Formulation and evaluation of diclofenac sodium dispersible tablets

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ABBREVIATIONS

ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC	Area under the curve
B/N	Batch number
BP	British Pharmacopoeia
cGMP	Current Good Manufacturing Practices
CoA	Certificate of Analysis
Cu	Copper
DSC	Differential scanning calorimetry
HCl	Hydrochloric acid
HPLC	High performance liquid chromatography
HSM	Hot-stage microscopy
ICH	International Conference on Harmonization
IR	Infrared spectroscopy
KBr	Potassium bromide
$KHCO_3$	Potassium bicarbonate
LOD	Limit of detection
LOQ	Limit of quantitation
MCC	Medicines Control Council
$NaHCO_3$	Sodium bicarbonate
NaOH	Sodium hydroxide

NMT	Not more than
NSAID	Non-steroidal, anti-inflammatory drug
PVC	Polyvinyl chloride
RH	Relative humidity
rpm	Rotations per minute
RSD	Relative standard deviation
RS	Reference standard
SD	Standard deviation
SOP	Standard operating procedure
SST	System suitable test
TGA	Thermogravimetric analysis
USP	United States Pharmacopoeia
UV	Ultraviolet
w/w	Weight/weight
w/v	Weight/volume
WHO	World health organization
XRPD	X-ray powder diffractometry

ABSTRACT

The Formulation and Evaluation of Diclofenac Sodium Dispersible Tablets

Diclofenac sodium is a non-steroidal, anti-inflammatory drug used for the relief of pain and inflammation. Many patients have difficulty swallowing tablets and consequently do not take medication as prescribed. To achieve optimum benefit of a drug, it is desirable to present it in a formulation which can rapidly disperse in water. This formulation is easier to swallow, therefore enhancing patient compliance.

The aim of this study was to develop a stable diclofenac sodium dispersible tablet for easier oral administration.

The first step in the product development was an investigative study into the physico-chemical properties, indications, side-effects and contra-indications of diclofenac sodium. Diclofenac sodium – excipient compatibility studies were performed as part of a preformulation study. Methods of evaluation included differential scanning calorimetry (DSC) and high performance liquid chromatography (HPLC). Four dispersible tablet formulations were developed. Kollidon CL-M® (crospovidone) and Disolcel® (croscarmellose sodium) were used as disintegrants in concentrations of 2% and 5% of the tablet mass. Tabletting was performed using a Cadmach® (India) single-punch tabletting machine. The four formulations were put on accelerated stability according to ICH guidelines for three months at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. HPLC was used to determine the identification, chromatographic purity and concentration of diclofenac sodium. Other tests included uniformity of mass, hardness, friability, disintegration, fineness of dispersion, loss on drying and dissolution.

Thermal compatibility studies revealed potential interactions between diclofenac sodium and the excipients. Since DSC results only serve as a rough indication of possible interactions, accelerated stability testing using HPLC was used as a more selective method to identify potential interactions between diclofenac sodium and excipients. The HPLC results revealed that no interactions exist between diclofenac sodium and the chosen excipients.

At the end of the stability period, no change in the physical appearance of the tablets was observed, except for the samples stored at 40°C/75% RH which showed a colour change from white to a very light brown after 3 months. Uniformity of mass remained within specification and average tablet mass and diameter remained relatively constant during stability testing. There was an increase in average thickness, hardness, disintegration time and percentage loss on

drying with time and increased stress conditions. This correlates with the decrease in friability observed with time. Differences in the disintegration times were noted between Kollidon CL-M® and Disolcel® formulations. The only formulation that disintegrated within 3 minutes was formulation B. Very few particles of formulation B were retained on the 710 µm sieve, indicating a homogeneous dispersion. Assay results for all four formulations were within specification throughout stability and no extra peaks ascribed to diclofenac related compound A or any other impurity were observed. After 30 minutes, more than 85% of diclofenac sodium in formulations A, B and D was dissolved. The diclofenac sodium in formulation C did not dissolve well. This correlates with the slow disintegration times of formulation C's tablets. Dissolution rates of formulations C and D decreased with time and increased stress conditions, with the effect more pronounced in the case of formulation C.

It can be concluded from the stability results that 5% Disolcel® as disintegrant was superior to a 2% concentration and to Kollidon CL-M® in concentrations of 2% and 5% of the tablet mass.

Formulation B (5% Disolcel®) was chosen as the most favourable formulation with the best marketing possibilities. Stability results were also used to determine storage conditions and set specifications for batch release and stability to ensure that all batches tested against these specifications, meet the requirements for quality, safety and efficacy.

UITTREKSEL

Die Formulering en Evaluering van Natriumdiklofenak Dispergeerbare tablette

Natriumdiklofenak is 'n nie-steroïde, anti-inflammatoriese geneesmiddel wat gebruik word vir die verligting van pyn en inflammasie. Baie pasiënte vind dit moeilik om tablette te sluk en neem gevolglik nie medikasie soos voorgeskryf nie. Om die optimale voordeel van 'n geneesmiddel te benut, is dit wenslik om dit in 'n doseervorm aan te bied wat vinnig in water kan dispergeer. Hierdie tipe doseervorm is makliker om te neem en verhoog sodoende pasiëntmeewerkendheid.

Die doel van hierdie studie was om 'n stabiele natriumdiklofenak dispergeerbare tablet te ontwikkel vir makliker orale toediening.

Die eerste stap in die nuwe produkontwikkeling was 'n uitgebreide literatuurstudie oor die fisies-chemiese eienskappe, indikasies, newe-effekte en kontra-indikasies van natriumdiklofenak. Studies om die verenigbaarheid van natriumdiklofenak met verskeie hulpstowwe te toets, is uitgevoer as deel van 'n pre-formulering studie. Metodes van evaluering het ingesluit DSC en HPLC. Vier dispergeerbare tabletformulerings is ontwikkel. Kollidon CL-M® en Disolcel® was gebruik as disintegreermiddels in konsentrasies van 2% en 5% van die tabletmassa. Tablettering is uitgevoer met 'n Cadmach® (India) enkelperstabletmasjien. Die vier formulerings is op versnelde stabiliteit geplaas volgens ICH-riglyne vir 3 maande by 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. HPLC is gebruik om die identifikasie, chromatografiese suiwerheid en konsentrasie van natriumdiklofenak te bepaal. Ander toetse het ingesluit massa-uniformiteit, hardheid, brosheid, disintegrasie, dispersiefynheid, verlies met verhitting en dissolusie.

Termiese verenigbaarheidstudies het potensiële interaksies tussen natriumdiklofenak en die hulpstowwe getoon. Aangesien DSC-resultate slegs as 'n indikasie van moontlike interaksies dien, is versnelde stabiliteitstoetsing gedoen waar HPLC gebruik is as 'n meer selektiewe metode om potensiële interaksies tussen natriumdiklofenak en die hulpstowwe aan te dui. Die HPLC-resultate toon geen interaksies tussen natriumdiklofenak en die gekose hulpstowwe nie.

Aan die einde van die stabiliteitsperiode is geen fisiese veranderinge by die tablette waargeneem nie, behalwe die tablette wat by 40°C/75%RH gestoor is waar 'n kleurverandering van wit na 'n ligbruin plaasgevind het. Massa-uniformiteit was binne die spesifikasies en die gemiddelde tabletmassa en diameter het relatief konstant gebly gedurende die stabiliteitstoetsing. 'n Toename in gemiddelde dikte, hardheid, disintegrasietyd en persentasie

verlies met verhitting is waargeneem oor tyd en met verhoogde streskondisies. Dit korreleer met die afname in brosheid waargeneem oor tyd. Verskille in die disintegrasietye is waargeneem tussen Kollidon CL-M® en Disolcel® formulerings. Die enigste formulering wat binne 3 minute gedisintegreer het, was formulering B. Byna geen partikels van formulering B is op die 710 µm sif agtergelaat nie, wat dui op 'n homogene dispersie. Die konsentrasie natriumdiklofenak van al vier formulerings was binne spesifikasie tydens stabiliteit en geen ekstra pieke wat toegeskryf kan word aan diklofenak verwante stof A of enige ander onsuiwerheid is opgemerk nie. Na 30 minute was meer as 85% van natriumdiklofenak in formulerings A, B en D in oplossing tydens dissolusietoetsing. Die dissolusietempo van formulering C was betekenisvol stadiger as dié van die ander 3 formulerings. Dit korreleer met die stadige disintegrasietye van formulering C se tablette. Dissolusietempo's van formulerings C en D het afgeneem oor tyd en met verhoogde streskondisies, met die effek meer merkbaar in die geval van formulering C.

Uit die stabiliteitsresultate kan afgelei word dat 5% Disolcel® as disintegreermiddel beter is as 'n 2% konsentrasie en beter as Kollidon CL-M® in konsentrasies van 2% en 5% van die tabletmassa.

Formulering B (5% Disolcel®) is gekies as die gunstigste formulering met die beste bemarkingsmoontlikhede. Stabiliteitsresultate was ook gebruik om bergingskondisies te bepaal en om spesifikasies te stel vir lotvrystelling en stabiliteit om te verseker dat alle lotte wat teen hierdie spesifikasies getoets word, aan die vereistes vir kwaliteit, veiligheid en effektiwiteit voldoen.

AIM AND OBJECTIVES

Diclofenac, a phenyl-acetic acid derivative, is a non-steroidal, anti-inflammatory and analgesic agent (Sweetman, 2002:31). It is available in several dosage forms such as solid forms for oral administration, parenteral-, ophthalmic-, rectal- and topical dosage forms. Indications range from rheumatoid arthritis to dysmenorrhea.

The aim of this study was to formulate a stable diclofenac sodium dispersible tablet. Advantages of a dispersible tablet include easier administration, enhanced patient compliance (Fielden, 1997:8) and a faster therapeutic effect.

The main objectives of this study were:

- To determine incompatibilities between diclofenac sodium and excipients chosen for formulation.
- To develop and validate a stability indicating method for the HPLC assay and the chromatographic purity of diclofenac sodium in diclofenac sodium dispersible tablets.
- To formulate a diclofenac sodium dispersible tablet with acceptable organoleptic properties.
- To determine the physical and chemical stability of the formulated diclofenac sodium dispersible tablets.
- To set final product specifications for release and stability purposes and determine appropriate storage conditions for the diclofenac sodium dispersible tablets.

CHAPTER 1

Diclofenac Sodium: Pharmaceutical and Pharmacological Properties

1.1 Introduction

Diclofenac, a phenyl-acetic acid derivative, is a non-steroidal, anti-inflammatory drug (NSAID). It is used mainly as the sodium salt for the relief of pain and inflammation in various conditions. Diclofenac sodium has an unpleasant taste and causes gastric irritation (Sweetman, 2002:31). The main aim of developing diclofenac sodium was to synthesise a NSAID with a high level of activity and good tolerability. Diclofenac sodium was developed after phenylbutazone made an appearance in 1952 and after mefenamic acid, ibuprofen and indomethacin were introduced in the 1960's (Sallmann, 1986:29).

In this chapter the pharmaceutical and pharmacological properties of diclofenac sodium will be discussed.

1.2 Description of diclofenac sodium

1.2.1 Nomenclature

1.2.1.1 Chemical names

(1) 2-[(2,6-dichlorophenyl) amino] benzene-acetic acid mono sodium salt.

(2) [o-(2,6-dichloro-anilino) phenyl] acetic acid sodium salt.

(3) Sodium [o-[(2,6-dichlorophenyl) amino] phenyl] acetate (Adeyeye & Li, 1990:124).

1.2.1.2 Nonproprietary name

Diclofenac Sodium.

1.2.1.3 Proprietary name/originator

Voltaren/Novartis®.

1.3 Formulae

1.3.1 Empirical formula

$C_{14}H_{10}Cl_2NNaO_2$ (BP, 2005).

1.3.2 Structural formula

The structural formula of diclofenac sodium is shown in figure 1.1.

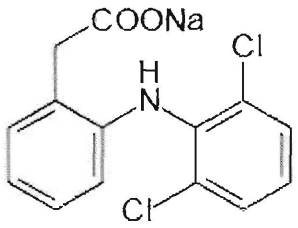

Figure 1.1: Structural formula of diclofenac sodium (Budavari, 2001:542).

1.4 Molecular weight

The molecular weight of diclofenac sodium is 318.1 g/mol (BP, 2005).

1.5 Appearance, colour and odour

Diclofenac sodium is an odourless, white or slightly yellowish, crystalline powder (Adeyeye & Li, 1990:124).

1.6 Pharmaceutics of diclofenac sodium

1.6.1 Preparations available

Diclofenac sodium preparations are available for oral, rectal, parenteral, topical and ophthalmic administration.

Oral forms

(1) Delayed-release (enteric coated) tablets (25 mg, 50 mg and 75 mg diclofenac sodium) (Dollery, 1999:D88, D89).

(2) Sustained-release tablets (75 mg and 100 mg diclofenac sodium) (Dollery, 1999:D88, D89).

(3) Capsules (Rotini & Marchi, 2002:1-3).

(4) Sustained-release capsules (Yoshikazu & Yoshinori, 1998:1).

(5) Lozenges (Fenghua *et al.*, 2005:1-22).

(6) Powder for oral solution (Applied pharma research S.A.).

Rectal forms

(1) Suppositories (12.5 mg, 25 mg, 50 mg and 100 mg diclofenac sodium) (Dollery, 1999:D89).

Parenteral forms

(1) Ampoules for intramuscular injection or intravenous infusion containing 25 mg diclofenac sodium/ml (Dollery, 1999:D89).

Topical forms

(1) Gel (3% w/w diclofenac sodium) (Bradley Pharmaceuticals®, Inc.).

(2) Topical spray (Wang, 1997:1-25).

(3) Diclofenac sodium cream/ointment (Sekine *et al.*, 1998:1-11).

(4) Adhesive transdermal formulation containing diclofenac sodium in suspension (Passoni *et al.*, 2003:1-10).

Ophthalmic form

(1) Sterile eye-drop solution (0.1% w/v diclofenac sodium) (Dollery, 1999:D89).

1.6.2 Dosage and administration

Diclofenac sodium is administered via routes mentioned in 1.6.1 with the maximum daily dose of 150 mg for adults, but doses should be reduced in the elderly (Gibbon, 2003:353).

Adult dose

(1) Oral: 25–50 mg 3 times daily with meals (Gibbon, 2003:353) or 100 mg sustained-release form which can be supplemented with 25 mg or 50 mg of the conventional tablet if needed (Dollery, 1999:D89).

(2) Rectal: 75–150 mg daily in divided doses (Sweetman, 2002:31) or 100 mg at night (Gibbon, 2003:353).

(3) Intramuscular: 75 mg once or twice daily. A second injection can be given within 24 hours in severe cases using the other buttock (Dollery, 1999:D89).

(4) Topical: The amount needed depends on the size of the affected area and enough gel must be applied to adequately cover the area. Apply twice daily (Bradley Pharmaceuticals®, Inc.).

(5) Ophthalmic doses: Instill 1–2 drops within the hour before surgery and 1 drop 15 minutes after surgery. Thereafter, 1 drop 4–5 times daily for 3 days (Novartis® ophthalmics).

Children

Diclofenac sodium is not recommended for general analgesic purposes in children. It has been used with good effect for juvenile chronic arthritis. In these limited cases the dosage for children over 2 years (oral or rectal) is 1–3 mg/kg/day in 2-3 divided doses (Gibbon, 2003:353).

1.6.3 Containers and storage

General storage principles for diclofenac sodium according to Dollery (1999:D89) are summarised as follows:

(1) Diclofenac preparations should be stored below 30°C.

(2) Oral forms should be protected from moisture.

(3) Injections should be protected from light.

(4) Eye drops should be discarded 30 days after opening (Novartis® ophthalmics).

1.7 Pharmacology of diclofenac sodium

1.7.1 Mechanism of action

Diclofenac sodium is a non-steroidal anti-inflammatory drug with analgesic and anti-pyretic properties. It inhibits cyclooxygenase 1 and -2 activity (Figure 1.2), hence reducing the production of prostaglandins and thromboxane associated with pain and inflammation (Dollery, 1999:D88). Prostaglandins act on a variety of cells such as vascular smooth muscle cells and spinal neurons. Its actions include muscular constriction and inflammatory mediation (Katzung, 2001:316). Diclofenac sodium also decreases arachidonic acid bioavailability (Katzung, 2001:604) and appears to reduce intracellular concentrations of free arachidonate in leukocytes (Hardman & Limbird, 2001:709).

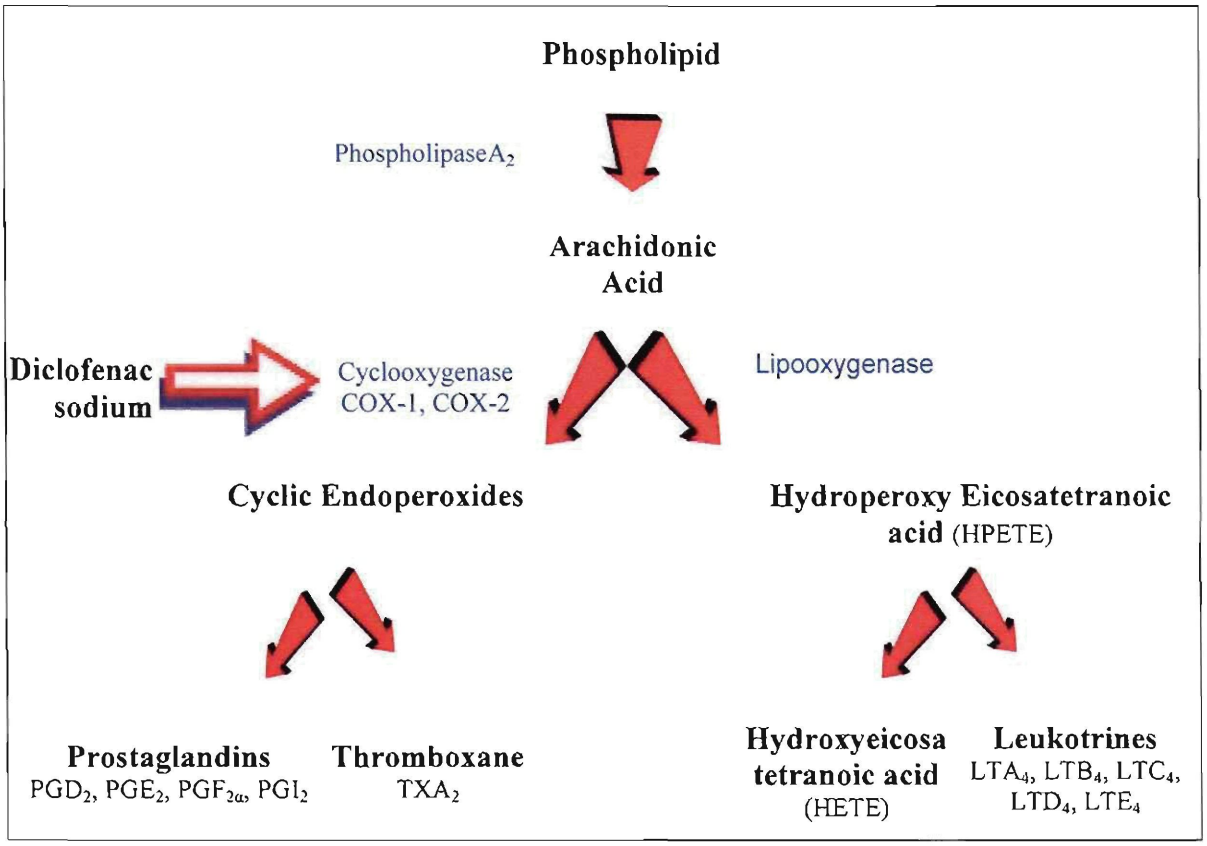

Figure 1.2: Arachidonic acid pathway (Kakkilaya, 2002).

1.7.2 Indications and therapeutic uses

The most common indications and therapeutic uses of diclofenac sodium according to Dollery (1999:D89) include rheumatoid arthritis, osteoarthritis, acute musculoskeletal disorders (e.g. tendinitis, sprains and dislocations), ankylosing spondylitis, acute gout, postoperative pain, renal colic and control of pain and inflammation in orthopedic, dental and other minor surgery. Diclofenac sodium is also used for dysmenorrhea (Hardman & Limbird, 2001:709).

Ophthalmic indications of diclofenac sodium include postoperative inflammation after cataract extraction, allergic conjunctivitis and corneal abrasions (Anon, 2006:9A). Gaynes and Fiscella (2002:237) also reported postoperative pain following refractive surgery and prevention and treatment of cystoid macular oedema as indications for diclofenac sodium.

1.7.3 Contraindications

Contraindications of diclofenac sodium include peptic ulcers (active or suspected), gastrointestinal bleeding, previous sensitivity to diclofenac sodium, asthma, concomitant NSAID (intravenous) or anti-coagulant use, operations associated with a high risk of haemorrhage (intravenous use) and history of confirmed or suspected cerebrovascular bleeding (intravenous use) (Dollery, 1999:D89). According to Gibbon (2003:352) suppositories are contraindicated in patients with proctitis or haemorrhoids.

1.7.4 Side-effects and special precautions

Diclofenac sodium may cause the following side-effects: gastrointestinal effects (ranging from mild irritation to erosion, peptic ulceration and bleeding), hypersensitivity reactions (bronchospasm, skin rashes, pruritus, urticaria and angioedema) and central nervous system effects (headache, dizziness and drowsiness). Hepatic dysfunction occurs occasionally (Gibbon, 2003:353).

Suppositories may cause local irritation (Gibbon, 2003:353).

Adverse topical effects include redness of the eye, a burning sensation immediately after instillation of the eye drops. It rarely causes itching, blurred vision or photosensitivity (Novartis® ophthalmics). Diclofenac sodium ophthalmic preparations should not be used by patients who wear soft contact lenses (Sweetman, 2002:30).

Diclofenac sodium injections may cause pain, and occasionally, tissue damage at the site of injection (Sweetman, 2002:30).

Diclofenac sodium is not recommended for children, nursing mothers or pregnant women (Hardman & Limbird: 2001:710).

1.7.5 Drug interactions

Dollery (1999:D90) reported the following interactions with diclofenac sodium:

(1) Lithium: Diclofenac sodium decreases renal clearance and increases plasma concentrations of lithium.

(2) Digoxin: Diclofenac has been reported to increase levels of digoxin.

(3) Diuretics: Diclofenac inhibits the activity of diuretics and potentiate the effects of potassium sparing diuretics.

(4) Methotrexate: Increased levels and toxicity of methotrexate.

Other drugs that cause interactions with diclofenac sodium according to Gibbon (2003:352-353) include:

(1) Oral anticoagulants: Enhanced risk of bleeding.

(2) Glucocorticosteroids: May enhance the potential toxicity of both medicines.

(3) Highly protein-bound agents (e.g. sulphonamides, phenytoin, verapamil, nifedipine): Diclofenac may displace such agents from plasma protein-binding sites, increasing their therapeutic effects and toxicity.

(4) Probenecid: May inhibit renal excretion of diclofenac.

Branthwaite and Nicholls (1991:252) also reported an interaction between cyclosporine and diclofenac sodium. Deterioration in renal function occurs with concomitant use.

1.8 Pharmacokinetics of diclofenac sodium

1.8.1 Absorption

Oral absorption is rapid, but according to Katzung (2001:604) diclofenac sodium's bioavailability is only 30–70% due to the first pass metabolism. The absorption rate, but not the extent, is decreased by food (Gibbon, 2003:352).

Peak concentrations in plasma are reached within 2 to 3 hours (Hardman & Limbird, 2001:709).

Diclofenac sodium is rapidly absorbed when given as rectal suppository and by intramuscular injection. It is also absorbed percutaneously (Sweetman, 2002:31).

Diclofenac sodium in an ophthalmic solution is promptly absorbed into the anterior chamber, where it reaches its highest concentration 2 hours and 24 minutes after topical application and remains at significantly elevated levels for longer than 4 hours (Costagliola *et al.*, 2005:611).

1.8.2 Distribution

Diclofenac sodium accumulates in the synovial fluid (Dollery, 1999:D88).

In a study of six mothers treated for 1 week with 100 mg diclofenac sodium daily, none of the 59 milk samples contained detectable amounts of unchanged drug (Dollery, 1999:D88).

Riess and Stierlin (1978:22) recorded that, within its therapeutic concentration range, 99.7% of diclofenac sodium is bound to the proteins in human serum. No less than 99.0–99.4% is accounted for by binding to serum albumin.

1.8.3 Metabolism

In man, diclofenac sodium is metabolised mainly by hydroxylations at various positions of the phenyl rings. The phenolic, urinary metabolites identified by Stierlin *et al.* (1979:606) include 4'-hydroxy diclofenac, 5-hydroxy diclofenac, 3'-hydroxy diclofenac and 4',5-dihydroxy diclofenac. Faigle *et al.* (1988:1191) isolated a fifth metabolite, namely 3'-hydroxy-4'-methoxy diclofenac.

Figure 1.3 illustrates the five metabolites of diclofenac sodium.

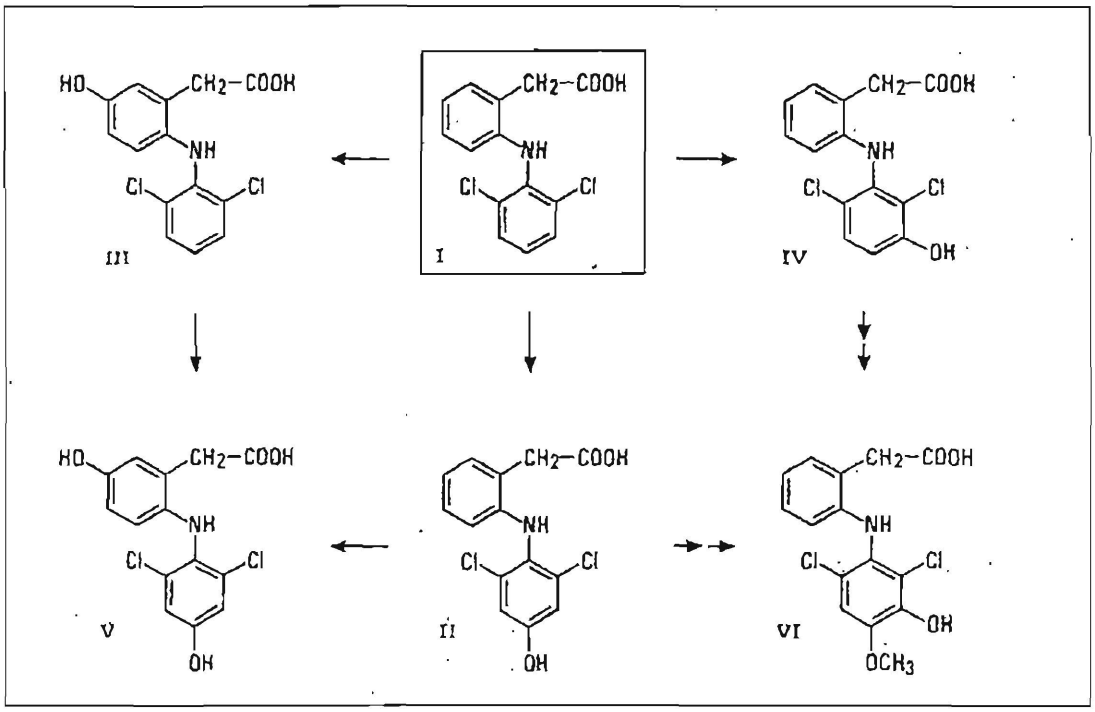

Figure 1.3: Phenolic metabolites of diclofenac sodium in man. I: Diclofenac (free acid); II: 4'-hydroxy diclofenac; III: 5-hydroxy diclofenac; IV: 3'-hydroxy diclofenac; V: 4',5-dihydroxy diclofenac; VI: 3'-hydroxy-4'-methoxy diclofenac (Faigle *et al.*, 1988:1196).

The phenolic metabolites are largely conjugated before excretion (Stierlin *et al.*, 1979:609). Formation of metabolite VI involves both oxidation and methylation (Faigle *et al.*, 1988:1196).

Experiments done by Degen *et al.* (1988:1449-1454) showed that only about 6% of a diclofenac sodium dose was found in urine in the form of free and conjugated diclofenac. Of the metabolites measured, 4'-hydroxy diclofenac was the most prominent one, corresponding to about 13% of the dose. Metabolites III – VI were of minor importance in urine and together they represented about 17% of the dose.

1.8.4 Metabolism of diclofenac sodium in patients with renal impairment

The results of the study done by Stierlin *et al.* (1978:35) demonstrate that the plasma concentration of unchanged diclofenac sodium is not increased when renal function is reduced.

The plasma concentrations of total diclofenac metabolites tend to be higher in patients with impaired renal function than in healthy patients. These metabolites are largely present in conjugated form. Conjugation reduces pharmacological activity; therefore patients with renal insufficiency may be given the same doses of diclofenac sodium as patients with normal kidney function (Stierlin *et al.*, 1978:35).

1.8.5 Elimination

Diclofenac sodium has a half-life of 1–2 hours (Gibbon, 2003:352). Studies done by Riess and Stierlin (1978:20) showed that excretion in a rat and dog is predominantly biliary, whereas in the rhesus monkey 80% of the dose is excreted via the kidneys. In man renal excretion exceeds biliary excretion.

Diclofenac sodium is excreted in the form of glucuronide and sulfate conjugates in the urine (65%) and bile (35%) (Hardman & Limbird, 2001:709). Little or no free unchanged diclofenac is excreted in the urine (Gibbon, 2003:352).

1.9 Conclusion

The pharmaceutical and pharmacological properties of diclofenac sodium discussed in this chapter showed that diclofenac sodium is a widely used anti-inflammatory and analgesic agent, available in several dosage forms such as solid forms for oral administration, parenteral-, ophthalmic-, rectal- and topical dosage forms.

Diclofenac sodium reduces the production of prostaglandins and thromboxane by inhibiting the enzyme cyclooxygenase 1 and -2.

Indications range from rheumatoid arthritis to dysmenorrhea with a maximum dose of 150 mg per day. The most common side-effect associated with the use of diclofenac sodium is gastric irritation. Contraindications include peptic ulcers and asthma.

Diclofenac sodium is well absorbed via the following routes: oral, topical, rectal and ophthalmic. Five metabolites have been identified which are eliminated mainly by renal excretion.

In the next chapter the physico-chemical properties of diclofenac sodium will be discussed. Several methods of characterisation will also be examined.

CHAPTER 2

Physico-chemical Properties of Diclofenac Sodium and Methods of Characterisation

2.1 Introduction

The purpose of this chapter is to provide general information on the physico-chemical properties of diclofenac sodium. Analytical methods used to identify and characterise diclofenac sodium are also described and/or investigated.

2.2 Physico-chemical properties of diclofenac sodium

Table 2.1 summarises the analytical specifications and results of diclofenac sodium generated by the supplier, obtained from the certificate of analysis (CoA).

Table 2.1: Physico-chemical properties of diclofenac sodium raw material, batch number D10-6001BFI (ANDENEX-CHEMIE, Hamburg, Germany)

Test	Specifications	Results
Description	A white or slightly yellowish, crystalline powder	White crystalline powder
Identification (IR)	Corresponds to the spectrum of diclofenac sodium reference standard	Passed
Identification (Clarity and colour)	Clear, absorbance measured at 440 nm is not greater than 0.05	Clear, 0.0005
pH	7.0 - 8.5	7.4
Loss on drying	Not more than 0.5%	0.1%
Heavy metals	Not more than 10 ppm	Passed
Chromatographic purity:		
- Related substances	Individual impurities < 0.2%	Nil
- Total impurities	Not more than 0.5%	Nil
Assay (by potentiometric titration)	Between 99.0 and 101.0% calculated on the dried basis	100.4%

2.2.1 Solubility

Diclofenac sodium is sparingly soluble in water, soluble in alcohol and slightly soluble in acetone (BP, 2005).

Table 2.2 defines the terms used in statements of approximate solubilities at a temperature between 15 and 25°C.

Table 2.2: Solubility definitions (BP, 2005)

Descriptive term	Approximate volume of solvent in milliliters per gram of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10 000
Practically insoluble	More than 10 000

The equilibrium solubility of diclofenac sodium was performed by Adeyeye and Li (1990:130). The solubility in various solvents (at 25 °C) is tabulated in Table 2.3.

Table 2.3: Solubility of diclofenac sodium in various solvents (Adeyeye & Li, 1990:130)

Solvent	Solubility (mg/ml)
Deionized water (pH 5.2)	>9
Methanol	>24
Acetone	6
Acetonitrile	<1
Cyclohexane	<1
pH 1.1 (HCl)	<1
pH 7.2 (Phosphate buffer)	6

2.2.2 Melting range

Diclofenac sodium melts at about 280.0°C, with decomposition (BP, 2005).

2.2.3 Density

Density values were obtained from the Drug Master File (SYN-TECH CHEM. & PHARM. CO., LTD).

2.2.3.1 Bulk density

0.3500-0.3900 g/ml.

2.2.3.2 Tapped density

0.6100-0.6700 g/ml.

2.2.4 Potential isomers

The diclofenac sodium molecule does not contain any asymmetric carbon atom (see Figure 1.1). There is not any potential isomerism in diclofenac sodium (Drug Master File, SYN-TECH CHEM. & PHARM. CO., LTD).

2.3 Methods of identification and characterisation of diclofenac sodium

X-ray powder diffractometry (XRPD), thermal behaviour and spectroscopic behaviour (infrared spectroscopy) of diclofenac sodium, batch number D10-6001BFI, had been investigated.

2.3.1 X-ray powder diffractometry

XRPD is a non-destructive method of characterisation. It is widely used for the identification of solid phases. Every crystalline form of a compound has a unique X-ray powder pattern, making XRPD particularly suited for the identification of different polymorphic forms of a compound (Suryanarayanan, 1995:188).

Two pseudo polymorphic forms of diclofenac sodium have been identified: Diclofenac sodium tetrahydrate (Reck *et al.*, 1988:771) and diclofenac sodium pentahydrate (Muangsin *et al.*, 2002:967). Literature does not specify the favourable form of diclofenac sodium for formulation.

2.3.1.1 Method and sample preparation

The X-ray powder diffraction data for the diclofenac sodium raw material and diclofenac sodium reference standard (diclofenac sodium RS)[1] was obtained using a Bruker D8 Advance diffractometer (Bruker, Germany). Table 2.4 describes the conditions for the recording of the XRPD patterns.

Table 2.4: Measurement conditions for XRPD analysis

Measurement conditions	
Target:	Cu
Voltage:	40 kV
Current:	30 mA
Divergence slit:	2 mm
Antiscatter slit:	0.6 mm
Detector slit:	0.2 mm
Scanning speed:	2°/min
Sample holder:	Aluminium sample holder
Sample size:	± 200 mg

2.3.1.2 Results and discussion

The X-ray powder diffraction patterns of diclofenac sodium RS and diclofenac sodium raw material are depicted Figure 2.1.

The XRPD pattern of the diclofenac sodium raw material was found to be similar compared to that of the diclofenac sodium reference standard.

2.3.2 Thermal methods

Thermal methods include differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and hot-stage microscopy (HSM). These techniques will be discussed in the following sections.

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[1] Diclofenac sodium reference standard: B/N X068409.

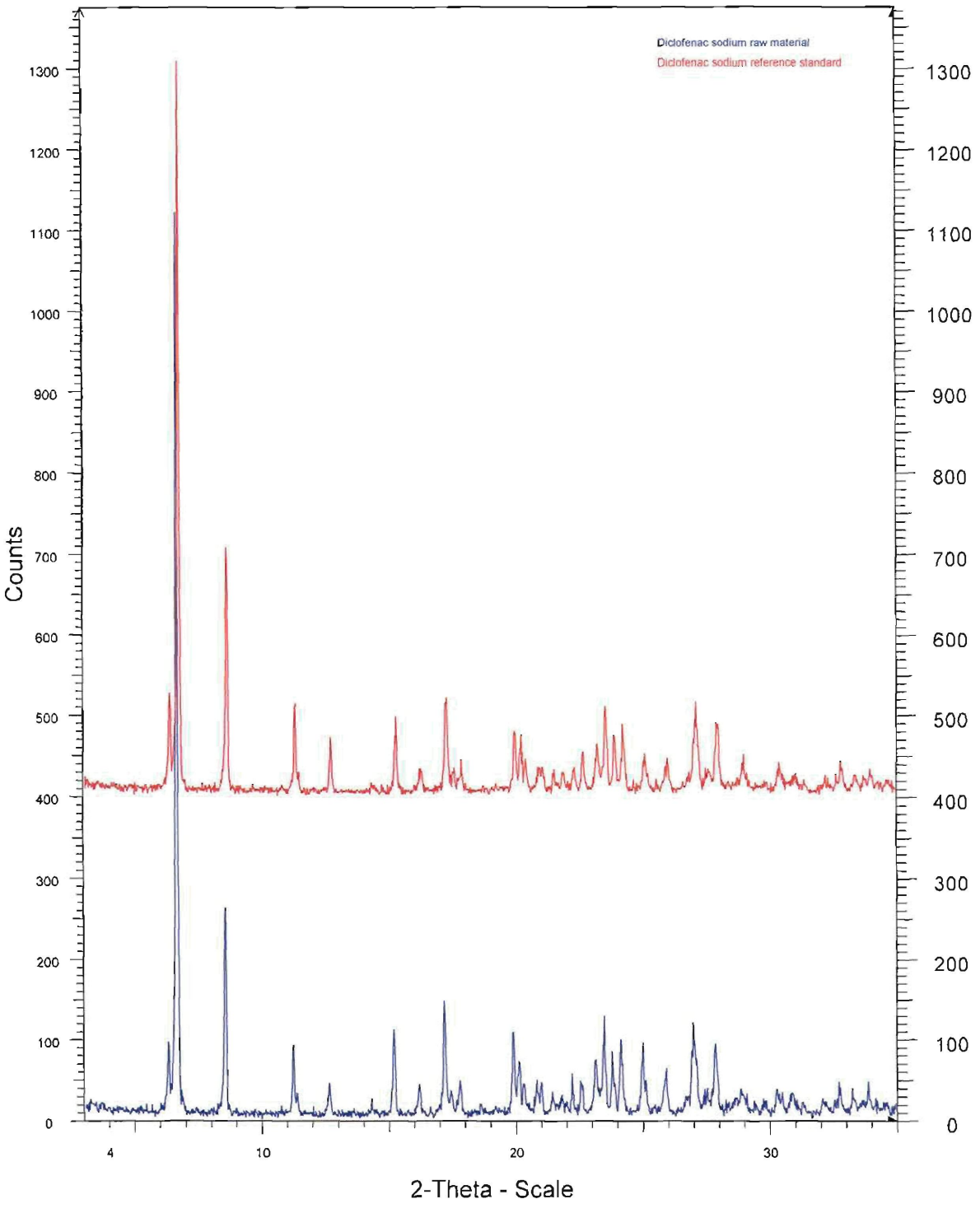


Figure 2.1: X-ray powder diffraction patterns of diclofenac sodium RS and diclofenac sodium raw material.

2.3.2.1 Differential scanning calorimetry (DSC)

DSC measures the difference between the temperature of a sample and a reference compound as the temperature of the system is changed, providing information on the enthalpy change of varous solid-state processes (Byrn *et al.*, 1999:81).

Thermal reactions observed in DSC thermograms can be endothermic or exothermic (McCauley & Brittain, 1995:224). Endotherms represent processes in which heat is absorbed and exotherms processes where heat is evolved (Byrn *et al.*, 1999:84). Examples of endothermal events include the following: melting, desolvation of solvated crystal systems, boiling, sublimation, vaporisation, decomposition or inter-crystal rearrangements. Exotermic reactions include crystallisation or oxidative decomposition of samples (McCauley & Brittain, 1995:224).

According to Wendlandt (referred to by Palomo *et al.*), the shape, number and location of these endo- and exothermic peaks are used to identify a substance (Palomo *et al.*, 1999:83, 84).

2.3.2.1.1 Method and sample preparation

DSC thermograms were recorded with a Mettler Toledo DSC822^{e}700 (Mettler, Switzerland) instrument. Table 2.5 describes the conditions for recording the DSC thermograms. The instrument was calibrated using ultra-pure indium as a calibration standard. DSC thermograms of diclofenac sodium reference standard and diclofenac sodium raw material were recorded.

Table 2.5: Measurement conditions for DSC analysis

Measurement conditions	
Atmosphere:	Nitrogen
Flow rate:	30 ml/min
Heating rate:	10°C/min
Cell:	40 µl Aluminium crimp cell
Sample size:	± 2 mg

2.3.2.1.2 Results and discussion

The DSC thermograms of diclofenac sodium RS and diclofenac sodium raw material are illustrated in Figure 2.2.

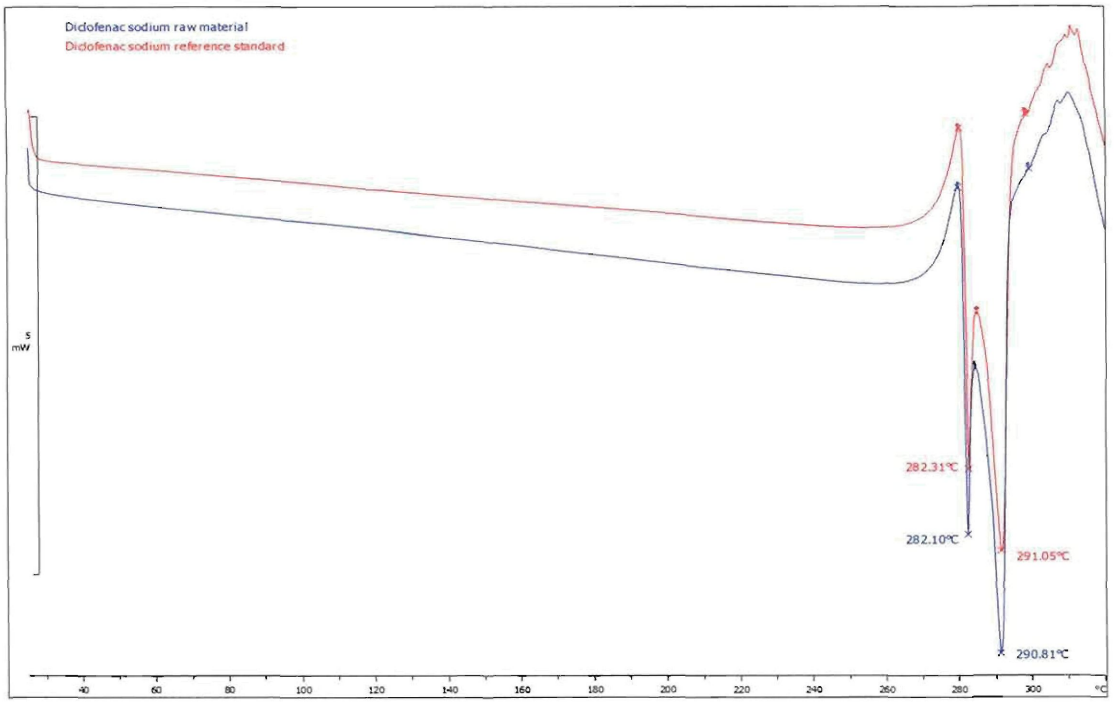


Figure 2.2: DSC thermograms of diclofenac sodium RS and diclofenac sodium raw material.

In the diclofenac sodium RS and diclofenac sodium raw material DSC thermograms, two endothermal events are visible at 282.10°C and 290.81°C. The first endotherm represents the melting point and the second decomposition. HSM was performed to examine physical changes of diclofenac sodium at these temperatures.

2.3.2.2 Hot-stage microscopy (HSM)

HSM is a thermal analytical technique where the sample can be heated at different rates in the sample chamber. It is advised to use HSM in conjunction with DSC and TGA (Steele, 2004:69).

2.3.2.2.1 Method and sample preparation

A Nikon Eclipse E400 thermo-microscope (Tokyo, Japan) with a Leitz 350 heating unit (Leitz – now known as Leica Microsystems – Wetzlar, Germany) and a Metratherm 1200d thermostat was used. A small amount of diclofenac sodium raw material was placed on a microscope slide and covered with a cover slide. The sample was observed under the thermomicroscope at a temperature range from 24-288°C. Photographs were taken using a Nikon Coolpix 5400 digital camera (Tokyo, Japan) which was attached to the microscope.

2.3.2.2.2 Results and discussion

Table 2.6 provides a summary of the HSM observations of diclofenac sodium at a temperature range of 24-288°C.

Table 2.6: Photomicrographs of diclofenac sodium obtained with hot stage microscopy (HSM)

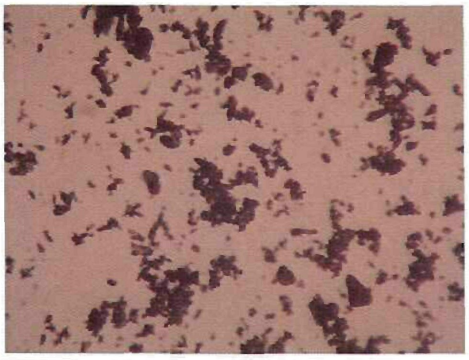
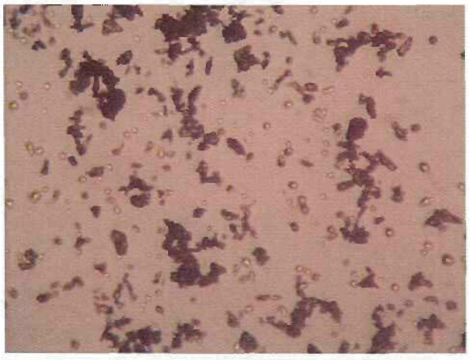
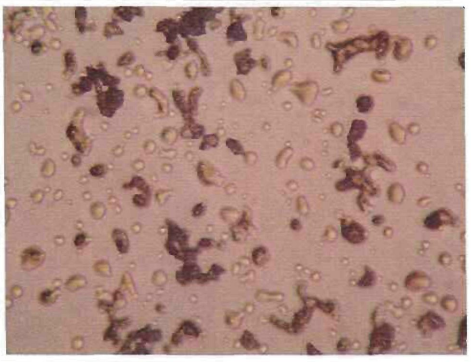
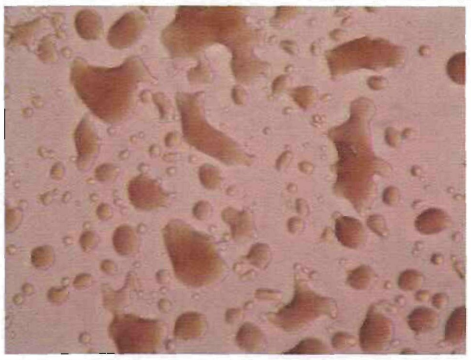
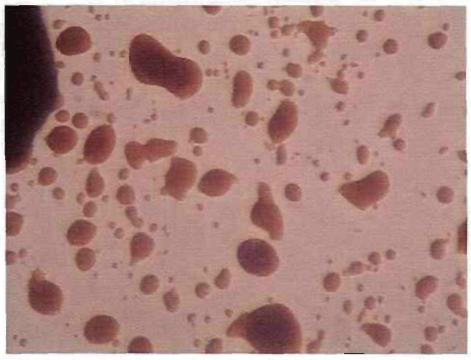
Photomicrograph	Temperature (°C)	Observation
	24	Diclofenac sodium powder at room temperature
	260	Melting of crystals started at 260°C
	265	Melting continued

Table 2.6: Continued

Photomicrograph	Temperature (°C)	Observation
	275	Melting completed
	288	Decomposed diclofenac sodium (a black powder was visible on the microscope slide)

HSM confirmed the DSC observations, namely that the endotherm at 282.10°C could be attributed to the melting of the sample and the 290.81°C endotherm to the decomposition of the sample.

2.3.2.3 Thermogravimetric analysis (TGA)

TGA can be used to detect the amount of weight lost on heating a sample (Komatsu *et al.*, 1994:1631). This method can detect the presence of water or solvent in different locations in the crystal structure (Gibson, 2004:70).

2.3.2.3.1 Method and sample preparation

Approximately 10 mg of the diclofenac sodium RS and diclofenac sodium raw material were weighed into an open platinum cell. Changes in mass at elevated temperatures were recorded with a Shimadzu TGA-50 instrument (Shimadzu, Kyoto, Japan). The samples were heated at a heating rate of 10°C/min under a nitrogen purge of 35 ml/min, to a maximum temperature of 240°C.

2.3.2.3.2 Results and discussion

TGA revealed no significant weight loss when heated from 25-240°C, indicating that the anhydrous form of diclofenac sodium was used.

2.3.3 Infrared spectroscopy (IR)

IR spectroscopy is used to detect the presence of functional groups (Palomo *et al.*, 1999:84). It is based on the measurement of the vibrational modes of bonded atoms, making it a primary tool for investigating molecular properties and polymorphic characterisation (Bernstein, 2002:125). According to Silverstein *et al.* (1981:95) it is unlikely that two compounds, except enantiomers, would give the same infrared spectrum.

2.3.3.1 Method and sample preparation

A Nicolet Nexus 470-FT-IR spectrometer (Nicolet instrument corporation, Maddison, Wisconsin, USA) was used to record the diclofenac sodium RS and –raw material IR spectra, over a range of 400-4000 cm^{-1}. The DRIFTS (diffuse reflectance infrared Fourier transform spectroscopic) method was used. KBr was used as background. The samples were dispersed in KBr and the IR spectra measured in a reflectance cell.

2.3.3.2 Results and discussion

The IR spectra of diclofenac sodium RS and diclofenac sodium raw material are depicted in Figure 2.3.

The IR spectrum of the diclofenac sodium raw material was found to be similar compared to that of the diclofenac sodium reference standard.

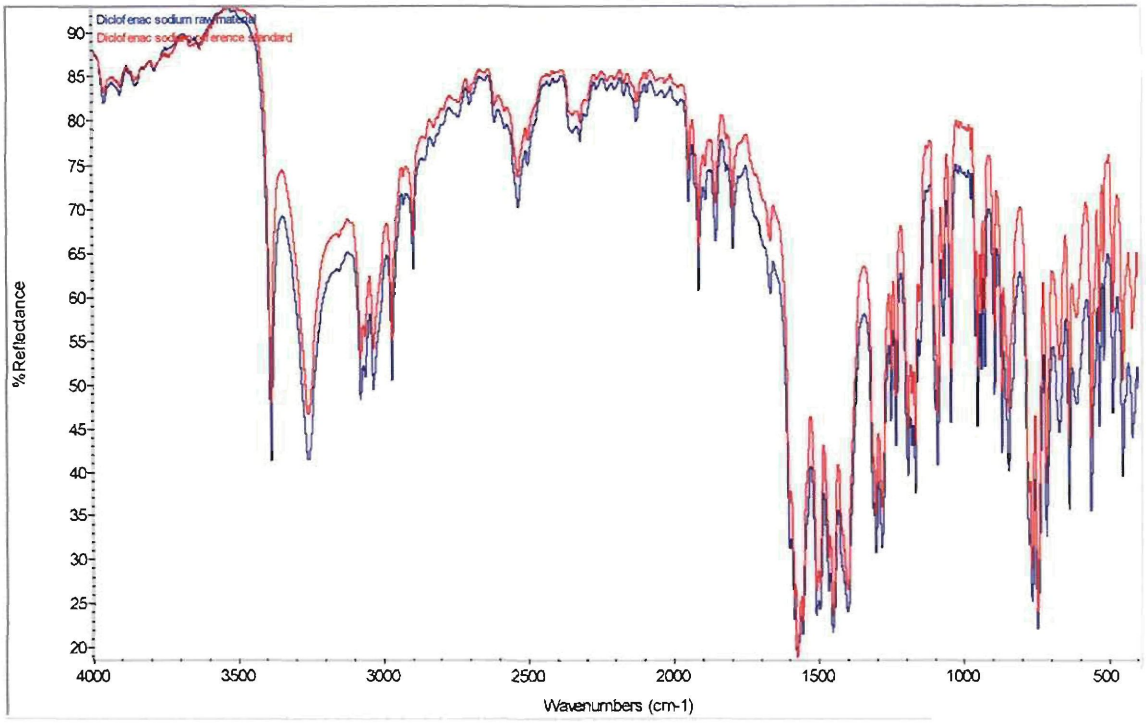


Figure 2.3: IR spectra of diclofenac sodium RS and diclofenac sodium raw material.

2.4 Conclusion

Physico-chemical properties of diclofenac sodium described in this chapter included solubility, melting range, density and potential isomers. The solubility of diclofenac sodium is pH dependent. In acidic solutions the solubility is less than 1 mg/ml and solubility increases with pH > 6.5. Diclofenac sodium melts at about 280°C, with decomposition. There is no potential isomerism in diclofenac sodium.

Methods of characterisation included X-ray powder diffractometry (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot-stage microscopy (HSM) and infrared spectroscopy (IR). The XRPD patterns and IR spectra of diclofenac sodium raw material were similar to that of a diclofenac sodium reference standard. DSC confirmed a melting point at about 282°C, with decomposition at about 291°C. This was confirmed by HSM. TGA analysis showed that the diclofenac sodium raw material was in the anhydrous form.

In the next chapter the compatibility between diclofenac sodium and selected excipients will be discussed.

CHAPTER 3

Diclofenac Sodium-Excipient Compatibility Studies

3.1 Introduction

Before commencing with formulation, compatibility studies must be performed as part of good development practice and a pre-formulation study. It is important to screen excipients for compatibility, i.e. active pharmaceutical ingredient (API) vs. excipients, because stability studies on formulated products are time consuming and expensive, emphasising the need to minimise the number of model formulations.

With compatibility studies, the chemical and physico-chemical compatibility of the API with possible excipients under stress conditions must be determined (WHO, 2005:138). The reason being, that the stability of a formulation depends, amongst other factors, on the compatibility of the API with the excipients. The excipients can affect the solid-state stability of a drug in various ways; directly as a chemical reaction between the drug and the excipients or mostly indirectly by sorption of moisture and/or catalysis (Botha & Lötter, 1990a:1946).

No attempt was made during this study to determine the nature of the interactions (if any), whether it is chemical, physical or complex formation.

Methods of evaluation for possible interactions included differential scanning calorimetry (DSC) and high performance liquid chromatography (HPLC).

3.2 Excipients used in compatibility studies

In Table 3.1 excipients used in the compatibility studies, as well as the functional description, supplier and batch number of each are given.

Table 3.1: Excipients used in compatibility studies

Chemical names (Trade names)	Functional description	Manufacturer/ supplier	Batch number
Colloidal silicon dioxide (Aerosil®)	Anti-caking agent, glidant, tablet disintegrant	DB Fine Chemicals	VA69311
Croscarmellose sodium (Disolcel®)	Tablet disintegrant	Mingtai Chemical	40308-S
Crospovidone (Kollidon CL-M®)	Tablet disintegrant	BASF	38-9264
Magnesium stearate[1] (Kemilub EM-F-V®)	Lubricant	Kirsch Pharma	472131
Microcrystalline cellulose (Avicel® pH 101)	Tablet binder/diluent	Hachimie	710
Peppermint flavour	Flavouring agent	Givaudan	8004074722
Potassium bicarbonate	Taste masking agent	Merck	1026855
Saccharine sodium	Sweetening agent	Merck	K33960142
Sodium bicarbonate	Taste masking agent	Merck	1028906

1: Magnesium stearate from vegetable origin

3.3 Compatibility study using differential scanning calorimetry (DSC)

DSC allows fast evaluation of possible incompatibilities between the API and excipients in formulations (Botha & Lötter, 1990b:674). It should be noted that DSC experiments for excipient screening are a rapid, but rough indication to identify possible interactions. It is possible that DSC responses may show no indication of interaction or a false-positive response indicative of an interaction. The reason for this is that DSC transitions are seen at temperatures significantly higher than the usual storage temperature, in regions where drugs and excipients are seen to melt. Under normal ambient conditions these chemical or physical processes may not occur (Lund, 1994:195).

3.3.1 Method and sample preparation

Diclofenac sodium was mixed with all the excipients listed in Table 3.1 in a 1:1 ratio. Thermograms of diclofenac sodium, each individual excipient and of the mixtures were recorded.

Analysis was done using the same apparatus and conditions as listed in Table 2.5.

3.3.2 Results

DSC thermograms of diclofenac sodium, each individual excipient and of the mixtures are depicted in Figures 3.1–3.19.

Table 3.2 provides a summary of the main endothermal events observed in the DSC thermograms of the API, various excipients and binary mixtures of the API and the excipients.

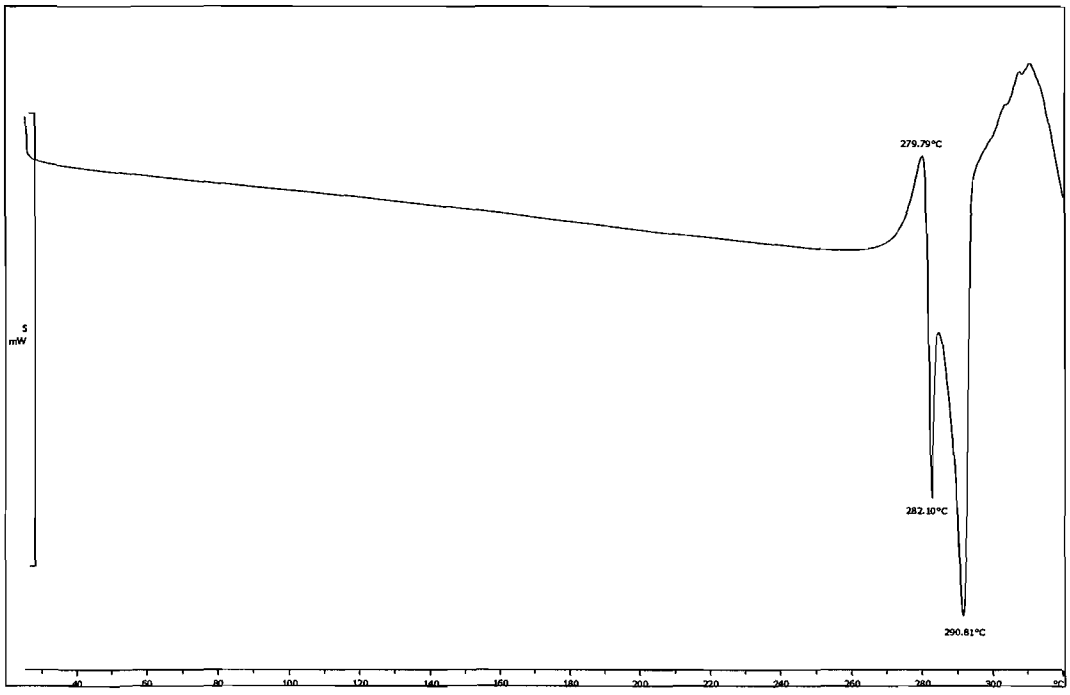


Figure 3.1: DSC thermogram of diclofenac sodium raw material.

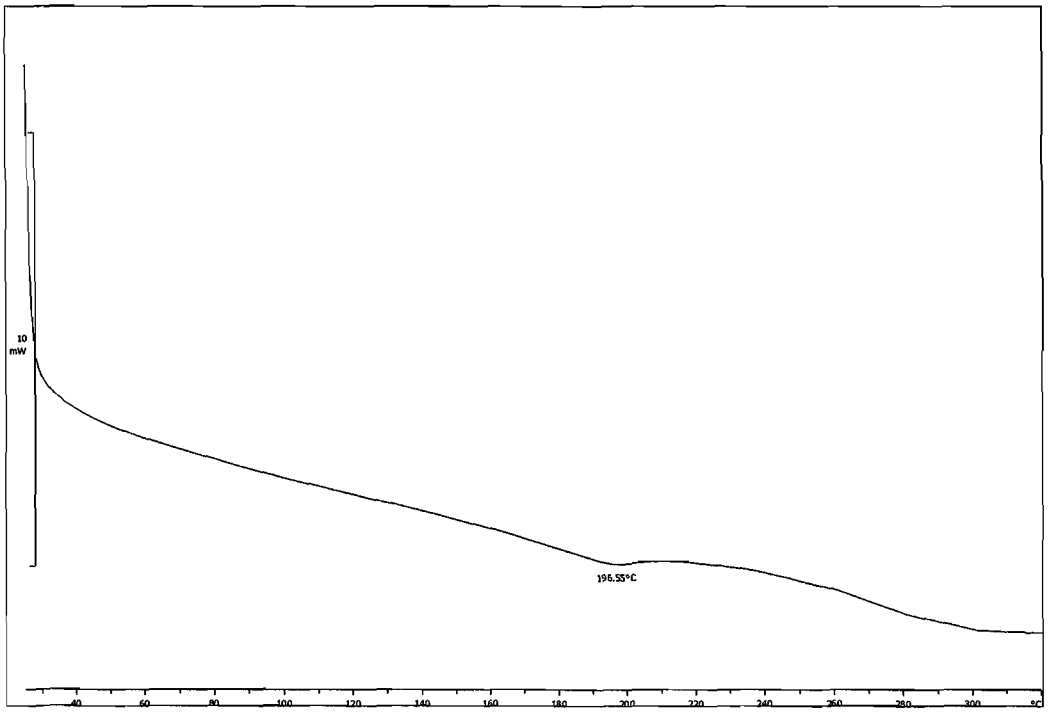


Figure 3.2: DSC thermogram of Aerosil®.

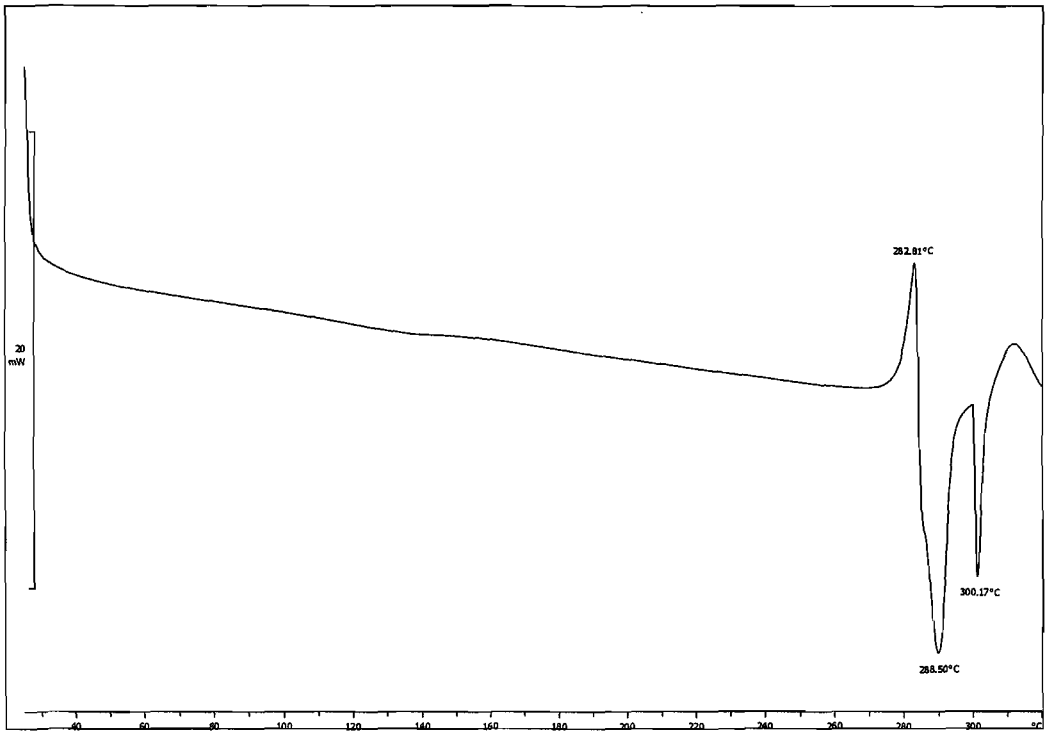


Figure 3.3: DSC thermogram of the 1:1 mixture of diclofenac sodium and Aerosil®.

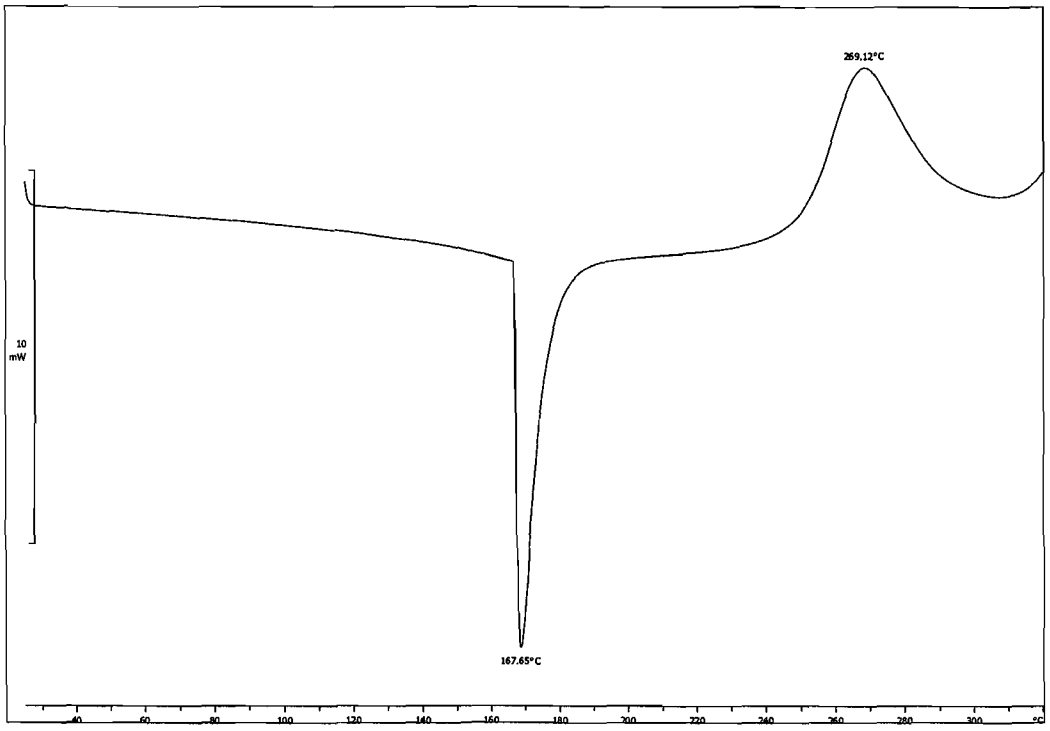


Figure 3.4: DSC thermogram of Disolcel®.

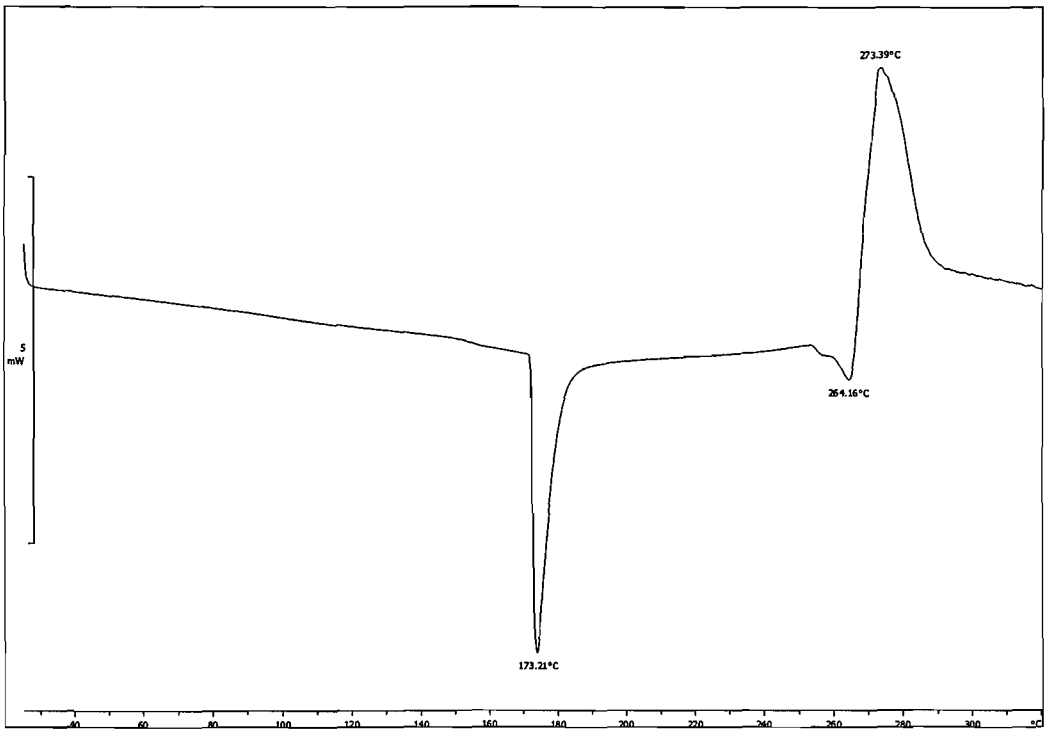


Figure 3.5: DSC thermogram of the 1:1 mixture of diclofenac sodium and Disolcel®.

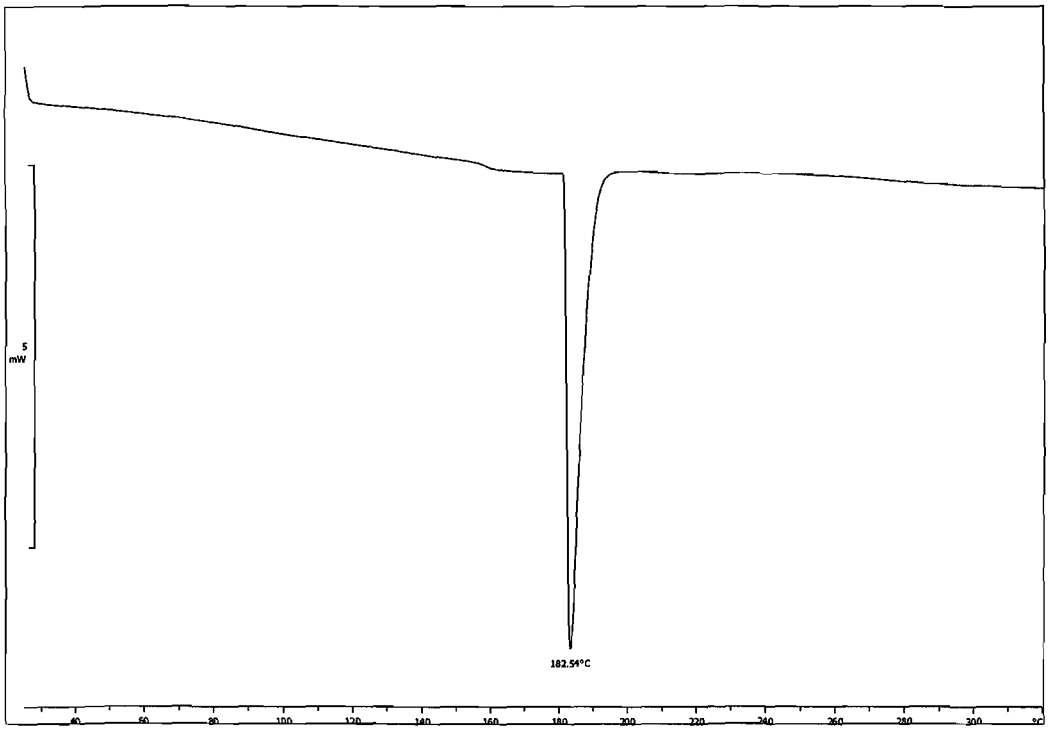


Figure 3.6: DSC thermogram of Kollidon CL-M®.

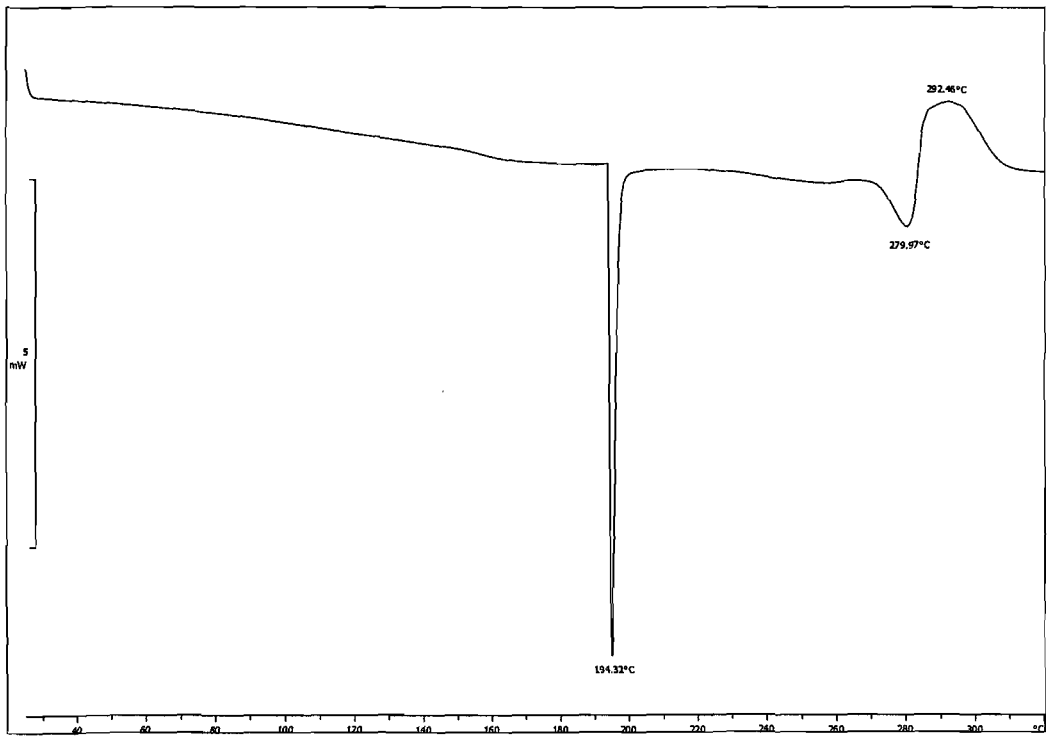


Figure 3.7: DSC thermogram of the 1:1 mixture of diclofenac sodium and Kollidon CL-M®.

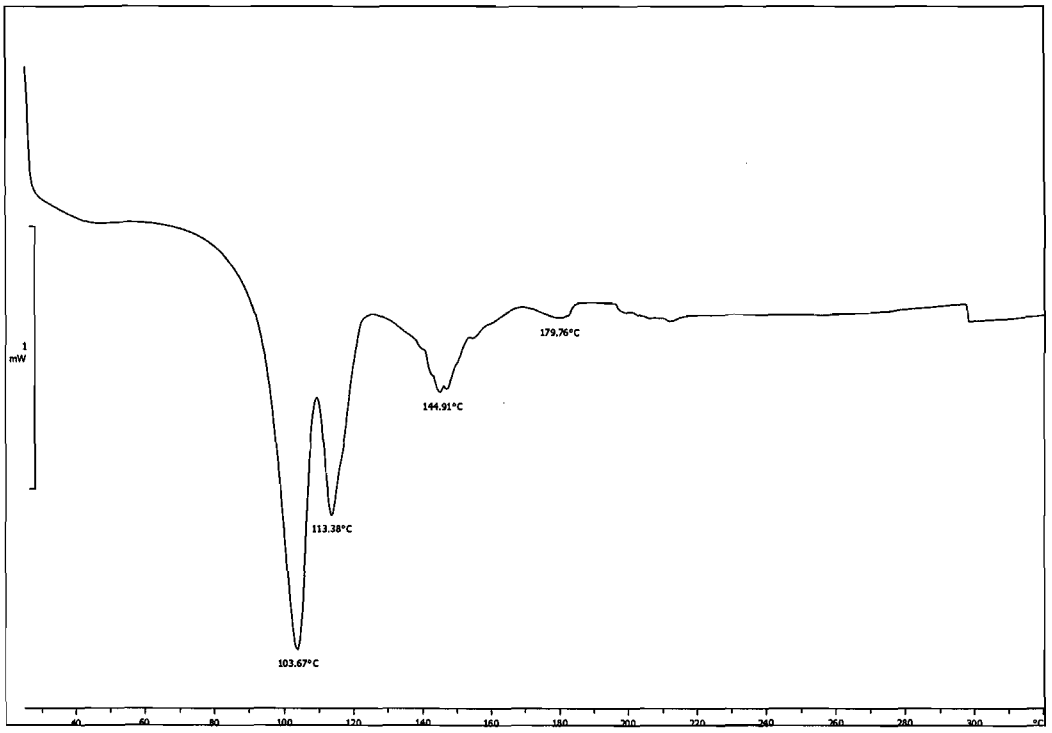


Figure 3.8: DSC thermogram of magnesium stearate.

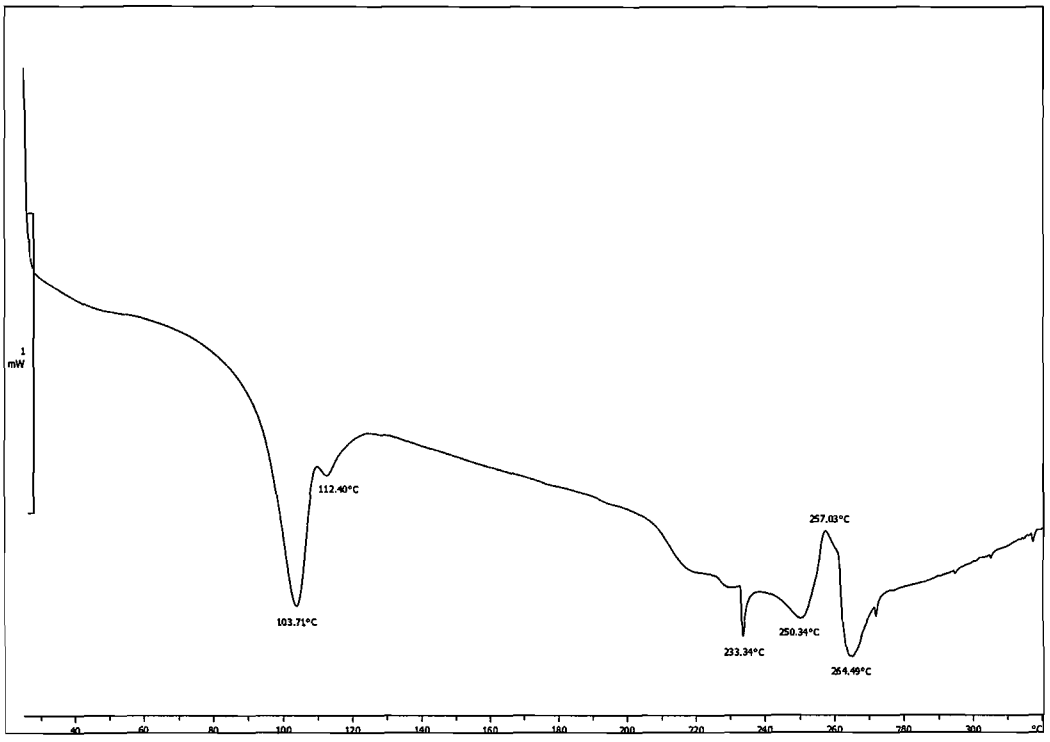


Figure 3.9: DSC thermogram of the 1:1 mixture of diclofenac sodium and magnesium stearate.

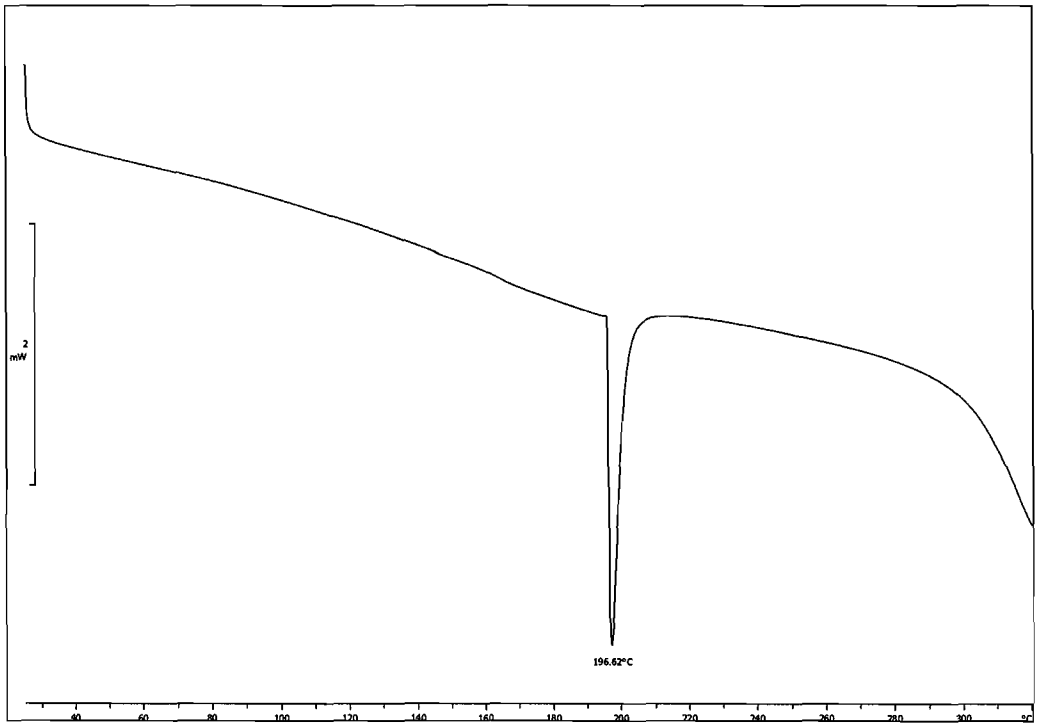


Figure 3.10: DSC thermogram of Avicel® pH 101.

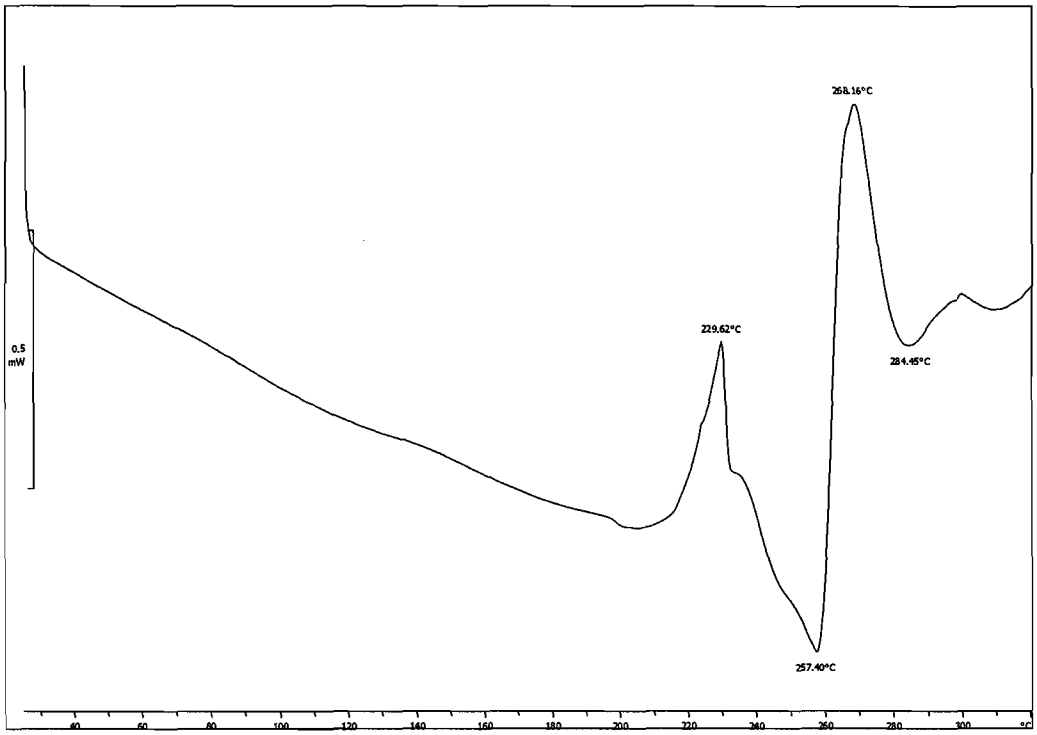


Figure 3.11: DSC thermogram of the 1:1 mixture of diclofenac sodium and Avicel® pH 101.

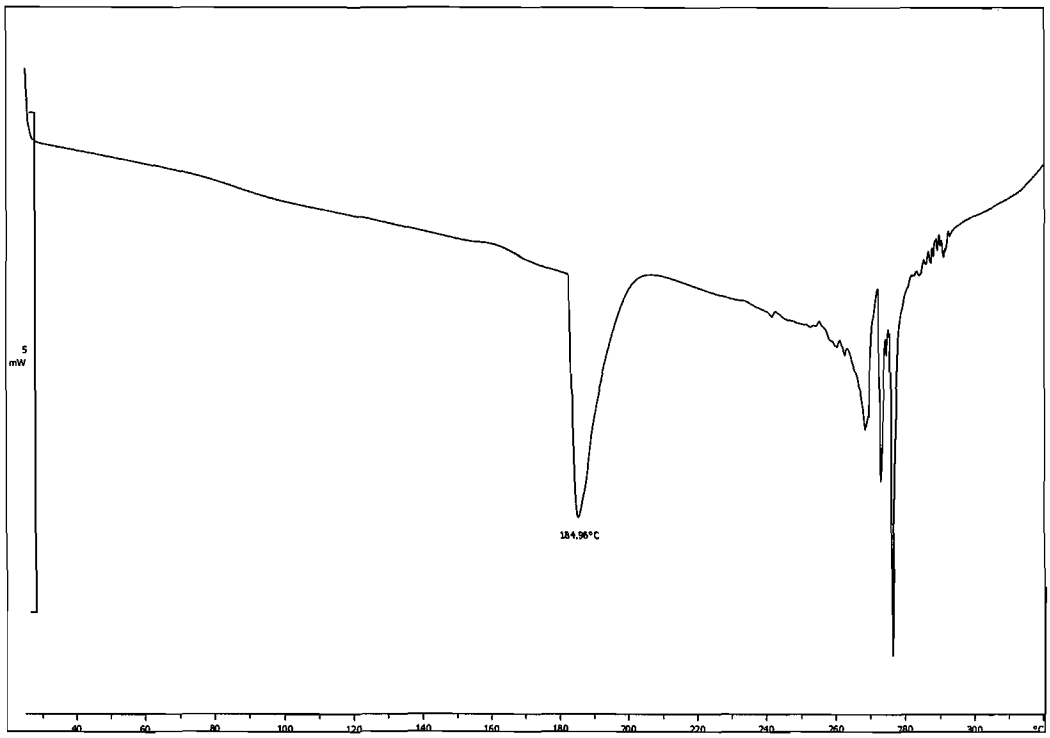


Figure 3.12: DSC thermogram of peppermint flavour.

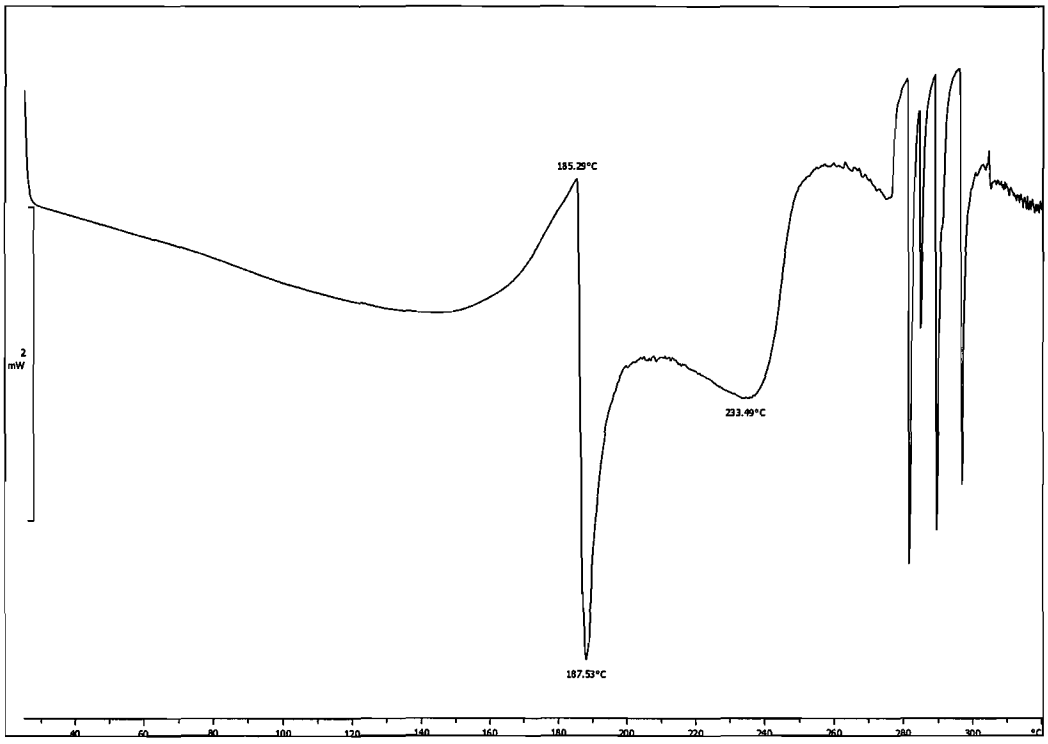


Figure 3.13: DSC thermogram of the 1:1 mixture of diclofenac sodium and peppermint flavour.

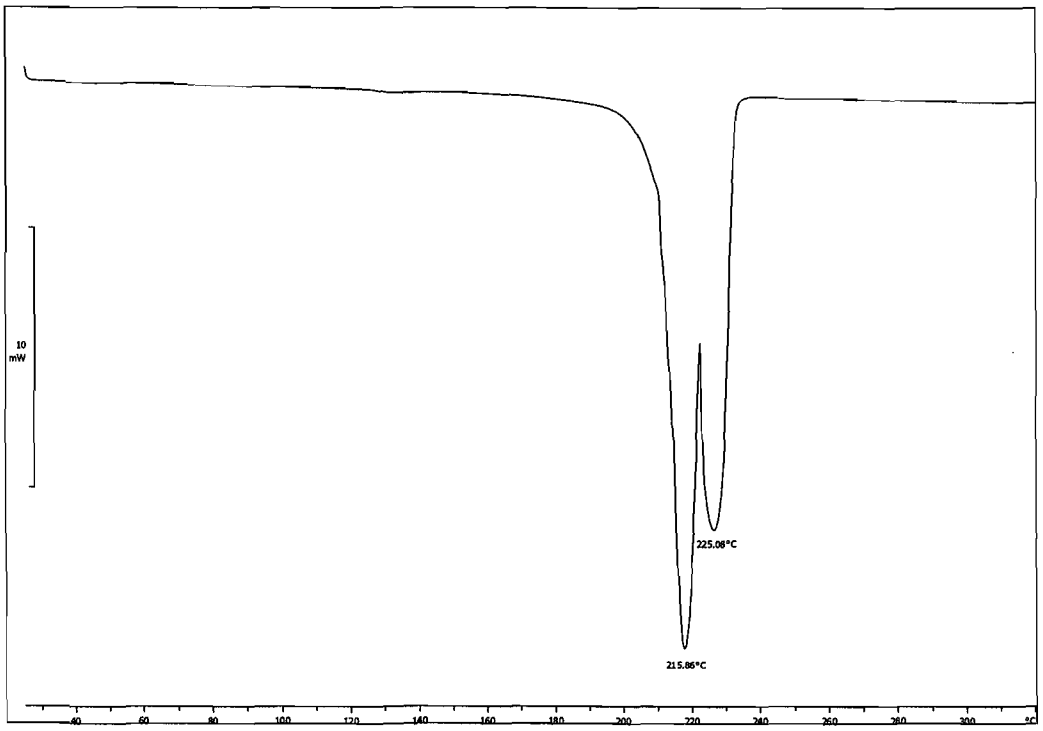


Figure 3.14: DSC thermogram of potassium bicarbonate.

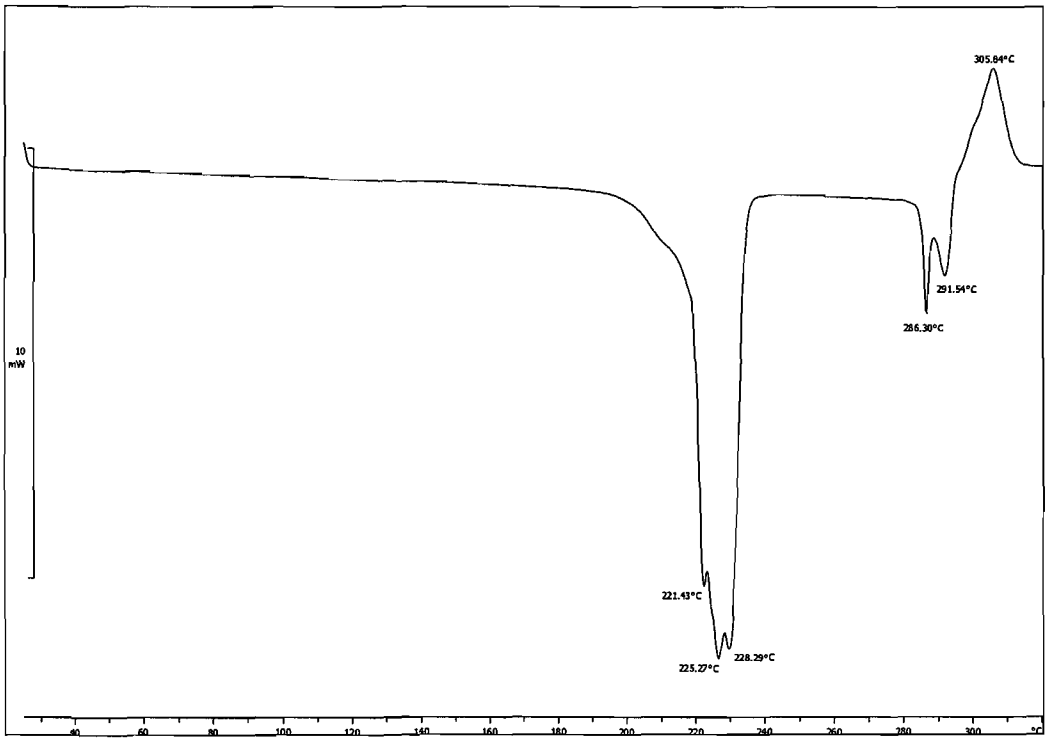


Figure 3.15: DSC thermogram of 1:1 mixture of diclofenac sodium and potassium bicarbonate.

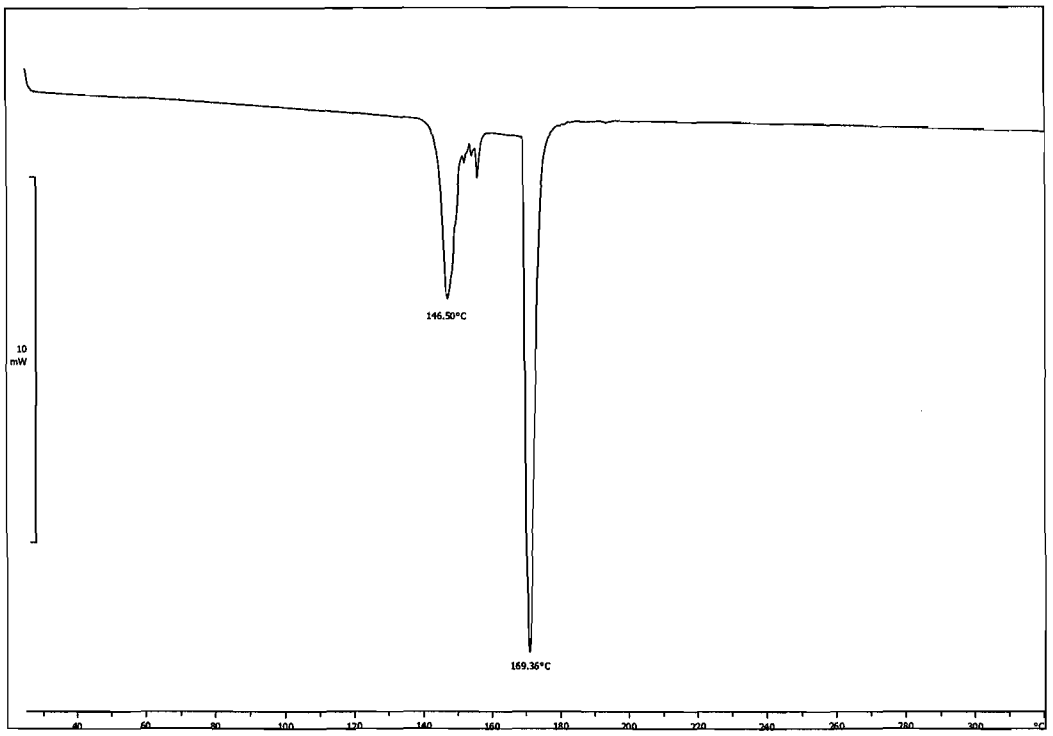


Figure 3.16: DSC thermogram of saccharine sodium.

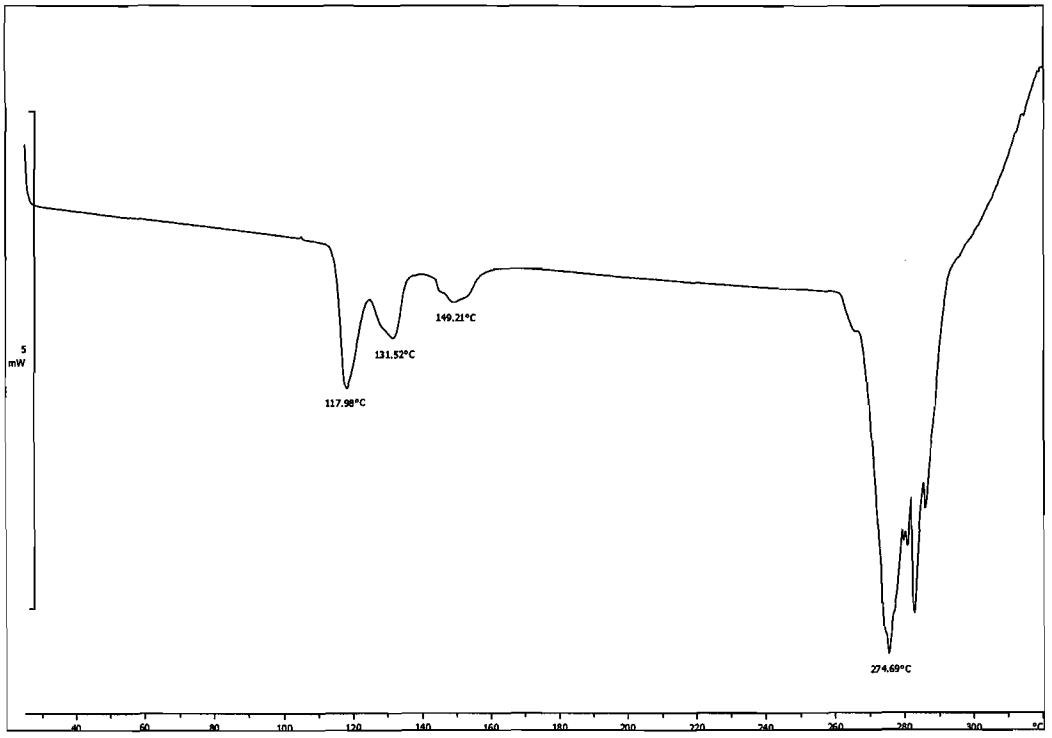


Figure 3.17: DSC thermogram of the 1:1 mixture of diclofenac sodium and saccharine sodium.

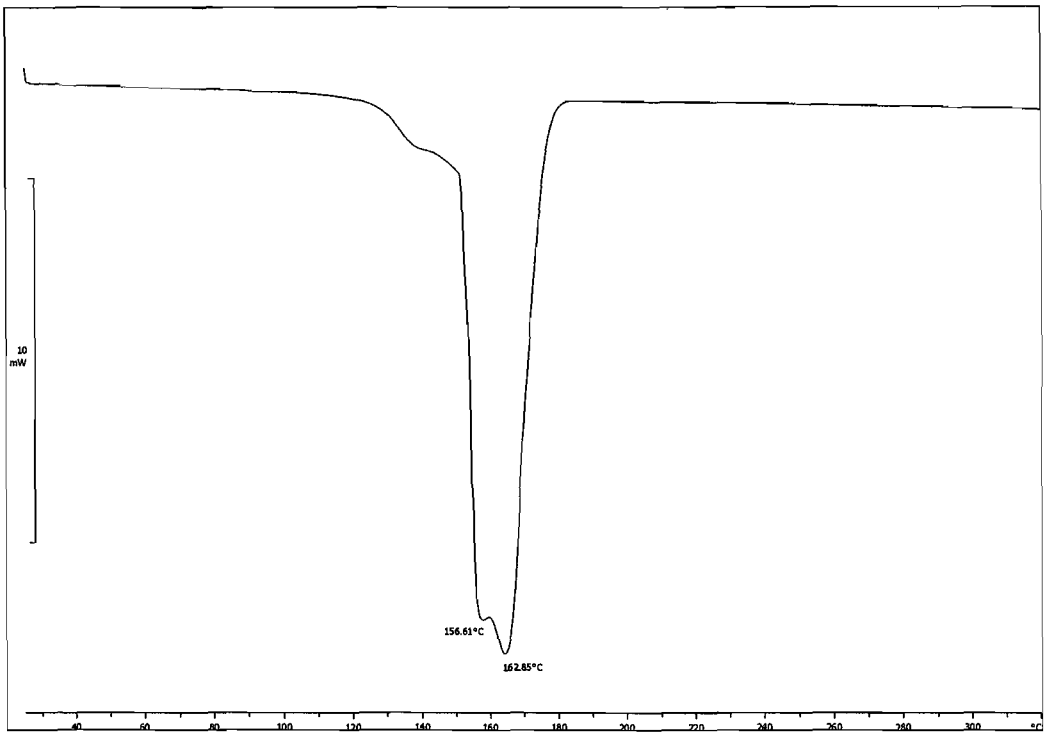


Figure 3.18: DSC thermogram of sodium bicarbonate.

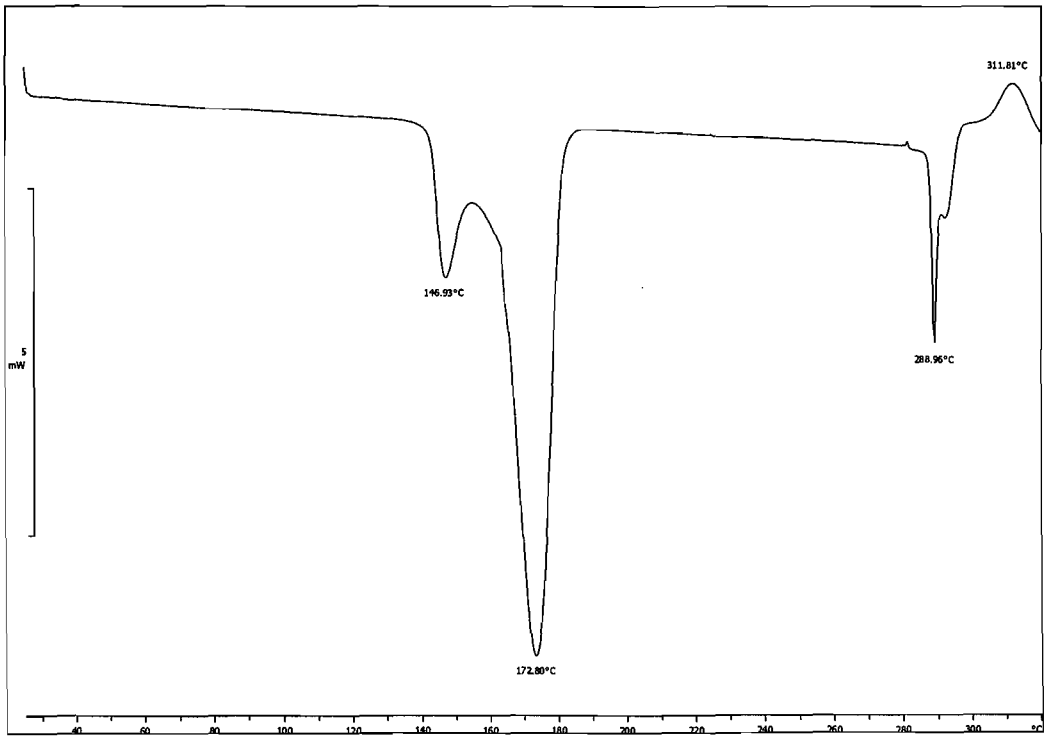


Figure 3.19: DSC thermogram of the 1:1 mixture of diclofenac sodium and sodium bicarbonate.

Table 3.2: Main endothermal events (°C) of diclofenac sodium (API), excipients and binary mixtures of the API and the excipients

API/Excipients	Endothermal events (°C) of individual API and excipients	Endothermal events (°C) of API/excipient mixtures
Diclofenac sodium	282.10 & 290.81	-
Colloidal silicon dioxide (Aerosil®)	No definite endotherm	288.50 & 300.17
Croscarmellose sodium (Disolcel®)	167.65	173.21 & 264.16
Crospovidone (Kollidon CL-M®)	182.54	194.32 & 279.97
Magnesium stearate (Kemilub EM-F-V®)	103.67, 113.38 & 144.91	103.71, 112.40, 233.34 250.34 & 264.49
Microcrystalline cellulose (Avicel® pH 101)	196.62	257.40 & 284.45
Peppermint Flavour	184.96	187.53 & 233.49
Potassium bicarbonate	215.86 & 225.08	221.43, 225.27, 228.29, 286.30 & 291.54
Saccharine sodium	146.50 & 169.36	117.98, 131.52, 149.21 & 274.69
Sodium bicarbonate	156.61 & 162.85	146.93, 172.80 & 288.96

3.3.3 Discussion

When two components are mixed, there is invariably some change in transition temperature, peak shape and area in the DSC thermograms. These changes are not due to any detrimental interaction. If no new thermal events occur or are lost, by mixing the components, no interaction can be assigned. The appearance of new peaks or a gross broadening or elongation of an exo- or endothermic change, indicate chemical interactions (Wells & Aulton, 1988:250). Any large shift in melting point signifies that a potential interaction has occurred, although it does not necessarily indicate an incompatibility (Botha & Lötter, 1990c:335).

All the DSC thermograms (Figures 3.1-3.19) of the API/excipient mixtures showed that possible interactions existed between the API and the excipient due to appearance of new peaks, broadening or elongation of exo- or endothermic peaks and disappearance of peaks.

Possible reasons for these changes:

- Most excipients had lower melting points (endothermal events) compared to diclofenac sodium, suggesting that diclofenac sodium might dissolve in the melted excipient, therefore producing unexpected thermal events.

- Prior to reaching 280°C, the excipient might already have undergone thermal decomposition (also shown as an endotherm), interfering with the melting point of diclofenac sodium.

- Potential interactions can occur due to the fact that the API/excipient mixtures are exposed to extreme stress conditions (high temperature and small surface area).

Since the DSC results only serve as a rough indication of possible interactions, accelerated stability testing using HPLC was used as a more selective method to identify potential interactions between the API and excipients.

3.4 Compatibility study using high performance liquid chromatography

High-performance liquid chromatography (HPLC) is a form of chromatography to separate, identify and quantify chemical entities that are in solution. Chemical entities are separated by injecting a sample mixture. Due to differences in their partitioning behaviour between the mobile liquid phase and the stationary phase, the different components in the mixture pass through the column at different rates (Tissue, 2000).

3.4.1 Method and sample preparation

The method described in the USP (USP29, 2006) for the determination of diclofenac sodium in diclofenac sodium delayed-release tablets was applied (see Annexure B for validation).

Before commencing with the stress studies, the excipients were injected individually to identify the retention time of the various chemical entities. In the method, a 100 % standard solution consists of 0.75 mg/ml diclofenac sodium. The amount of each excipient in relation to this concentration of diclofenac sodium was made up in 100 ml volumetric flasks and injected into the chromatograph. Diclofenac sodium has a retention time of ± 11 minutes (see Figure 3.20). The only excipient that showed absorbance under the chromatographic conditions used was sodium saccharine at a retention time of ± 4 minutes. With the other excipients, no peaks were identified, as these excipients do not absorb UV light in the

254 nm wavelength. A placebo formula containing all of the excipients was prepared, made up in solvent and injected into the chromatograph. Again, only the sodium saccharine peak was identified at ± 4 minutes (see Figure 3.21).

Diclofenac sodium/excipient mixtures were prepared in a 1:1 ratio (in duplicate), the amount of diclofenac sodium and the excipient in each sample accurately known. The two sets of API/excipient mixtures were stored at 50°C and re-evaluated after 2 weeks. The peak areas (AUC) of diclofenac sodium in the various samples were compared to that obtained from a freshly prepared standard solution of diclofenac sodium raw material, containing 0.75 mg/ml diclofenac sodium.

The diclofenac sodium content was determined by the following equation:

$$\%\,Diclofenac\ sodium = \frac{A_{sa} \times M_{st} \times DF_{sa} \times 100}{A_{st} \times M_{sa} \times DF_{st}}$$

Where: A_{sa} = Area of sample peak

A_{st} = Area of standard peak

M_{sa} = Sample mass of diclofenac sodium (in mg)

M_{st} = Standard mass (in mg)

DF_{sa} = Dilution factor of sample solution

DF_{st} = Dilution factor of standard solution

After the storage period of 2 weeks, samples were also visually examined for potential caking, liquification, discoloration and odour or gas formation (Carstensen, 2000b:255). Any such observation would indicate a potential interaction between the API and the excipient.

3.4.2 Results

The HPLC chromatograms of diclofenac sodium and a placebo formula are represented in Figures 3.20 and 3.21 respectively.

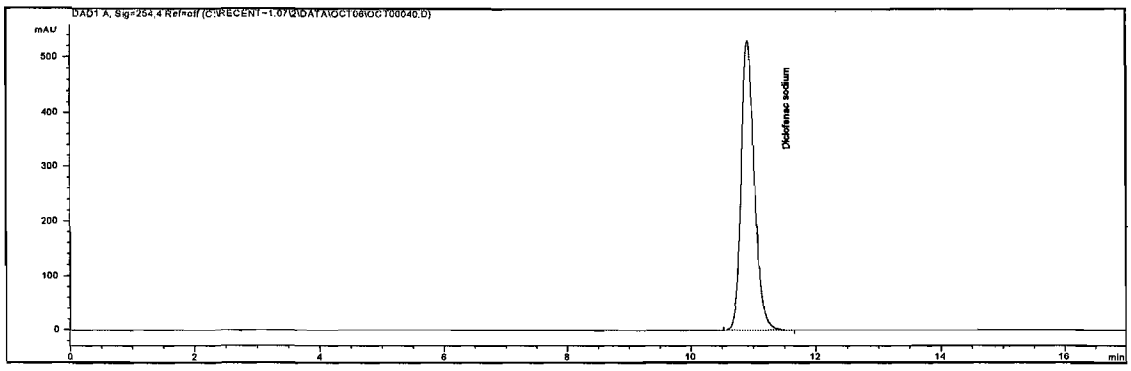


Figure 3.20: HPLC chromatogram of diclofenac sodium.

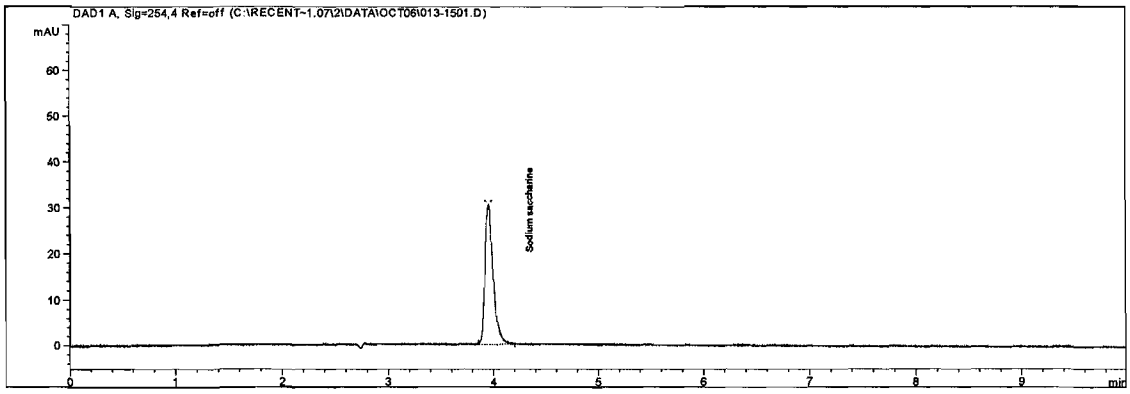


Figure 3.21: HPLC chromatogram of placebo formula.

The diclofenac sodium peak areas (in mAU) and the recovery percentages are tabulated in Table 3.3.

Table 3.3: Percentage diclofenac sodium recovered after 2 weeks of stress testing at 50°C

Excipient (1:1 mixture with diclofenac sodium)	Mass of diclofenac sodium (mg)	Area of diclofenac sodium sample (Injection1) (mAU)	Area of diclofenac sodium sample (Injection 2) (mAU)	Mean area of diclofenac sodium sample (mAU)	% Recovery[2]	% Recovery (mean)
Aerosil® (1)	74.98	7600	7606	7603	100.16	99.87
Aerosil® (2)	75.09	7574	7563	7569	99.57	
Disolcel® (1)	75.49	7626	7619	7623	99.75	100.0
Disolcel® (2)	75.12	7520	7512	7516	100.24	
Kollidon CL-M® (1)	75.01	7563	7567	7565	99.62	99.3
Kollidon CL- M® (2)	75.35	7621	7611	7616	99.84	
Magnesium stearate (1)	75.19	7618	7608	7613	100.01	100.23
Magnesium stearate (2)	75.52	7680	7677	7679	100.44	
Avicel® pH101 (1)	75.22	7525	7527	7526	98.83	99.21
Avicel® pH101 (2)	75.13	7583	7566	7575	99.59	
Peppermint flavour(1)	75.45	7447	7433	7440	97.40	98.24
Peppermint flavour(2)	75.12	7543	7536	7540	99.08	

[2] The peak area of diclofenac sodium standard solution (freshly prepared and analysed on day 14) to which the samples were compared: 7619 mAU

Table 3.3: Continued

Excipient (1:1 mixture with diclofenac sodium)	Mass of diclofenac sodium (mg)	Area of diclofenac sodium sample (Injection1) (mAU)	Area of diclofenac sodium sample (Injection 2) (mAU)	Mean area of diclofenac sodium sample (mAU)	% Recovery	% Recovery (mean)
$KHCO_3$ (1)	75.05	7593	7593	7593	99.94	99.62
$KHCO_3$ (2)	75.56	7587	7602	7595	99.29	
Saccharine sodium (1)	75.28	7583	7583	7583	99.50	99.50
Saccharine sodium (2)	75.52	7607	7604	7606	99.49	
$NaHCO_3$ (1)	75.69	7686	7682	7684	100.28	99.68
$NaHCO_3$ (2)	75.30	7553	7551	7552	99.07	

No sample showed any physical changes, except one diclofenac sodium/peppermint flavour sample. A slight discoloration was observed.

3.4.3 Discussion

In all the studies the recovered diclofenac sodium was within the satisfactory range of 98.0-102.0%. The retention time of the diclofenac sodium peak did not change and no extra peaks were detected in the HPLC chromatograms. It can thus be deduced that there will be no potential interactions between the API and various excipients.

The physical appearance of the samples was also satisfactory, except for the one diclofenac sodium/peppermint flavour sample where a slight discoloration was observed. Since this mixture was in a 1:1 ratio and the diclofenac sodium-peppermint flavour ratio in the dispersible tablet formula is significantly smaller (1:0.015), this potential physical interaction could be considered negligible

3.5 Summary of DSC- and HPLC results

Table 3.4 provides a summary of DSC and HPLC results obtained by thermal analysis and stress studies.

Table 3.4: DSC- and HPLC results of the compatibility study of diclofenac sodium and various excipients

Diclofenac sodium and excipients	Potential interaction	
	DSC	HPLC
Colloidal silicon dioxide (Aerosil®)	√	X
Croscarmellose sodium (Disolcel®)	√	X
Crospovidone (Kollidon CL-M®)	√	X
Magnesium stearate (Kemilub EM-F-V®)	√	X
Microcrystalline cellulose (Avicel® pH 101)	√	X
Peppermint Flavour	√	X
Potassium bicarbonate ($KHCO_3$)	√	X
Saccharine sodium	√	X
Sodium bicarbonate ($NaHCO_3$)	√	X

√ - Potential interaction X - No interaction, therefore compatible

3.6 Conclusion

The aim of this chapter was to identify excipients, which were considered for formulation, that are not compatible with diclofenac sodium and those that will not have any impact on the stability of diclofenac sodium.

Thermal compatibility studies showed potential interactions between diclofenac sodium and the various excipients. Since DSC results only serve as a rough indication of potential interactions, the decision to include all of the excipients listed in Table 3.1 in the dispersible tablet formulation was based upon the stressed samples analysed with HPLC.

The HPLC results revealed that no interactions existed between diclofenac sodium and the mentioned excipients. Recovery of diclofenac sodium in 1:1 mixtures with the excipients after 2 weeks of storage at 50°C was between 98.24 and 100.23%. Except for one diclofenac sodium/peppermint flavour mixture where a slight discoloration occurred. Physical examination of the mixtures after 2 weeks showed no signs of discoloration, caking, liquification, discoloration and odour or gas formation.

Based on the HPLC and physical examination results, it can be concluded that no interactions will occur between diclofenac sodium and the chosen excipients during the stability period after formulation.

In the next chapter the formulation of a diclofenac sodium dispersible tablet with the chosen excipients will be discussed.

CHAPTER 4

Formulation of Diclofenac Sodium Dispersible Tablets

4.1 Introduction

Tablets are the most widely used pharmaceutical dosage form and are easy to use, convenient to handle, less expensive to manufacture than other oral dosage forms and deliver the intended dose with a high degree of accuracy (Alderborn, 2002:398).

Specifications tablets should fulfill regarding their chemical, physical and biological properties are listed below:

- The tablet should include the correct dose of the drug.
- The appearance should be elegant.
- The weight, size and appearance should be consistent.
- The drug should be released from the tablet in a controlled and reproducible way.
- The tablet should not include excipients, contaminants or microorganisms that could cause harm to patients.
- The tablet should be of sufficient mechanical strength to withstand fracture and erosion during handling.
- The tablet should be chemically, physically and microbiologically stable during the lifetime of the product.
- The tablet product should be acceptable by the patient.
- The tablet should be packed in a safe manner (Alderborn, 2002:398, 399).

Tablets consist of one or more active substances with or without excipients such as diluents, binders, disintegrating agents, glidants, lubricants, colourants and flavouring substances (BP, 2005). Excipients are added to a formulation in order to facilitate the preparation, functioning of the dosage form as a delivery system and patient acceptability (Ashford, 2002:250).

Excipients are divided into two major classes by function (Banker *et al.*, 1980:72):

Those which affect the compressional characteristics of the tablet:

- Diluents
- Binders and adhesives
- Lubricants and glidants

Those which affect the biopharmaceutics, chemical and physical stability, and marketing considerations:

- Disintegrants
- Colourants
- Flavours and sweeteners
- Miscellaneous components (buffers, etc.)

There are many different types of tablets which can be designed to fulfill specific therapeutic needs. Examples include immediate-release, delayed-release, controlled-release, chewable, effervescent, buccal and dispersible tablets (Davies, 2004:380). Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration, giving a homogeneous dispersion (BP, 2005).

Methods of tablet formulation include direct compression and granulation. Direct compression describes the process where powder blends of the drug substance and excipients are compressed on a tablet machine. Granulation involves particle enlargement, whereby powders are formed into permanent aggregates. This can be achieved by wet- or dry granulation (Davies, 2004:420,421).

In this study, direct compression was used as method of formulation.

Advantages of direct compression (Sheth *et al.*, 1980:148):

- Economy (reduced processing time and labour cost, fewer manufacturing steps, less space and lower consumption of power).
- Elimination of heat and moisture.

- Prime particle dissociation.
- Increased stability.
- Better particle size uniformity.

In this chapter, the formulations and processes used to formulate laboratory scale batches of diclofenac sodium dispersible tablets will be discussed. Two different disintegrants in two different concentrations will be used to determine the effect on stability, disintegration, dissolution and other tablet characteristics.

4.2 Advantages of a diclofenac sodium dispersible tablet formulation

Many patients have difficulty swallowing tablets and hard gelatin capsules and consequently do not take medication as prescribed. To achieve optimum therapeutic benefit of a drug, it is desirable to present it in a formulation which can rapidly disperse in water, so that when needed, the drug can be taken in the form of an aqueous dispersion. As previously mentioned, dispersible tablets are dispersed in water to give homogeneous dispersions. This formulation is much easier to swallow, therefore enhancing patient compliance (Fielden, 1997:8). The time of onset of the therapeutic effect ought to be faster than that of normal tablets, since the drug is already in an aqueous dispersion. However, in this study, no experiments were done to prove this.

4.3 Components of the dispersible tablet formulation

4.3.1 Active pharmaceutical ingredient (API)

Diclofenac sodium's pharmacological, pharmaceutical and physico-chemical properties have been discussed in chapter 1 and 2. Diclofenac sodium will comprise ± 16% of the total tablet mass.

4.3.2 Excipients

The excipients chosen, the concentration ranges normally used and their characteristics/function are summarised in Table 4.1.

Table 4.1: Excipients used in the dispersible tablet formulation with their concentration range and characteristics/function

Excipient	Concentration range (%)	Characteristics / function	Reference
Colloidal silicon dioxide (Aerosil®)	0.1-0.5	• Glidant • Light, loose, odourless, tasteless, amorphous white powder • Small particle size (15 nm)	Rowe *et al.*, 2003:161
Croscarmellose sodium (Disolcel®)	0.5-5.0	• Disintegrant • Odourless, white powder	Rowe *et al.*, 2003:181
Crospovidone (Kollidon CL-M®)	2.0-5.0	• Disintegrant • Free-flowing, tasteless, odourless, white to creamy white hygroscopic powder	Rowe *et al.*, 2003:184
Magnesium stearate (Kemilub EM-F-V®)	0.25-5.0	• Lubricant • Fine, white powder of low bulk density	Rowe *et al.*, 2003:354
Microcrystalline cellulose (Avicel® pH 101)	20-90	• Binder/diluent • White, odourless, tasteless, crystalline powder	Rowe *et al.*, 2003:108
Peppermint Flavour	0.25-2.0	• Flavouring agent • Fine white powder	Fielden, 1997:16
Potassium bicarbonate	44% of API mass	• Taste masking agent	Reiner & Reiner, 2005:7,13
Saccharine sodium	0.5-5.0[1]	• Sweetening agent[2] • White, odourless or faintly aromatic, crystalline powder[2]	1. Fielden, 1997:16 2. Rowe *et al.*, 2003:532
Sodium bicarbonate	44% of API mass	• Taste masking agent	Reiner & Reiner, 2005:7,13

4.4 Formulation process

Prior to finalising the final four formulations, many dispersible tablet formulations were studied as a guide to examine different excipients used in different concentrations and in different combinations. Different excipients were evaluated and several trial formulations were tabletted.

4.4.1 Excipient selection

Kriel (2003:57) tested various filling agents/diluents in his study. Formulations with lactose did not disintegrate within the specified time. Dicalcium phosphate (Emcompress®) and Avicel® pH 200 (microcrystalline cellulose) were tested, but gave an unacceptable feel in the mouth. Avicel® pH 101 gave the best feel in the mouth, due to the small particle size. However, a glidant then has to be added to improve the powder's flowability. Avicel® pH 101 was chosen as diluent together with Aerosil® as glidant.

Croscarmellose sodium and crospovidone (so-called super disintegrants) were chosen above starch as disintegrants, due to their excellent disintegrant activity at low concentrations and better compression properties (Davies, 2004:417,418).

Magnesium stearate was chosen as lubricant due to its superior lubrication properties and low concentration needed in the formulation (Alderborn, 2002:409).

4.4.2 Taste improvement

Diclofenac sodium is characterised by a particularly unpleasant and bitter taste. Since taste is one of the most important parameters that governs patient compliance, it is desirable to provide a palatable formulation free from after-taste.

A tablet formula, containing diclofenac sodium and the excipients mentioned above, was mixed using passionfruit flavour as flavouring agent. The dispersed tablet had an extremely bitter taste. Other flavouring agents were tested and peppermint was chosen as the one masking the bitter taste the best.

Sodium saccharine was used as sweetener, first in a concentration of 0.5%, but a concentration of 1.0% yielded the best taste improvement.

To further enhance the taste, two alkali metal bicarbonates (potassium- and sodium bicarbonate) were added to the formula. It has been found that the addition of flavouring

agents such as mint, and alkali metal bicarbonates, produces a synergistic effect which eliminates the astringency effect of diclofenac salt formulations. The amount of alkali metal bicarbonates to be added is between 40 and 80% of the API weight (Reiner & Reiner, 2005:13).

Trial formulations were made where potassium- and sodium bicarbonate were included separately and together in a 50:50 ratio. The formulation with both alkali metal bicarbonates resulted in the best taste. The combination was used in a concentration of 44% of the diclofenac sodium weight (50 mg).

4.4.3 Manufacturing formulations

After consideration and experimentation with other patented and commercial dispersible tablet formulations, the formulations given in Tables 4.2-4.5 were manufactured.

Table 4.2: Formulation A (300 mg tablet)

API/excipient	Amount per tablet (%)	Amount per tablet (mg)
Diclofenac sodium	16.67	50
Colloidal silicon dioxide (Aerosil®)	2.3	6.9
Croscarmellose sodium (Disolcel®)	2	6
Magnesium stearate (Kemilub EM-F-V®)	1	3
Microcrystalline cellulose (Avicel® pH 101)	69.45	208.35
Peppermint flavour	0.25	0.75
Potassium bicarbonate	3.67	11
Saccharine sodium	1	3
Sodium bicarbonate	3.67	11

Table 4.3: Formulation B (300 mg tablet)

API/excipient	Amount per tablet (%)	Amount per tablet (mg)
Diclofenac sodium	16.67	50
Colloidal silicon dioxide (Aerosil®)	2.3	6.9
Croscarmellose sodium (Disolcel®)	5	15
Magnesium stearate (Kemilub EM-F-V®)	1	3
Microcrystalline cellulose (Avicel® pH 101)	66.45	199.35
Peppermint flavour	0.25	0.75
Potassium bicarbonate	3.67	11
Saccharine sodium	1	3
Sodium bicarbonate	3.67	11

Table 4.4: Formulation C (300 mg tablet)

API/excipient	Amount per tablet (%)	Amount per tablet (mg)
Diclofenac sodium	16.67	50
Colloidal silicon dioxide (Aerosil®)	2.3	6.9
Crospovidone (Kollidon CL-M®)	2	6
Magnesium stearate (Kemilub EM-F-V®)	1	3
Microcrystalline cellulose (Avicel® pH 101)	69.45	208.35
Peppermint flavour	0.25	0.75
Potassium bicarbonate	3.67	11
Saccharine sodium	1	3
Sodium bicarbonate	3.67	11

Table 4.5: Formulation D (300 mg tablet)

API/excipient	Amount per tablet (%)	Amount per tablet (mg)
Diclofenac sodium	16.67	50
Colloidal silicon dioxide (Aerosil®)	2.3	6.9
Crospovidone (Kollidon CL-M®)	5	15
Magnesium stearate (Kemilub EM-F-V®)	1	3
Microcrystalline cellulose (Avicel® pH 101)	66.45	199.35
Peppermint flavour	0.25	0.75
Potassium bicarbonate	3.67	11
Saccharine sodium	1	3
Sodium bicarbonate	3.67	11

4.4.4 Manufacturing method

(1) Each formulation's API and excipient masses (for 2000 tablets) were divided by three[3].

(2) The ingredients of each third were weighed separately (except the lubricant) and sifted through a 500 µm sieve.

(3) The tablet powder was placed in containers and tightly closed.

(4) Each third of the powder mixture was mixed in a Turbula® (USA) mixer at 69 rpm for 15 minutes.

(5) The lubricant was then added to the three powder mixtures and mixed for another 5 minutes.

(6) The three powder mixtures were then added together in a large container and mixed manually.

(7) Tabletting was then performed using a Cadmach® (India) single-punch tabletting machine with a punch diameter of ± 9.05 mm. Press parameters were adjusted until tablets of consistent mass and hardness were obtained. The manufactered tablets are shown in Figure 4.1.

[3] Due to equipment constraints, the total powder mixture couldn't be mixed together in a V-mixer.

(8) Tablets were packed in PVC containers with screw caps, each containing a silica sachet. [4]

Figure 4.1: Photo of diclofenac sodium dispersible tablets.

4.4.5 In-process developmental tests

Before tabletting the final amount of tablets, the first few tablets of each formulation were tested for uniformity of mass, hardness and disintegration time. Tablet mass varied within 5% of the theoretical tablet mass. Since press parameters had to be adjusted after each formulation was tabletted, the hardness of the four formulations varied between 45N and 110 N. Simple disintegration tests were performed where a tablet was added to ± 50 ml water, each time measuring the time it took for the tablet to disintegrate. Disintegration times were less than 3 minutes.

[4] Steps 2-8 were followed for all 4 formulas.

4.5 Conclusion

The aim of this formulation process was to develop diclofenac sodium dispersible tablet formulations that exhibit ideal properties for its intended purpose. Dispersible tablets are dispersed in water to give homogeneous dispersions which are easier to swallow, therefore enhancing patient compliance.

Four final dispersible tablet formulations were developed after several excipients and flavouring agents were evaluated for formulation. Crospovidone and croscarmellose sodium were used as disintegrants in concentrations of 2 and 5% of the tablet mass.

During tabletting the tablet powder revealed good flow and lubrication properties. Initial disintegration experiments revealed that all the formulations disintegrated within 3 minutes in ± 50 ml water at ambient temperature. Tablet mass varied within 5% of the theoretical tablet mass, but hardness varied between 45N and 110N.

In the next chapter, the stability programme of the diclofenac sodium dispersible tablets will be discussed.

CHAPTER 5

Stability Testing

5.1 Introduction

The aim of stability testing is to provide evidence on how the quality of a pharmaceutical product is influenced by a variety of environmental factors such as temperature, humidity and light. Using this evidence, a shelf life for the product and recommended storage conditions can be established (ICH Q1A(R2), 2003). Organoleptic, physico-chemical, chemical and microbial test results must be within the predefined tolerance ranges to ensure the quality, efficacy and safety of the product (Grimm & Krummen, 1993:17).

Pharmaceutical dosage forms degrade by means of four processes (Wells, 2002:129):

- Hydrolysis
- Oxidation
- Photolysis
- Trace metal catalysis

The stability of pharmaceutical dosage forms can be influenced by the following factors (Grimm & Krummen, 1993:18):

Manufacturing related factors:

- Batch size
- Equipment
- Different quality of active pharmaceutical ingredients (APIs), excipients and packaging materials
- Sequence in which the ingredients of the formulation were added

External factors:

- Temperature

- Humidity
- Light
- Oxygen
- pH

Formulated products are exposed to high stress conditions to establish the stability of the product. High stress conditions (conditions of temperature and humidity) enhance the degradation of the product and therefore reduce the time required for testing (Wells, 2002:109).

In this chapter the accelerated stability test conditions and tests done on the formulated diclofenac sodium dispersible tablets, will be discussed.

5.2 Stability programme

Four diclofenac sodium dispersible tablet formulations were formulated in this study (see Chapter 4) and put on a stability programme for three months, at conditions specified by the International Conference on Harmonization (ICH Q1A(R2), 2003). Stability tests were performed at initial, 1 month, 2 months and 3 months.

5.2.1 Storage conditions

Where "significant change" occurs at 40°C/75% RH, additional testing at an intermediate storage condition (30°C/65% RH) should be conducted. "Significant change" is defined as failure of the API to meet specified requirements (MCC Stability Guideline, 2006:5). Samples were put in the 30°C/65% RH incubator at the start of the programme and tested during stability to prevent delays in the stability programme should significant changes occur at 40°C/75% RH.

The following storage conditions were used (ICH Q1A(R2), 2003):

- 25°C/60% RH
- 30°C/65% RH
- 40°C/75% RH

5.2.2 Stability tests

Adherence to cGMP guidelines as set out in in-house standard operating procedures (Handford *et al.,* 2005:1-30) is essential to perform any analytical procedure.

Safety equipment e.g. laboratory coat, latex gloves, safety glasses and mask were worn where applicable in accordance with the standard operating procedures (Liebenberg *et al.,* 2005:1-26).

All equipment used during the stability tests were calibrated and in good working order and validated analytical procedures were used (Fourie *et al.,* 2006:1-4).

The following stability tests were conducted:

- Visual assessment (description)
- Uniformity of weight (mass)
- Dimensions (thickness, diameter)
- Hardness
- Friability
- Disintegration
- Fineness of dispersion
- Loss on drying
- Identification
- Assay
- Chromatographic purity
- Dissolution

5.3 Test methods

5.3.1 Visual assessment (description)

A visual assessment of the tablets was performed. Colour, taste, odour and physical appearance were examined. Any change in the physical characteristics of the tablets during manufacturing, storage or stability testing, should be investigated and appropriate action taken (ICH Q6A, 1999).

5.3.2 Uniformity of weight (mass) and average mass

This test is performed on tablets to ensure the consistency of dosage units in a batch (USP29, 2006:<9057>).

5.3.2.1 Method

(1) A Sartorius® analytical balance (Germany) was used to weigh the tablets.

(2) 20 tablets were selected randomly from each batch.

(3) Each tablet was weighed on a calibrated balance and the mass recorded (BP, 2005).

(4) The average tablet mass and standard deviation were calculated and recorded.

(5) After each procedure the tablets were powdered for the assay and loss on drying tests.

5.3.2.2 Specifications

Not more than 2 of the individual masses deviate from the average mass by more than ± 5% and none deviates by more than twice that percentage (BP, 2005).

5.3.3 Dimensions

The thickness and diameter of the tablets were measured to ensure the consistency of the tablet size.

5.3.3.1 Method

(1) The thickness and diameter of the 20 tablets selected for uniformity of mass were measured with a Vernier Caliper and recorded.

(2) The average thickness and diameter and standard deviation were calculated and recorded.

5.3.3.2 Specifications

To be determined during stability.

5.3.4 Hardness

This test is intended to determine the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing (BP, 2005).

5.3.4.1 Method

(1) A PTB-311 Pharma Test® hardness testing apparatus (Germany) was used during the procedure.

(2) Ten tablets were selected randomly from each formulation.

(3) Each tablet was placed between the jaws and the resistance to crushing measured in newton (N).

(4) Before each determination, all fragments of tablets were removed from the crushing surfaces.

(5) A summary of the results was recorded with mean, minimum and maximum forces measured (BP, 2005).

5.3.4.2 Specifications

To be determined during stability.

5.3.5 Friability

Friability of tablets is an indication of the physical strength of the tablets and supplements other physical measurements, such as tablet breaking force (hardness) (BP, 2005).

5.3.5.1 Method

(1) A Pharma Test® friabilator (Germany) was used during the procedure.

(2) 20 tablets of each batch were brush-cleaned before testing.

(3) The tablets were accurately weighed and placed in the drum.

(4) The drum was rotated for 4 minutes (100 times).

(5) The tablets were removed from the drum, brush-cleaned and weighed again (BP, 2005).

(6) The weight difference of the tablets before and after the procedure was recorded and the percentage friability calculated using the following equation (May *et al.,* 2005:6):

$$\%\,Friability = \frac{mass\,loss \times 100}{mass\,before}$$

5.3.5.2 Specifications

- If any tablets are obviously cracked, cleaved or broken after tumbling, the sample fails the test.
- A mass loss not greater than 1.0% is considered acceptable (BP, 2005).

5.3.6 Disintegration

For tablets to be effective, they must disintegrate in order for the API to dissolve (Carstensen, 1998:248). This test determines whether tablets disintegrate within the prescribed time when placed in a liquid medium at specified conditions (BP, 2005).

5.3.6.1 Method

(1) A Pharma Test® disintegration apparatus (Germany) was used.

(2) The vessel was filled with distilled water (23°C).

(3) One tablet from each batch was placed in the 6 tubes of the basket.

(4) The time it took for each tablet to disintegrate (no fragments visible on the screen of the test apparatus) was recorded (BP, 2005).

5.3.6.2 Specifications

- Dispersible tablets should disintegrate within 3 minutes.
- If 1 or 2 tablets fail to disintegrate within this time, repeat the test on 12 additional tablets. The requirements of the test are met if not less than 16 of the 18 tablets have disintegrated within 3 minutes (BP, 2005).

5.3.7 Fineness of dispersion

This test is performed to ensure a smooth homogeneous dispersion is formed when a tablet is placed in water.

5.3.7.1 Method

(1) Two tablets of each batch were placed in 100 ml of distilled water until completely dispersed.

(2) The dispersion was poured through a 710 µm sieve (BP, 2005).

5.3.7.2 Specifications

To be determined during stability.

5.3.8 Loss on drying

This test is performed to determine the amount of volatile matter of any kind that is driven off under the conditions specified (USP29, 2006:<731>).

5.3.8.1 Method

(1) 1 g of tablet powder of each batch was weighed (in duplicate) into dry, clean, shallow screw cap glass bottles with heat resistant screw caps (masses of the bottles accurately known).

(2) Bottles were shaken gently to evenly distribute the tablet powder.

(3) Bottles and caps were labeled for identification.

(4) The powder was then dried in a pre-heated Binder® oven (Germany) at 105°C.

(5) After 3 hours the bottles were removed, caps replaced and placed in a dessicator to cool to room temperature.

(6) The bottles with tablet powder were weighed again (USP29, 2006:<731>).

(7) The weight difference between the initial mass and final mass was recorded and expressed as a percentage of the initial powder mass, using the following equation:

$$\%\,Moisture = \frac{mass\,of\,sample\,before\,drying - mass\,of\,sample\,after\,drying \times 100}{mass\,of\,sample\,before\,drying}$$

5.3.8.2 Specifications

To be determined during stability.

5.3.9 Identification

Identification testing should establish the identity of the API in the formulation (ICH Q6A, 1999).

5.3.9.1 Method

The HPLC method for the determination of diclofenac sodium content was used (See validated method in Annexure B).

5.3.9.2 Specifications

The HPLC retention time of the API in the tablet sample conforms to that of diclofenac sodium RS obtained in the assay (USP29, 2006).

5.3.10 Assay

The ICH stability guidelines states that a stability-indicating assay should be performed on all new pharmaceutical products (ICH Q6A, 1999). This test is performed to determine the strength/content of the tablets.

5.3.10.1 Method

This test was done according to the HPLC method validated in Annexure B.

5.3.10.2 Specifications

Diclofenac sodium dispersible tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of diclofenac sodium (USP, 2006).

5.3.11 Chromatographic purity

Impurities arising from degradation of the API and impurities that arise during the manufacturing process of the pharmaceutical product should be monitored (ICH Q6A, 1999).

5.3.11.1 Method

(1) The chromatographic purity method to determine the amount of diclofenac related compound A ([N-(2,6-dichlorophenyl)indolin-2-one]) in diclofenac sodium delayed-release tablets was used (USP29, 2006) (See also validated method in Annexure B).

(2) The chromatographs were enlarged 100 times to see if any related compound/impurity peaks could be detected.

(3) If any peaks were detected, the following equation would be used to calculate the percentage of the related compound in relation to the quantity of diclofenac sodium:

$$\% \text{ Diclofenac related compound A} = 10(C/A)(r_u/r_s)$$

Where: A = Quantity (mg) of diclofenac sodium in the tablets as determined in the assay

C = Concentration (µg/ml) of diclofenac related compound A in the standard solution

r_u = Diclofenac related compound A peak response (sample)

r_s = Diclofenac related compound A peak response (standard) (USP29, 2006).

(4) Calculate the percentage of each other impurity, other than diclofenac related compound A, if present, in relation to the diclofenac sodium in the tablets with the equation:

$$\% \text{ Impurity} = 10(C/A)(r_i/r_s)$$

Where: r_i = Peak response for each impurity (sample) (USP29, 2006).

5.3.11.2 Specifications

- Not more than 0.5% of diclofenac related compound A is found.
- Not more than 1.0% of any individual impurity is found and not more than 1.5% of total impurities are found (USP29, 2006).

5.3.12 Dissolution

This test measures the time required for an API in an oral solid dosage form to dissolve under a specified set of conditions (Lieberman & Lachman, 1982:381). According to Abrahamsson and Ungell (2004:241) the purpose of dissolution testing is to investigate API release from formulations and to determine the effect of different storage conditions on these formulations. Dissolution results also support bioavailability studies.

5.3.12.1 Choice of dissolution medium

The choice of dissolution medium is dependant on the API solubility and stability at different pH values (Abrahamsson & Ungell, 2004:251).

Comparative dissolution studies were carried out between the four different formulations using the conditions as set out in the MCC Dissolution Guideline. The purpose of these comparative dissolution studies was to establish the ideal dissolution medium for stability and to compare the effect of different disintegrants used in the formulations on dissolution.

5.3.12.1.1 Comparison of dissolution profiles

A simple model independent approach uses a difference factor (f_1) and a similarity factor (f_2) to compare dissolution profiles (Moore & Flanner, 1996:65). Similarity factors were used to compare dissolution results. The following criteria are set by the MCC (MCC Dissolution Guideline, 2003:6):

(1) If both the test and reference product show more than 85% dissolution within 15 minutes, the profiles are considered similar. If not,

(2) Calculate the f_2 value (similarity factor). If $f_2 \geq 50$, the profiles are regarded similar.

The similarity factor (in percentage) was calculated using the following mathematical equation (MCC Dissolution Guideline, 2003:6):

$$f_2 = 50 \bullet \log\left(\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t (R_t - T_t)^2\right]^{-0.5} \bullet 100\right)$$

Where: n = Number of dissolution time points

R_t = Reference dissolution value at time t

T_t = Test dissolution value at time t

w_t = Optional weighting factor

5.3.12.1.2 Sampling intervals

For bioequivalence studies and product development, multi-point intervals are recommended for immediate release dosage forms (Abrahamsson & Ungell, 2004:251). In this study the following sampling intervals were used: 10, 15, 20, 30, 45 and 60 minutes.

5.3.12.1.3 Parameters

Dissolution conditions as set out in the MCC Dissolution Guideline (2003:5,6):

Medium 1: Phosphate buffer pH 6.8 (900 ml)

Medium 2: Sörensen buffer pH 4.5 (900 ml)

Medium 3: 0.1 N HCl (900 ml)

USP apparatus 2 (paddles) (USP29, 2006:<711>): 75 rpm

Twelve units (2 sets of dissolution tests) of each formulation were included in the dissolution studies in all three media.

5.3.12.1.4 Method

(1) A Vankel 7000® dissolution apparatus (USA) was used. The apparatus consisted of six glass vessels with paddles.

(2) The following dissolution media were prepared according to USP methods (USP29, 2006):

- Phosphate buffer pH 6.8: 81.66 g potassium dihydrogen phosphate and 10.752 g sodium hydroxide were measured and dissolved in 12 liters of distilled water and the pH adjusted to pH 6.8.
- Sörensen buffer pH 4.5: 9.6 g disodium hydrogen phosphate dodecahydrate and 105 g potassium dihydrogen phosphate were measured and dissolved in 12 liters of distilled water and the pH adjusted to pH 4.5.
- 0.1 N HCl: 98 ml of HCl (32%) was diluted to 10 liters with distilled water.

(3) The dissolution media were divided into the six vessels (900 ml each).

(4) The dissolution media in the vessels were maintained at 37°C and the speed of the paddles set at 75 rpm.

(5) Six tablets were randomly selected from each tablet formulation, weighed and each tablet weight recorded.

(6) The six tablets were then introduced into the vessels.

(7) After each elapsed time interval, 10 ml was extracted from each vessel and filtered through a Millex HV 0.45 µm PVDF filter (Millipore) into glass test tubes.

(8) 5 ml of each extracted sample was diluted to 10 ml with dissolution medium.

(9) The following standard solution was prepared:

- About 27.78 mg of diclofenac sodium RS was transferred into a 100 ml volumetric flask.
- 10 ml of 0.1 M NaOH was added to dissolve the diclofenac sodium and the volumetric flask made up to volume with dissolution medium.
- 5 ml of this solution was diluted to 50 ml with dissolution medium.

(10) The amount of diclofenac sodium dissolved was determined from UV absorbances at 276 nm, compared to a standard solution, on a Beckman DU® 650i spectrophotometer (USA).

5.3.12.1.5 Results

The dissolution rates (%), f_1 and f_2 values of formulation A (2% croscarmellose sodium) in comparison with formulation B (5% croscarmellose sodium) are given in tables 5.1-5.3.

Table 5.1: Dissolution rates of formulations A and B in 0.1 N HCl

Time (minutes)	% Dissolved	
	Formulation A	Formulation B
10	24.52	24.20
15	26.97	23.02
20	24.72	19.79
30	23.83	15.73
45	16.95	12.66
60	14.49	11.84
f_1 (n=6)	23	
f_2 (n=6)	66	

Table 5.2: Dissolution rates of formulations A and B in Sörensen buffer pH 4.5

Time (minutes)	% Dissolved	
	Formulation A	Formulation B
10	44.54	43.52
15	46.81	45.19
20	45.28	43.34
30	42.09	40.39
45	40.99	37.71
60	38.65	34.85
f_1 (n=6)	5	
f_2 (n=6)	79	

Table 5.3: Dissolution rates of formulations A and B in phosphate buffer pH 6.8

Time (minutes)	% Dissolved	
	Formulation A	Formulation B
10	87.52	91.63
15	94.79	99.35
20	95.06	99.55
30	95.20	99.57
45	95.32	99.83
60	97.15	100.75
f_1	N/A	
f_2	≥85% in 15 minutes	

The dissolution rates (%), f_1 and f_2 values of formulation C (2% crospovidone) in comparison with formulation D (5% crospovidone) are given in Tables 5.4-5.6.

Table 5.4: Dissolution rates of formulations C and D in 0.1 N HCl

Time (minutes)	% Dissolved	
	Formulation C	Formulation D
10	34.24	32.53
15	33.94	28.91
20	23.90	23.62
30	19.96	20.24
45	15.80	15.18
60	12.62	12.39
f_1 (n=6)	6	
f_2 (n=6)	81	

Table 5.5: Dissolution rates of formulations C and D in Sörensen buffer pH 4.5

Time (minutes)	% Dissolved	
	Formulation C	Formulation D
10	60.49	57.42
15	64.35	60.48
20	60.02	56.84
30	57.61	54.94
45	52.20	50.90
60	49.42	49.24
f_1 (n=6)	4	
f_2 (n=6)	77	

Table 5.6: Dissolution rates of formulations C and D in phosphate buffer pH 6.8

Time (minutes)	% Dissolved	
	Formulation C	Formulation D
10	73.78	82.26
15	88.24	91.95
20	93.89	94.19
30	96.78	95.85
45	98.51	97.49
60	100.04	99.38
f_1	N/A	
f_2	≥85% in 15 minutes	

The dissolution rates (%), f_1 and f_2 values of formulation B (5% croscarmellose sodium) in comparison with formulation D (5% crospovidone) are given in Tables 5.7-5.9. Dissolution profiles of formulations B and D in all three media are given in Figures 5.1-5.3.

Table 5.7: Dissolution rates of formulations B and D in 0.1 N HCl

Time (minutes)	% Dissolved	
	Formulation B	Formulation D
10	24.20	32.53
15	23.02	28.91
20	19.79	23.62
30	15.73	20.24
45	12.66	15.18
60	11.84	12.39
f_1 (n=6)	24	
f_2 (n=6)	65	

Table 5.8: Dissolution rates of formulations B and D in Sörensen buffer pH 4.5

Time (minutes)	% Dissolved	
	Formulation B	Formulation D
10	43.52	57.42
15	45.19	60.48
20	43.34	56.84
30	40.39	54.94
45	37.71	50.90
60	34.85	49.24
f_1 (n=6)	35	
f_2 (n=6)	42	

Table 5.9: Dissolution rates of formulations B and D in phosphate buffer pH 6.8

Time (minutes)	% Dissolved	
	Formulation B	Formulation D
10	91.63	82.26
15	99.35	91.95
20	99.55	94.19
30	99.57	95.85
45	99.83	97.49
60	100.75	99.38
f_1	N/A	
f_2	≥85% in 15 minutes	

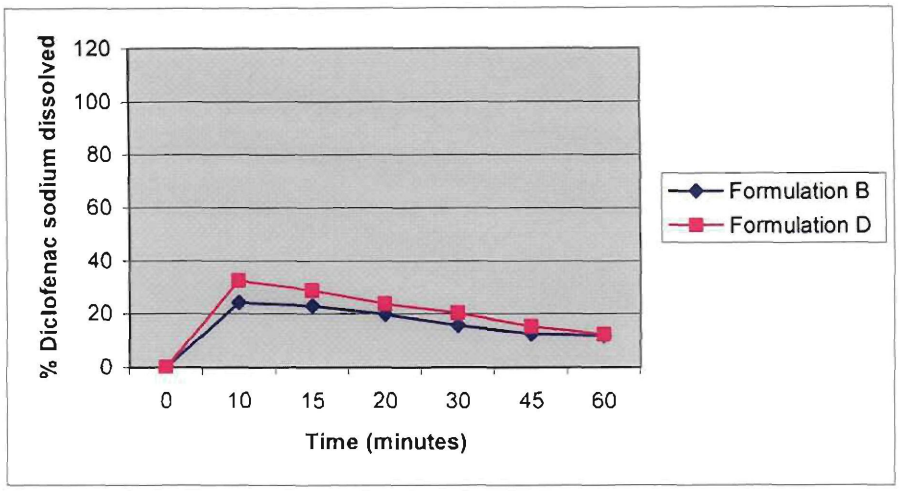


Figure 5.1: Dissolution profiles of formulations B and D in 0.1 N HCl.

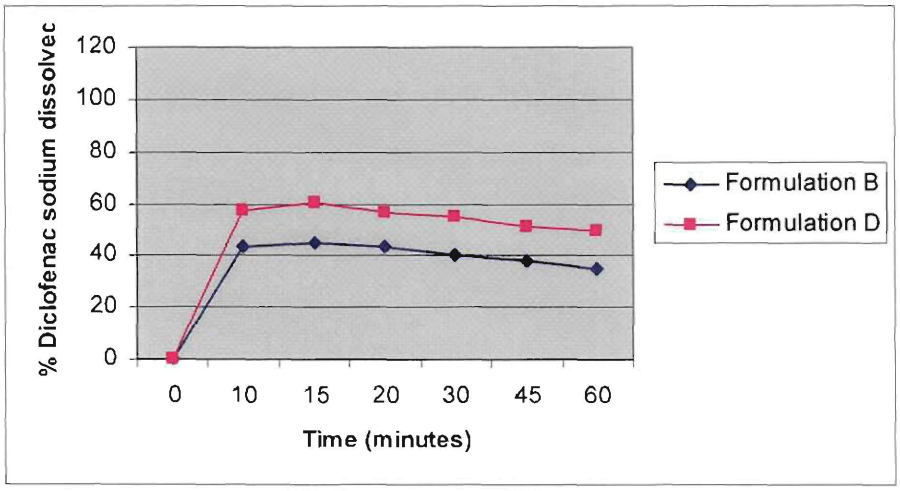


Figure 5.2: Dissolution profiles of formulations B and D in Sörensen buffer pH 4.5.

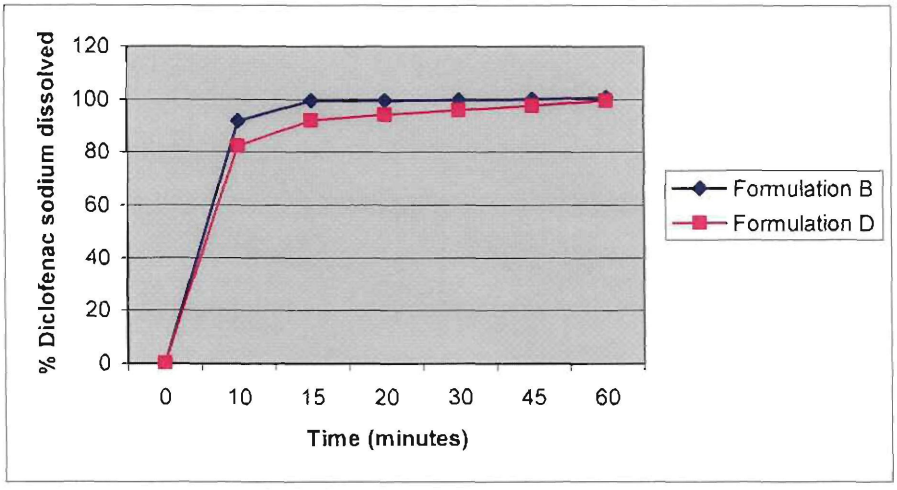


Figure 5.3: Dissolution profiles of formulations B and D in phosphate buffer pH 6.8.

5.3.12.1.6 Discussion

The similarity factor (f_2) and the difference factor (f_1) were not calculated for comparison of the dissolution profiles of the four formulations in phosphate buffer pH 6.8. According to the MCC Dissolution Guideline (2003:6) these calculations are not necessary, since for all the formulations 85% or more of the labeled amount of diclofenac sodium dissolved within 15 minutes in this dissolution medium.

Comparison of dissolution profiles of formulation A and B and formulation C and D in 0.1 N HCl and Sörensen buffer pH 4.5 gave f_2 values higher than 50. Therefore, the dissolution profiles of formulation A and B and formulation C and D in 0.1 N HCl and Sörensen buffer pH 4.5 can be considered similar.

The f_2 value for comparison of the dissolution profiles of formulation B and D in 0.1 N HCl is ≥ 50, therefore, the profiles can be considered similar. The f_2 value of formulation B and D in Sörensen buffer pH 4.5 is ≤ 50. Therefore the dissolution profiles of formulation B and D in Sörensen buffer pH 4.5 are not similar.

The dissolution results obtained for all four formulations in 0.1 N HCl were very low. This is due to the low solubility of diclofenac sodium at low pH-values. Herzfeldt and Kümmel (1983:779) reported a solubility for diclofenac sodium of less than 4×10^{-4}% w/v at pH 1.2 to 3.

The dissolution results obtained for all four formulations in Sörensen buffer pH 4.5 were also relatively low. At pH 4 Herzfeldt and Kümmel (1983:779) reported a solubility for diclofenac sodium of 0.0021% w/v, which is in line with the results obtained.

A decrease in the percentage diclofenac sodium dissolved was observed for all four formulations in 0.1 N HCl and Sörenson buffer pH 4.5. Information about the stability of diclofenac sodium is scarce, but the cyclization of diclofenac sodium to an indolinone derivative (a lactam) in acidic aqueous solutions was reported (Larsen & Bundgaard, 1980:104). This could explain the downward curve in the dissolution profiles obtained at lower pH-ranges.

The dissolution profiles obtained for formulations A and B in phosphate buffer pH 6.8 show that, although the profiles are comparable, the onset of dissolution was faster in the case of formulation B (croscarmellose sodium 5% as disintegrant). The same applies to the dissolution profiles of formulations C and D, where formulation D (crospovidone 5%) showed faster dissolution rates at the earlier time points. When the dissolution profiles of formulations B and D are compared, formulation B showed faster dissolution at earlier time

points, indicating that the disintegrating properties of croscarmellose sodium at 5% is superior to that of crospovidone at 5%.

5.3.12.1.7 Conclusion

The phosphate buffer pH 6.8 was chosen as the most favourable dissolution medium for dissolution stability testing of the diclofenac sodium dispersible tablets.

5.3.12.2 Method

Use the method as specified in 5.3.12.1.4 with phosphate buffer pH 6.8 as dissolution medium.

5.3.12.3 Specifications

- To be determined during stability.
- Typical acceptance criteria for the amount of active ingredient dissolved, expressed as a percentage of the labeled content (Q), are in the range of 75% to 80% dissolved.
- Dissolution profiles of immediate-release products typically show a gradual increase reaching 85% to 100% at about 30 to 45 minutes (USP29, 2006:<1092>).

5.3 Conclusion

The stability tests performed on the four dispersible diclofenac sodium tablet formulations, test methods and specifications were discussed in this chapter. Tests performed included a visual assessment of the tablets, uniformity of weight, dimensions, hardness, friability, fineness of dispersion, loss on drying, identification, assay, chromatographic purity and dissolution.

Comparative dissolution studies performed to determine the dissolution medium of choice for stability studies indicated that phosphate buffer pH 6.8 was the most favourable medium. The dissolution profiles obtained also indicated that the disintegration properties of 5% croscarmellose sodium were superior to that of croscarmellose sodium at a concentration of 2% and the disintegration properties of crospovidone at 5% and 2%.

The stability test results are discussed in chapter 6. Results will be used to choose the most favourable formulation, set product specifications for release and stability and to establish specific storage conditions.

CHAPTER 6

Test Results and Discussion

6.1 Introduction

A summary of the test results obtained from stability testing performed on the four diclofenac sodium dispersible tablets formulations is given in this chapter.

6.2 Visual assessment (description)

Four batches of round, white tablets with no markings and a diameter of ± 9.05 mm were manufactured. Tablets had a smooth surface with sharp edges. No evidence of capping were observed.

All the formulations had a peppermint flavour and odour with a bitter after-taste in the back of the throat. This remained unchanged throughout the stability programme.

The visual appearance of all the formulations remained unchanged throughout the stability period, except the samples stored for 3 months at 40°C/75%RH where a slight colour change from white to a very light brown was observed.

6.3 Uniformity of mass and average mass

6.3.1 Results

The average tablet mass of the four formulations is tabulated in Tables 6.1-6.4.

Table 6.1: Average tablet mass (mg) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	301	302	301	302
30°C/65% RH	-	299	302	301
40°C/75% RH	-	301	300	299

Table 6.2: Average tablet mass (mg) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	298	297	299	302
30°C/65% RH	-	299	303	300
40°C/75% RH	-	304	300	300

Table 6.3: Average tablet mass (mg) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	301	302	300	300
30°C/65% RH	-	308	303	305
40°C/75% RH	-	309	306	305

Table 6.4: Average tablet mass (mg) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	292	291	295	295
30°C/65% RH	-	297	299	298
40°C/75% RH	-	297	299	300

6.3.2 Discussion

The average mass of the all the formulations remained relatively constant at increased stress conditions and at different time intervals (Tables 6.1 – 6.4). The uniformity of mass fell within the specification for all the formulations at all time intervals, therefore confirming that not more than 2 of the individual masses deviate from the average mass by more than ± 5% and none deviates by more than twice that percentage.

6.4 Dimensions

6.4.1 Results

The average diameter and thickness of the four formulations are tabulated in Tables 6.5-6.12.

Table 6.5: Average diameter (mm) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	9.05	9.10	9.08	9.09
30°C/65% RH	-	9.05	9.09	9.10
40°C/75% RH	-	9.09	9.10	9.05

Table 6.6: Average diameter (mm) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	9.04	9.09	9.09	9.08
30°C/65% RH	-	9.05	9.10	9.10
40°C/75% RH	-	9.10	9.09	9.06

Table 6.7: Average diameter (mm) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	9.05	9.08	9.11	9.09
30°C/65% RH	-	9.06	9.10	9.10
40°C/75% RH	-	9.11	9.10	9.09

Table 6.8: Average diameter (mm) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	9.09	9.08	9.10	9.09
30°C/65% RH	-	9.07	9.10	9.10
40°C/75% RH	-	9.09	9.11	9.11

Table 6.9: Average thickness (mm) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.15	4.21	4.20	4.20
30°C/65% RH	-	4.21	4.21	4.21
40°C/75% RH	-	4.22	4.21	4.22

Table 6.10: Average thickness (mm) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.14	4.20	4.20	4.21
30°C/65% RH	-	4.21	4.26	4.26
40°C/75% RH	-	4.24	4.26	4.22

Table 6.11: Average thickness (mm) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.49	4.57	4.51	4.50
30°C/65% RH	-	4.55	4.56	4.59
40°C/75% RH	-	4.60	4.56	4.56

Table 6.12: Average thickness (mm) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	3.66	3.80	3.69	3.69
30°C/65% RH	-	3.70	3.74	3.71
40°C/75% RH	-	3.77	3.76	3.75

6.4.2 Discussion

The diameter remained relatively constant throughout the stability programme, but an increase in thickness with time was observed in all four formulations. The thickness of formulation D was significantly less than that of the other 3 formulations. This could be due to a greater force exerted by the tabletting punch, resulting in thinner, harder tablets.

6.5 Hardness

6.5.1 Results

The average tablet hardness in Newton for each formulation is tabulated in Tables 6.13-6.16.

Table 6.13: Average tablet hardness (N) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	60.3	61.0	61.5	67.0
30°C/65% RH	-	58.6	66.4	66.9
40°C/75% RH	-	62.7	68.8	70.3

Table 6.14: Average tablet hardness (N) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	54.8	56.4	56.3	57.3
30°C/65% RH	-	51.3	56.7	58.7
40°C/75% RH	-	56.8	76.6	86.0

Table 6.15: Average tablet hardness (N) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	47.3	45.0	46.4	51.2
30°C/65% RH	-	44.9	55.5	56.5
40°C/75% RH	-	55.7	62.1	71.4

Table 6.16: Average tablet hardness (N) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	105.2	104.8	102.7	111.6
30°C/65% RH	-	106.3	102.0	118.2
40°C/75% RH	-	101.5	117.6	131.1

Graphic displays of the hardness results for each formulation during the stability period are given in Figures 6.1-6.4.

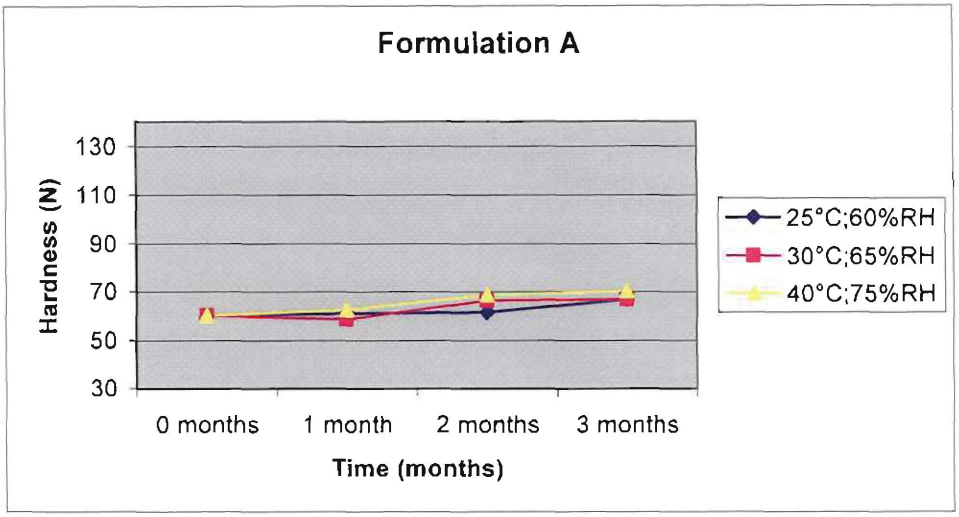


Figure 6.1: **Graphic representation of the hardness (N) results of formulation A over the stability period of three months.**

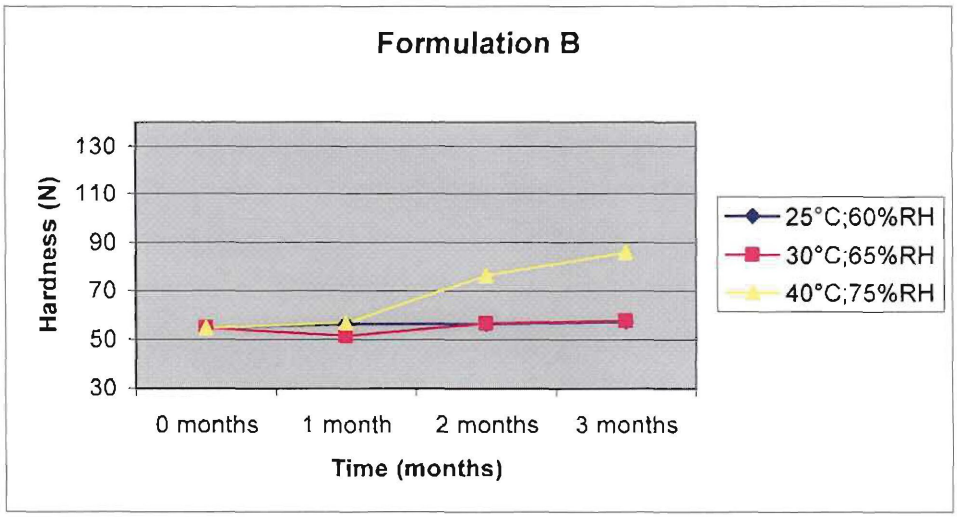


Figure 6.2: **Graphic representation of the hardness (N) results of formulation B over the stability period of three months.**

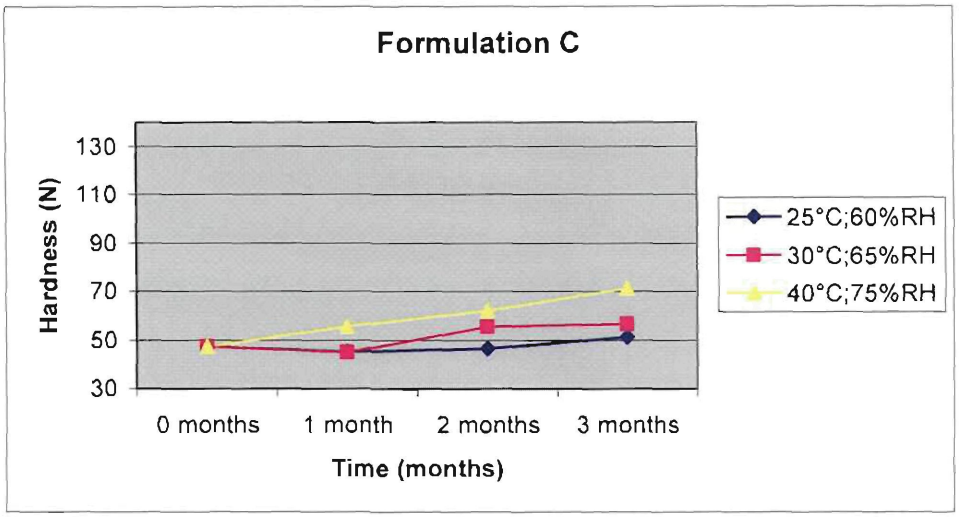


Figure 6.3: Graphic representation of the hardness (N) results of formulation C over the stability period of three months.

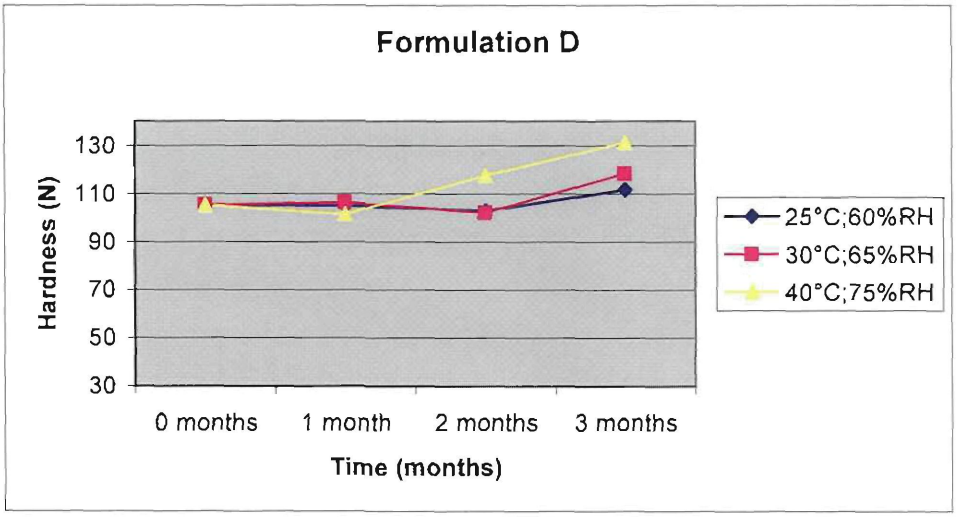


Figure 6.4: Graphic representation of the hardness (N) results of formulation D over the stability period of three months.

6.5.2 Discussion

Formulation A:

There was an increase in hardness after 2 months storage at 30°C/65% RH and 40°C/75% RH. After 3 months, an increase was observed at all three storage conditions.

Formulation B:

After 2 and 3 months, the samples stored at 40°C/75% RH showed a significant increase in hardness.

Formulation C:

There was an increase in hardness after 1 month storage at 40°C/75% RH, and after 2 months storage at 30°C/65% RH and 40°C/75% RH. After 3 months, an increase was observed at all three storage conditions.

Formulation D:

The hardness of the tablets of formulation D was significantly higher than that of the other 3 formulations, confirming the observation and explanation of the thinner tablets of formulation D in 6.4.2. After 2 months storage at 40°C/75% RH, an increase in hardness was observed. The tablets at all three storage conditions showed in increase in hardness after 3 months.

A possible reason for the increase in hardness of the tablets of all four formulations can be ascribed to recrystallisation of a compound or excipient due to moisture absorbed during the stability period (Carstensen, 2000a:296).

6.6 Friability

6.6.1 Results

The amount of tablet mass (in percentage) lost due to friability is tabulated in Tables 6.17-6.20.

Table 6.17: Friability (%) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	1.5	1.1	1.0	0.7
30°C/65% RH	-	1.0	0.8	0.6
40°C/75% RH	-	0.8	0.8	0.7

Table 6.18: Friability (%) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	1.6	1.5	1.2	0.7
30°C/65% RH	-	1.2	1.1	0.7
40°C/75% RH	-	0.8	0.8	0.6

Table 6.19: Friability (%) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	1.9	1.4	1.4	1.0
30°C/65% RH	-	1.2	1.2	1.2
40°C/75% RH	-	1.0	0.9	0.7

Table 6.20: Friability (%) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	0.5	0.2	0.2	0.1
30°C/65% RH	-	0.2	0.2	0.1
40°C/75% RH	-	0.1	0.1	0.1

The friability results of formulations A, B, C and D obtained during stability testing are graphically represented in Figures 6.5-6.8.

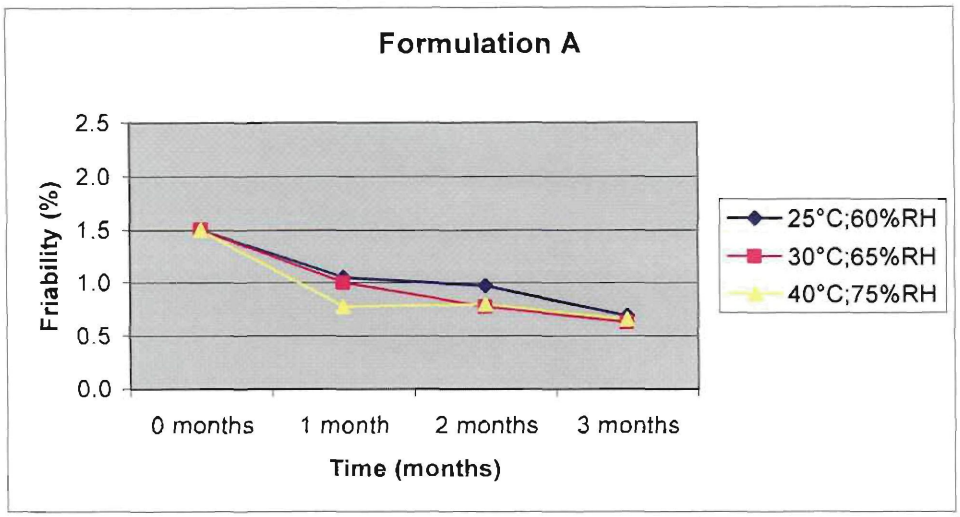


Figure 6.5: **Graphic representation of the friability (%) results of formulation A over the stability period of three months.**

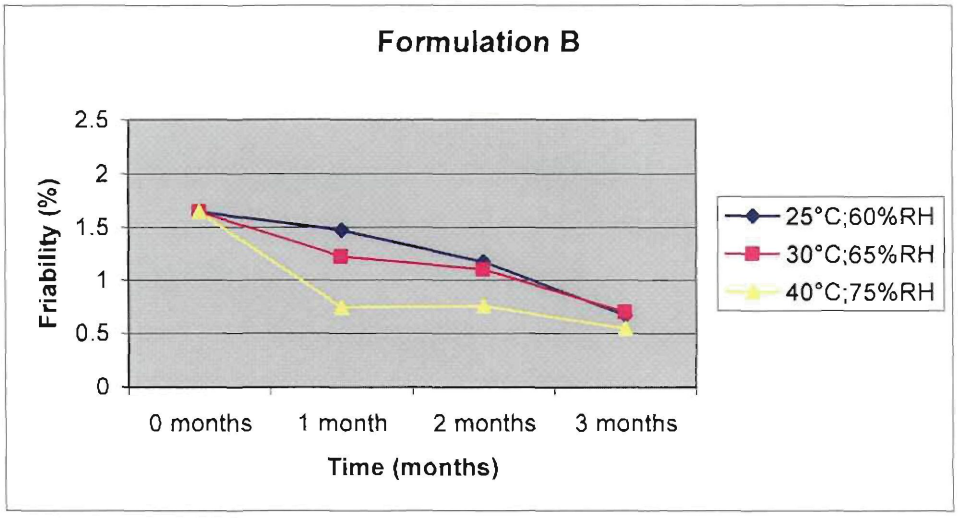


Figure 6.6: **Graphic representation of the friability (%) results of formulation B over the stability period of three months.**

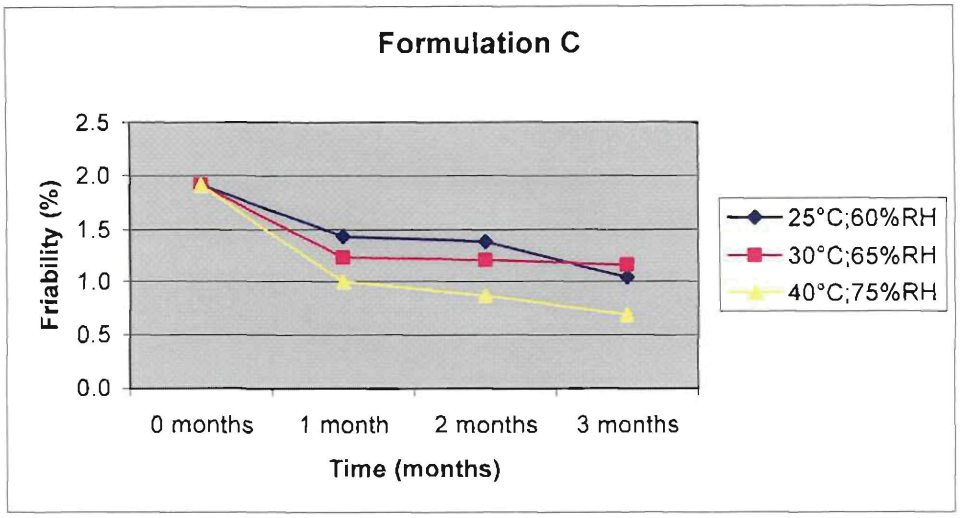


Figure 6.7: Graphic representation of the friability (%) results of formulation C over the stability period of three months.

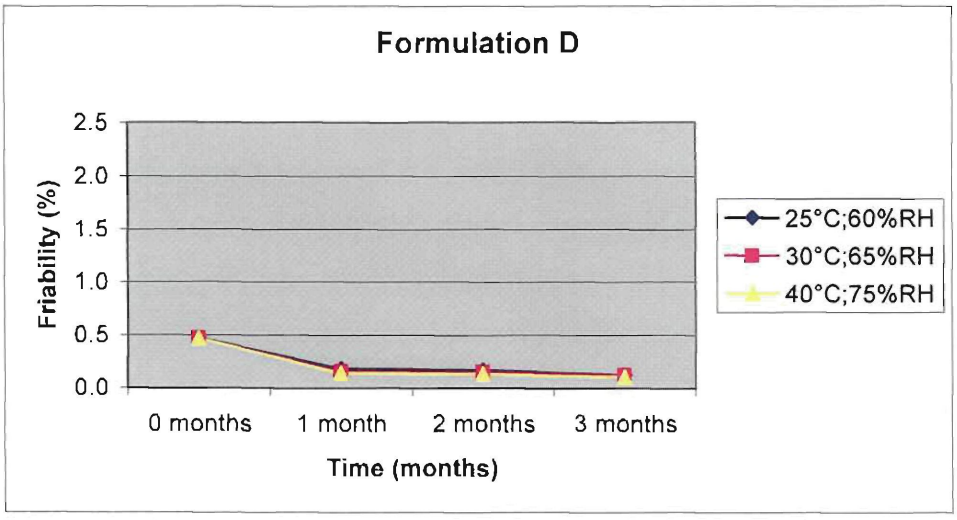


Figure 6.8: Graphic representation of the friability (%) results of formulation D over the stability period of three months.

6.6.2 Discussion

The percentage tablet mass lost during friability of all four formulations decreased noticeably with time and increased stress conditions. The largest decrease was observed after 1, 2 and 3 months at the 40°C/75% RH storage condition.

A definite correlation can be drawn between the increased hardness of the tablets after 3 months and the decreased friability values. The harder the tablet, the smaller the tablet

mass lost during friability testing. The percentage friability of the thinner, harder tablets of formulation D was significantly less than that of the other 3 formulations.

The percentage friability of all 4 formulations, except the thinner, harder formulation D, was higher than the general specification of 1% at some time points. The friability specification for batch release and stability can be set at 2% according to the results obtained, because no signs of chipping of the tablets or any broken tablets were observed in any of the formulations throughout the stability period. If chipping or breaking of the tablets is a concern and picked up during stability, the packing of the tablets in blisters can solve the problem.

6.7 Disintegration

6.7.1 Results

The time it took each of the six tablets per formulation to disintegrate, is tabulated in Tables 6.21-6.24.

6.7.2 Discussion

Disintegration times increased with time and increased stress conditions.

Formulation A:

Tablets disintegrated within 3 minutes, except the 40°C/75% RH samples at 2 and 3 months.

Formulation B:

All the tablets of formulation B disintegrated within 3 minutes.

Formulation C:

Although tablets appeared to disintegrate within 3 minutes during the in-process developmental tests, the tablets failed to meet the disintegration specification during stability.

Formulation D:

Tablets disintegrated within 3 minutes at the start of the stability programme, but disintegration time increased to more than 3 minutes after 1, 2 and 3 months of storage.

The increase in time for the tablets to disintegrate correlates with the increase in hardness and decrease in friability observed. From the results obtained, it is clear that only formulation B complied to the specification of 3 minutes for disintegration.

Table 6.21: Disintegration times (minutes) of formulation A measured over 3 months at different storage conditions

Storage condition and interval	Disintegration time (minutes)					
Initial	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
	0'28	0'29	0'52	0'54	1'01	1'02
1 month	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	0'44	0'52	1'16	1'18	1'21	1'30
30°C/65% RH	0'36	0'44	0'46	1'06	1'42	1'56
40°C/75% RH	0'38	0'48	0'56	1'12	1'16	2'04
2 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	1'07	1'30	1'40	1'56	2'16	2'39
30°C/65% RH	0'54	1'04	1'43	2'29	2'36	2'50
40°C/75% RH	2'24	2'39	>3'00	>3'00	>3'00	>3'00
3 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	0'53	1'16	1'33	1'39	1'45	2'02
30°C/65% RH	1'00	1'20	1'43	1'50	1'59	2'40
40°C/75% RH	2'08	2'27	>3'00	>3'00	>3'00	>3'00

Table 6.22: **Disintegration times (minutes) of formulation B measured over 3 months at different storage conditions**

Storage condition and interval	Disintegration time (minutes)					
Initial	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
	0'16	0'18	0'19	0'20	0'24	0'34
1 month	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	0'21	0'23	0'26	0'27	0'30	0'35
30°C/65% RH	0'24	0'28	0'30	0'32	0'35	0'42
40°C/75% RH	0'48	0'51	0'56	1'06	1'13	2'29
2 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	0'22	0'23	0'24	0'27	0'29	0'41
30°C/65% RH	0'34	0'37	0'41	0'43	0'56	1'00
40°C/75% RH	1'30	2'10	2'11	2'25	2'31	2'49
3 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	0'24	0'27	0'29	0'30	0'30	0'36
30°C/65% RH	0'30	0'31	0'42	0'43	0'54	1'02
40°C/75% RH	0'43	1'04	1'24	1'39	2'26	2'39

Table 6.23: Disintegration times (minutes) of formulation C measured over 3 months at different storage conditions

Storage condition and interval	Disintegration time (minutes)					
Initial	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
	2'45	2'51	2'58	>3'00	>3'00	>3'00
1 month	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	2'52	>3'00	>3'00	>3'00	>3'00	>3'00
30°C/65% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
2 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
30°C/65% RH	2'58	>3'00	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
3 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
30°C/65% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00

Table 6.24: **Disintegration times (minutes) of formulation D measured over 3 months at different storage conditions**

Storage condition and interval	Disintegration time (minutes)					
Initial	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
	1'58	2'01	2'02	2'06	2'25	2'50
1 month	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	2'15	2'20	2'34	>3'00	>3'00	>3'00
30°C/65% RH	2'34	2'48	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	2'49	>3'00	>3'00	>3'00	>3'00	>3'00
2 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	2'29	2'35	2'50	>3'00	>3'00	>3'00
30°C/65% RH	2'14	2'55	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	2'56	>3'00	>3'00	>3'00	>3'00	>3'00
3 months	**Tablet 1**	**Tablet 2**	**Tablet 3**	**Tablet 4**	**Tablet 5**	**Tablet 6**
25°C/60% RH	2'07	2'48	>3'00	>3'00	>3'00	>3'00
30°C/65% RH	2'15	>3'00	>3'00	>3'00	>3'00	>3'00
40°C/75% RH	>3'00	>3'00	>3'00	>3'00	>3'00	>3'00

6.8 Fineness of dispersion

6.8.1 Results

The amount of particles of each formulation that were retained on the 710 µm sieve, are given in Tables 6.25-6.28.

Table 6.25: Amount of particles of formulation A retained measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	±15	±12	±20	±30
30°C/65% RH	-	±20	±20	±30
40°C/75% RH	-	±30	±30	±20

Table 6.26: Amount of particles of formulation B retained measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	0	2	0	0
30°C/65% RH	-	2	1	0
40°C/75% RH	-	1	2	2

Table 6.27: Amount of particles of formulation C retained measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	±20	±30	±30	±30
30°C/65% RH	-	±35	±30	±30
40°C/75% RH	-	±35	±45	±35

Table 6.28: Amount of particles of formulation D retained measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	8	7	11	±20
30°C/65% RH	-	15	15	±15
40°C/75% RH	-	6	6	±30

6.8.2 Discussion

Very few particles of formulation B (5% croscarmellose sodium) were retained on the sieve when poured through, indicating that it was a homogeneous dispersion. The other 3 formulations were not very homogeneous, as a lot of particles were retained on the sieve. Croscarmellose sodium appears to be superior to crospovidone as disintegrant and is more effective when present in a concentration of 5% of the tablet mass, confirming the results obtained in the comparative dissolution studies in 5.3.12.1.5.

6.9 Loss on drying

6.9.1 Results

The moisture lost (in percentage) of each formulation during drying, is tabulated in Tables 6.29–6.32.

Table 6.29: Moisture lost (%) of formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.2	4.2	4.1	4.4
30°C/65% RH	-	5.9	5.9	6.0
40°C/75% RH	-	6.1	5.9	6.1

Table 6.30: Moisture lost (%) of formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.6	4.8	4.4	4.7
30°C/65% RH	-	5.9	5.4	5.2
40°C/75% RH	-	6.5	6.4	6.7

Table 6.31: Moisture lost (%) of formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.3	4.6	4.6	4.6
30°C/65% RH	-	6.1	5.8	5.9
40°C/75% RH	-	6.6	6.2	6.4

Table 6.32: Moisture lost (%) of formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	4.6	4.6	4.5	4.9
30°C/65% RH	-	5.9	6.6	6.9
40°C/75% RH	-	6.0	6.1	6.5

The percentage moisture lost during the 3 months stability testing of formulations A, B, C and D is graphically represented in Figures 6.9-6.12.

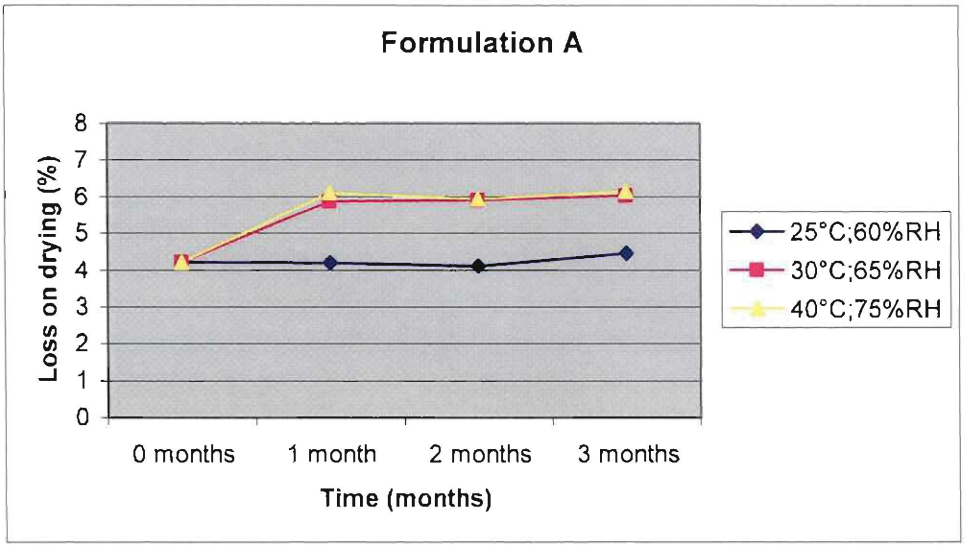


Figure 6.9: Graphic representation of the loss on drying (%) results of formulation A over the stability period of three months.

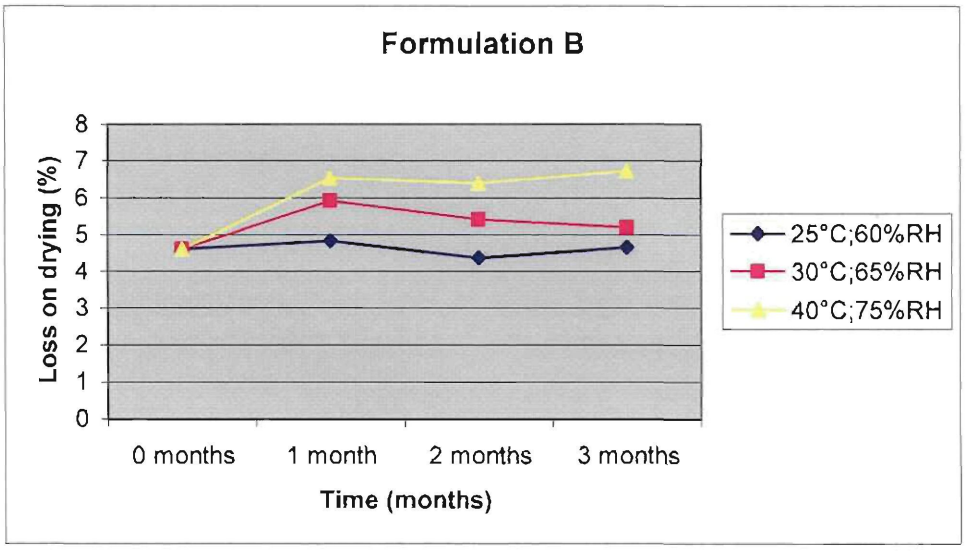


Figure 6.10: Graphic representation of the loss on drying (%) results of formulation B over the stability period of three months.

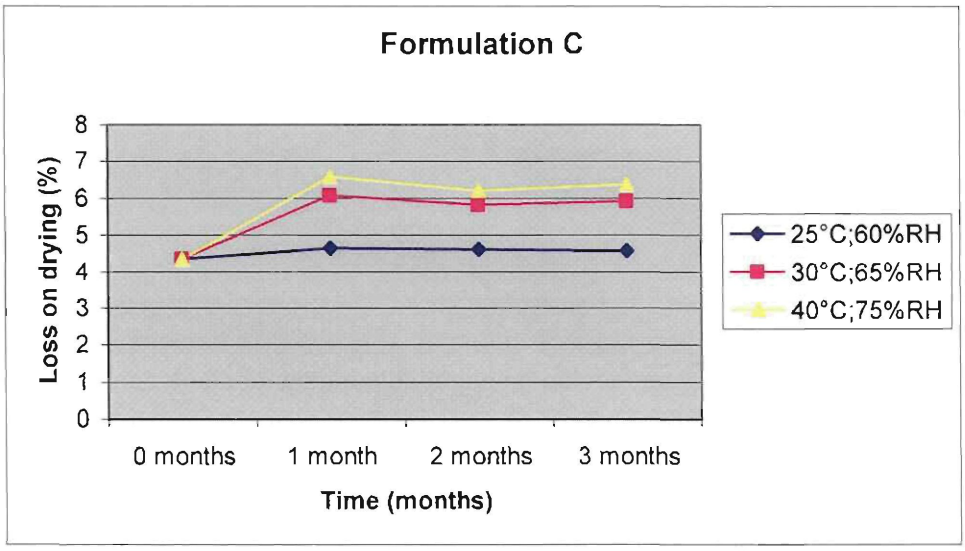


Figure 6.11: Graphic representation of the loss on drying (%) results of formulation C over the stability period of three months.

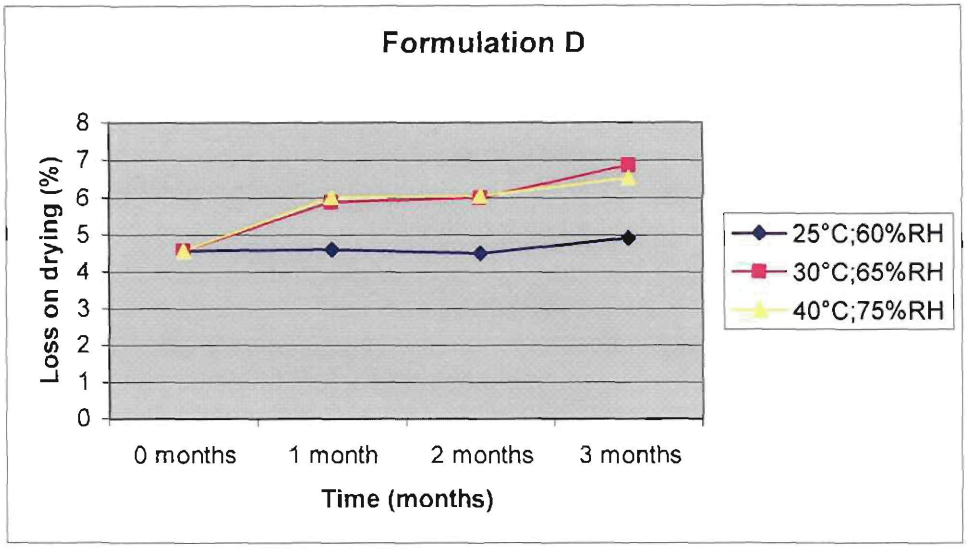


Figure 6.12: Graphic representation of the loss on drying (%) results of formulation D over the stability period of three months.

6.9.2 Discussion

Formulation A:

When stored at 25°C/60% RH, the formulation did not absorb a large percentage of moisture and results did not deviate much from the initial percentage moisture lost. Larger percentages moisture lost was observed in the samples stored at 30°C/65% RH and 40°C/75% RH.

Formulation B:

The percentage moisture lost at 25°C/60% RH remained relatively constant. The samples stored at 30°C/65% RH and 40°C/75% RH showed an increase in moisture lost after 2 and 3 months.

Formulation C:

After 1, 2 and 3 months, the percentage moisture lost increased with increased stress conditions.

Formulation D:

The samples stored at 30°C/65% RH and 40°C/75% RH showed increased percentages of moisture lost after 1, 2 and 3 months.

According to Carstensen (2000a:296) more moisture is absorbed by the tablets during storage at 40°C/75%RH. As mentioned in 6.5.2, the sorbed moisture can cause recrystallisation, therefore increasing tablet hardness.

6.10 Identification and assay

6.10.1 Results

For all four formulations the diclofenac sodium peak in the tablet samples eluted at the same time as diclofenac sodium peak in the standard solution with more or less the same peak area, during assay for content using HPLC.

The amount of diclofenac sodium present in each formulation is expressed as a percentage of the labeled amount (50 mg) in Tables 6.33-6.36.

Table 6.33: Amount of diclofenac sodium (%) in formulation A measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	97.4	99.5	96.0	95.1
30°C/65% RH	-	96.7	94.3	93.6
40°C/75% RH	-	97.5	96.0	93.6

Table 6.34: Amount of diclofenac sodium (%) in formulation B measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	97.1	97.0	96.3	96.6
30°C/65% RH	-	99.4	96.2	95.0
40°C/75% RH	-	98.5	96.3	93.0

Table 6.35: Amount of diclofenac sodium (%) in formulation C measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	99.3	99.3	97.5	96.0
30°C/65% RH	-	102.8	97.4	95.0
40°C/75% RH	-	100.6	97.8	93.1

Table 6.36: Amount of diclofenac sodium (%) in formulation D measured over 3 months at different storage conditions

Storage condition	Time interval			
	Initial	1 month	2 months	3 months
25°C/60% RH	94.7	94.4	94.4	93.5
30°C/65% RH	-	96.3	95.2	95.1
40°C/75% RH	-	95.0	94.9	90.6

The percentage diclofenac sodium in each formulation is graphically represented in Figures 6.13-6.16.

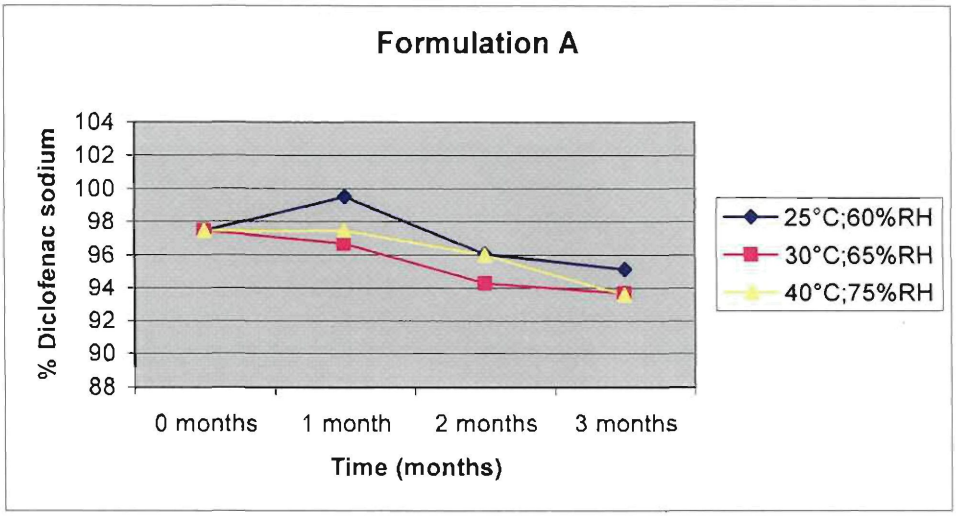


Figure 6.13: Graphic representation of the percentage diclofenac sodium present in formulation A over the stability period of three months.

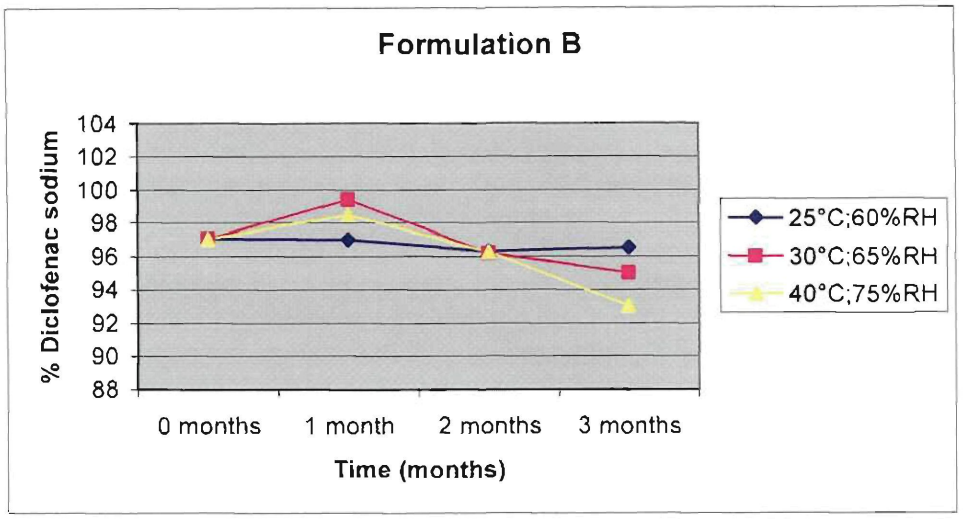


Figure 6.14: Graphic representation of the percentage diclofenac sodium present in formulation B over the stability period of three months.

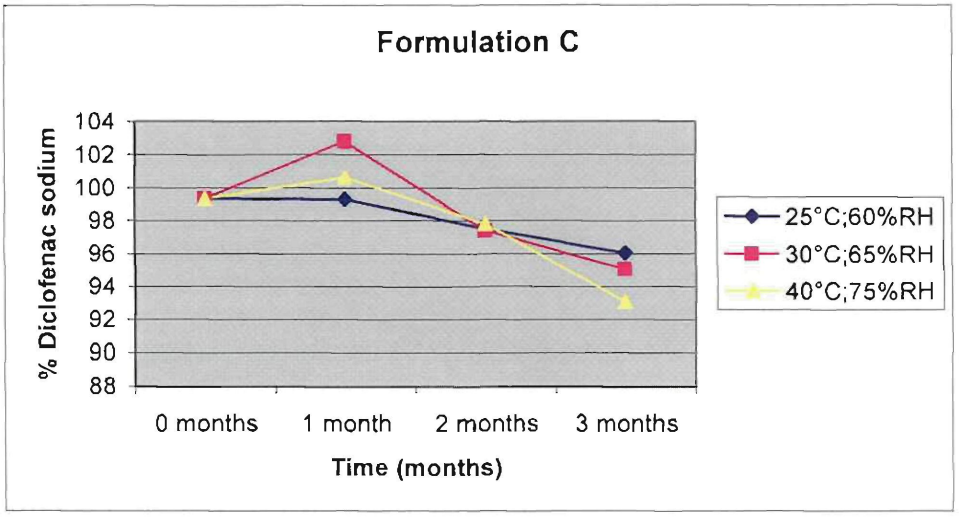


Figure 6.15: Graphic representation of the percentage diclofenac sodium present in formulation C over the stability period of three months.

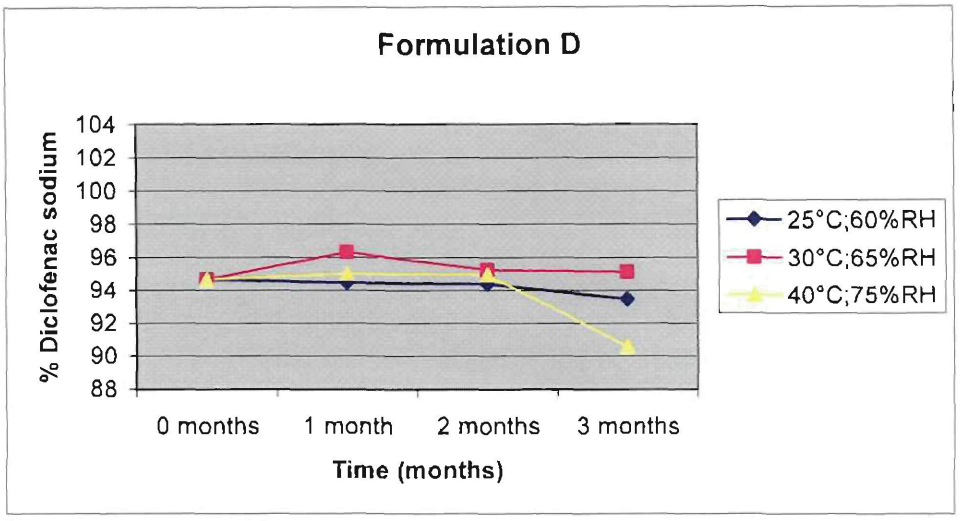


Figure 6.16: Graphic representation of the percentage diclofenac sodium present in formulation D over the stability period of three months.

6.10.2 Discussion

The HPLC retention time of diclofenac sodium in the tablet sample conforms to that of diclofenac sodium RS obtained in the assay, therefore confirming the positive identification of diclofenac sodium in all tablet samples.

The amounts of diclofenac sodium of all the formulations were within the specification limits of 90.0-110.0%. The diclofenac sodium assay of the tablets of formulation A stored at 25°C/60% RH, showed a decline from 97.4% at initial to 93.6% after 3 months at 40°C/75% RH. The same phenomenon was observed for the other formulations with a decline in percentage diclofenac sodium from 97.1% at initial to 93.0% after 3 months at 40°C/75% RH for formulation B, 99.3% to 93.1% in the case of formulation C and 94.7% to 90.6% in the case of formulation D.

6.11 Chromatographic purity

6.11.1 Results

No extra peaks were identified throughout the stability programme.

6.11.2 Discussion

No extra peaks ascribed to diclofenac related compound A ([N-(2,6-dichlorophenyl)indolin-2-one]) or any other impurity was identified during the stability period. All the samples therefore conformed to the set specifications, namely not more than 0.5% of diclofenac related compound A is found, not more than 1.0% of any individual impurity is found and not more than 1.5% of total impurities are found.

6.12 Dissolution

6.12.1 Results

Dissolution results are given in Tables 6.37-6.40 as the average percentages of the diclofenac sodium dissolved at a specific time point.

Table 6.37: Amount of diclofenac sodium (%) dissolved of formulation A measured over 3 months at different storage conditions (average of 6 tablets)

Storage condition and interval	Withdrawal time (minutes)					
Initial	10 min	15 min	20 min	30 min	45 min	60 min
	87.5	94.8	95.1	95.2	95.3	97.9
1 month	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	95.4	97.3	98.4	98.9	99.0	99.3
30°C/65% RH	96.3	96.8	99.0	99.2	99.4	100.0
40°C/75% RH	93.8	97.0	97.8	98.6	98.9	99.5
2 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	94.7	97.8	98.9	99.7	100.0	100.3
30°C/65% RH	93.9	95.6	96.3	96.6	96.7	98.0
40°C/75% RH	95.2	98.8	99.8	99.9	100.0	100.6
3 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	95.8	99.7	100.1	101.0	101.0	101.1
30°C/65% RH	89.6	89.9	91.0	91.6	98.5	99.4
40°C/75% RH	96.8	98.7	99.5	99.5	99.8	100.1

Table 6.38: Amount of diclofenac sodium (%) dissolved of formulation B measured over 3 months at different storage conditions (average of 6 tablets)

Storage condition and interval	Withdrawal time (minutes)					
Initial	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
	91.6	99.4	99.6	99.6	99.8	100.8
1 month	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
25°C/60% RH	98.9	99.9	100.3	100.2	100.3	100.4
30°C/65% RH	93.0	96.1	96.8	97.7	98.2	99.2
40°C/75% RH	98.8	98.9	98.9	99.5	100.3	101.3
2 months	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
25°C/60% RH	98.1	99.5	99.6	100.4	101.2	101.9
30°C/65% RH	99.7	99.1	100.4	101.0	101.5	101.7
40°C/75% RH	99.8	100.1	100.6	101.2	101.7	101.6
3 months	**10 min**	**15 min**	**20 min**	**30 min**	**45 min**	**60 min**
25°C/60% RH	98.9	98.9	98.8	99.0	99.5	100.0
30°C/65% RH	97.2	97.4	97.3	97.4	97.5	99.1
40°C/75% RH	96.7	98.9	98.9	99.0	99.1	100.6

Table 6.39: Amount of diclofenac sodium (%) dissolved of formulation C measured over 3 months at different storage conditions (average of 6 tablets)

Storage condition and interval	Withdrawal time (minutes)					
Initial	10 min	15 min	20 min	30 min	45 min	60 min
	73.8	88.2	93.9	95.9	97.3	98.0
1 month	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	50.9	62.4	70.8	73.6	92.6	97.5
30°C/65% RH	37.1	48.0	57.7	68.6	84.3	94.5
40°C/75% RH	39.6	51.9	72.5	86.8	94.5	96.6
2 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	45.1	55.7	69.7	82.2	94.6	98.5
30°C/65% RH	46.2	54.7	63.2	77.4	89.0	95.1
40°C/75% RH	38.7	46.8	51.7	61.0	75.1	84.3
3 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	50.1	59.7	69.0	81.3	91.8	97.4
30°C/65% RH	52.3	61.9	71.8	84.3	94.6	98.7
40°C/75% RH	43.0	52.2	59.8	70.6	80.3	88.7

Table 6.40: **Amount of diclofenac sodium (%) dissolved of formulation D measured over 3 months at different storage conditions (average of 6 tablets)**

Storage condition and interval	Withdrawal time (minutes)					
Initial	10 min	15 min	20 min	30 min	45 min	60 min
	82.3	92.0	94.2	95.9	97.5	99.4
1 month	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	76.6	85.7	91.0	95.9	96.9	98.7
30°C/65% RH	75.8	84.4	89.8	94.0	96.2	95.8
40°C/75% RH	70.7	79.2	82.2	89.4	95.7	99.7
2 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	79.8	89.2	94.5	98.1	99.6	100.4
30°C/65% RH	77.9	88.0	89.3	94.6	96.4	97.3
40°C/75% RH	72.0	81.9	86.8	94.7	97.8	98.1
3 months	10 min	15 min	20 min	30 min	45 min	60 min
25°C/60% RH	81.0	88.5	91.4	94.8	96.5	97.6
30°C/65% RH	83.5	92.4	95.4	97.3	98.6	99.7
40°C/75% RH	64.6	68.2	80.7	96.0	97.8	99.3

The initial dissolution results and the results of the samples stored for 3 months at 40°C/75% RH are presented in Figures 6.17-6.20.

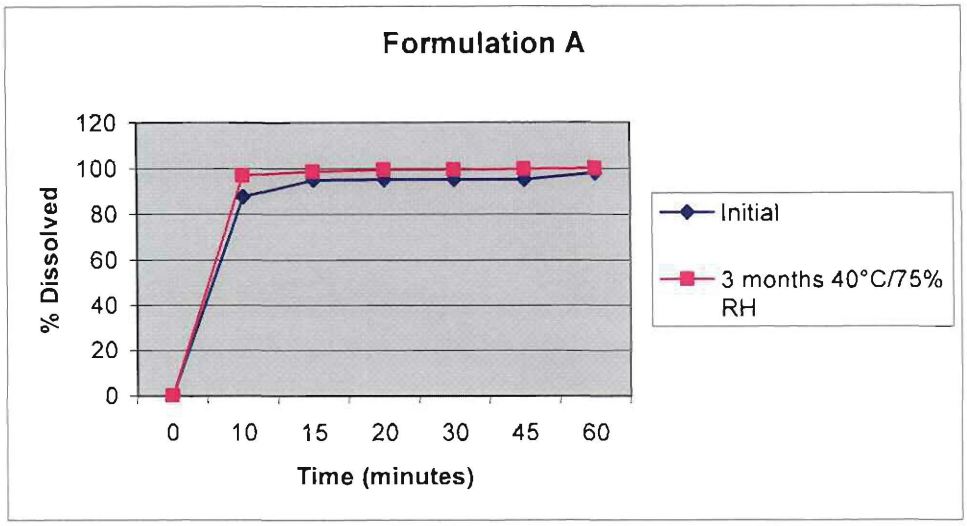


Figure 6.17: Graphic representation of the initial and 3 months (40°C/75% RH) dissolution results for formulation A.

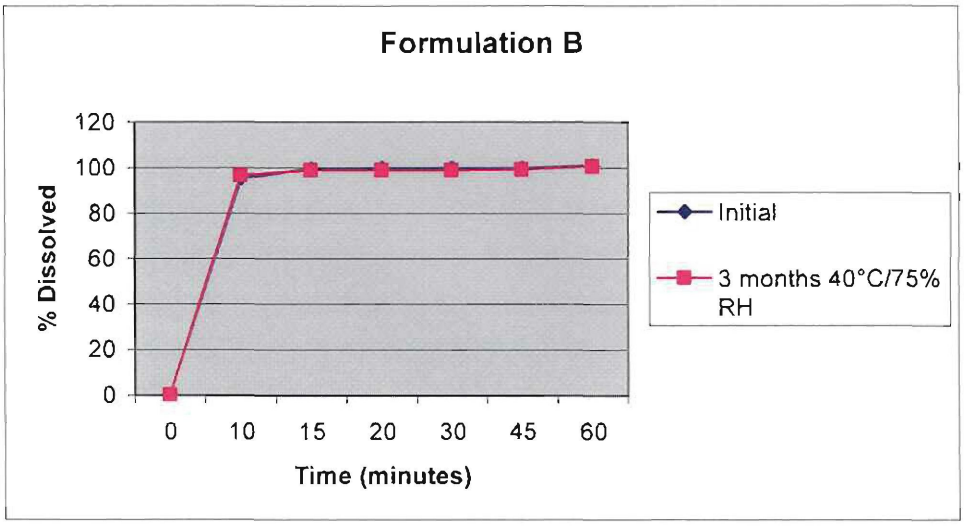


Figure 6.18: Graphic representation of the initial and 3 months (40°C/75% RH) dissolution results for formulation B.

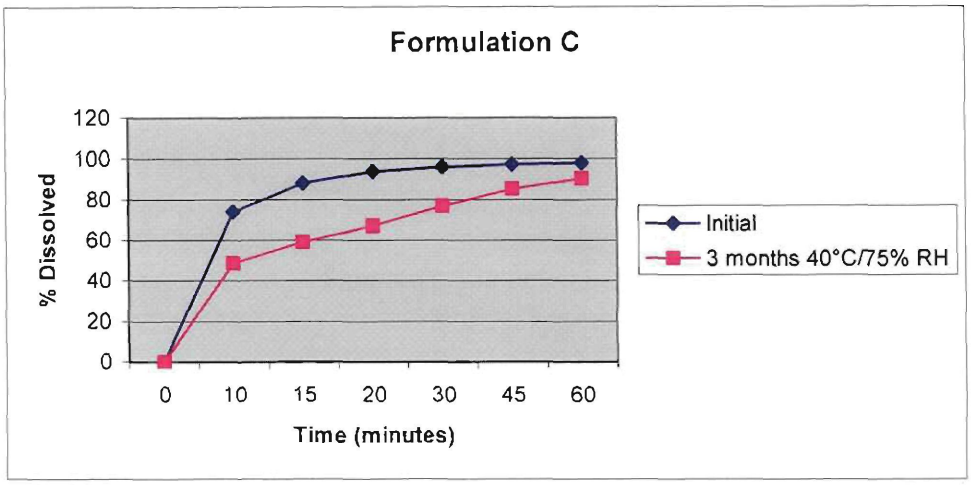


Figure 6.19: Graphic representation of the initial and 3 months (40°C/75% RH) dissolution results for formulation C.

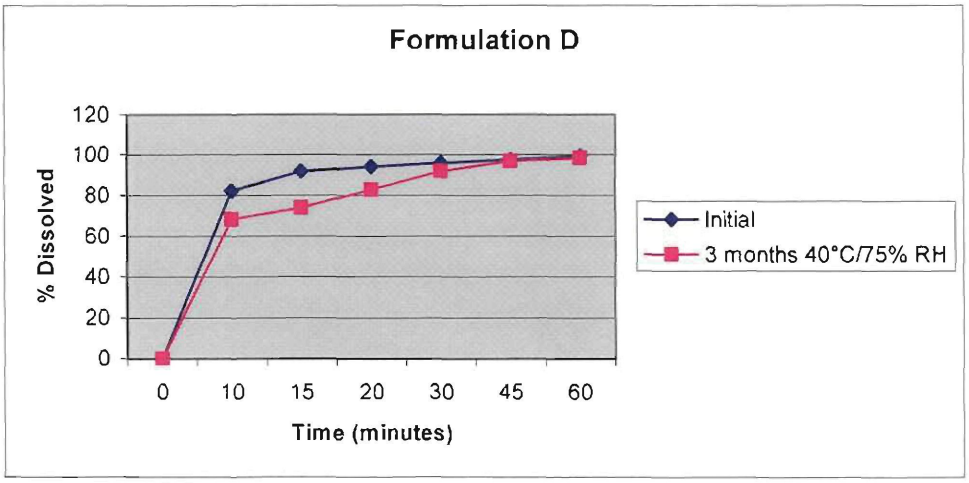


Figure 6.20: Graphic representation of the initial and 3 months (40°C/75% RH) dissolution results for formulation D.

6.12.2 Discussion

Formulation A:

Formulation A showed fast dissolution rates at all storage conditions and all time points with dissolution rates > 85% within 10 minutes.

Formulation B:

Accelerated stability testing did not affect the dissolution rates of formulation B which showed dissolution of > 85% within 10 minutes throughout the stability programme.

Formulation C:

The dissolution rate of formulation C showed a significant decline with increased stress conditions (Figure 6.19). The results indicate that crospovidone sodium at a concentration of 2% is not effective as a disintegrant.

Formulation D:

The dissolution rate of formulation D also showed a decline with increased stress conditions. However, the decline is not as significant as in the case of formulation C, proving that crospovidone in a concentration of 5% is more effective than at 2%.

The dissolution rates of all the formulations, except formulation C, met the general specification of 75% dissolved within 30 or 45 minutes, with formulation B showing the fastest dissolution.

6.13 Choosing the most favourable formulation

From the results obtained during the accelerated stability testing performed on four different formulations (A, B, C and D) of diclofenac sodium dispersible tablets, it would seem that formulation B is the most favourable formulation with the best marketing possibilities. This statement is based on the following results obtained during stability testing:

- **Visual assessment**
  The tablets of formulation B did not undergo any change in physical appearance, except for the samples at 40°C/75% RH after storage for 3 months, where a slight colour change from white to a very light brown was observed.

- **Uniformity of mass, average mass, diameter and thickness**
  The uniformity of mass was within specification throughout stability. The average tablet mass and diameter of formulation B remained relatively constant throughout stability. There was a slight increase in the thickness of the tablets at all temperature conditions.

- **Hardness**
  The hardness of formulation B remained relatively constant at 25°C/60% RH and 30°C/65% RH, but increased slightly at 40°C/75% RH after 2 months.

- **Friability**

  The percentage friability of formulation B was higher than 1% at initial and after 2 months storage at 25°C/60%RH and 30°C/65%RH. However, the tablets showed no signs of chipping and no broken tablets were observed.

- **Disintegration**

  The tablets of formulation B was the only tablets of the 4 formulations that disintegrated within the specified time limit of 3 minutes.

- **Fineness of dispersion**

  Very few particles of formulation B were retained on the 710 µm sieve, indicating a homogeneous dispersion.

- **Loss on drying**

  Formulation B showed a slight increase in the percentage loss on drying during stability. This increase was more pronounced at 40°C/75% RH.

- **Assay**

  The percentage diclofenac sodium present in the tablets of formulation B ranged between 97.1% and 93.0%, all within the specification of 90.0-110.0%.

- **Chromatographic purity**

  No extra peaks ascribed to diclofenac sodium related compound A or any other impurity was identified throughout the stability programme.

- **Dissolution**

  All the tablets of formulation B subjected to dissolution testing showed dissolution of more than 90% within 10 minutes. This confirmed the results obtained during comparative dissolution testing (5.3.12.1.5) to choose the most suitable dissolution medium. The results obtained during stability testing also proved that 5% croscarmellose sodium as disintegrant was superior to a 2% concentration and crospovidone in concentrations of 2% and 5% of the tablet mass.

6.14 Setting specifications for batch release and stability

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product

should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval (ICH Q6A, 1999).

Specifications are one part of a total control strategy for the drug substance and/or drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterisation during development, upon which specifications are based, and adherence to cGMP; e.g., suitable facilities, a validated manufacturing process, validated test procedures, raw material testing, in-process testing, stability testing, etc. (ICH Q6A, 1999).

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterisation, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and/or drug product (ICH Q6A, 1999).

Drug products can have more restrictive criteria for the release of a drug product than criteria applied to the shelf-life. An example include assay and impurity (degradation product) levels. The experience and data accumulated during the development and accelerated studies performed on a drug product, form the basis for the setting of specifications. It should be kept in mind that the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification, which could involve loosening, as well as thightening, acceptance criteria as appropriate (ICH Q6A, 1999).

The acceptance criteria listed in Table 6.41 for the release and shelf-life of diclofenac sodium dispersible tablet (formulation B) are based on results obtained during the three month accelerated stability testing period. A reasonable range of expected analytical and manufacturing variability was considered.

Table 6.41 contains a summary of the accelerated stability results obtained for diclofenac sodium dispersible tablets (formulation B), as well as the chosen acceptance criteria (specifications) for batch release and shelf-life purposes.

Where references were found in pharmacopoeias, these specifications were used. In this study, the USP29 (2006) criteria for assay and chromatographic purity were used, and the BP (2005) criteria for uniformity of mass and disintegration.

Table 6.41: Stability programme and record for diclofenac sodium dispersible tablets formulation B

Test	Specification	Result									
		Initial	1 month			2 months			3 months		
			25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH
Appearance	A white to off-white, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	White, round tablet with no markings	Very light brown tablet with no markings
Odour	Peppermint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint	Pepper-mint
Taste	Peppermint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste	Pepper-mint with a bitter after-taste
Uniformity of mass	NMT 2 of the individual masses deviate from the average mass by more than 5% and none deviates by more than twice that percentage	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
Average mass	300 (285-315) mg	298 mg	297 mg	299 mg	304 mg	299 mg	303 mg	300 mg	302 mg	300 mg	300 mg

Table 6.41: Continued

Test	Specification	Result									
		Initial	1 month			2 months			3 months		
			25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH
Thickness	4.22 (3.80-4.60) mm	4.14 mm	4.20 mm	4.21 mm	4.24 mm	4.20 mm	4.26 mm	4.26 mm	4.21 mm	4.26 mm	4.22 mm
Diameter	9.05 (8.63-9.53) mm	9.04 mm	9.09 mm	9.05 mm	9.10 mm	9.09 mm	9.10 mm	9.09 mm	9.08 mm	9.10 mm	9.06 mm
Hardness	65 (35-95) N	54.8N	56.4N	51.3N	56.8N	56.3N	56.7N	76.6N	57.3N	58.7N	86.0N
Friability	NMT 2%	1.6%	1.5%	1.2%	0.8%	1.2%	1.1%	0.8%	0.7%	0.7%	0.6%
Disintegration	NMT 3 minutes	Within 1 minute	Within 1 minute	Within 1 minute	Within 3 minutes	Within 1 minute	Within 1 minute	Within 3 minutes	Within 1 minute	Within 1 minute	Within 3 minutes
Fineness of dispersion	NMT 10 particles retained in 710 µm sieve	None retained	2 particles retained	2 particles retained	1 particle retained	None retained	1 particle retained	2 particles retained	None retained	None retained	2 particles retained
Loss on drying	NMT 8%	4.6%	4.8%	5.9%	6.5%	4.4%	5.4%	6.4%	4.7%	5.2%	6.7%
Assay (HPLC)											
Release	50.0 (47.5-52.5) mg diclofenac sodium/tablet	48.6 mg/tablet	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Shelf-life	50.0 (45.0-55.0) mg diclofenac sodium/tablet	N/A	48.5 mg/tablet	49.7 mg/tablet	49.3 mg/tablet	48.2 mg/tablet	48.1 mg/tablet	48.2 mg/tablet	48.3 mg/tablet	47.5 mg/tablet	46.5 mg/tablet

Table 6.41: Continued

Test	Specification	Result									
		Initial	1 month			2 months			3 months		
			25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH	25°C/60% RH	30°C/65% RH	40°C/75% RH
Chromato-graphic purity (HPLC)											
Diclofenac related compound A	NMT 0.5%	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected
Individual	NMT 1.0%	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected
Total	NMT 1.5%	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected	No peaks detected
Dissolution	NLT 75% of diclofenac sodium is released within 30 minutes	99.6%	100.2%	97.7%	99.5%	100.4%	101.0%	101.2%	99.0%	97.4%	99.0%

6.15 Establishing storage conditions

From the accelerated stability results it is clear that increased stress conditions, namely higher temperatures and humidity, affect the physical and chemical stability of diclofenac sodium dispersible tablets. The USP (USP29, 2006) indicates that diclofenac sodium tablets should be stored in tight, light-resistant containers. The package insert should also state that diclofenac sodium dispersible tablets should be protected from moisture and stored at temperatures below 30°C.

6.16 Conclusion

In this chapter, the results of accelerated stability testing performed on 4 diclofenac sodium dispersible tablet formulations, were reported. Based on the results obtained, the most favourable formulation was chosen, batch release and shelf-life specifications were determined and storage conditions for the final product were set.

Visual assessment of all the formulations indicated no change in physical appearance, oudour and taste throughout the stability period, except a colour change from white to a very light brown after 3 months at 40°C/75%RH.

The mass uniformity of all formulations complied with the specifications during stability, with the average mass and diameter remaining relatively constant and the average thickness showing a slight increase at all conditions of temperature and humidity.

The hardness of all formulations showed an increase with increased stress conditions. The hardness of formulation D was significantly higher than that of the other 3 formulations.

The percentage friability of all 4 formulations decreased during stability, correlating with the increase in hardness. No sign of chipping or any broken tablets was observed.

Only formulation B complied with the specification for disintegration, namely that all 6 tablets should disintegrate within 3 minutes. Disintegration times increased with time and increased stress conditions.

The amount of particles retained on a 710 µm sieve was the lowest in formulation B, indicating a homogeneous dispersion. The amount of particles retained was the highest in the case of the disintegrants present in a concentration of 2%, indicating that the use of croscarmellose sodium and crospovidone in concentrations of 2% is not recommended.

In all 4 formulations, the percentage loss on drying increased during stability, ranging from 4.2% at initial to 6.9% after 3 months at 30°C/65%RH.

The identification of diclofenac sodium was positive in all 4 formulations. Assay values decreased during stability, but remained within the specifications of 90.0-110.0%. The lowest assay value was obtained after 3 months at 40°C/75%RH in the case of formulation D, namely 90.6%.

No extra peaks ascribed to diclofenac related compound A or any other impurity was identified during stability in any of the formulations.

Dissolution rates for formulations A and B were rapid from initial to the end of the stability programme. The dissolution rates of formulations C and D showed a marked decrease during stability, with the decrease more significant in the case of formulation C.

Based on the results and observations made during the accelerated stability testing on all four formulations, formulation B was chosen as the most favourable formulation with the best marketing possibilities.

The results of the stability testing were also used to set specifications for batch release and shelf-life of diclofenac sodium dispersible tablets. These specifications are established to ensure that all batches, tested according to the set specifications, comply with standards for quality, safety and efficacy.

Diclofenac sodium dispersible tablets must be stored in tight, light-resistant containers at temperatures below 30°C.

CHAPTER 7

Summary and Conclusion

The aim of this study was to formulate a stable diclofenac sodium dispersible tablet. This formulation is easier to swallow, therefore enhancing patient compliance.

7.1 Summary

An investigative study of the physico-chemical properties, indications, side-effects and contra-indications of diclofenac sodium was performed as first step in the product development.

Diclofenac sodium – excipient compatibility studies were performed as part of a preformulation study. Results indicated no possible interactions between diclofenac sodium and the chosen excipients.

An HPLC method for the assay and chromatographic purity of diclofenac sodium in diclofenac sodium dispersible tablets was developed and validated.

Comparative dissolution studies were performed on all four formulations in order to choose a dissolution medium for batch release and stability purposes.

Four dispersible tablet formulations were developed. Crospovidone and croscarmellose sodium were used as disintegrants in concentrations of 2% and 5% of the tablet mass.

The following excipients were used:

- Binder/diluent: Microcrystalline cellulose
- Disintegrants: Croscarmellose sodium and crospovidone
- Glidant: Colloidal silicon dioxide
- Lubricant: Magnesium stearate
- Flavouring agent: Peppermint flavour
- Sweetening agent: Sodium saccharine
- Taste masking agents: Sodium bicarbonate and potassium bicarbonate

The four formulations were put on accelerated stability according to ICH guidelines for three months at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH.

The following stability tests were conducted:

- Visual assessment (description)
- Uniformity of weight (mass) and average mass
- Dimensions (thickness, diameter)
- Hardness
- Friability
- Disintegration
- Fineness of dispersion
- Loss on drying
- Identification
- Assay
- Chromatographic purity
- Dissolution

Initial test results were used as a baseline for detection of any changes occuring during the stability programme.

At the end of the stability period, no change in the physical appearance of the tablets was observed, except for the samples stored at 40°C/75% RH which showed a colour change from white to a very light brown after 3 months. The assay values remained within the specification of 90.0-110.0% in all four formulations. No extra peaks ascribed to diclofenac related compound A or any other impurity were observed in any of the formulations. The percentage loss on drying increased during stability. The least amount of particles retained on a 710 µm sieve during the test for fineness of dispersion, was in the case of formulation B. Differences in the disintegration times were noted between crospovidone and croscarmellose sodium formulations. The only formula that disintegrated within the specified time of 3 minutes was formulation B. These differences were also noted during dissolution testing in

phosphate buffer pH 6.8, where the croscarmellose sodium formulations showed quicker dissolution that was not influenced by stability testing at accelerated conditions. The dissolution results correlated with the decrease in friability and increase in hardness obtained during the stability in the crospovidone formulations.

7.2 Conclusion

According to the results obtained, the formulation containing 5% croscarmellose sodium as disintegrant (formulation B) proved to be the best. The test results of this formulation were all within specifications. This formulation with croscarmellose sodium (5%) as disintegrant can be used for futher developement and has definite marketing possibilities.

Further investigations that are required on this formulation include:

- Conducting accelerated stability studies over a longer period of time (6 months).
- *In vivo* testing of the formulated diclofenac sodium dispersible tablet.

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ANNEXURE A

Validation Parameter Definitions

Validation of an analytical method is the process by which it is established, through conducting laboratory studies, that the performance characteristics of the method meet the requirements for the intended analytical applications (USP29, 2006:<1225>). Therefore, the objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose.

The steps necessary for the validation of an analytical method are given in figure A.1.

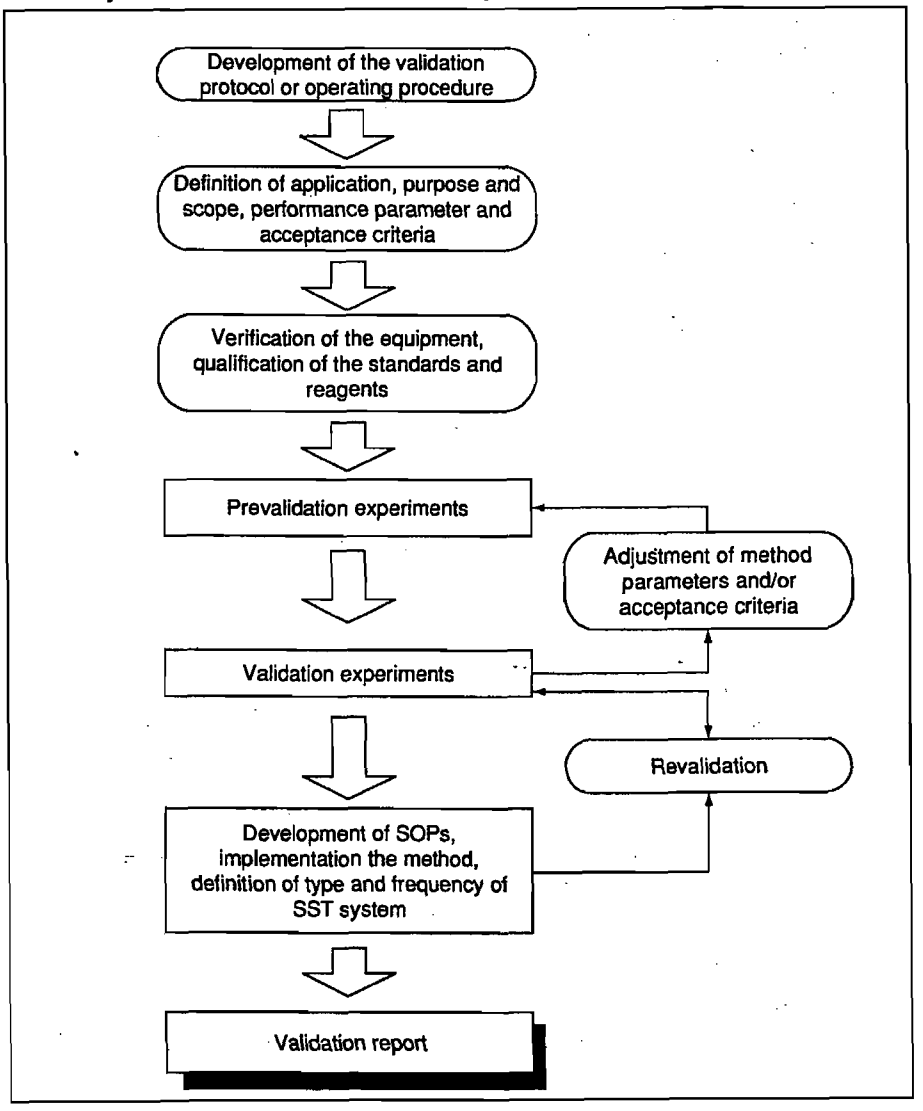

Figure A.1: Steps taken during the validation of an analytical method (Yuwono & Indrayanto, 2005:246).

Types of analytical procedures to be validated and their characteristics are discussed. Information was taken from the guideline Q2 (R1) on the validation of analytical procedures prepared by the ICH (2005).

A.1 Types of analytical procedures

The three most common types of analytical procedures are:

A.1.1 Identification tests

Identification tests are intended to ensure the identity of an analyte in a sample. This can be achieved by comparison of a property of the sample, for example chromatographic behaviour, to that of a reference standard.

A.1.2 Test for impurities

Testing for impurities can either be a quantitative test or a limit test. Both tests are intended to accurately reflect the purity characteristics of the sample.

A.1.3 Assay procedures

Assay procedures are intended to measure the analyte present in a given sample. The assay represents a quantitative measurement of the major component(s) in the drug substance. The same validation characteristics may also apply to assays associated with other analytical procedures, for example dissolution.

A.2 Types of analytical procedures

Typical validation characteristics that should be considered are listed below:

- Accuracy
- Precision
    - Repeatability
    - Intermediate precision

- Specificity
- Linearity and range
- Limit of detection
- Limit of quantitation
- Robustness

A.2.1 Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value, and the value found.

A.2.2 Precision

The precision of an analytical procedure expresses the closeness of agreement among individual test results when the method is applied repeatedly to multiple samplings of a homogeneous sample under the prescribed conditions. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements. Precision may be considered at three levels:

A.2.2.1 Repeatability (intra-day)

Repeatability, or intra-day assay variance, expresses the precision under the same operating conditions over a short period of time.

A.2.2.2 Intermediate precision (inter-day)

Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.

A.2.2.3 Reproducibility

Reproducibility expresses the precision between laboratories. This is used in collaborative studies and usually applied to standardisation of methodology.

A.2.3 Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components, which may be expected to be present, for example impurities, degradants and matrix.

Lack of specificity of an individual analytical procedure may be compensated for by other supporting analytical procedures such as:

- Identification to ensure the identity of the analyte.
- Purity tests to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte.
- Assay to provide an exact result, which allows an accurate statement on the potency or content of the analyte in a sample.

A.2.4 Linearity and range

The linearity of an analytical procedure is its ability (within a given range) to obtain test results that are directly proportional to the concentration of analyte in the sample.

The range of an analytical procedure is the interval between the upper and lower concentration of analyte in the sample (including these concentrations) for which it has been established that the analytical procedure has a suitable level of precision, accuracy and linearity.

A.2.5 Limit of detection

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected, but not necessarily quantitated, as an exact value.

A.2.6 Limit of quantitation

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used for the determination of impurities and/or degradation products.

A.2.7 Robustness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters. It provides an indication of the method's reliability during normal usage.

Table A.1 lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures.

Table A.1: Important validation characteristics for validation of different types of analytical procedures

Type of analytical procedure	Identification	Testing for impurities		Assay
		Quantitative	Limit	- Dissolution (measurement only) - Content/potency
Accuracy	-	+	-	+
Precision				
- Repeatability	-	+	-	+
- Intermediate precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Limit of detection	-	- (3)	+	-
Limit of quantitation	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

-: characteristic is not normally evaluated.

+: characteristic is normally evaluated.

(1): in cases where reproducibility has been performed, intermediate precision is not needed.

(2): lack of specificity of one analytical procedure could be compensated for by other supporting analytical procedure(s).

(3): may be needed in some cases.

ANNEXURE B

Method Validation for the HPLC Assay and Chromatographic purity of Diclofenac Sodium in Diclofenac Sodium Dispersible Tablets

B.1 Summary

The validation results are summarised in Table B.1.

Table B.1: Summary of validation results

Parameter	Acceptance criteria	Results
Specificity	The placebo should not generate any peaks that will interfere with the determination of the active ingredients. Extra peaks formed under stress conditions should be discernible from those of the active ingredients.	Complies
Linearity and Range	**Diclofenac sodium:** The method is linear over the range: 60–140% of the expected sample concentration. R^2 is not less than 0.99. **Diclofenac related compound A:** The method is linear over the range: 0.2-1.0% of the expected diclofenac sodium concentration. R^2 is not less than 0.99.	**Diclofenac sodium:** Complies: Linear over the range of 0.45-1.05 mg/ml (60-140% of expected concentration) with R^2 = 0.9999 **Diclofenac related compound A:** Complies: Linear over the range 1.5-7.5 µg/ml (0.2-1.0% of the expected diclofenac sodium concentration) with R^2 = 1.00
Accuracy	Recovery must be between 98.0–102.0%.	Complies Diclofenac sodium: 100.5%
Precision	**Diclofenac sodium:** RSD of 2.0% or less. **Diclofenac related compound A:** RSD of 5.0% or less.	**Diclofenac sodium:** Complies: Intra-day = 0.8% Inter-day = 0.8% **Diclofenac related compound A:** Complies: 1.3%

Table B.1: Continued

Parameter	Acceptance criteria	Result
Ruggedness (Stability)	The sample solution should not be used for a period longer than it takes to degrade by 2.0%.	Diclofenac sodium is stable for 8 hours
Ruggedness (System repeatability)	The peak area of both the assay and impurity testing should have an RSD of 2.0% or less. The retention times of both the assay and impurity testing should have an RSD of 2.0% or less.	**Diclofenac sodium:** 0.1% for peak area 0.2% for retention time **Diclofenac related compound A:** 1.2% for peak area 0.1% for retention time
Limit of detection (LOD)	The concentration determined at the LOD has a signal-to-noise ration of 3:1.	Diclofenac related compound A: 0.48 µg/ml
Limit of quantitation (LOQ)	The concentration determined at the LOQ has a signal-to-noise ration of 10:1.	Diclofenac related compound A: 0.15 µg/ml
Robustness	The method should be able to tolerate about 5.0% variance in chromatographic conditions.	Complies

B.2 Method reference

USP29, 2006.

B.3 Chromatographic conditions

(1) Analytical instrument: HP 1100 series HPLC (Germany) equipped with a pump, auto sampler, UV detector and Chemstation Rev.10.02 data acquisition and analysis software or equivalent.

(2) Column: Luna C8(2) column, 250 x 4.6 mm, 5µm (Phenomenex®).

(3) Mobile phase: Methanol:Phosphate buffer (700:300).

(4) Phosphate buffer: Mix equal volumes of 0.01 M phosphoric acid and 0.01 M monobasic sodium phosphate. If necessary, adjust with additional portions of the appropriate component to a pH of 2.5 ± 0.2.

(5) Solvent: methanol:water (70:30).

(6) Flow rate: 1.0 ml/min.

(7) Injection volume: 10 µl.

(8) Detection: UV at 254 nm (Diode array detection).

(9) Retention time: ± 7 minutes for diclofenac related compound A.

± 11 minutes for diclofenac sodium.

(10) Run time: 15 minutes.

B.4 Diclofenac Related Compound A stock solution preparation

(1) Transfer 5 mg of Diclofenac Related Compound A RS[5] to a 50 ml volumetric flask.

(2) Dissolve in and dilute to volume with methanol.

B.5 Standard preparation

(1) Transfer 37.5 mg of Diclofenac sodium RS[6] (mass accurately known) to a 50 ml volumetric flask.

(2) Add 2 ml of Diclofenac Related Compound A stock solution.

(3) Fill to volume with solvent.

(4) Transfer the standard into an autosampler vial and analyse.

B.6 Sample preparation

(1) Accurately weigh 20 tablets and grind to a fine powder.

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5 Diclofenac related compound A reference standard: USP, B/N H.

6 Diclofenac sodium reference standard: B/N X068409.

(2) Weigh approximately 450 mg (equivalent to 75 mg diclofenac sodium) of powdered tablet sample (mass accurately known) into a 100 ml volumetric flask.

(3) Add about 40 ml of solvent and sonicate for 5 minutes.

(4) Fill to volume with solvent.

(5) Filter the solution through a 0.45 μm filter, discarding the first 5 ml of filtrate.

(6) Transfer the sample into an autosampler vial and analyse.

B.7 Calculations

The dispersible tablet contains 50 mg diclofenac sodium per tablet. The compliance range is set at 90.0–110.0% diclofenac sodium.

The equation for the calculation of content:

$$mg/tablet = \frac{A_{sa} \times M_{st} \times DF_{sa} \times P \times mass\ of\ 20\ tablets(mg)}{A_{st} \times M_{sa} \times DF_{st} \times 100 \times 20}$$

Where: A_{sa} = Area of sample peak

A_{st} = Area of standard peak

M_{sa} = Sample mass (in mg)

M_{st} = Standard mass (in mg)

P = Potency of standard in %

DF_{sa} = Dilution factor of sample solution

DF_{st} = Dilution factor of standard solution

B.8 Validation test procedure and acceptance criteria

B.8.1 Diclofenac sodium

B.8.1.1 Specificity

The composition of the placebo[7] used is given in Table B.2.

Table B.2: Dispersible tablet placebo mixture constitution (20 tablets)

Excipient	Quantity (g)
Aerosil®	0.138
Avicel® pH 101	4.167
Disolcel®	0.12
$KHCO_3$	0.22
Kollidon CL-M®	0.12
Magnesium stearate	0.06
$NaHCO_3$	0.22
Peppermint flavour	0.015
Sodium saccharine	0.06

(1) Weigh 375 mg of placebo powder and prepare a sample as described in the method under sample preparation.

(2) Make 4 standard diclofenac sodium RS dilutions (1:1) with water, 0.1 M hydrochloric acid, 0.1 M sodium hydroxide and 10% hydrogen peroxide.

(3) Store these solutions overnight in closed test tubes at 40°C to degrade.

(4) Inject the samples into the chromatograph with a run time of 15 minutes.

(5) Examine the chromatograms to determine whether any additional peaks were formed.

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[7] In this placebo formula two disintegrants (Disolcel® and Kollidon CL-M®) were included. The reason being that both disintegrants were used separately in 4 different formulations during formulation. If no interaction occurs with the 50:50 mixture, it is safe to assume that no interaction will occur when used separately.

Acceptance criteria

- The placebo should not contain any peaks that will interfere with the determination of the active.
- Extra peaks formed in the stressed standards should be discernible from those of the active.

B.8.1.2 Linearity and Range

(1) Prepare the following standard solution: Transfer 75 mg diclofenac sodium RS into a 50 ml volumetric flask. Dilute to volume with solvent.

(2) Dilute 3 ml, 4 ml, 5 ml, 6 ml and 7 ml of this solution to 10 ml with solvent to obtain standards from 60–140% of the expected sample concentration.

(3) Inject into the chromatograph in duplicate.

Acceptance criterion

- Linear regression analysis should yield a regression coefficient (R^2) of ≥ 0.99.

B.8.1.3 Accuracy

(1) Prepare a placebo as described in B.8.1.1.

(2) Accurately weigh 9 times 375 mg of placebo powder into 100 ml volumetric flasks.

(3) Spike with known amount of active (in triplicate) at concentrations of approximately 80%, 100% and 120% of the expected sample concentration.

- 80%: 60 mg diclofenac sodium.
- 100%: 75 mg diclofenac sodium.
- 120%: 90 mg diclofenac sodium.

(4) Dilute with solvent.

(5) Inject in duplicate.

Acceptance criterion

- Recovery must be between 98.0–102.0% for diclofenac sodium.

B.8.1.4 Precision

B.8.1.4.1 Intra-day precision (Repeatability)

(1) Weigh 3 times 360 mg (80%), 3 x 450 mg (100%) and 3 x 540 mg (120%) of diclofenac sodium dispersible tablet powder into 100 ml volumetric flasks.

(2) Add about 40 ml of solvent to each flask and sonicate for 5 minutes.

(3) Dilute to volume with solvent.

(4) Filter through a 0.45 µm filter.

(5) Inject samples into the chromatograph in duplicate.

B.8.1.4.2 Inter-day precision

(1) Analyse the same sample as described in B.8.1.4.1 (at 100% of the sample concentration) on 2 more occasions on different days to determine the between-day variability of the method.

(2) On one occasion (day 3) a different analyst should perform the analysis on a different set of equipment.

Acceptance criteria

- B.8.1.4.1: Repeatability must be better than 2.0% (n = 9).
- B.8.1.4.2: Inter-day precision must be better than 2.0% (n = 9).

B.8.1.5 Ruggedness

B.8.1.5.1 Stability of the sample solutions

(1) Prepare a sample as described under sample preparation in the method.

(2) Inject the sample into the chromatograph.

(3) Leave the sample in the auto sampler tray and re-analyse over a period of 8 hours to determine the stability of the sample.

Acceptance criterion

- Sample solutions should not be used for a period longer than it takes to degrade by 2%, and in the case of degradation, special precautions should be followed to compensate for the loss.

B.8.1.5.2 System repeatability

(1) Prepare a single standard at 100% of the sample concentration as described in the method.

(2) Inject six times consecutively in order to test the repeatability of the peak area, as well as the retention time.

Acceptance criteria

- The peak area of diclofenac sodium should have an RSD of 2.0% or less.
- The retention times of diclofenac sodium should have an RSD of 2.0% or less.

B.8.2 Diclofenac related compound A

B.8.2.1 Specificity

(1) Prepare a standard solution as described under standard preparation.

(2) Analyse by means of HPLC.

(3) Examine the chromatograms to determine whether the peaks are well separated from each other.

Acceptance criterion

- The diclofenac related compound A peak and diclofenac sodium peak should be well separated from each other.

B.8.2.2 Linearity and Range

(1) Prepare the following diclofenac related compound A solution: Transfer 3.75 mg diclofenac related compound A into a 50 ml volumetric flask. Dilute to volume with methanol.

(2) Dilute the diclofenac related compound A solution to prepare solutions that represent the following diclofenac sodium standard solution concentrations: 1.0%; 0.8%; 0.6%; 0.4% and 0.2%.

(3) Inject into the chromatograph in duplicate.

Acceptance criterion

- Linear regression analysis should yield a regression coefficient (R^2) of ≥ 0.99.

B.8.2.3 Precision

(1) Prepare a standard solution containing diclofenac related compound A (B.5).

(2) Analyse by means of HPLC (6 injections).

Acceptance criterion

- The percentage relative area must have an RSD of 5.0% or less.

B.8.2.4 Ruggedness

B.8.2.4.1 System repeatability

See B.8.1.5.2.

Acceptance criteria

- The peak area of diclofenac related compound A should have an RSD of 2.0% or less.
- The retention times of diclofenac related compound A should have an RSD of 2.0% or less.

B.8.2.5 Limit of detection (LOD)

The LOD is usually defined as a peak with a signal-to-noise ratio of at least 3:1. Signal refers to the baseline-corrected absorbance of the analyte peak, and noise refers to the width of the baseline (Snyder *et al.*, 1997:645).

Several approaches for determining LOD are possible. Approaches other than those listed may be acceptable (ICH Q1A(R2), 2005):

(1) **Based on visual evaluation**

The limit of detection is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

(2) **Based on signal-to-noise**

This approach can only be applied to analytical procedures which exhibit baseline noise. Compare measured signals from samples with known low concentrations of analyte with those of blank samples and establish the minimum concentration at which the analyte can be reliably detected.

(3) **Based on the standard deviation of the response and the slope**

The slope may be estimated from the calibration curve of the analyte. The estimate of the slope may be based on the standard deviation of the blank, or on the calibration curve.

Method

(1) Prepare and inject the solutions as described under B.8.2.2.

(2) Calculate the signal-to-noise ratio for one of the concentrations of the related substance (chromatograph obtained from linearity and range) by measuring the peak-

to peak noise and the signal (measured from the midpoint of the noise to the apex of the signal peak) (Snyder *et al.*, 1997:645,655).

(3) Calculate the concentration which gives a signal-to-noise ratio of 3:1.

(4) This concentration is the limit of detection.

Acceptance criterion

- The concentration determined as the limit of detection has a signal-to-noise ratio of 3:1.

B.8.2.6 Limit of quantitation (LOQ)

The LOQ is usually defined as a peak with a signal-to-noise ratio of at least 10:1. According to the ICH Q1A(R2) guideline (2005) several approaches for determining LOQ are possible. Approaches other than those listed may be acceptable:

(1) **Based on visual evaluation**

The limit of detection is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

(2) **Based on signal-to-noise**

This approach can only be applied to analytical procedures which exhibit baseline noise. Compare measured signals from samples with known low concentrations of analyte with those of blank samples and establish the minimum concentration at which the analyte can be reliably quantified.

(3) **Based on the standard deviation of the response and the slope**

The slope may be estimated from the calibration curve of the analyte. The estimate of the slope may be based on the standard deviation of the blank, or on the calibration curve.

Method

(1) With the signal-to-noise ratio calculated in B.8.2.5, calculate the concentration which gives a signal-to-noise ratio of 10:1.

(2) This concentration is the limit of quantitation.

Acceptance criterion

- The concentration determined as the limit of quantitation has a signal-to-noise ratio of 10:1.

B.8.3 Robustness

(1) Make deliberate changes to the chromatographic conditions to determine the method's tolerance towards changes.

(2) Change the flow rate, injection volume, wavelength, and mobile phase pH and use a similar column from a different manufacturer.

Acceptance criterion

- The method should be able to tolerate about 5.0% variance in the chromatographic conditions.

B.8.4 System and method performance characteristics (System suitability)

(1) Generate an extended performance report on the standard solution, integrating the relevant peaks.

(2) Calculate the number of theoretical plates for diclofenac sodium.

(3) Calculate the resolution between the diclofenac related compound A and diclofenac sodium peaks.

(4) Use the tangent method to calculate the parameters.

(5) Use the data obtained to set realistic performance limits that should be met before the analysis can be performed.

Acceptance criteria

- USP tailing factor must be less than 1.5 for diclofenac sodium.

- RSD must be less than 2.0%.
- The resolution and plate count have to be determined through the validation for the specific system.

B.9 Validation results

B.9.1 Diclofenac sodium

B.9.1.1 Specificity

A chromatogram of the standard solution is depicted in Figure B.1. Figure B.2 is a chromatogram obtained from a sample solution. Figure B.3 is a chromatogram of a placebo solution. In order to determine peak purity, the stress solutions were diluted three times to ensure that the spectrum would not be over ranged. Figures B.4–B.7 show chromatograms of the standard solutions that have been stressed overnight as described in B.8.1.1. After being stressed, the analyte peaks were analysed by means of diode array peak purity testing to determine whether the peaks were still pure. The peak purity results are given in Figure B.8.

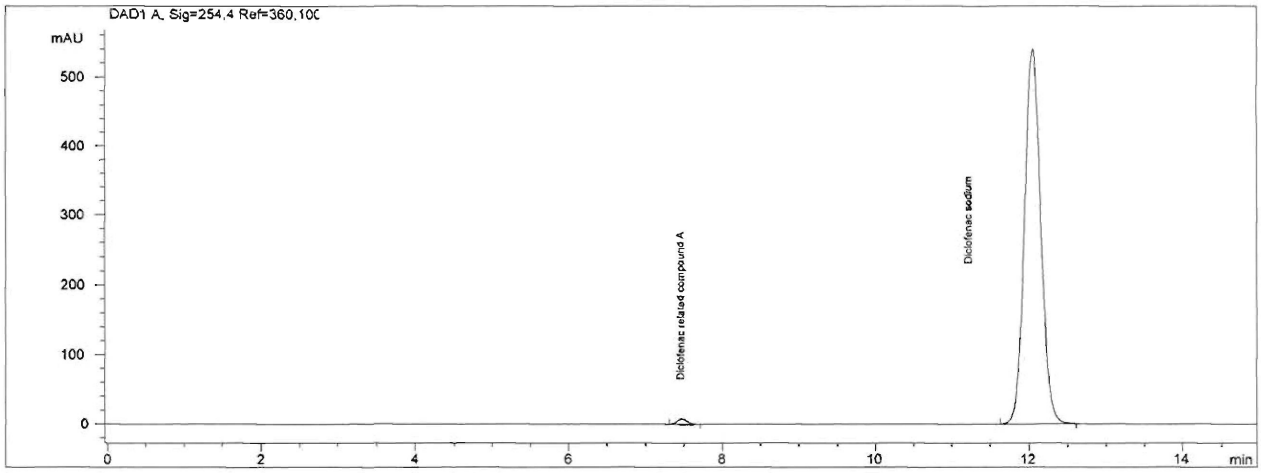

Figure B.1: HPLC chromatogram of a standard solution containing diclofenac related compound A.

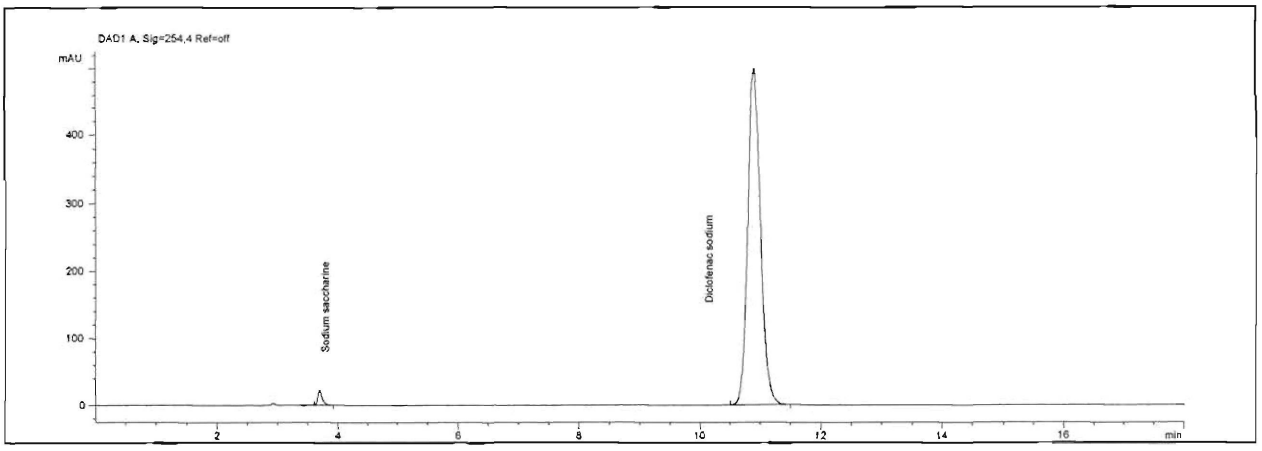

Figure B.2: HPLC chromatogram of a sample solution.

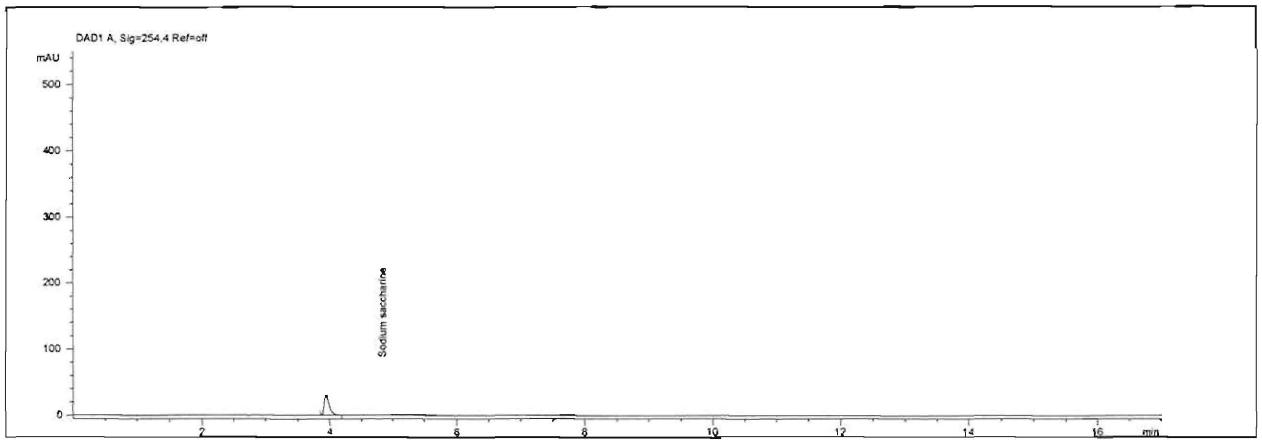

Figure B.3: HPLC chromatogram of placebo.

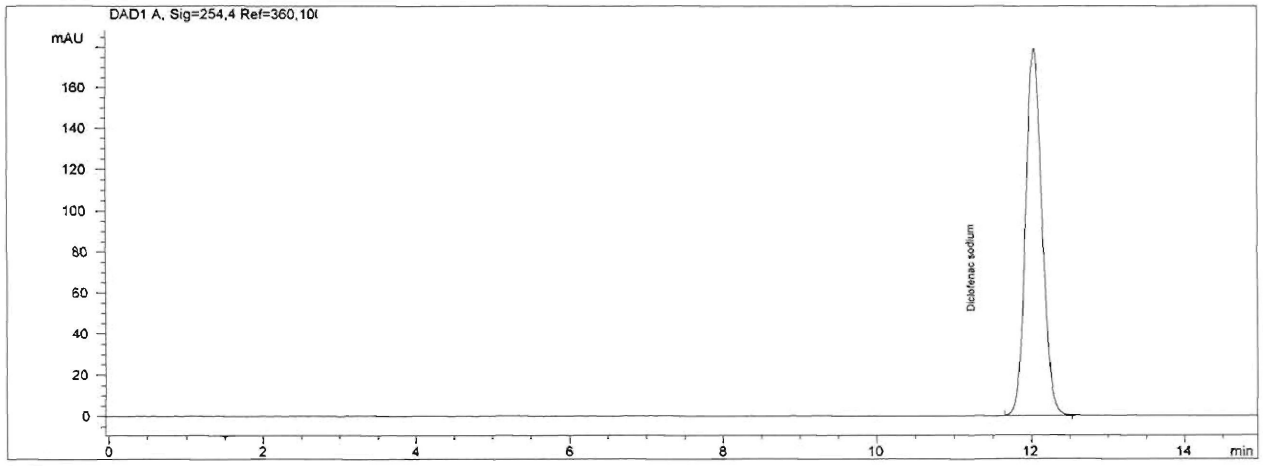

Figure B.4: HPLC chromatogram of a standard solution stressed in water at 40°C.

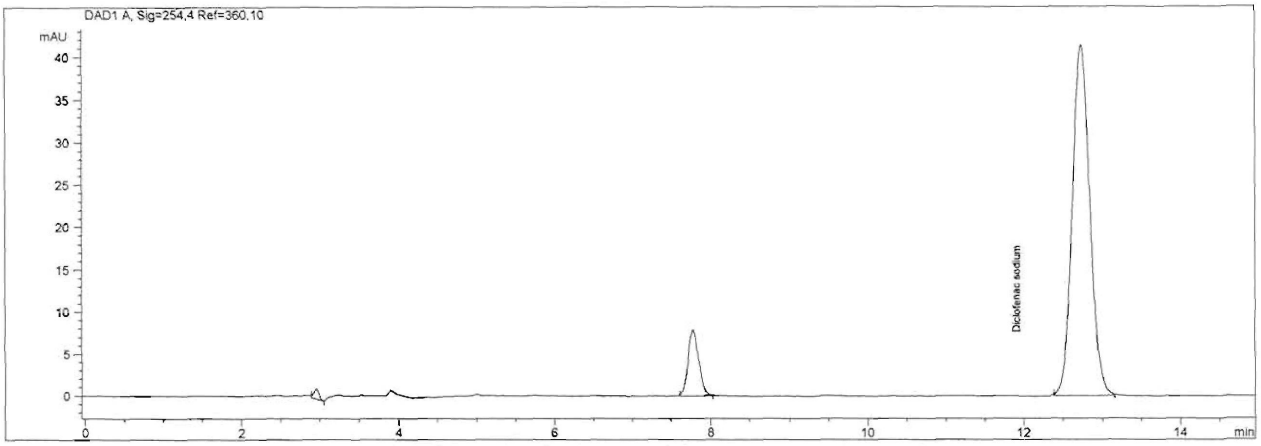

Figure B.5: HPLC chromatogram of a standard solution stressed in 0.1 M hydrochloric acid at 40°C.

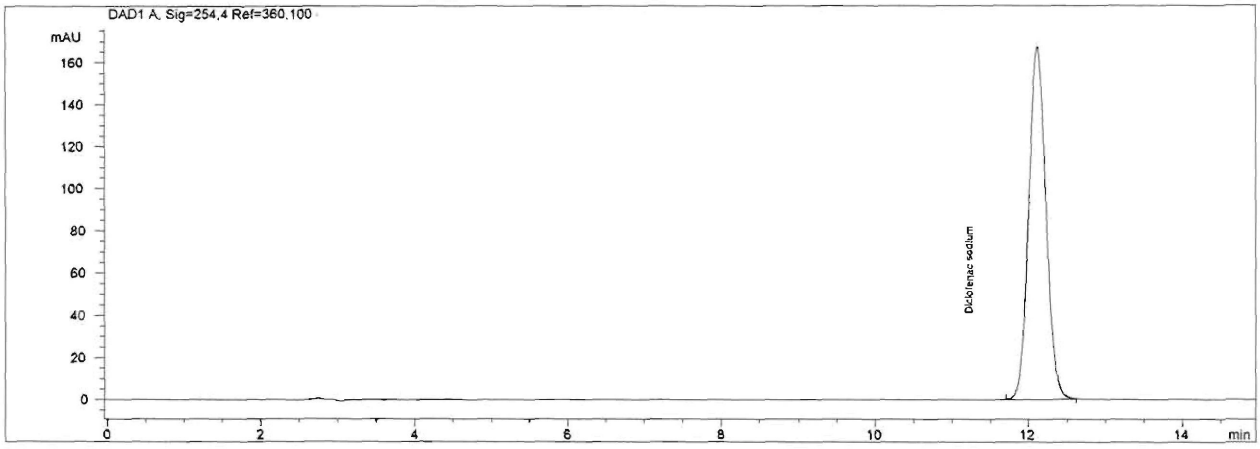

Figure B.6: HPLC chromatogram of a standard solution stressed in 0.1 M sodium hydroxide at 40°C.

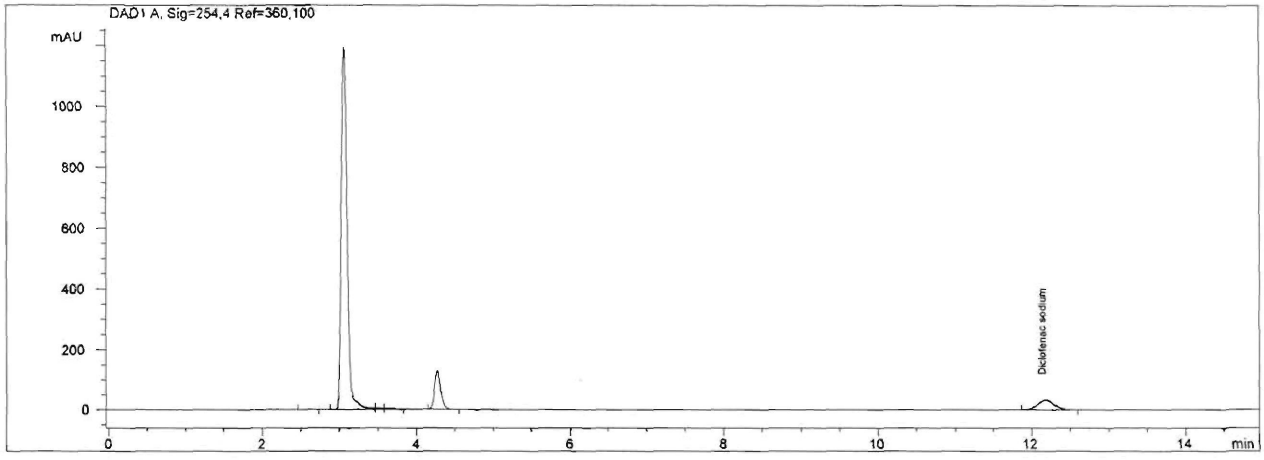

Figure B.7: HPLC chromatogram of a standard solution stressed in 10% hydrogen peroxide at 40°C.

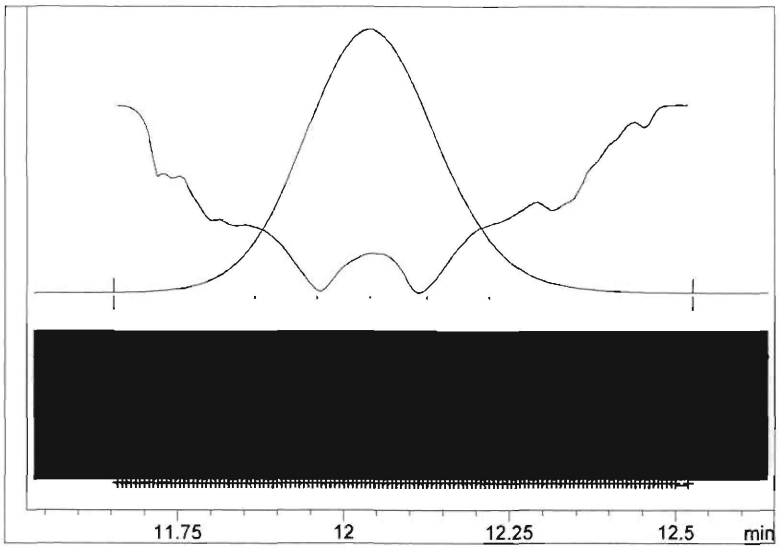

Figure B.8: Peak purity test results for diclofenac sodium.

Conclusion

(Acceptance criteria: The placebo should not contain any peaks that will interfere with the determination of the active and extra peaks formed in the stressed standards should be discernible from those of the active).

None of the ingredients in the placebo interfered with the analyte peak. Extra peaks formed during forced degradation did not interfere with the analyte peak.

Peak purity testing of all the remaining peaks after forced degradation showed that the peaks were still pure, thus proving that the method is stability-indicating.

B.9.1.2 Linearity and range

Linearity and range results for diclofenac sodium are presented in Table B.3.

Table B.3: Results for diclofenac sodium to determine linearity and range

mg/ml	% Relative to standard concentration	Area 1	Area 2	Mean
0.45	60	4592	4595	4594
0.60	80	6146	6134	6140
0.75	100	7597	7608	7603
0.90	120	9145	9160	9153
1.05	140	10655	10634	10645

Regression statistics are given in Table B.4.

Table B.4: Regression statistics of diclofenac sodium results

R squared	0.9999	Lower 95%	Upper 95%
Intercept	69.5	-47.8780	186.8780
Slope	10076.667	9926.0706	10227.2628

Conclusion

(Acceptance criterion: Linear regression analysis should yield a regression coefficient (R^2) of ≥ 0.99).

The method is linear over the concentration range 0.45–1.05 mg/ml (60-140% of the expected sample concentration) as shown in Figure B.9. The regression coefficient (R^2) is 0.9999. The method is suitable for single point calibration.

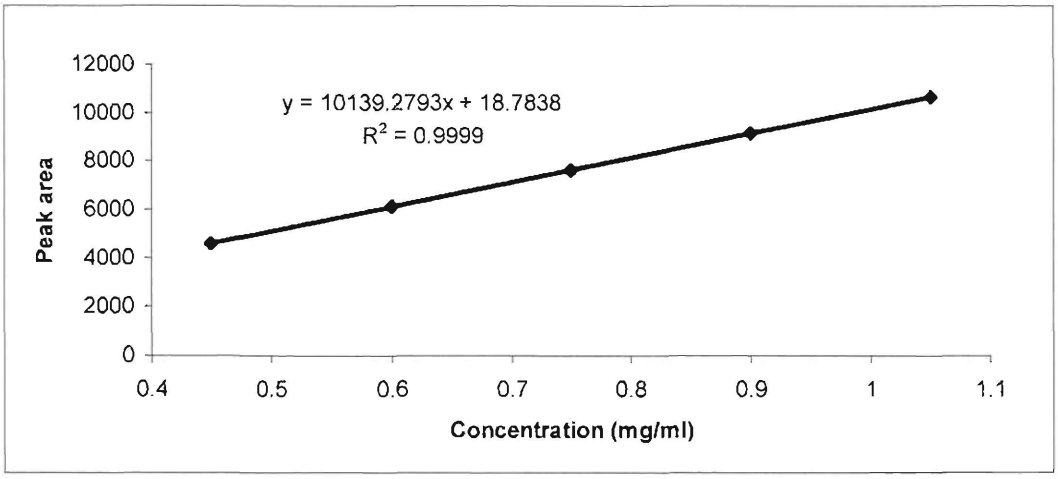

Figure B.9: Linear regression graph for diclofenac sodium to determine linearity and range.

B.9.1.3 Accuracy

Accuracy results for diclofenac sodium and the statistical analysis thereof are given in Tables B.5 and B.6, respectively.

Table B.5: Results for diclofenac sodium to determine accuracy

Concentration spiked				Recovery	
mg/ml	Area 1	Area 2	Mean	mg/ml	%
0.60	6142	6149	6146	0.606	101.0
0.60	6137	6141	6139	0.606	100.9
0.60	6135	6131	6133	0.605	100.8
0.75	7663	7648	7656	0.755	100.7
0.75	7595	7570	7583	0.748	99.7
0.75	7647	7643	7645	0.754	100.5
0.90	9167	9132	9150	0.903	100.3
0.90	9136	9142	9139	0.902	100.2
0.90	9128	9127	9128	0.900	100.0

Table B.6: Statistical analysis of diclofenac sodium accuracy determination results

Mean %	100.5
SD	0.4
% RSD	0.4
95% confidence intervals	
Lower limit	100.1
Upper limit	100.8
Estimated median	100.6
Confidence Level (95.0%)	0.4

Conclusion

(Acceptance criteria: Recovery must be between 98.0–102.0% for diclofenac sodium).

Over the range of 80.0–120.0% of the sample concentration, accuracy was satisfactory with a mean recovery of 100.5 %.

B.9.1.4 Precision

B.9.1.4.1 Intra-day precision

Intra-day results for diclofenac sodium are given in Table B.7.

Table B.7: Results for diclofenac sodium to determine intra-day precision

				Recovery	
Tablet powder (mg)	**Area 1**	**Area 2**	**Mean area**	**mg/ml**	**%**
360.55	5894	5898	5896	0.592	98.7
360.50	5840	5833	5837	0.586	97.7
360.36	5852	5857	5855	0.588	98.0
450.16	7287	7283	7285	0.731	97.5
450.12	7422	7434	7428	0.746	99.5
450.14	7347	7343	7345	0.737	98.3
540.06	8709	8721	8715	0.875	97.2
540.09	8805	8799	8802	0.884	98.2
540.08	8826	8933	8880	0.891	99.0
				Mean	98.2
				SD	0.7
				RSD %	0.8

Conclusion

(Acceptance criteria: Repeatability must be better than 2.0%).

Intra-day precision was satisfactory with an RSD of 0.8%.

B.9.1.4.2 Inter-day precision

Inter-day precision results for diclofenac sodium and ANOVA single factor statistics thereof are given in Tables B.8 and B.9, respectively.

Table B.8: Results for diclofenac sodium to determine inter-day precision

	Day 1	Day2	Day 3	Between days
	7285	7302	7174	
	7428	7447	7225	
	7345	7433	7233	
Mean	7353	7394	7211	7320
SD	71.7	80	32	61.03
% RSD	0.98	1.08	0.44	0.83

Table B.9: ANOVA single factor statistics for the determination of diclofenac sodium

Groups	Count	Sum	Average	Variance	
Day 1	3	22058	7352.667	5156.333	
Day 2	3	22182	7394	6397	
Day 3	3	21632	7210.667	1024.333	
ANOVA					
Source of variation	**SS**	**Df**	**MS**	**F**	**P-value**
Between groups	55483.56	2	27741.78	6.616914	0.030357
Within groups	25155.33	6	4192.556		
Total	80638.89	8			

SS = sum of squares

df = degrees of freedom

MS = mean squares

F = F ratio

Conclusion

(Acceptance criteria: Inter-day precision must be better than 2.0%).

Inter-day precision was satisfactory with an RSD of 0.8%.

B.9.1.5 Ruggedness

B.9.1.5.1 Stability of sample solutions

Results of a sample solution re-analysed over a period of 8 hours are presented in Table B.10.

Table B.10: Results for diclofenac sodium to determine ruggedness

Time (hours)	Peak area	%
0	7133	100.0
1	7125	99.9
2	7133	100.0
3	7153	100.3.
4	7160	100.4
5	7159	100.4
6	7171	100.5
7	7165	100.4
8	7172	100.5
Mean	7152	100.3
SD	17.7	0.2
RSD	0.3	0.2

Conclusion

(Acceptance criterion: Sample solutions should not be used for a period longer than it takes to degrade by 2%).

No degradation was observed over an 8-hour period.

B.9.1.5.2 System repeatability

A standard was injected six times in order to test the repeatability of the peak area and retention time of diclofenac sodium. The results are presented in Table B.11.

Table B.11: Results for diclofenac sodium to determine system repeatability

	Area	Retention time (minutes)
	7533	10.94
	7538	10.92
	7541	10.92
	7533	10.94
	7543	10.93
	7544	10.90
Mean	7539	10.93
SD	4.84	0.02
% RSD	0.06	0.14

Conclusion

(Acceptance criteria: The peak area of diclofenac sodium should have an RSD of 2.0% or less and the retention times of diclofenac sodium should have an RSD of 2.0% or less).

System performance was satisfactory with RSD values of 0.1% for both peak area and retention time.

B.9.2 Diclofenac related compound A

B.9.2.1 Specificity

See Figure B.1 for chromatogram of diclofenac sodium standard containing diclofenac related compound A.

Conclusion

(Acceptance criterion: The diclofenac related compound A peak and diclofenac sodium peak should be well separated from each other).

The peaks were well separated from each other.

B.9.2.2 Linearity and Range

Linearity and range results for diclofenac related compound A are given in Table B.12.

Table B.12: Results for diclofenac related compound A to determine linearity and range

µg/ml	% Relative to diclofenac sodium standard solution	Area 1	Area 2	Mean
1.5	0.2	25.46	25.5	25.48
3	0.4	51.9	51.01	51.46
4.5	0.6	77.11	77.29	77.2
6	0.8	103.3	103.1	103.2
7.5	1	128.6	129.2	128.9

Regression statistics are given in Table B.13.

Table B.13: Regression statistics of diclofenac related compound A results

R squared	1.0000	**Lower 95%**	**Upper 95%**
Intercept	-0.345	-0.6415	-0.0485
Slope	17.246	17.1864	17.3056

Conclusion

(Acceptance criterion: Linear regression analysis should yield a regression coefficient (R^2) of ≥ 0.99).

The method is linear over the concentration range 1.5-7.5 µg/ml (0.2-1.0% of the expected diclofenac sodium standard solution concentration) as shown in Figure B.10. The regression coefficient (R^2) is 1.00.

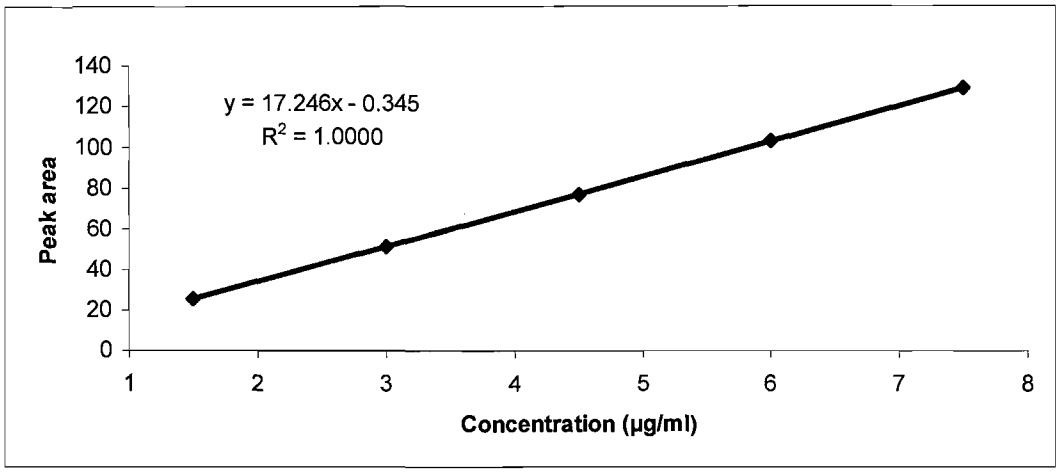

Figure B.10: Linear regression graph for diclofenac related compound A to determine linearity and range.

B.9.2.3 Precision

Precision results for a 4 µg/ml diclofenac related compound A solution are given in Table B.14.

Table B.14: Results for diclofenac sodium related compound A to determine precision

Area Diclofenac related compound A	Area Diclofenac sodium	% Relative area
61.14	7533	0.81
61.32	7538	0.81
63.13	7542	0.84
61.52	7533	0.82
61.48	7543	0.82
61.64	7544	0.82
	Mean	0.82
	SD	0.01
	% RSD	1.34

Conclusion

(Acceptance criterion: The percentage relative area must have an RSD of 5.0% or less).

Precision was satisfactory with a RSD of 1.3%.

B.9.2.4 Ruggedness

B.9.2.4.1 System repeatability

A standard was injected six times in order to test the repeatability of the peak area and retention time of diclofenac related compound A. The results are presented in Table B.15.

Table B.15: Results for diclofenac related compound A to determine system repeatability

	Area	Retention time (minutes)
	61.14	6.69
	61.32	6.68
	63.13	6.68
	61.52	6.68
	61.48	6.68
	61.64	6.67
Mean	61.71	6.68
SD	0.72	0.01
% RSD	1.17	0.09

Conclusion

(Acceptance criteria: The peak area of diclofenac related compound A should have an RSD of 2.0% or less and the retention times of diclofenac related compound A should have an RSD of 2.0% or less).

System performance proved well with RSD values of 1.2% for peak area and 0.1% for retention time, respectively.

B.9.2.5 Limit of detection

Figure B.11 was used to calculate the experimental signal to noise ratio of a 0.2% (relative to the diclofenac sodium standard solution) diclofenac related compound A solution. It yielded a ratio of 31:1.

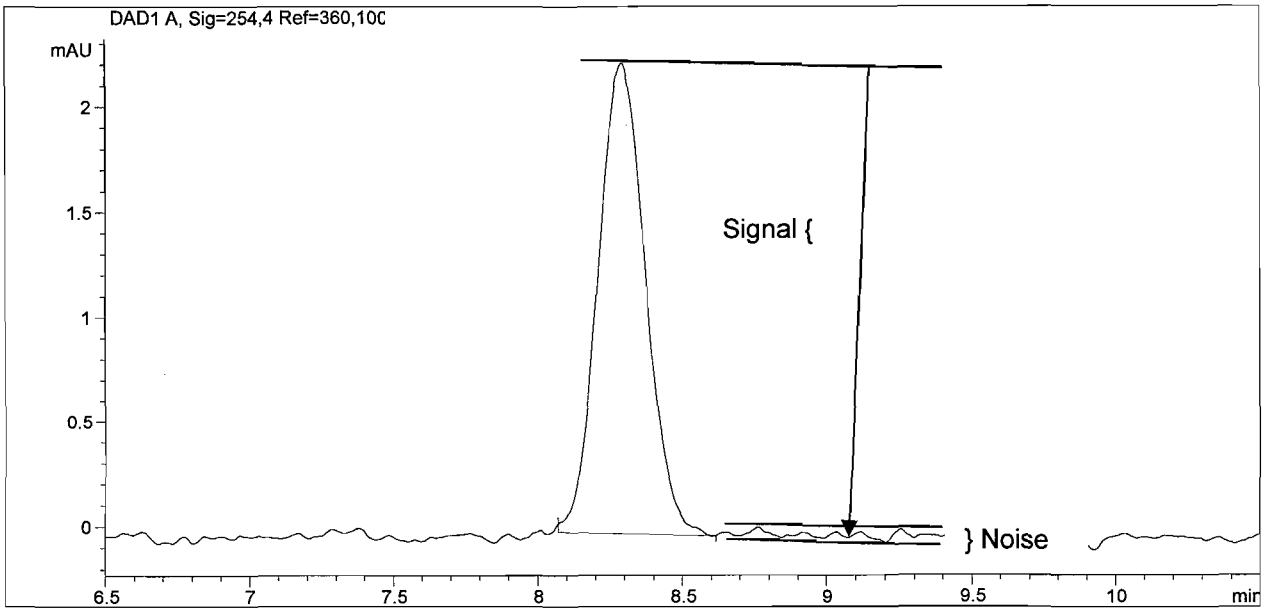

Figure B.11: Representation of a 1.5 µg/ml diclofenac related compound A solution.

Conclusion

(Acceptance criterion: The concentration determined as the limit of detection has a signal-to noise ratio of 3:1).

A concentration of about 0.48 µg/ml will yield a signal-to-noise ratio of 3:1.

B.9.2.6 Limit of quantitation

Figure B.11 was used to calculate the experimental signal to noise ratio of a 0.2% (relative to the diclofenac sodium standard solution) diclofenac related compound A solution. It yielded a ratio of 31:1.

Conclusion

(Acceptance criterion: The concentration determined as the limit of quantitation has a signal-to noise ratio of 10:1).

A concentration of about 0.15 µg/ml will yield a signal-to-noise ratio of 10:1.

B.9.3 Robustness

The following changes in the chromatographic operating parameters were found to be acceptable:

Column: Discovery C8 column, 250 x 4.6 mm, 5µm (Supelco®).

Mobile phase pH: pH 2.3–2.7.

Injection volume: 8–12 µl.

Flow rate: 0.8–1.2 ml/min.

Wavelength: 252–256 nm.

Conclusion

(Acceptance criterion: The method should be able to tolerate about 5.0% variance in the chromatographic conditions).

The method was able to tolerate small changes in the chromatographic conditions.

B.9.4 Chromatographic performance parameters

Retention time (minutes):

Diclofenac sodium: ± 11 minutes

Diclofenac related compound A: ± 7 minutes

USP tailing factor:

Diclofenac sodium: 1.131

Diclofenac related compound A: 1.150

Number of theoretical plates/column:

Diclofenac sodium: 12878

Diclofenac related compound A: 14109

Capacity factor (k'):

Diclofenac sodium: 2.874

Diclofenac related compound A: 1.368

Resolution between peaks: 13.923

B.9.5 System suitability parameters

The system is suitable for analysis if the following criteria are met:

- RSD of 6 injections not more than 2.0%.
- The column must have more than 7500 theoretical plates for diclofenac sodium and diclofenac related compound A.
- The resolution between the peaks should not be less than 6.5.
- USP tailing factor must be less than 1.5.

B.9.5 Conclusion

The method performed well and should be suitable to analyse diclofenac sodium and test for chromatographic purity in dispersible tablets during stability testing.

ANNEXURE C

Poster presented at the 28th Annual Conference of the Academy of Pharmaceutical Sciences of South Africa

The formulation and evalution of diclofenac sodium dispersible tablets

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Purpose

The aim of this study was to develop a stable diclofenac sodium dispersible tablet.

Background

Diclofenac sodium is a non-steroidal, anti-inflammatory drug used for the relief of pain and inflammation[1]. Many patients have difficulty swallowing tablets and consequently do not take medication as prescribed. To achieve optimum benefit of a drug, it is desirable to present it in a formula which can rapidly disperse in water. This formulation is easier to swallow, therefore enhancing patient compliance.

Materials & Methods

Diclofenac sodium – excipient compatibility studies were performed as part of a preformulation study. Methods of evaluation included differential scanning calorimetry (DSC) and high performance liquid chromatography (HPLC). Four dispersible tablet formulations were developed. Crospovidone and croscarmellose sodium were used as disintegrants in concentrations of 2% and 5% of the tablet mass. Tabletting was performed using a Cadmach® (India) single-punch tabletting machine. The four formulations were put on accelerated stability according to ICH guidelines for three months at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. HPLC was used to determine the chromatographic purity and concentration of diclofenac sodium. Other tests included uniformity of mass, hardness, friability, disintegration, fineness of dispersion, loss on drying and dissolution.

Results

Thermal compatibility studies revealed potential interactions between diclofenac sodium and the excipients. Since DSC results only serve as a rough indication of possible interactions[2], accelerated stability testing using HPLC was used as a more selective method to identify potential interactions between diclofenac sodium and excipients. The HPLC results revealed that no interactions exist between diclofenac sodium and the chosen excipients.
At the end of the stability period, no change in the physical appearance of the tablets was observed and the assay values remained within the specification of 90.0-110.0% in all four formulations. Differences in the disintegration times were noted between crospovidone and croscarmellose sodium formulations. The only formula that disintegrated within the specified time of 3 minutes, was formulation B (Table 1). These differences were also noted during dissolution testing in phosphate buffer pH 6.8, where the croscarmellose sodium formulations showed quicker dissolution that was not influenced by stability testing at accelerated conditions. The dissolution results correlated with the decrease in friability and increase in hardness obtained during the stability in the crospovidone formulations.

Fig.1: Picture of diclofenac sodium dispersible tablets manufactured during the study

Table 1: Formula B (300 mg tablet)

API/excipient	Amount per tablet (%)	Amount per tablet (mg)
Diclofenac sodium	16.67	50
Colloidal silicon dioxide (Aerosil®)	2.3	6.9
Croscarmellose sodium (Disolcel®)	5	15
Magnesium stearate (Kemilub EM-F-V®)	1	3
Microcrystalline cellulose (Avicel® pH 101)	66.45	199.35
Peppermint Flavour	0.25	0.75
Potassium bicarbonate	3.67	11
Saccharine sodium	1	3
Sodium bicarbonate	3.67	11

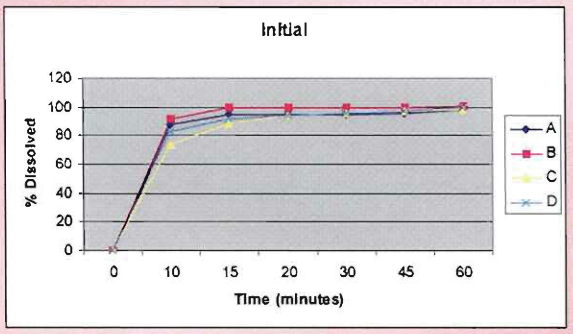

Fig.2: Initial dissolution results of the four formulations

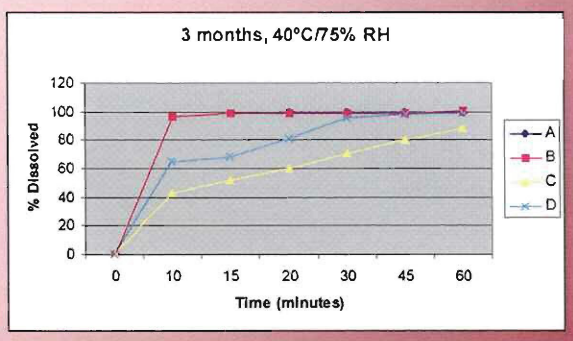

Fig.3: Dissolution results of the four formulations after 3 months at 40°C/70%

Conclusion

According to the results obtained, the formulation containing 5% croscarmellose sodium as disintegrant (formula B) proved to be the best.

References

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