THE TRANSDERMAL ABSORPTION OF DRUGS THAT ARE SUITABLE FOR USE AGAINST MORNING SICKNESS DURING PREGNANCY

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ABSTRACT

THE TRANSDERMAL ABSORPTION OF DRUGS THAT ARE SUITABLE FOR USE AGAINST MORNING SICKNESS DURING PREGNANCY

The aim of this study was to determine the transdermal absorption of appropriate anti-emetic drugs for use during pregnancy.

Some of the objectives were obtained through a literature study done on the advantages of transdermal drug delivery over other drug delivery systems e.g. peroral drug delivery, factors that could influence transdermal drug delivery and the essential physicochemical characteristics required of drugs for effective transdermal drug delivery. After investigating the physicochemical characteristics of drugs which are normally prescribed for treatment of morning sickness (oral administration) two drugs (chlorpromazine hydrochloride and doxylamine succinate) were identified as promising candidates for transdermal delivery.

Transdermal absorption of chlorpromazine hydrochloride and doxylamine succinate (dissolved in ethanol) in combination with penetration enhancers - oleic acid (5 %) and phosphatidylcholine (5 %) - and solvents known for their enhancing properties - Transcutol® (50 %) and Labrafil M 1944 CS® (50 %) were investigated. Hairless mice were used in the *in vivo* diffusion study. A diffusion cell was implanted under the dorsal skin of the anaesthetised hairless mouse (n = 6). Sodium chloride - 0.9 % - (saline) were used as receptor fluid. Drug concentrations were determined at half-hour intervals, over a period of 12 hours. A Spectra Physics HPLC-system was used for the analysis. A Lichrospher® 100RP-18 (250 x 4 mm) column (Merck, Darmstadt) was used for chlorpromazine hydrochloride. The injection volume was 100 µl and the samples were analysed at a fixed wavelength of 254 nm. The mobile phase (2 $ml.min^{-1}$) consisted of acetonitrile - tetrahydrofuran - water (60:30:10). For doxylamine succinate a Nova-Pak® CN HP 60 Å 4 µm (3.9 x 150 mm) column (Waters, Milford, Massachusetts) was used, with a mobile phase (2 $ml.min^{-1}$) of acetonitrile - methanol - 5 mM potassium dihydrogen orthophosphate buffer containing 0.72 mM triethylamine and adjusted to pH 5.30 with glacial acetic acid (70:10:20). The injection volume was 100 µl and the

100 µl and the samples were analysed at a fixed wavelength of 262 nm.

According to the AUC and flux values determined after application, chlorpromazine hydrochloride in combination with oleic acid showed promising results. The AUC and flux values were 586.83 ± 298.57 $ng.ml^{-1}.h$ and 45.95 ± 22.70 $\mu g.cm^{-2}.h^{-1}$ respectively. The other formulations with chlorpromazine did not show any significant absorption.

AUC and flux values obtained after application of doxylamine succinate together with the various penetration enhancers, solvents and solubilising agents showed transdermal absorption that followed the order of doxylamine succinate together with phosphatidylcholine > doxylamine succinate with oleic acid as enhancer > doxylamine succinate in combination with Labrafil M 1944 CS® > doxylamine succinate together with Transcutol®. Doxylamine succinate in ethanol did not show any significant absorption.

From this study followed that:

- chlorpromazine hydrochloride with oleic acid as penetration enhancer showed excellent transdermal absorption ($AUC_{(0 - 12\ h)}$ = 586.83 ± 298.57 $ng.ml^{-1}.h$ and flux = 45.49 ± 22.70 $\mu g.cm^{-2}.h^{-1}$);

- chlorpromazine hydrochloride in ethanol did not show any significant absorption. Using phosphatidylcholine, Transcutol® and Labrafil M 1944 CS® as enhancers, solvents and solubilising agents, did not improve transdermal absorption to such an extend that it were of therapeutic importance;

- doxylamine succinate in ethanol in combination with oleic acid showed good transdermal absorption ($AUC_{(0 - 12\ h)}$ = 462.66 ± 116.60 $ng.ml^{-1}.h$ and flux = 40.46 ± 14.77 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate combined with phosphatidylcholine had the ideal concentration-time profile for transdermal drug delivery, with concentrations comparable to therapeutic levels obtained for 11 hours ($AUC_{(0 - 12\ h)}$ = 841.29 ± 59.09 $ng.ml^{-1}.h$ and flux = 67.77 ± 12.70 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate together with Transcutol® also showed good transdermal absorption ($AUC_{(0\ -\ 12\ h)}$ = 351.78 ± 241.70 $ng.ml^{-1}.h$ and flux = 27.83 ± 19.38 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate and Labrafil M 1944 CS® showed good transdermal absorption ($AUC_{(0\ -\ 12\ h)}$ = 725.90 ± 342.21 $ng.ml^{-1}.h$ and flux = 52.96 ± 26.65 $\mu g.cm^{-2}.h^{-1}$) and concentrations comparable to therapeutic levels were maintained for 11.5 hours and

- doxylamine succinate in ethanol did not show any significant transdermal drug delivery.

In continuation of this study the following should be investigated:

- the transdermal delivery of chlorpromazine hydrochloride in combination with other penetration enhancers;

- formulation of transdermal drug delivery systems (TTS) with doxylamine succinate in combination with oleic acid, phosphatidylcholine, Transcutol® and Labrafil M 1944 CS® respectively;

- transdermal absorption of doxylamine succinate in combination with other penetration enhancers and

- other routes of drug delivery e.g. intranasal administration, could be investigated as alternative to peroral administration of anti-emetic drugs.

Key words: Transdermal, Absorption, Anti-emetic, Morning sickness, Pregnancy Chlorpromazine, Doxylamine.

OPSOMMING

TRANSDERMALE ABSORPSIE VAN ANTI-EMETIESE GENEESMIDDELS, GESKIK VIR GEBRUIK TYDENS SWANGERSKAP

Die doel van hierdie studie was om die transdermale absorpsie van geskikte anti-emetiese geneesmiddels vir gebruik tydens swangerskap te bepaal.

'n Literatuurstudie is gedoen oor die voordele van transdermale toedieningsroete bo ander roetes van toediening bv. die orale roete, faktore wat 'n invloed kan hê op transdermale geneesmiddel toediening en fisies-chemiese eienskappe van geneesmiddels wat noodsaaklik blyk te wees vir effektiewe transdermale aflewering. Na afloop van die bestudering van die fisies-chemiese eienskappe van geneesmiddels wat reeds gebruik word vir die behandeling van swangerskapsnaarheid (oraal toegedien), is chloorpromasien hidrochloried en doksielamien suksinaat geselekteer as geskikte kanidate vir moontlike transdermal absorpsie.

Die transdermale absorpsie van chloorpromasien hidrochloried en doksielamien suksinaat (opgelos in etanol) in kombinasie met absorpsie bevorderaars - oliesuur (5 %) en fosfatidielcholien (5 %), sowel as oplosmiddels wat bekend is vanwee hul absorpsie bevorderings effekte - Transcutol® (50 %) en Labrafil M 1944 CS® (50 %) is ondersoek. Haarlose muise is gebruik vir die *in vivo* diffusie studie. 'n Diffusiesel is onder die dorsale vel van die muis ingeplant, terwyl die muis onder narkose gehou is. Die reseptor vloeistof wat gebruik is, was 0.9 % natriumchloried (normale soutoplossing). 'n Spectra Physics HPLC-sisteem is gebruik om die geneesmiddel konsentrasies met intervalle van 30 minute oor 'n tydperk van 12 uur bepaal. 'n Lichrospher® 100RP-18 (250 x 4 mm) kolom (Merck, Darmstadt) is gebruik vir die analise van chloorpromasien hidrochloried. Die monsters is geanaliseer by 'n vaste golflengte van 254 nm en die mobiele fase (2 $ml.min^{-1}$) wat gebruik is, het bestaan uit asetonitriel - tetrahidrofuran - water (60:30:10). Vir die analise van doksielamien suksinaat is gebruik gemaak van 'n Nova-Pak® CN HP 60 Å 4 µm (3.9 x 150 mm) kolom (Waters, Milford, Massachusetts), kaliumdiwaterstofortofosfaat buffer (70:10:20) tesame met 0.72 mM trietielamien. Die mobiele fase is ingestel tot 'n pH van 5.30 met ysasynsuur. Analises is uitgevoer by 'n

vaste golflengte van 262 nm.

Die AUC en fluks wat bereken is, na afloop van absorpsie, dui daarop dat chloorpromasien hidrochloried in kombinasie met oliesuur belowende resultate gelewer het. Die AUC en fluks was onderskeidelik 586.83 ± 298.57 $ng.ml^{-1}.h$ en 45.95 ± 22.70 $\mu g.cm^{-2}.h^{-1}$. Die ander formules wat chloorpromasien bevat het, het geen betekenisvolle absorpsie getoon nie.

Die AUC en fluks, bereken vir doksielamien, dui daarop dat al die absorpsie bevorderaars, oplosmiddels en solubiliserings middels transdermale absorpsie tot gevolg gehad het en wel in die volgorde doksielamien suksinaat saam met fosfatidielcholien > doksielamien suksinaat in kombinasie met oliesuur > doksielamien suksinaat tesame met Labrafil M 1944 CS® > doksielamien suksinaat saam met Transcutol®. Doksielamien suksinaat in etanol het geen betekenisvolle absorpsie getoon nie.

Vanuit hierdie studie blyk dit dat:

- chloorpromasien hidrochloried in kombinasie met oliesuur uitstekende transdermale absorpsie getoon het ($AUC_{(0 - 12\ h)}$ = 586.83 ± 298.57 $ng.ml^{-1}.h$ en fluks = 45.49 ± 22.70 $\mu g.cm^{-2}.h^{-1}$);

- chloorpromasien hidrochloried in etanol geen betekenisvolle absorpsie getoon het nie. Absorpsie bevorderaars, oplosmiddels en solubiliserings middels soos fosfatidielcholien, Transcutol® en Labrafil M 1944 CS® het nie die absorpsie sodanig verbeter dan dit van terapeutiese waarde was nie;

- doksielamien suksinaat in etanol tesame met oliesuur het goeie transdermale absorpsie getoon ($AUC_{(0 - 12\ h)}$ = 462.66 ± 116.60 $ng.ml^{-1}.h$ en fluks = 40.46 ± 14.77 $\mu g.cm^{-2}.h^{-1}$);

- doksielamien suksinaat gekombineerd met fosfatidielcholien het die ideale konsentrasie-tyd kurwe vir transdermale absorpsie getoon ($AUC_{(0 - 12\ h)}$ = 841.29 ± 59.097 $ng.ml^{-1}.h$ en fluks = 67.77 ± 12.70 $\mu g.cm^{-2}.h^{-1}$) Konsentrasies wat vergelykbaar is met terapeutiese vlakke is gehandhaaf vir 11 ure;

- doksielamien suksinaat saam met Transcutol® het ook bevredigende

- doksielamien suksinaat saam met Transcutol® het ook bevredigende transdermale absorpsie getoon ($AUC_{(0\ -\ 12\ h)}$ = 351.78 ± 241.70 $ng.ml^{-1}.h$ en fluks = 27.83 ± 19.38 $\mu g.cm^{-2}.h^{-1}$);

- doksielamien suksinaat tesame met Labrafil M 1944 CS® het uitstekende absorpsie getoon ($AUC_{(0\ -\ 12\ h)}$ = 725.90 ± 342.21 $ng.ml^{-1}.h$ en fluks = 52.96 ± 26.65 $\mu g.cm^{-2}.h^{-1}$) met konsentrasies wat vergelykbaar is met terapeutiese vlakke. Hierdie konsentrasies is gehandhaaf vir 'n tydperk van 11.5 ure en

- doksielamien suksinaat in etanol het geen noemenswaardige transdermale absorpsie getoon nie.

Ter voortsetting van hierdie studie behoort die volgende aspekte bestudeer te word:

- die transdermale toediening van chloorpromasien hidrochloried in kombinasie met ander absorpsie bevorderaars;

- formulering van transdermale terapeutiese sisteme (TTS) met doksielamien suksinaat in kombinasie met oliesuur, fosfatidielcholien, Transcutol® en Labrafil M 1944 CS® onderskeidelik;

- transdermale absorpsie van doksielamien suksinaat in kombinasie met ander absorpsie bevorderaars en

- ander roetes van geneesmiddel toediening bv. nasale toediening, kan bestudeer word as alternatief vir orale toediening van anti-emetiese geneesmiddels.

Sleutelwoorde: Transdermaal, Absorpsie, Anti-emeties, Swangerskapsnaarheid, Swangerskap, Chloorpromasien, Doksielamien.

TABLE OF CONTENTS

CHAPTER 1

TRANSDERMAL DELIVERY OF ANTI-EMETIC DRUGS

CHAPTER 2

EXPERIMENTAL PROCEDURES AND VALIDATION OF EXPERIMENTAL TECHNIQUES

CHAPTER 3

TRANSDERMAL DELIVERY OF CHLORPROMAZINE HYDROCHLORIDE AND DOXYLAMINE SUCCINATE

STATEMENT OF THE PROBLEM

Transdermal drug delivery is often dismissed as a relatively minor player in modern pharmaceutical sciences. One commonly hears that the skin is too good a barrier to permit transdermal drug delivery, and that it is not even worth considering as an alternative route for drug administration (Guy, 1996:1765).

Peroral administration of anti-emetic drugs is the principle route for the treatment of morning sickness. Oral therapy is effective, but many of the drugs are subject to considerable first-pass effects and metabolism in the gut wall (Reynolds, 1993:578-159). Transdermal drug delivery offers an alternative to conventional therapy. The main advantages of transdermal drug delivery compared to peroral dosage regimens are that the pharmacokinetic variability associated with the gastro-intestinal tract (effect of pH, motility, transit time of food intake) and metabolism within the gastro-intestinal tract and first-pass effect in the liver are avoided with the transdermal route (Ridout *et al.*, 1988:115).

The aim of this study is to determine the transdermal absorption of appropriate anti-emetic drugs for use during pregnancy. A literature study will be conducted with the following objectives:

- ☆ comparison of the transdermal route of administration with other routes of drug administration;
- ☆ investigation of the factors that could influence transdermal drug delivery;
- ☆ statement of the essential physicochemical characteristics that are essential for effective transdermal drug delivery;
- ☆ investigation of the physicochemical characteristics of drugs which are normally prescribed for treatment of morning sickness;

- ☆ identification of drugs that are safe for use during pregnancy, which also meet the criteria for effective transdermal drug delivery and

- ☆ introduction of possible solutions for drugs that don't meet the required criteria for transdermal drug delivery.

In vivo transdermal drug delivery studies will be conducted on hairless mice to:

- ✧ determine the transdermal absorption of the chosen drugs;

- ✧ compare the pharmacokinetic parameters (flux and AUC-values) of these drug, with values obtained for nitroglycerin - used as a model drug for transdermal drug delivery and

- ✧ indicate whether the chosen drugs showed sufficient transdermal absorption for incorporation into a transdermal therapeutic system (TTS).

CHAPTER 1

TRANSDERMAL DELIVERY OF ANTI-EMETIC DRUGS

1.1 INTRODUCTION

In the past decade, there has been a continuous increase in the pharmaceutical industry's interest in the development of transdermal drug delivery systems, which offer an effective way to deliver many drugs topically into the systemic circulation. This type of delivery system offers many advantages such as bypassing the "first-pass" effect and ease of self-administration (Beckett, 1982:156-157). However, it also has its limitations. Were it not for the skin's extraordinary barrier properties, one would see many more drugs on the market available for transdermal administration. The fact is that most drugs lack sufficiently high permeability through the skin to produce therapeutic effects.

Transdermal therapeutic systems (TTS) could be of great benefit in certain situations and conditions. TTS avoid the variables associated with peroral administered drugs, e.g. gastro-intestinal pH and drug and food interactions, they also avoid the gastrointestinal metabolism and first-pass effect in the liver which is so characteristic of peroral administration (Abdou, 1989:245). TTS provide controlled, constant drug delivery over periods of 24 hours to 7 days and provide a simple medication regimen where the patient may self-medicate when necessary (Beckett, 1982:156).

The only anti-emetic drug currently available on the market as a TTS is Scopoderm TTS® (scopolamine/hyoscine), an anti-emetic used as prophylaxis for motion sickness. The lack of anti-emetic TTS open a wide field for research, especially for an anti-emetic TTS for use during pregnancy.

Effective treatment of nausea and vomiting during pregnancy will not only be beneficial to the mother-to-be but also to her employer. Work productivity will not decrease because of absence from work and the employee will be less irritable. An anti-emetic TTS will be of great benefit during pregnancy. The constant drug delivery can eliminate the nausea and vomiting by assuring that the active drug is present in the blood at

therapeutic levels at all times. TTS give an alternative method of treatment to someone who is nauseous and does not want to eat or drink, even a tablet or capsule, because this may aggravate the condition or even induce vomiting, here the TTS give an alternative method of treatment.

In order to attain the objectives of this research project, a literature study was conducted to investigate the following aspects:

- advantages of transdermal drug delivery over other drug delivery systems e.g. peroral drug delivery;
- factors which could influence transdermal drug delivery;
- essential physicochemical characteristics required of drugs for effective transdermal drug delivery;
- investigation of pharmacological action of anti-emetics;
- epidemiology of morning sickness during pregnancy;
- physicochemical characteristics of drugs which are normally prescribed for treatment of morning sickness (oral administration);
- identification of drugs suitable for use during pregnancy, which also meet the criteria for effective transdermal drug delivery and
- possible solutions for drugs that don't meet the required criteria for transdermal drug delivery.

1.2 TRANSDERMAL DRUG DELIVERY

1.2.1 Comparison of transdermal and peroral drug delivery

The advantages and disadvantages listed in Table 1.1 are limited to comparisons between oral and topical therapy.

***TABLE 1.1**: Advantages and disadvantages of administration of drugs by different routes e.g. transdermal and peroral administration (Beckett, 1982:156-157).*

TRANSDERMAL	ORAL
Drug delivery of 5 to 7 days.	Drug delivery 24 hours irrespective of biological half-life.
Only a small dose can be administered.	Small and large doses may be administered.
Rate of drug release not influenced by food.	Food has a negligible effect on rate of drug release.
Drug administration in general visible to others.	Drug administration need not be visible to others.
Narrow range of physicochemical properties of drugs can at present be accommodated.	Wide range of physicochemical properties can be used.
Can be used if vomiting occurs.	Cannot be used if vomiting occurs.
Small area for absorption; local irritation.	Large area for absorption; less irritation.
Occlusion usually required; problems of skin flora.	Seldom problems.
Relatively long delay in achieving appropriate plasma concentrations of drug.	Short delay in achieving appropriate plasma concentrations of drug.
Avoid first-pass metabolism.	Cannot avoid first-pass metabolism.

TABLE 1.1 (continue)

TRANSDERMAL	ORAL
Release of drug is controlled by the system and not the skin, the influence of both inter and intra-patient variability are minimized.	Inter and intra-patient variablilty plays a larger role.
Acceptance by patient of route - doubtful. Application of a transdermal system once daily or twice weekly assists with obtaining patient compliance.	Acceptance by patient of route - good.
Can remove source of drug supply after application.	Cannot remove source of drug supply after application.

1.2.2 Factors that could influence transdermal drug delivery

The human skin is made up of three distinct layers (Abdou, 1989:437):

- the epidermis;
- the dermis and
- the subcutaneous fat layer.

Each of these layers consists of various components which are involved in the process of absorption of any chemical substance by the skin.

The ultimate goal of TTS is to facilitate the entrance of drug substances into the blood stream. Because of the different histological characteristics of the human skin layers, it is an immensely complex process.

There are six key events which must occur prior to the appearance of the drug in the blood stream or systemic circulation (Guy *et al.*, in Cairncross, 1993:21):

✧ drug transportation or diffusion within the TTS to the interface of the TTS and the stratum corneum;

- ✧ drug partition from the TTS into the stratum corneum;
- ✧ drug diffusion through the layers of the stratum corneum;
- ✧ drug partition from the stratum corneum into the stratum lucidum;
- ✧ drug diffusion through the stratum lucidum, stratum granulosum, stratum malpighii, stratum germinativum and dermis and
- ✧ drug entrance into the blood vessels, which are present in the dermis, thereby becoming systemically available.

The movement of the drug across and through the various layers of the skin will be rate-limited by the slowest step of the overall absorption process. For the majority of substances, the rate-limiting step is the diffusion through the stratum corneum (Abdou, 1989:438). This delay caused by the resistance of the stratum corneum to the absorption of the drug, together with the time taken for the drug to move through the remaining underlying tissues, is termed the "lag-time" (Cairncross, 1993:21-22).

In order to facilitate the passive diffusion of the drug from the TTS into the blood vessels, a concentration gradient must exist between the TTS and the tissue of the skin (York, 1988:3). Upon application of the TTS, a high concentration of the drug exists in the TTS whilst no drug is present in the skin. This concentration gradient will be the precipitating factor in the movement of the drug from the patch - stratum corneum interface to within the stratum corneum. As the drug enters the blood vessels, it is diluted and distributed in the general circulation thus causing a near zero concentration of the drug in the blood also termed a "sink" condition (Barry, 1988:384). This then maintains the concentration gradient between the TTS, skin tissues and the general circulation which is responsible for the passive diffusion of the drug from the TTS into the blood vessels.

It is widely recognized that permeation of the drug substance through the skin may occur through two main pathways, namely transepidermal and transappendageal or transfollicular. Transappendageal diffusion occurs through the sweat and sebaceous glands. Although it is possible that many substances permeate the skin simultaneously via both routes, the skin surface occupied by the appendages is so small, approximately

1 %, that the amount diffused transappendageally is virtually insignificant (Bhargava *et al.*, 1984:56).

1.2.2.1 Biosystem factors affecting percutaneous absorption

1.2.2.1.1 Composition of the stratum corneum

The stratum corneum (SC) comprises both hydrophilic and lipophilic components (Friberg *et al.*, 1990:29). The water content of which may vary depending on environmental conditions and body location. The fact that the SC consists of a hydrophilic and lipophilic component is the cause of the SC acting selectively in the absorption of the majority of substances and being the rate limiting step of the absorption process.

The water content may increase as a result of water diffusing from underlying epidermal layers or owing to excessive environmental humidity. When this occurs, permeability of all substances, polar and non-polar, increases (Ansel, 1985:294).

1.2.2.1.2 Dermatological conditions

Physical injuries to the skin surface, such as cuts, abrasions and burns, destroy the barrier function of the stratum corneum and enhances the absorption of almost any substance (Govil, 1988:387).

Skin diseases for example, atopic dermatitis, any inflammatory/allergic conditions, seborrhoeic dermatitis and exfoliative dermatitis may all alter the integrity of the stratum corneum and allow increased permeability by any substance.

1.2.2.1.3 Reservoir effect

When a transdermal patch is applied to the skin, the steady-state systemic dosage may not be reached for some time because of absorption of the drug in the skin. If skin absorption is large, the time required to saturate the skin with drug may be long compared to the time the device is on the skin (Baker and Kochinke, 1989:278). This leads to the drug not being bioavailable immediately.

1.2.2.1.4 Anatomical differences

Anatomical differences including skin type, skin thickness and the anatomical skin site of application can influence the permeation of drugs through the skin (Cairncross, 1993:30).

1.2.2.1.5 Skin metabolism

There is evidence which suggests that certain drugs permeating the skin are also metabolized to a certain degree, but this does not seem to be true for all drugs.

The epidermis contains catabolic enzymes which may either inactivate a drug or activate a prodrug. The skin is able to oxidise, reduce, hydrolyse and conjugate the drug in such a way that the use of prodrugs should be considered (Martin *et al.*, 1987:24).

1.2.2.1.6 Exercise

An increase in skin temperature is unavoidable following exercise. Vasodilatation occurs during any physical exertion and cutaneous vasodilatation, in part, is given as the reason for increased plasma concentrations of a drug. The increase in the amount of blood at the skin enables increased drainage of the drug from the subcutaneous reservoir with the resultant elevation in drug plasma concentration (Cairncross, 1993:30).

Another reason for the elevated plasma concentration of the active drug in patients or subjects exercising whilst using a patch may be attributed to occlusion of the skin by the patch with a resultant moisture accumulation under the patch. The moisture hydrates the skin, causing changes in the permeation characteristics of hydrophilic and lipophilic active drugs (Cairncross, 1993:31).

1.2.2.1.7 Temperature

An increase in skin temperature is not only the result of physical exertion, but can also be ascribed to the skin site, environmental conditions, fever and stress. An increase in the skin temperature has a profound effect on the increased

permeation of a drug and therefore on the efficacy of TTS (Gummer, 1989:180).

The opposite effect is observed during a decrease in skin temperature. The decrease observed in the permeation of the drug is the result of the vasoconstriction of blood vessels within the skin as a mechanism to minimise heat loss (Cairncross, 1993:31).

1.2.2.1.8 Circulatory effects

Both exercise and skin temperature have an influence on the cutaneous blood vessels, but there are various other factors which may also affect these blood vessels. Medications such as vasodilators and vasoconstrictors which affect the peripheral circulation, rubefacients such as nicotinic acid or intravenous nicotine as well as physical manipulation of the skin and the effect of the response of the autonomic nervous system to a number of external stimuli are all factors which affect the cutaneous blood vessels (Barry, 1988:393).

1.2.3 Drugs suitable for transdermal drug delivery

Not every drug available is a candidate for inclusion in controlled TTS. The characteristics of the drug and the various materials which are used in the manufacturing of the TTS have to be carefully taken into consideration during the development of the TTS. The following factors may play a role:

- Neither the drug, the adhesive nor other components may induce irritation or hypersensitivity on immediate application or after a prolonged period of use (Guy and Hadgraft, 1989:61).

- The drug candidate must be sufficiently potent, with effective doses of only a few milligrams, e.g. a total of 15 mg per day (Guy and Hadgraft, 1989:59). According to Cleary (1993:20), the maximum total amount of drug that can be delivered may be as high as 50 mg per day.

- The drug and system should possess the proper physicochemical characteristics to permit drug release from the system and facilitate sufficient partitioning into the stratum corneum for permeation into the systemic vasculature (Barry, 1988:399).

- Drugs with a low melting point penetrate the skin better than drugs with a high melting point (Baker and Kochinke, 1989:299).

- The TTS should adhere well to the patient's skin and their physical size, appearance and placement on the body should not be a deterrent for use (Cairncross, 1993:5).

- The TTS should not permit the proliferation of skin bacteria beneath the occlusion (Ansel, 1985:295).

- There should be a medical rationale for wishing to administer the drug candidate in the form of TTS e.g. (Cairncross, 1993:5-6):

    - drugs that are suitable and indicated for treatment of a chronic disease requiring long-term use (Cairncross, 1993:5).

    - drugs exhibiting poor bioavailability after peroral administration (Shah *et al.*, 1992:1462).

    - drugs characterised by a narrow therapeutic index, which may result in severe or serious side effects during repetitive pulse administration of an effective dose (Cairncross, 1993:5).

    - drugs characterised by a short biological half-life, necessitating frequent administration of conventional dosage forms (Shah *et al.*, 1992:1462).

    - drugs that are such that the avoidance of the first-pass effect would be desirable.

It should be considered if continuous, zero-order release of the drug is at all necessary or applicable for the disease requiring treatment (Cairncross, 1993:6).

1.2.4 Transdermal therapeutic systems (TTS)

1.2.4.1 The basic structure of TTS

Transdermal patches form part of the larger group of pharmaceutical products known as controlled release dosage forms.

TTS are uniquely designed to deliver drugs to the surface of the human skin in such a manner that the TTS theoretically rather than the skin, control the rate of drug absorption. This means that the drug should be released by the TTS at a rate well below the maximum that can be absorbed by the skin tissues (Barry, 1988:389).

Despite the differences in the various TTS being marketed and researched at present, TTS have a number of basic components common to all systems (Bhargava et al., 1984:60):

- *The drug component:* The drug is selected to exhibit the desired therapeutic effectiveness, appropriate pharmacokinetic behavior and physicochemical properties that permit effective transfer from the delivery area to the target site.

- *The drug delivery module:* The drug delivery module comprises:

    - the drug reservoir which stores a large excess of the drug in a stable form without losing its structural integrity at stress conditions. The reservoir must have little or no affinity for the drug, be non-irritating and be able to hydrate the skin particularly the stratum corneum;

    - the rate controller which establishes and maintains the prescribed rate of drug administration;

    - the energy source which facilitates the transfer of the drug from the reservoir to the surface of the skin. The energy necessary to achieve the constant rate of delivery of the drug contained in the reservoir is provided by the concentration gradient across the membrane and

- the delivery portal which provides the exit for the drug from the delivery module.

- *The platform:* The platform houses and protects the drug and delivery module and must be compatible with local tissues.

- *The therapeutic program:* The therapeutic program which specifies the rate and duration of drug release from the system.

1.2.4.2 The various TTS

The main differences between the systems are the varying types of reservoirs, rate controllers and the manner in which the adhesive is mounted. These differences allow the sub-division of the various systems.

1.2.4.2.1 Membrane-moderated TTS

In membrane-moderated systems, the drug reservoir is totally encapsulated in a shallow compartment molded from a drug-impermeable metallic plastic laminate and a rate-controlling polymeric membrane (Fig. 1.1).

The rate of drug release from this type of transdermal drug delivery system can be tailored by varying the polymer composition, the permeability coefficient, and/or the thickness of the rate-controlling membrane and adhesive (Chien, 1987:31-32).

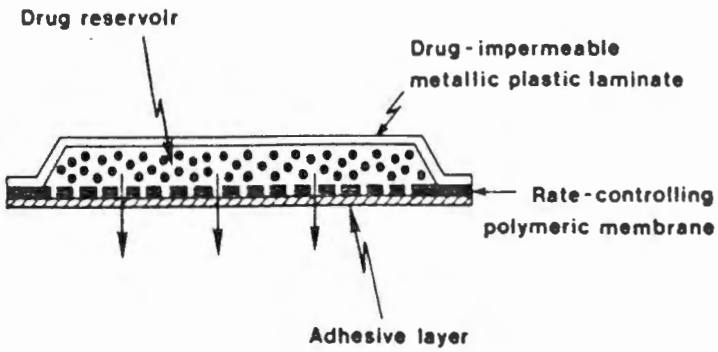


FIGURE 1.1: *Cross-sectional view of a membrane-moderated delivery system (Chien, 1987:32).*

1.2.4.2.2 Adhesive dispersion TTS

In a simplified version of the membrane-moderated drug delivery system, instead of completely encapsulating the drug reservoir in a compartment fabricated from drug-impermeable metallic plastic backing, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer. Then the medicated adhesive is spread, by solvent casting or hot melt, into a flat sheet of drug-impermeable backing support to form one or more layers of drug reservoir (Fig. 1.2) (Chien, 1987:34).

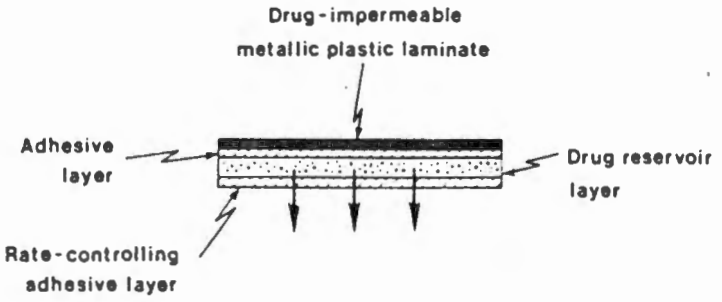


FIGURE 1.2: *Cross-sectional view of an adhesive dispersion-type transdermal drug delivery system (Chien, 1987:36).*

1.2.4.2.3 Matrix diffusion-controlled TTS

The drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix, the medicated polymer is then molded into a medicated disc with a defined surface area and controlled thickness. This drug-reservoir-containing polymer disc is mounted onto an occlusive plastic backing (Fig 1.3) (Chien, 1987:37-38).

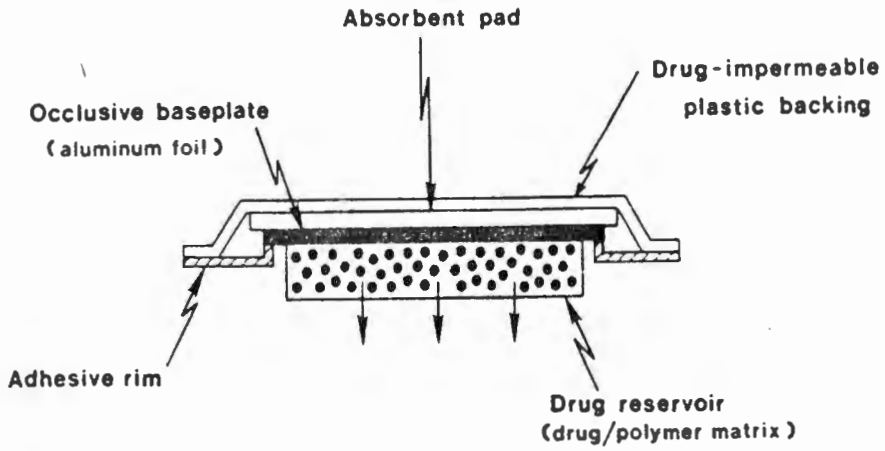


FIGURE 1.3: *Cross-sectional view of a matrix-diffusion-controlled transdermal drug delivery system (Chien, 1987:38).*

1.2.4.2.4 Microreservoir dissolution-controlled TTS

The microreservoir-type drug delivery system can be considered a hybrid of the reservoir and matrix dispersion-type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of a water-soluble polymer and then dispersing the drug suspension homogeneously in a lipophilic polymer, by high-shear mechanical force, to form thousands of unleachable, microscopic spheres of drug reservoirs (Fig. 1.4) (Chien, 1987:39).

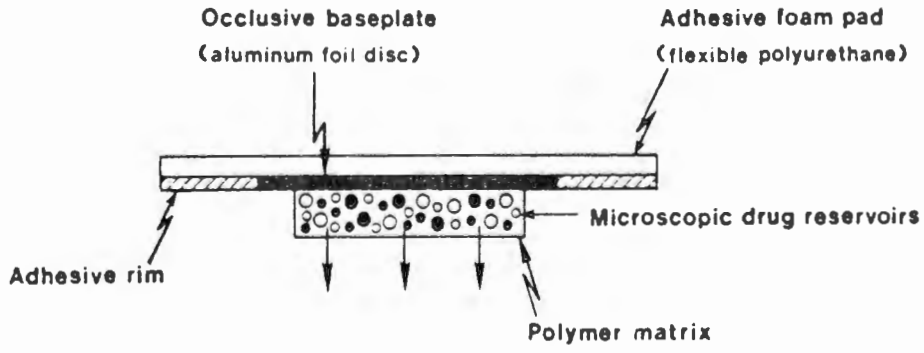


FIGURE 1.4: *Cross-sectional view of a microreservoir dissolution-controlled transdermal drug delivery system (Chien, 1987:42).*

1.2.4.3 Drug related factors which affect the release rate and permeation rate

1.2.4.3.1 Drug solubility

The solubility of the drug is the most important of the physicochemical factors which influence the dissolution and bioavailability of the drug (Abdou, 1989:368).

The concept of drug solubility within TTS is extremely complicated because of the uniqueness of this type of dosage form. The drug must exhibit optimal solubility characteristics in a range of media namely in the polymer coating membrane, in the liquid compartment and in the polymer matrix. However, the one important factor which is highlighted, is that it is the solubility of the drug in the fluid, be it water, aqueous glycerol or any other neutral media, which is of importance rather than its solubility in the polymer matrix. It is also only the dissolved or soluble drug fraction which is involved in diffusion within the matrix and diffusion out of the TTS into the first skin layers (Tyle *et al.*, 1990:19).

1.2.4.3.2 Ionic-state

Most drugs are weak acids or bases and according to the pH-partition theory, may exist in an ionised or non-ionised form, depending upon the pH of the matrix or reservoir of the TTS. The movement of the drug through membranes, natural or synthetic, is governed to a large extent by the degree of ionisation. Membranes are more permeable to the non-ionised forms, because of their greater lipid solubility (Abdou, 1989:59). Ionised drugs are either highly charged, or they may bind with water becoming larger molecules and, therefore, lose their capacity to permeate. The slower rate of permeation by the ionised drugs through the membranes of TTS will, therefore result in a slower release rate. Although this characteristic may be seen to be a drawback in certain instances, it may be a useful quality for TTS which are supposed to provide the rate-controlling step (Kuo *et al.*, 1989:1200).

1.2.4.3.3 Crystalline form

Polymorphism, the existence of the drug substance in more than one crystalline form, may occur during the synthesis of the drug substance or during the manufacture and storage of the final product. The different forms have to be identified as they may affect bioavailability and product stability owing to their unique and different pharmacological and physical properties, including solubility and melting point. Improved rate and extent of bioavailability could be obtained with the same amount of drug substance which exhibits the "desired" polymorphic state (Abdou, 1989:70).

1.2.4.3.4 Particle size

One of the most important physical drug parameters which affects the bioavailability of a drug in oral therapy is particle size. This has also shown to be an important determination of the release rate of the drug from TTS (Abdou, 1989:59).

1.2.4.3.5 Molecular size and mass

Molecular mass and size play a role in determining the release of the drug from the TTS as the drug molecules have to diffuse through the components of the matrix as well as through the membrane of the TTS. The molecular size and mass of the drug is also important in determining the further diffusion of the drug through the stratum corneum and underlying tissues. An optimal drug diffusion rate is documented for molecular masses of 800 to 1000 (Parikh *et al.*, 1984:291), but according to Zats in Cairncross (1993:53) there is evidence that molecules as large as 5000 and macromolecules such as heparin, dextrin and albumin can penetrate the skin, albeit a bit slower.

1.2.4.3.6 Isomers

If there is a preferred isomer, the specification should include a test to ensure isomeric purity.

1.2.4.3.7 Drug concentration

The concentration of the drug is the driving force behind the movement of the drug within the TTS and subsequently into the first layers of the skin. When the concentration of the drug in the TTS is increased, the danger of toxicity should be taken into account, especially if the product is not used correctly by the patient, or if dose-dumping occurs should the rate-controlling membrane rupture (Cairncross, 1993:55).

1.2.4.3.8 Diffusion coefficient

Percutaneous absorption of most drugs is a passive diffusion process that can be described by Fick's first law of diffusion. This principle is illustrated in equation 1.1, in which the amount of drug transported through a unit area of the skin per unit time *(J)* is the product of the diffusion coefficient of the drug in the skin *(D)*, the vehicle-skin partition coefficient of the drug *(K)*, and the drug concentration in the vehicle or delivery system *(C)* divided by the thickness of the skin *(h)* in cm.

$$J = \frac{DKC}{h} \qquad (1.1)$$

Equation 1.2 illustrates that when the permeation process attains a steady-state, the flux can be calculated from (Kurihara-Mergstrom and Good, 1987:53)

$$J_S = \frac{V_r}{A} \cdot \frac{dc}{dt} \qquad (1.2)$$

where

J_s = steady state flux and also the slope of plots of the amount penetrated versus time ($\mu g.cm^{-2}.h^{-1}$)

V_r = the receiver volume (ml)

A = the diffusional area (cm^2)

dc/dt = The steady-state rate of change in concentration in the receiver compartment ($\mu g.ml^{-1}.h^{-1}$)

According to Barry (1988:390) the diffusion coefficient of a drug in the TTS or skin is dependent on the properties of the drug and the medium through which it is diffusing. One drug property which is well documented as having a major influence on the diffusion coefficient is that of the molecular mass. Other important parameters which have been documented are the drug state, e.g. ionised or non-ionised, with non-ionised forms diffusing more freely than ionised forms.

1.2.4.3.9 Log P (octanol/water partition coefficient)

The lipid/water partition coefficient denotes the ratio of the concentrations of drug in two (practically) immiscible phases (Ritschel, 1988:41). The lipid/water partition coefficient of the drug is the basic determinant for specific drug permeability through the stratum corneum. Substances which are either highly insoluble in water and/or have very low lipid solubility will have low rates of diffusion through the stratum corneum. For the skin the maximum partition coefficient at which maximum flux occurs is approximately 1000/1 in η-octanol/water, where η-octanol presents the oil phase (Parikh *et al.*, 1984:291). A drug with a log P value of < 2 is considered to be a potential candidate for transdermal delivery (Guy and Hadgraft, 1989:70-71). According to Guy (1996:1766) compounds with a log P value between 1 and 3, with relatively low molecular weights and modest melting points, are likely to have decent passive skin permeablities.

1.3 ANTI-EMETICS AND ANTI-NAUSEANTS

1.3.1 The cause and treatment of nausea

Various mechanisms, both peripheral and central, may play a role in the emergence of nausea and vomiting. The vomiting center in the hypothalamus receives impulses from the chemo-effector trigger zone (CETZ), from cortical centers such as emotional, visual and olfactory areas, and from peripheral sources, including the inner ear and gastro-intestinal tract. The CETZ can be stimulated by chemicals, toxins, pyrogens and other endogenous substances, as well as medicines e.g. digoxin, cisplatin, morphine, ipacacuanha, etc.

Dopaminergic mechanisms predominate at the CETZ, while mainly muscarinic mechanisms operate at the vomiting center (Gibbon and Swanepoel, 1991:38).

The choice of the most appropriate therapy for nausea and vomiting depends on the cause. Drugs are not required for every case, and a proper assessment is always necessary.

Atropine, hyoscine and **certain antihistamines** have prominent antimuscarinic activity and act on the vomiting center.

Hyoscine (Scopolamine) is most effective in preventing and treating motion sickness, but it has considerable potential for causing adverse effects. Due to the transdermal slow-release formulation the adverse effects has been reduced, making it a more acceptable and effective agent for motion sickness.

Antihistamines (such as promethazine) may be useful in motion sickness. In labyrinthine disorders, cyclizine or cinnarizine is widely used.

Domperidone is a dopamine blocker selective for the CETZ. Less selective dopamine blockers are metoclopramide, promethazine and neuroleptics such as prochlorperazine.

Metoclopramide is indicated in nausea and vomiting associated with the post-operative period, infections, drugs, toxins (including post-operative cancer chemotherapy), uraemia and radiation sickness. It is ineffective in Meniere's disease, motion sickness, or vertigo, nausea and vomiting from other labyrinthine disturbances.

Prochlorperazine, a phenothiazine derivative of the piperazine type, is a neuroleptic with anticholinergic activity and a relatively low potential to cause sedation.

Glucocorticosteroids are of value, in combination with anti-emetics, in controlling nausea and vomiting provoked by chemotherapeutic agents. Dexamethasone or methylprednisolone are best documented. High doses are advocated, e.g. dexamethasone 10 - 20 mg, administered IV or orally for up to 72 hours. Equivalent doses of methylprednisolone are 50 - 100 mg.

Benzodiazepines, lorazepam in particular, may be useful adjuncts in the control of nausea and vomiting induced by chemotherapeutic agents.

$5HT_3$ (serotonin) antagonists (e.g. ondansetron, granisetron, tropisetron) are recently introduced agents which have been found useful in the management of chemotherapy- and radiotherapy-induced emesis. There is no proven superior efficacy of these agents over the steroid-anti-emetic-benzodiazepine combination (Gibbon and Swanepoel, 1991:38). Frequently used anti-emetics that are shown in table 1.2.

***TABLE 1.2:** Anti-emetics and anti-nauseants.*

Generic name	Proprietary name	Chemical group	Indications	Dosage form	Contra-indications	Adverse effects
Betahistine	Serc®	Histamine analogue	*Meniere's disease *Vascular headache	Tablets		Headache.
Buclizine	Longifene® Vomifene®	Piperazine Histamine H_1-Receptor Antagonist	*Hay fever *Nausea & vomiting *Food & drug allergy	Tablets Syrup	Use with caution in glaucoma and prostate hypertrophy	Sedation, CNS effects, Hypotension, Allergic reaction, GI disturbance.
Cinnarizine	Stugeron®	Piperazine Histamine H_1-Receptor Antagonist	*Vertigo *Meniere's disease	Tablets Capsules	Use with caution in glaucoma and prostate hypertrophy	Sedation, GI disturbance, Allergic skin reaction, CNS effects, Blurred vision.
Cyclizine	Valoid®	Piperazine Histamine H_1-Receptor Antagonist	*Motion sickness *Vertigo *Nausea & vomiting caused by labyrinthine disorders	Tablets Syrup Supp. Injections	Use with caution in glaucoma and prostate hypertrophy	CNS depression or stimulation, cardiovascular effects, hematological disturbances.

TABLE 1.2: (continue).

Generic name	Proprietary name	Chemical group	Indications	Dosage form	Contra-indications	Adverse effects
Difenidol	Vontrol®		*Nausea & vomiting *Vertigo	Tablets Supp.		Drowsiness, Depression, Skin rash, Malaise, Headache, Heartburn.
Dimenhy-drinate	Dramamine®	Ethanolamine Histamine H_1-Receptor Antagonist	*Motion sickness *Vertigo *Meniere's disease *Nausea & vomiting	Tablets Liquid	Liver dysfunction	Drowsiness, CNS effects, Hypotension, GI disturbances, Dry mouth.
Doxylamine	Somnil® Asic®	Ethanolamine Histamine H_1-Receptor Antagonist	*Motion sickness *Vertigo *Nausea & vomiting caused by labyrinthine disorders	Tablets	Use with caution in glaucoma and prostate hypertrophy	CNS depression or stimulation, cardiovascular effects, hematological disturbances.
Phosphora-ted carbo-hydrate	Emetrol® Emex®		*Nausea & vomiting *Morning sickness	Solution Syrup	Liver disfunction, Diabetics, Renal failure	
Prochlor-perazine	Stemetil® Mitil® Scripto-metic®	Phenothiazine	*Vomiting *Vertigo associated with Meniere's disease *Migraine	Tablets Syrup Supp Injections	Tachycardia, Liver disfunction.	Acute dystonic reaction.

TABLE 1.2: (continue).

Generic name	Proprietary name	Chemical group	Indications	Dosage form	Contra-indications	Adverse effects
Prometha-zine	Phenergan® Avomine® Betametha-zine®	Phenothiazine Histamine H_1-Receptor Antagonist	*Motion sickness *Vertigo *Nausea and vomiting *Allergic conditions	Tablets Elixir Injection	Epilepsy, Cardiac disease, hepatic dis-orders, asthma, narrow angle glaucoma or prostate hypertrophy	CNS effects, drowsiness, dizziness, fatigue.
Scopola-mine	Scopoderm TTS®	Tertiery Anti-muscrainic	*Motion sickness *Nausea	TTS	Glaucoma.	Dry mouth, Drowsiness, Hypotension, Blurred vision.

* Table 1.2 was composed from Gibbon and Swanepoel (1991:38-41).

1.3.2 The use of anti-emetic drugs against morning sickness

1.3.2.1 Morning sickness during pregnancy

"Morning sickness" commonly occurs during early pregnancy. It has been estimated that about 50 % of expectant mothers may experience it during the first 3 months of gestation. Symptoms reach a peak during week 10 to 11 and usually subside by week 14. Typically, the condition consist of early morning nausea and retching rather than vomiting, but up to 2 % of pregnant women may experience protracted vomiting (hyperemesis gravidarum) leading to electrolyte imbalance, weight loss, coma and convulsions. The basis of this condition is not known, but has been variously considered to involve psychosomatic, endocrine, allergic and metabolic aspects (Mitchelson, 1992:444).

Zhang and Cai (1991:454-457) stated that women with chronic liver disease had a threefold increased risk of severe vomiting during pregnancy. Paternal smoking was associated with a twofold increased risk of maternal vomiting. Their study indicates

that passive smoking is a risk factor for vomiting during pregnancy, which may, in turn, increase the risk of fetal growth retardation.

Endocrine studies show that vomiting and hyperemesis gravidarum may be associated with elevated serum levels of human chorionic gonadotrophin (HCG) occurring in the first few weeks of pregnancy. Levels declined back to control levels by week 15 to 20. Studies of urinary HCG levels have yielded conflicting results. Serum levels of corticotrophin (ACTH), cortisol, follicle-stimulating hormone (FSH), human growth hormone and thyrotrophin are similar in vomiting and non-vomiting women.

Hyperemesis gravidarum has no effect on birth-weight and may be associated with a reduced risk of spontaneous abortion or premature labour. However, a slightly increased risk of congenital abnormalities may be associated with vomiting in pregnancy whether or not anti-emetic therapy is administered (Mitchelson, 1992:445).

1.3.2.2 Pharmacology of anti-emetic drugs suitable for use during pregnancy

Therapy of morning sickness and hyperemesis gravidarum is aimed at minimising risks to the developing fetus. Dietary modification may be sufficient, since many patients obtain relief of symptoms by taking small, frequent carbohydrate meals and by avoiding smelly or fatty foods. Both dry meals and plenty of liquids have been advocated. A phosphorated carbohydrate solution (Emetrol®) consisting of fructose, dextrose and ortophosphoric acid was beneficial in the treatment of morning sickness. The mode of action is unknown, but it has been shown that phosphoric acid and sugars slow the rate of gastric emptying (Mitchelson, 1992:445).

Histamine H_1-receptor antagonists and dopamine receptor antagonists may be effective drugs in the treatment of morning sickness, because circulating gonadotrophins sensitize vomiting pathways involving dopamine and histamine H_1 receptors (Mitchelson, 1992:445). There are a few anti-emetic drugs that are safe to use during pregnancy (shown in table 1.3), however none of them are available as TTS.

TABLE 1.3: *Recommended anti-emetic treatment of vomiting associated with morning sickness and hyperemesis gravidarum.*

Chemical Group	Drug
Antimuscarinic	Dicyclomine
Histamine H_1-receptor antagonists	
Ethanolamines	Doxylamine
Phenothiazines	Promethazine
Piperazines	Cyclizine
	Meclizine
Phenothiazine neuroleptic (aliphatic)	Chlorpromazine
	Prochlorperazine
Vitamins	Pyridoxine

To decide on an appropriate anti-emetic drug(s) for use during pregnancy, a few aspects must be taken into account, e.g. safety of the neonate after exposure to the drug and some physicochemical properties of the drug.

1.3.2.2.1 Dicyclomine Hydrochloride (Asic®)

The combination of doxylamine, pyridoxine, and dicyclomine (Bendectin®) was originally marketed in 1956. The drug was reformulated in 1976 (United States and Canada) to eliminate dicyclomine because it was found that it did not contribute to its effectiveness as an anti-emetic. Over 33 million women have taken this product during pregnancy, making it one of the most heavily prescribed drugs for this condition. The manufacturer ceased producing the drug combination in 1983 because of litigation over its alleged association with congenital limb defects. Although no longer available as a fixed combination, the individual components are still marketed by various manufacturers (Briggs *et al.*, 1986:156).

Absorption and Fate: Tertiary amines are rapidly absorbed from the gastro-intestinal tract and also enter the circulation through the mucosal surfaces of the body. Exact distribution of anticholinergics has not been fully determined. However tertiary amines appear to be distributed throughout the entire body and readily crosses the blood-brain

barrier (USP DI, 1994:213). The plasma half-life ($t_{½}$) is approximately 5 hours (Moffat., 1986:536).

Adverse effects: Side effects include dryness of mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, dilatation of the pupils (mydriasis), flushing and dryness of the skin, transient bradycardia followed by tachycardia, with palpitations. Occasionally vomiting, confusion, giddiness and staggering may occur (Reynolds, 1993:419).

1.3.2.2.2 Doxylamine Succinate (Asic®)

Doxylamine succinate is an ethanolamine derivative. It is given by mouth for the symptomatic relief of hypersensitivity reactions and pruritic skin disorders (Reynolds, 1993:938).

Absorption and Fate: Well absorbed after oral or parenteral administration. Hepatic biotransformation occurs (USP DI, 1994:299).

The therapeutic plasma concentrations for doxylamine succinate is 5 - 300 $ng.ml^{-1}$ (Baselt, 1980:231). LD_{50} in mice and rabbits ($mg.kg^{-1}$) are: 470 and 250 orally; 62 and 49 i.v.; in mice, male rats and female rats ($mg.kg^{-1}$) are: 460, 440 and 445 s.c. (Budavari, 1989:541). The elimination half-life ($t_{½z}$) is 10,1 hours (Freedman and Greenblatt, 1985:450).

Adverse effects: Most antihistamines vary in incidence and severity with each patient as much as with each drug, though some of the drugs give rise to more side effects than others. Many antihistamines have CNS-depressant activity, the most common side effect of the traditional antihistamines is sedation. Paradoxal CNS stimulation may occur especially in children, with insomnia, nervousness, euphoria, irritability, tremors and rarely nightmares. Systemic or topical therapy with antihistamines may produce hypersensitivity reactions, particularly of the skin, and cross-sensitivity to related drugs may occur (Reynolds, 1993:926).

1.3.2.2.3 Promethazine Theoclate (Avomine®)

Promethazine is a phenothiazine antihistamine that is sometimes used as an anti-emetic in pregnancy and as an adjunct to narcotic analgesics during labour.

Absorption and Fate: Promethazine is well absorbed after oral or intramuscular administration. Peak plasma concentrations have been observed 2 to 3 hours after administration by these routes, although there is low systemic bioavailability after oral administration due to high first-pass metabolism in the liver. Promethazine is widely distributed, it enters the brain and crosses the placenta. Values ranging from 76 to 93 % have been reported for plasmaprotein binding. Promethazine undergoes extensive metabolism, predominantly to promethazine sulphoxide, and also to N-desmethylpromethazine. It is excreted slowly via the urine and bile chiefly as metabolites. Elimination half-lives of 5 to 14 hours have been reported (Reynolds, 1993:944). According to Taylor *et al.*, (1983:288) the distribution half-life ($t_{½\alpha}$) of promethazine is 1,4 h and the elimination half-life ($t_{½z}$) is 12,2 hours. The volume of distribution (V_d) is 13 *l*/kg and the plasma clearance (*Cl*) is 16 $ml.min^{-1}.kg^{-1}$ (Moffat, 1986:933). The log P (oct/pH7.4) of promethazine theoclate is 2,9 (Lund, 1994:1023).

Adverse effects: Cardiovascular side effects are commonly seen after injection, and bradycardia, tachycardia, transient minor increases in blood pressure and occasional hypotension have been reported with promethazine hydrochloride. Jaundice and blood dyscrasias have been reported, and extrapyramidal effects may occur at high doses. Venous thrombosis has been reported at the site of intravenous injections, and arteriospasm and gangrene may follow inadvert intra-arterial injection (Reynolds, 1993:944).

Also see adverse effects of doxylamine succinate

1.3.2.2.4 Cyclizine Hydrochloride

Cyclizine is a piperazine antihistamine which is used as an anti-emetic. The drug is teratogenic in animals but apparently not in humans (Briggs *et al.*, 1986:111).

Adverse effects: See adverse effects of doxylamine succinate (Histamine H_1-antagonist).

Absorption and fate: The plasma half-life ($t_{½}$) is 24 hours (Moffat, 1986:298).

1.3.2.2.5 Meclizine Hydrochloride

Meclizine/Meclozine is a piperazine antihistamine which is frequently used as an anti-emetic. Since late 1962, the question of the effect of meclizine on the fetus has been argued in numerous situations (Briggs *et al.*, 1986:261/m).

Absorption and Fate: Both meclizine base and meclizine hydrochloride have been administered by the rectal route, doses are similar to those given by mouth (Reynolds, 1993:941). The half-life of meclizine is 6 hours (USP DI, 1994:1825).

Adverse effects: See adverse effects of doxylamine succinate (Histamine H_1-antagonist).

1.3.2.2.6 Chlorpromazine (Largactil®).

Chlorpromazine is a propylamino phenothiazine. The drug readily crosses the placenta. Chlorpromazine has been used for the treatment of nausea and vomiting of pregnancy during all stages of gestation, including labour, since the mid-1950's. The drug seems to be safe and effective for this indication (Briggs *et al.*, 1986:85).

Absorption and Fate: Chlorpromazine is readily, although sometimes erratically, absorbed from the gastro-intestinal tract but is subject to considerable first-pass metabolism in the gut wall. It is also extensively metabolised in the liver and is excreted in the urine and bile in the form of numerous active and inactive metabolites; there is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations following oral administration are much lower than those following intramuscular administration. Moreover, there is very wide intersubject variation in plasma concentrations; no simple correlation has been found between plasma concentrations of chlorpromazine and its metabolites, and their therapeutic effect. This phenothiazine has a large volume of distribution and a high metabolic clearance

resulting in low blood concentrations particularly when the oral route is used (Reynolds, 1993:578-579). The plasma half-life has been reported to be about 30 hours, and there is limited evidence that chlorpromazine induces its own metabolism. The elimination half-life ($t_{½z}$) is 10,9 ± 6,1 hours (Yeung *et al.*, 1987:807), and the distribution half life ($t_{½\alpha}$) is 0,11 ± 0,17 hours (Nawaz, 1979:126-136). The effective concentration is 30 - 350 $ng.ml^{-1}$ and the toxic dose is 750 - 1000 $ng.ml^{-1}$ (Reynolds, 1993:1669). The minimum effective concentration is 50 - 300 $ng.ml^{-1}$ (Ritschel, 1992:356). The log P (oct/pH7.4) of chlorpromazine is 3,4 (Lund, 1994:800). Chlorpromazine is very extensively bound (about 95 to 98 %) to plasma proteins. It is widely distributed in the body and crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma. Chlorpromazine and its metabolites also cross the placental barrier and are excreted in milk (Reynolds, 1993:578-579).

1.3.2.2.7 Prochlorperazine (Stemetil®)

Prochlorperazine is a piperazine phenothiazine. The drug readily crosses the placenta. Prochlorperazine has been used to treat nausea and vomiting of pregnancy. Most studies have found the drug to be safe for this indication (Briggs *et al.*, 1986:372).

1.3.2.2.7.1 Prochlorperazine Maleate and Mesylate

Absorption and Fate: Prochlorperazine is readily, although sometimes erratically absorbed from the gastro-intestinal tract but is subject to considerable first-pass metabolism (Reynolds, 1993:578). The LD_{50} in mice ($mg.kg^{-1}$) is: 400 s.c.; 120 i.p.; 90 i.v. and 400 orally (Budavari, 1989:1231). The distribution half-life ($t_{½\alpha}$) is 20,9 ± 5,3 min, and the elimination half-life ($t_{½z}$) is 21,9 ± 5,3 hours (Shidhar *et al.*, 1993:423-430). According to Isah *et al.* (1991:677) the half-life at the end of 14 days was 18 ± 4 hours, due to accumulation of prochlorperazine and its metabolite following repeated dosing. The log P (oct/pH7) of prochlorperazine mesylate is 2,4 (Lund, 1994:1020).

Also see absorption and fate of chlorpromazine.

Adverse effects: Sever dystonic reactions have followed the use of prochlorperazine, particularly in children and adolescents. Transient numbness of the gum and tongue has

occurred after the use of buccal tablets of prochlorperazine maleate (Reynolds, 1993:612).

Note: Avoid skin contact with liquid forms of this medication, contact dermatitis has resulted (USP DI, 1994:2230).

1.3.2.2.8 Pyridoxine Hydrochloride (Vomifene®)

Pyridoxine (vitamin B6), a water-soluble B complex vitamin, acts as an essential co-enzyme involved in the metabolism of amino acids, carbohydrates and lipids. The first use of pyridoxine for severe nausea and vomiting of pregnancy was reported in 1942. Individual injections ranged from 10 to 100 mg with total doses up to 1500 mg being given (Briggs *et al.*, 1986:390). Pyridoxine has not been proven effective for treatment of morning sickness (USP DI, 1994:2364).

Absorption and Fate: Pyridoxine, pyridoxal and pyridoxamine are readily absorbed from the gastro-intestinal tracts following oral administration and are converted to the active forms pyridoxal phosphate and pyridoxamine phosphate. Pyridoxal crosses the placenta and also appears in breast milk (Reynolds, 1993:1055). The plasma half-life has been reported to be 15 - 20 days (USP DI, 1994:2365).

Adverse effects: Long-term administration of large doses of pyridoxine is associated with the development of severe peripheral neuropathies, it has been stated that this may occur with doses in excess of about 2 g daily. Many drugs may alter either the metabolism or bioavailability of pyridoxine, such agents include isoniazid, penicillamine and oral contraceptives (Reynolds, 1993:1054).

Safety of the neonate after exposure to the drug: A minimal relationship was found between congenital heart disease and Bendectin® (a preparation which contained doxylamine, dicyclomine and pyridoxine) use in early pregnancy (Briggs *et al.*, 1986:157). A prospective study found no increased incidence of either severe congenital abnormalities or perinatal mortality rates in women who had been prescribed Bendectin®, prochlorperazine, meclizine or cyclizine (Reynolds, 1993:927). A study by Pastuszak (1995:42) concluded that the combination of doxylamine

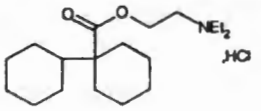
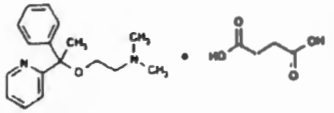
succinate/pyridoxine hydrochloride should be the drug of choice for treatment of nausea and vomiting during pregnancy. Walters (1987:291) also found a lack of evidence for teratogenicity associated with doxylamine succinate. The Collaborative Perinatal Project could not find evidence to suggest a relationship to large categories of major or minor malformations or to individual defects after promethazine, meclizine or prochlorperazine exposure in the 1st trimester (Briggs *et al.*, 1986:261, 372). Pyridoxine is considered save for use during pregnancy, but its efficacy in treating nausea and vomiting is not determined. No risks of congenital limb defects was found to be associated with the use of dicyclomine hydrochloride (McCredie *et al.*, 1984:526). Meclizine is the anti-emetic that present the lowest risk of teratogenicity (Leathem, 1986:667).

Phenothiazines, such as chlorpromazine, promethazine and prochlorperazine should be reserved for treating persistent vomiting that threatens the matermal nutritional status (Leathem, 1986:667). Phenothiazine drug therapy is not recommended for nausea in the 1st trimester of pregnancy, but on rare occasions a phenothiazine e.g. chlorpromazine, may be indicated for the short-term management of severe vomiting. Intoxication and withdrawal symptoms may occur in neonates exposed to high doses of anti-psychotics towards the end of pregnancy; sedation, hypotonia, extrapyramidal symptoms, and cholestatic jaundice have been reported (Reynolds, 1993:576). Most reports describing the use of chlorpromazine in pregnancy have concluded that it does not adversely affect the fetus or newborn (Briggs *et al.*, 1986:85). In a study by Rafla (1987:1557) two cases of congenital limb abnormalities were reported that may have resulted from maternal use of prochlorperazine maleate as therapy for hyperemesis gravidarum in the first twelve weeks of pregnancy.

1.3.2.3 Physicochemical characteristics of anti-emetic drugs suitable for use during pregnancy

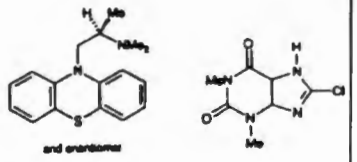
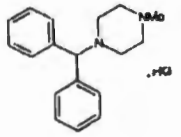
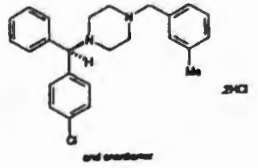
There are various anti-emetic drugs that are suitable for use during pregnancy, all of these drugs are administered orally. In order to eliminate the drugs that don't meet the criteria for transdermal delivery, one must compare the physicochemical properties of these drugs. Table 1.4 contain some of the essential physicochemical properties of orally administered anti-emetic drugs.

TABLE 1.4: Characteristics of drugs suitable for use against morning sickness during pregnancy.

DRUG	CHEMICAL STRUCTURE & FORMULA	MOLECULAR MASS	SOLUBILITY	MELTING POINT	DOSE	pKa
DICYCLOMINE HYDROCHLORIDE	 $C_{19}H_{35}NO_2 . HCl$ [1]	345.96 [1]	1 in 13 parts of water 1 in 5 parts of alcohol 1 in 2 parts of chloroform practically insoluble in ether [2]	169°C to 174°C [1]	10 to 20 mg three to four times a day, up to 169 mg daily [3]	9.0 [4]
DOXYLAMINE SUCCINATE	 $C_{17}H_{22}N_2O . C_4H_6O_4$ [5]	388.47 [5]	1 in 1 part of water 1 in 2 parts of alcohol 1 in 2 parts of chloroform 1 in 370 parts of ether [5]	103°C to 108°C [5]	12,5 to 25 mg every four to six hours, up to 150 mg daily [6]	4.4 [7] 9.2 [7]

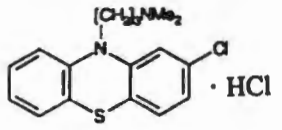
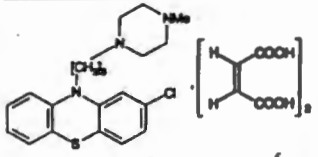
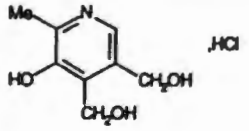
1. USP, (1995:499) 2. Reynolds, (1995:499) 3. USP DI, (1994:219) 4. USP DI, (1994:212) 5. USP, (1995:559)
6. USP DI, (1994:312) 7. Moffat, (1986:576)

TABLE 1.4 (continue)

PROMETHAZINE THEOCLATE	 $C_{17}H_{20}N_2S$. $C_7H_7ClN_4O$ [1]	499.0 [1]	very slightly soluble in water 1 in 70 parts of alcohol 1 in 2,5 parts of chloroform practically insoluble in ether [2]	222°C with decomposition [3]	25 mg every four to six hours, although more than 100 mg in 24 hours is not often necessary [4]	9.1 [5]
CYCLIZINE HYDROCHLORIDE	 $C_{18}H_{22}N_2$.HCl [6]	302.85 [7]	1 in 115 parts of water and alcohol 1 in 75 parts of chloroform practically insoluble in ether [8]	about 285°C with decomposition	50 mg three times daily, although up to 200 mg may be given in 24 hours [8]	7.7 [9]
MECLIZINE HYDROCHLORIDE	 $C_{25}H_{27}ClN_2$. 2HCl [10]	463.88 [10]	practically insoluble in water and ether slightly soluble in chloroform slightly soluble in diluted acids and alcohol [11]	224°C [12]	25 to 50 mg daily [13]	3.1 [14] 6.2 [14]

1. (BP, (1995:553)
2. Reynolds, (1993:943)
3. Reynolds, (1993:944)
4. USP DI, (1993:345)
5. BP, (1995:552)
6. BP, (1995:191)
7. USP, (1995:437)
8. Reynolds, (1993:935)
9. USP DI, (1994:1066)
10. BP, (1995:415)
11. Reynolds, (1993:941)
12. Elks and Ganelli, (1990:759)
13. USP DI, (1995:353)
14. Williams, (1995:954)

TABLE 1. 4 (contime)

CHLORPROMAZINE HYDROCHLORIDE	 $C_{17}H_{19}ClN_2S$. HCl[1]	355.33 [1]	very soluble in water 1 in 1 part of alcohol 1 in 1,5 parts of alcohol and chloroform practically insoluble in ether[2]	195 to 198°C [1]	10 to 25 mg every four hours, up to 1g a day [3]	9.3 [4]
PROCHLORPERAZINE MALEATE	 $C_{20}H_{24}ClN_3S$. $2C_4H_4O$ [5]	606.2 [6]	practically insoluble in water 1 in 1200 parts of alcohol slightly soluble in warm chloroform [7]	about 200°C [8]	5 to 10 mg three to four times a day, up to 40 mg a day [9]	3.7 [10] 8.1 [10]
PROCHLORPERAZINE MESYLATE	$C_{20}H_{24}ClN_3S$. $2CH_4SO_3$ [11]	556.2 [11]	1 in less than 0,5 parts of water 1 in 40 parts of alcohol slightly soluble in chloroform practically insoluble in ether[7]	about 242°C [8]	5 to 10 mg three to four times a day, up to 40 mg a day [9]	3.7 [10] 8.1 [10]
PYRIDOXINE HYDROCHLORIDE	 $C_8H_{11}NO_3$. HCl [12]	295.6 [12]	1 in 5 parts of water 1 in 100 to 115 parts of alcohol practically insoluble in chloroform and ether [13]	about 205°C with decomposition [12]	Initial: 30 to 600 mg daily. Maintenance: 10 to 20 mg daily for three weeks, followed by 2 to 5 mg per day for several weeks [14]	8.96 [15] 5 [15]

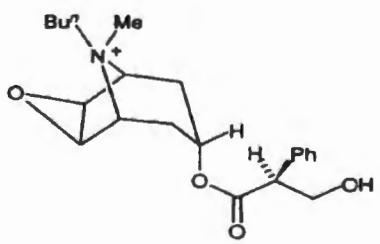
1. USP, (1995:354) 2. Reynolds, (1993:573) 3. USP DI, (1994:2221) 4. Williams, (1995:950) 5. USP, (1995:1304) 6. BP, (1995:546)
7. Reynolds, (1993:612) 8. Lund, (1994:1020) 9. USP DI, (1994:2230) 10. Williams, (1995:546) 11. BP, (1995:546) 12. BP, (1995:565)
13. Reynolds, (1993:1054) 14. USP DI, (1994:2364) 15. Williams, (1995:957)

1.3.3 Anti-emetic drugs available as TTS

Scopoderm TTS® is the only anti-emetic TTS currently available in South Africa.

Hyoscine (scopolamine) is a competitive inhibitor of the muscarinic receptor of acethylcholine and it has been shown to be one of the most effective agents for preventing motion sickness. However, a relatively high incidence of side effects and a short duration of action has restricted the usefulness of this agent when administered orally or parenterally, to counter this, a novel transdermal preparation of hyoscine has been developed. Pharmacokinetic studies indicate that this new method for administering hyoscine controls the absorption process and the rate of drug entry into the systemic circulation over an extended period (72 hours), providing a means of delivery which is similar to a slow intravenous infusion. However, recent evidence suggest that the response to transdermal hyoscine treatment is variable and this may reflect pharmacokinetic differences between individuals. Controlled therapeutic trials have indicated that a single transdermal hyoscine patch is significantly superior to placebo and oral meclozine (meclizine) in preventing motion sickness. Trials comparing transdermal hyoscine with oral dimenhydrinate have failed to establish any significant differences in efficacy between the 2 drugs in small numbers of subjects, although there was always a more favorable trend towards the transdermal system. In patients with acute vertigo, transdermal hyoscine and oral meclizine were equally efficacious and both were significantly better than placebo in reducing the number of attacks of vertigo (Clissold and Heel, 1985:190).

Scopolamine / Hyoscine



$C_{17}H_{21}NO_4$

Dose: Hyoscine hydrobromide 300 μg may be taken by mouth 30 minutes before a journey to prevent motion sickness; followed by 300 μg every 6 hours if required up to a maximum of 3 doses in 24 hours.

Hyoscine is also given to prevent motion sickness via a transdermal delivery system which is placed behind the ear and supplies 500 μg over 3 days (Reynolds, 1993:426).

Molecular mass: 303,4 (Reynolds, 1993:245).

***Solubility*:** Scopolamine butylbromide - Soluble 1 in 1 of water, 1 in 50 of alcohol, and 1 in 5 of chloroform.

Scopolamine hydrobromide - Freely soluble in water, soluble in alcohol, slightly soluble in chloroform, insoluble in ether (USP DI, 1994:361).

***Absorption and Fate*:** Hyoscine is readily absorbed from the gastro-intestinal tract following oral doses of hydrobromide. It is almost entirely metabolised, probably in the liver. Only a small proportion of an oral dose has been reported to be excreted unchanged in the urine. It crosses the blood-brain barrier and has been stated to cross the placenta. Hyoscine is also well absorbed following application to the skin. The elimination half-life ($t_{½z}$) of scopolamine is 4,5 ± 1,7 hours. (Putcha *et al.*, 1989:483), the effective concentration is 40 $pg.ml^{-1}$ (Reynolds, 1993:1706). The good transdermal absorption of N-methyl scopolamine can be explained by the formation of an ion pair by the skin allowing penetration through the lipid bilayers of the stratum corneum (Vollmer, *et al.*, 1993:245).

***Adverse effects*:** Side-effects of hyoscine and other antimuscarinic agents include dryness of the mouth with difficulty in swallowing and talking, thirst, reduced bronchial secretions, flushing and dryness of the skin. Central stimulation sometimes proceeds depression, especially after large doses of hyoscine or in severe pain, but the main central symptom is drowsiness leading to coma. Caution has been advised in elderly patients and in patients with impaired metabolic, liver or kidney function, as adverse CNS effects such as disorientation, delirium, or somnolence, have been stated to be more likely in these patients. There have been rare reports of an increase in frequency of seizures in epileptic patients (Reynolds, 1993:419-426).

Although transdermal hyoscine has been associated with a lower incidence of side effects than orally or parenterally administered hyoscine hydrobromide, adverse systemic effects have still been frequently reported. Most commonly cited have been dry mouth, drowsiness and impairment of ocular accommodation, including blurred vision and mydriasis (some ocular effects reported may be due to finger-to-eye contamination). Adverse central nervous system (CNS) effects, difficulty in urinating, rashes and erythema have been reported only occasionally. Thus, preliminary evidence suggests transdermal hyoscine may offer an effective and conveniently administered alternative for the prevention of motion-induced nausea and vomiting in certain situations. However, the duration of its clinical effectiveness, and its relative efficacy and tolerability compared with other agents needs to be confirmed in a few additional well-designed studies (Clissold and Heel, 1985:190).

1.4 ANTI-EMETIC DRUGS THAT ARE SUITABLE FOR TRANSDERMAL DELIVERY DURING PREGNANCY

Drugs formulated in transdermal delivery systems typically have the following combination of physicochemical characteristics (Pfister and Hsieh, 1990:132):

- molecular weight < 400 Da, Cairncross (1993:53) states that an optimal drug diffusion rate is documented for molecular masses of 800 to 1000.
- daily dosage < 20 mg, according to Cleary (1993:20) the maximum amount of drug that can be delivered may be as high as 50 mg per day.
- low melting point and
- low polarity.

In principle, however, more than 90 % of existing drugs do not have this combination of characteristics and therefore cannot be directly formulated into transdermal delivery systems without some degree of formulation enhancement (Pfister and Hsieh, 1990:132).

1.4.1 Safe drugs that are suitable for transdermal delivery

Taking into account the properties that is necessary for drugs to be suitable for transdermal absorption, e.g. low melting point (Pfister and Hsieh, 1990:132), daily dosage of less than 50 mg (Cleary, 1993:20), a molecular mass of less than 1000 (Parikh *et al.*, 1984:291) and minimum skin sensitisation or irritation potential (Guy and Hadgraft, 1989:61), it became apparent that the following anti-emetic drugs could be suitable for transdermal delivery:

1. Chlorpromazine hydrochloride
2. Doxylamine succinate

The majority of drugs are precluded from consideration for transdermal application because of their limited ability to penetrate the skin at a sufficient rate. For such compounds, methods to enhance penetration must be considered. Alteration of the barrier properties of the stratum corneum can be achieved through the use of chemical penetration enhancers, providing an additional driving force for transport, or by chemically modifying the drug itself through prodrug formation.

1.4.2 Penetration enhancers

Three pathways are suggested for drug penetration through the skin: polar, nonpolar, and polar/nonpolar. The enhancers act by altering one of these pathways. The key to altering the polar pathway is to cause protein conformational changes or solvent swelling. The key to altering the nonpolar pathway is to alter the rigidity of the lipid structure and fluidise the crystalline pathway (this substantially increases diffusion). The fatty acid enhancers (binary vehicles) act on both polar and nonpolar pathways by altering the multilaminate pathway for penetrants. The extent of skin permeability enhancement seems to depend on the alkyl chain length of the fatty acid. Maximum enhancement can be achieved with the fatty acid containing six units of CH_2 groups (Chien, 1987:70). Enhancers can increase the drug diffusivity in the stratum corneum (SC) by dissolving the skin lipids or by denaturing skin proteins. The methods employed for modifying the barrier properties of the SC to enhance drug penetration (and absorption) through the skin can be categorized as (1) chemical and (2) physical methods of enhancement (Shah, 1994:20).

1.4.2.1 Chemical enhancers

The chemical enhancers act by increasing drug permeability through the skin by causing reversible damage to the SC, or by increasing (and optimising) thermodynamic activity of the drug when functioning as a cosolvent. Increasement of the partition coefficient of the drug to promote its release from the vehicle into the skin is another mechanism of action. The chemical enhancers can also operate by controlling the SC to promote drug diffusion, promote penetration and establish a drug reservoir in the SC (Shah, 1994:20-21).

Enhancers are classified as polar or nonpolar according to their solubility parameters. The Hildebrand solubility parameter measures the cohesive forces and sum of all the intermolecular attractive forces related to the extent of mutual solubility of many chemical species (Pfister and Hsieh, 1990:134).

Relative hydrophilicity increases with the value of the Hildebrand solubility parameter. Enhancers with solubility parameters <12 will intervene with the lipid component of the skin, but those with solubility parameters >12 will selectively partition into the polar components in the skin. Because the resistance barrier to drug transport is typically the SC, an effective enhancer must first partition into the SC, where it increases drug solubility or diffusivity (Pfister and Hsieh, 1990:134).

1.4.2.1.1 Penetration enhancers that could be used to improve transdermal absorption

A few of the chemical enhancers that could be used for permeation enhancement of the chosen anti-emetic drugs are discussed below. These enhancers show minimum irritation and toxicity.

1. Alcohol enhancers

The enhancement effect of short-chain alcohols appears to be related to their ability to swell, and perhaps extract SC lipids. Short-chain alcohols are very readily absorbed by the skin, thus, rather large amounts of alcohol are required to obtain a prolonged enhancement effect. The high delivery rate of short-chain alcohol enhancers often produces skin irritation. The use of short-chain alcohols in

combination with other compounds, for example, ethanol and glycerin, can minimise irritation (Baker and Santus, 1993:4).

Long-chain alcohols plasticise the skin. The amount of long-chain alcohol required to produce enhancement is much less than when ethanol is used. The long-chain alcohol mentioned most frequently is n-dodecanol.

The third group of alcohol-based enhancers are multifunctional alcohols. The most commonly mentioned members of this group are propylene glycol and glycerol. These two enhancers are frequently used to lower the irritation effect of other enhancers (Baker and Santus, 1993:4-6).

2. Amide enhancers

Dimethylacetamide was the first compound in this class of enhancers to be used. This amide, along with other aprotic solvents, has been shown to enhance skin permeation by interacting with the skin lipids. Unfortunately, dimethylacetamide, although a powerful enhancer is generally thought to be too irritating to be used as an enhancer. Amides with long aliphatic chains are preferred, either alone or in combination with other enhancers (Baker and Santus, 1993:7).

3. Amino acid enhancers

Amino acid and water soluble proteins can enhance the absorption of drugs. In particular, it is thought that N-alkyl-amino acid improves drug absorption by loosening the skin's keratin layer (Baker and Santus, 1993:8).

4. Azone & azone-like enhancers

Azone has a significant enhancement effect on a number of drugs. The meganism by which Azone and similar substances enhance skin permeation is still unknown. One hypothesis suggests that they use an ion-paring mechanism, whereas another postulates that Azone affects the fluidity of structured lipids in the skin's intercellular channels (Baker and Santus, 1993:9).

5. Essential oil enhancers

As percutaneous enhancers, they are believed to act by disrupting the ordered lipid structure of the stratum corneum and by increasing partitioning of the drug from its aqueous vehicle into the SC. Use of naturally occurring terpenes is reported to avoid the side-effects associated with the more traditional enhancers, such as DMSO and Azone. This category includes essential oils such as rosemary, spearmint, wintergreen and peppermint oil (Baker and Santus, 1993:11).

6. Fatty acid and fatty acid ester enhancers

Fatty acids are a distinct group of penetration enhancers with several favorable properties: they are relatively small molecules and also common components of human skin lipids (Lampe in Tanojo, 1996:110), including the stratum corneum (Lange *et al.* in Tanojo, 1996:90).

The most important of these enhancers are oleic acid, the methyl and ethyl esters of oleic and lauric acid and the isopropyl ester of myristic acid. Fatty acids, and particularly oleic acid, are often used alone or in combination with solvent enhancers such as alcohols and glycols (Baker and Santus, 1993:12).

The mode of action for the capacity of oleic acid as a skin penetration enhancer is still under in-depth investigation. It has been suggested that penetration enhancement can be achieved by increasing drug solubility in the vehicle by disrupting the intercellular lipid and/or intracellular proteins (Goodman in Tanojo, 1996:100) by fluidising of the skin lipid structure, or by forming separate domains which break up the continuity of the multilamellar structure and may hence induce highly permeable pathways in these domains (Tanojo, 1996:100). Mak *et al.* (1990:73) suggest that oleic acid increases the motional freedom (i.e. disordering) of the hydrocarbon region of the intercellular lipid domains of the stratum corneum. Results obtained by Naik *et al.* (1995:300) indicate that oleic acid primarily modulates the extracellular lipid domain of the stratum corneum. Permeation enhancers such as oleic acid which reduce the diffusional resistance of the skin by interacting with the lipid matrix, have been postulated to act by increasing lipid

fluidity, in a manner analogous to enhanced membrane permeability resulting from thermally induced stratum corneum lipid disordering.

Mak *et al.,* (1990:73) found that as the concentration of applied oleic acid was increased from 0,5 % to 1 %, there was also an increase in stratum corneum lipid disorder. However, further increase in concentration, from 1 % to 10 % did not cause additional disorder. They sought to determine whether the apparent saturation was limited by either (a) the fatty acid's ability to maximally perturb the lipid domains, or (b) the saturation solubility of oleic acid in the stratum corneum. They found that the lipid perturbing effect of oleic acid saturates when the stratum corneum concentration of the enhancer exceeds about 5 - 10 $\mu g.mg^{-1}$ of stratum corneum. It is possible that, when oleic acid is present at levels above this critical value, it forms a separate phase within the stratum corneum lipids, and as a result is no longer able to perturb the endogenous lipid domains. This hypothesis is currently under investigation. Regardless of the mechanism, however, the concentration dependence of oleic acid-induced lipid disorder and of penetration enhancement show similar saturation effects. *In vivo* results suggest that changes in stratum corneum lipid order, as measured by C-H stretching frequency shifts, are likely to be directly related to increased permeation of co-applied drugs. In conclusion, topical application of oleic acid induces human stratum corneum disorder *in vivo* (Mak *et al.,* 1990:74).

A study conducted by Tanojo (1996:119) demonstrates that minute amounts of oleic acid are capable of inducing changes in tissue morphology in the viable epidermis. The morphological changes in skin do not occur as long as the stratum corneum is properly functioning. A topical application of oleic acid can be considered harmless due to the fact that oleic acid does not readily penetrate across the stratum corneum into the viable epidermis. Therefore, an intact skin barrier should be considered of major importance for studies which aim at a reversibly alteration of stratum corneum resistance without interfering with the living epidermal cells, especially with regard to cutaneous irritancy (Tanojo, 1996:119). A toxicity study in mice showed that with an LD50 of 230 ± 18 $mg.kg^{-1}$ oleic acid is less toxic that any straight-chain fatty acid having 9 or more carbon atoms (Orö, 1961:150).

A test conducted by Tanojo (1996:152) showed no visible tissue damage to human skin upon exposure to oleic acid. When oleic acid was applied topically on the freshly excised human skin no alterations in epidermal tissue morphology were observed. No epidermal tissue damage was seen *in vivo* after topical application of oleic acid on healthy skin of living humans. This phenomena indicate a potential key role of the stratum corneum in the control of the tissue damage by oleic acid. On the other hand, the results also indicate that topically applied oleic acid does not permeate across the stratum corneum (Tanojo, 1996:152). These enhancers are not irritating to the skin, even when used in an occluded patch and after repeated application at the same skin site (Baker and Santus, 1993:13-14).

Oleic acid - 5 % (0,16 M) - slightly delays the onset of action, (t_0, lag-time) but does not change the maximum response time (t_{max}) (Tanojo, 1996:144).

7. Macrocyclic enhancers

Macrocyclic compounds are reported to enhance skin absorption by temporarily increasing the solubility of the drug in the skin. When the enhancer is removed, the skin returns to its normal state (Baker and Santus, 1993:14).

8. Phospholipids and phosphate enhancers

The intercellular lamellar sheets (lipid bilayer) of the stratum corneum are regarded as the practical barrier of the skin. One of the common polar lipids found in mammalian plasma membranes are phosphatidylcholine (Yokomizo and Sagitani, 1996:272).

Phospholipids are a kind of surfactant and it has been reported that several surfactants increase skin permeability (Yokomizo and Sagitani, 1996:268), by acting directly on the stratum corneum (Yokomizo and Sagitani, 1996:271). Firstly, phospholipids may exert a direct influence on the permeability characteristics of the stratum corneum. Secondly, phospholipid is incorporated into the viable cells via the stratum corneum and makes a lipophilic route for the permeability of drugs. Thirdly, exogenous phospholipid disorders the lamellar structure in the viable cells. Phospholipids have a high affinity to epidermal tissue and change the fluidity of cell

membranes and enhance the percutaneous penetration of drugs (Yokomizo and Sagitani, 1996:273).

According to Mahjour *et al.* (1990:249-250) higher skin permeability may be due to an increase in drug partition coefficient between the vehicle and the skin, or a direct effect of the phospholipid solution on the skin, thereby reducing the skin's resistance to permeation of the compounds. Phospholipids are surfactants, and it has been reported that several surfactants increase skin permeability. The enhancing effect is mainly due to the reduction of skin resistance to drug permeation and not to an increase in drug solubility (Mahjour *et al.*, 1990:251).

In a study conducted by Kato *et al.* (1986:400) the phase solubility diagram showed no significant change in drug solubility after the transdermal application of 1 % phospholipid. Two possible reasons for the improvement of transdermal delivery were considered. One is a thermodynamic change of the penetrant in the vehicle that takes place as a result of the addition of phospholipids, the other is a permeability change in the skin barrier resulting from the interaction of the phospholipid with components of the skin. The addition of phospholipids in amounts ranging from 0 to 5 % does not alter the solubility of the drug. Accordingly, the enhancing effect of the phospholipid must be due to a change in the permeability of the skin barrier although the mechanism by which this occurs remains unclear.

In a study conducted by Yokomizo (1996:225) treatment with 5 % phospholipids was superior to penetration with 1 % phospholipids in the percutaneous penetration of indomethacin *in vitro*. In this study, phospholipids were almost recovered from the donor side. This result suggests that a high concentration of phospholipid molecules in vehicles contacting the stratum corneum of the skin surface is needed to strongly enhance the percutaneous penetration of a drug.

Since phospholipids are degraded in the skin, they are considered to be safe for application to the skin (Yokomizo and Sagitani, 1996:268).

Lag times, estimated from cumulative concentration-time curves (Mahjour *et al.*, 1990:247) only slightly changes, after the application of 1 % phospholipid (Yokomizo and Sagitani, 1996:269).

9. Soft penetration enhancers

The compounds in this category of enhancer are designed to degrade into nontoxic compounds after absorption. Typical examples of these so-called soft enhancers are the cyclic derivatives of dioxane and dioxolane (Baker and Santus, 1993:16).

10. Sulphoxide enhancers

The sulphoxides, particularly dimethyl sulphoxides (DMSO), were widely used as enhancers in the 1970's and early 1980's. Despite its popularity, DMSO is poorly tolerated and potentially toxic, which imposes serious limitations on its use in transdermal systems (Baker and Santus, 1993:16-17).

11. Transcutol®

Transcutol® is amphiphilic, freely miscible with polar and non-polar solvents. It is non-irritating and non-toxic and can be used in topical, transdermal and oral formulations (Product information, Gattefossé Co.).

Transcutol®, a monoethyl ether of diethylene glycol, may enhance drug flux across stratum corneum by diffusing into and altering the solubility parameter (Williams in Harrison *et al,*. 1996:543). Evidence for the meganism by which Transcutol® acts as enhancer is limited. However Transcutol® does not appear to have a fluidising effect on structured lipids (Harrison *et al.,* 1996:545).

In a study conducted by Harrison *et al.,* (1996:544) Transcutol® was used as a solvent in a 1:1 mixture of Transcutol® and water. Panchagnula and Ritschel (1991:610) made use of mixtures containing 5, 10, 15, 25 50, 75 and 100 % of Transcutol® and found that 50 % was the optimum concentration to be used.

Transcutol® can increase drug flux without an apparent change in lag time (Harrison *et al.,* 1996:542).

12. Labrafil M 1944 CS®

Labrafil M 1944 CS® is an unsaturated polyglycolysed glyceride made of mono-, di- and triglicerides and polyethylene glycol mono- and diesters. It can be used as a non

ionic amphiphilic excipient or a solubilising agent in peroral solutions, nasal solutions, sprays, emulsions, hard shell capsules, softgel capsules and microemulsions or as a solubilising agent (Product information, Gattefossé Co.). Bonina *et al.* (1993:45 - 55) demonstrated the ability of Labrafil® to facilitate the flux and the diffusivity of caffeine across the stratum corneum. They concluded that the potential of a vehicle to increase the affinity between stratum corneum and drug should be considered with regard to transdermal and topical drug delivery. Paulesu *et al.* (1988:200) found that Labrafil® did not significantly improve the absorption of interferon administered by oral route, but it modified the pattern of the areas under the curve. The peak was delayed when Labrafil® was present and remained fairly constant until the end of the experiment. Labrafil M 1944 CS® is a composition of palmitic acid, stearic acid, oleic acid, linoleic acid and other mono-, di- and triglycerides and polyethylene glycol mono- and diesters. The mode of action of Labrafil M 1944 CS® is not clear, but it might be similar to that of the fatty acid and fatty acid ester enhancers - increasing drug solubility or fluidising the skin lipid structure (Goodman in Tanojo, 1996:100 and Tanojo, 1996:100).

The toxicity by nasal route (rat) is >20 $ml.kg^{-1}$ (Product information, Gattefossé Co.).

Chemical enhancers may be useful in increasing transdermal penetration of drugs. Important factors to be taken into consideration is potential toxicity and skin irritation. Potential chemical penetration enhancers include ethanol in combination with propylene glycol and glycerol, phospholipid enhancers, e.g. phosphatidylcholine, essential oils, e.g. wintergreen or rosemary oil and oleic acid. Solvents such as Transcutol® and Labrafil M 1944 CS® might also be tested.

1.4.2.2 Physical enhancers

The iontophoresis and ultrasound techniques are examples of physical means of enhancement that have been used for enhancing percutaneous penetration (and absorption) of various therapeutic agents. One of the major concerns in the usage of iontophoresis is that the device may cause painful destruction of the skin with high current settings (Shah, 1994:21).

The acceptance of skin penetration enhancers as adjuvants will depend on the degree to which their effects are transient. The structure and biochemistry of the skin is integral to its barrier function. If the skin's ability to maintain its barrier is altered, thus permitting easier penetration of pharmaceuticals, it is likely due to impairment of the skin's structural or biochemical integrity. Therefore, modification of the barrier function of the epidermis is reversible only upon reversal of the structural/biochemical changes caused by the enhancer (Haberkamp, 1994:43-44).

Since the drug concentration in the skin is limited by its physicochemical properties, it is not expected that the drug concentration within the skin membrane can be increased tremendously by the use of enhancers. It has been postulated that the effect of penetration enhancers on flux is more likely to be greater on the diffusion coefficient of the drug substance in the skin layers than on the drug concentration (Ng, 1994:95).

Physical enhancers could be beneficial in enhancing percutaneous penetration of drugs. However, this means of enhancement is not recommended due to possible pain and irreversibility to the skin's barrier function.

1.4.3 Prodrugs

Prodrug formation is the chemical modification of a biologically active compound to form a new chemical entity that is in itself inactive but from which the active parent compound is regenerated *in vivo*. In the case of prodrugs used for the enhancement of drug transport through the skin, that function is normally completed when the prodrug reaches the viable epidermis, since it is the SC that serves as the transport barrier for most drugs (Anderson, 1993:69-70).

Enhancement of transport via prodrug formulation, presupposes that the chemical modification is a reversible one and that bioconversion to the parent drug will occur at the intended site of action or prior to reaching this site. For topically administered drugs acting systemically, bioconversion may occur at any site accessible to the general circulation. As long as this bioconversion occurs at a sufficient rate, one may be inclined to ignore any possible impact of bioconversion within the skin. Drug flux may be dependent, in some cases, on the rate of prodrug bioconversion within the skin (Anderson, 1993:71).

The necessary conversion or activation of prodrugs to the parent drug molecules in the body can take place by a variety of reactions. The most common prodrugs are those requiring a hydrolytic cleavage mediated by enzymatic catalysis. Active drug species containing hydroxyl or carboxyl groups, i.e. scopolamine, doxylamine succinate, pyridoxine hydrochloride and prochlorperazine maleate, can often be converted to prodrug esters from which the active forms are regenerated by esterases within the body, e.g. in the blood. In other cases, active drug substances are regenerated from their produgs by biochemical reductive or oxidative processes. Besides usage of the various enzyme systems of the body to carry out the necessary activation of prodrugs, the buffered and relatively constant value of the physiological pH (7,4) may be useful in triggering the release of a drug from a prodrug. In these cases, the prodrugs are characterized by a high degree of chemical lability at pH 7,4 while preferably exhibiting a higher stability at, for example, pH 3,4 (Bundgaard, 1987:13-14).

More recently, newer chemistry has been developed which permits the use of endogenous esterases to convert derivatised drugs to their active forms. Thus a number of amines, amides and imides have been converted to esterase-sensitive prodrugs (Bundgaard, 1987:3).

Prodrugs that could be used for the chosen anti-emetic drugs for use during pregnancy (amides, imides and other NH-acidic compounds) are discussed below.

1. N-Mannich bases

N-Mannich bases have been proposed as potentially useful prodrug candidates for NH-acidic compounds such as various amides, imides, carbamates as well as for aliphatic or aromatic amines. They are generally formed by reacting as NH-acidic compounds with formaldehyde and a primary or secondary aliphatic or aromatic amine. The process can be considered as an N-aminomethylation or N-amidomethylation (in the case of the NH-acidic component being an amide) (Bundgaard, 1987:21).

$$R\text{-}CONH_2 + CH_2O + R_1R_2NH \rightleftharpoons R\text{-}CONH\text{-}CH_2\text{-}NR_1R_2 + H_2O$$

By appropriate selection of the amine compound, it should be feasible to obtain prodrugs of a given amide-type drug with varying degree of *in vivo* lability. Besides, other physicochemical properties such as aqueous solubility, dissolution rate and lipophilicity can be modified for the parent compounds (Bundgaard, 1987:25).

N-Mannich bases prepared from secondary amines showed very high solubilities in salt form, whereas the Mannich bases derived from primary amines did not show increased solubility even as salts. This different behavior was attributed to the occurrence of intramolecular hydrogen bonding in the latter derivatives (Bundgaard, 1987:27).

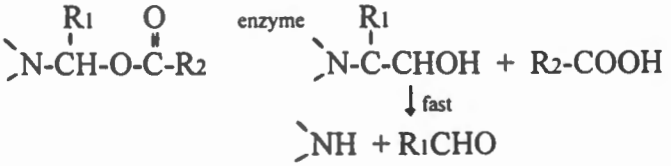
Various N-Mannich bases of theophylline and the morpholino N-Mannich base of 5-fluorouracil have shown that these derivatives are effective as prodrugs for the delivery of the parent drug through skin. The N-Mannich bases exhibit enhanced water as well as enhanced lipid solubilities as compared to the parent drugs and are relatively stable in aprotic solvents such as isopropyl myristate which was used as a vehicle for the diffusion experiments with hairless mouse skin. The enhanced solubilities of the derivatives relative to the parent drugs may be ascribed partly to decreased crystal lattice energy as reflected in the decreased melting points (Bundgaard, 1987:31).

2. *N-Acyloxyalkyl derivatives*

In recent years, N-Acyloxyalkylation has become a commonly used approach to obtain prodrugs at various amides, imides, tertiary or N-heterocyclic amines and other NH-acidic compounds (Bundgaard, 1987:39). N-Acyloxylation of simple, acidic primary and secondary amines does not appear to be useful because of the extreme lability of such derivatives in aqueous solution, but for tertiary amines chemically stable compounds (quaternary ammonium salts) are obtained. Due to a high susceptibility to undergo enzymatic hydrolysis, these compounds are useful as prodrugs of tertiary or N-heterocyclic amines (Bundgaard, 1987:58-59).

The usefulness of this approach stems from the fact that by varying the acyl portion of the derivatives it is possible to control the rate of regeneration of the parent drug and to obtain prodrugs with varying physicochemical properties such as water

and to obtain prodrugs with varying physicochemical properties such as water solubility or lipophilicity. Whereas the derivatives show good stability in aqueous solution *in vitro* similar to other esters, they are in general rapidly cleaved *in vivo* by virtue of enzyme mediated hydrolysis. The regeneration of the parent NH-acidic drug takes place via a two step reaction.



Enzymatic cleavage of the ester grouping results in the formation of an N-hydroxyalkyl derivative which subsequently is assumed to decompose instantaneously into the corresponding aldehyde and the NH-acidic drug (Bundgaard, 1987:39-40).

The most commonly used acyloxyalkyl derivatives are acyloxymethyl compounds, i.e. derivatives from which formaldehyde is released from an N-hydroxymethyl intermediate (Bundgaard, 1987:40).

3. N-Acyl derivatives

N-Acylation of amines to give amide prodrugs has been used only to limited extent due to the relative stability of amides *in vivo*. However, certain activated amides are sufficiently chemically labile and also, certain amides formed with amino acids may be susceptible to undergo enzymatic cleavage *in vivo* (Bundgaard, 1987:53).

Prodrugs seems to provide a useful means of enhancing drug transport through the skin, but because of the complex chemical modification that is needed for prodrug formation it is wishful to avoid this method of penetration enhancement as far as possible. The use of prodrugs will only be considered as a last option to try to improve drug penetration through the skin.

and perhaps vomiting are not induced because there is no need to take oral anti-emetics by the already nauseous women. There are no TTS available on the market for treatment of nausea and vomiting during pregnancy. This provides the perfect opportunity for research.

Transdermal drug delivery seems to be an effective and well tolerated way of administering systemic drugs, but only a few drugs possess the physicochemical and pharmacokinetic properties needed for transdermal absorption, e.g. low melting point (approximately 150°C or less), daily dosage of less than 50 mg and a molecular mass of less than 1000. The physicochemical properties can be altered through modification of the drug by means of prodrug formation - i.e. chemical modification of a biologically active compound to form a new chemical entity that is in itself inactive but from which the active parent compound is regenerated *in vivo* - or by the use of penetration enhancers - acting by alteration of the three pathways suggested for drug penetration through the skin: polar, nonpolar, and polar/nonpolar. These modifications could provide more effective and rapid absorption of the drugs.

The quality of life of pregnant woman, who suffer from morning sickness can be improved via the transdermal delivery of drugs for the treatment and/or prophylaxis of morning sickness.

CHAPTER 2

EXPERIMENTAL PROCEDURES AND VALIDATION OF EXPERIMENTAL TECHNIQUES

2.1 INTRODUCTION

Chlorpromazine hydrochloride is a propylamino phenothiazine, that has been used for the treatment of nausea and vomiting during pregnancy since the mid-1950's. The drug seems to be safe and effective for this indication (Briggs *et al.,* 1986:85). Chlorpromazine is readily absorbed from the gastro-intestinal tract but is subject to considerable first-pass effect and metabolism in the gut wall (Reynolds, 1993:578-579). Transdermal delivery of this drug would avoid the first-pass metabolism. Most analytical methods for the determination of chlorpromazine, make use of high performance liquid chromatography (HPLC) with either fluorescence or UV detection.

Doxylamine succinate is an ethanolamine derivative (Reynolds, 1993:938), it is the best documented anti-emetic for use against morning sickness in pregnancy (Pray, 1994:26). It is well absorbed after peroral or parenteral administration, but hepatic biotransformation occurs (USP DI, 1994:299). High performance liquid chromatography (HPLC) methods were used to determine the concentrations of chlorpromazine and doxylamine that penetrated the skin after topical application.

2.2 OBJECTIVE

The objective of this part of the study was to develop analytical methods that are easy to use and sensitive enough for the quantitative determination of chlorpromazine hydrochloride and doxylamine succinate in saline solution following transdermal delivery in hairless mice.

2.3 EXPERIMENTAL PROCEDURES

2.3.1 Reagents and raw materials

2.3.1.1 Chlorpromazine hydrochloride

Chlorpromazine hydrochloride was supplied by Sigma (St. Louis, USA). Glacial acetic acid and perchloric acid used in the assay of chlorpromazine hydrochloride were supplied by SAARCHEM (Muldersdrift, South Africa). HPLC analytical grade acetonitrile and tetrahydrofuran (BDH, Poole, England) were used. Double distilled deionised water was prepared by a Milli-Q 50 water purification system (Millipore, Milford, USA). Sodium chloride 0,9 % m/v was supplied by Intramed (Port Elizabeth, South Africa).

2.3.1.2 Doxylamine succinate

Doxylamine succinate was supplied by SAARCHEM (Muldersdrift, South Africa.) Glacial acetic acid and perchloric acid used in the assay of doxylamine succinate were supplied by SAARCHEM (Muldersdrift, South Africa). HPLC analytical grade methanol (BDH, Poole, England) and acetonitrile (BDH, Poole, England) were used, as well as potassium dihydrogen orthophosphate, triethylamine and glacial acetic acid supplied by SAARCHEM (Muldersdrift, South Africa). Double distilled deionised water was prepared by a Milli-Q 50 water purification system (Millipore, Milford, USA). Sodium chloride 0,9 % m/v was supplied by Intramed (Port Elizabeth, South Africa).

2.3.2 Assays

2.3.2.1 Assay of chlorpromazine hydrochloride

According to the USP (1995:354) chlorpromazine hydrochloride may not contain less than 98.0 percent and not more than 101.5 percent of $C_{17}H_{19}ClN_2S$ HCl, calculated on the dried basis. The assay of chlorpromazine hydrochloride was done titrimetrically with 0.1 N perchloric acid, and the endpoint was determined potentiometrically. The assay of the raw material was done in duplicate and found to be 99.35 % and 99.27 % respectively. The average assay of chlorpromazine hydrochloride was 99.3 %. The chlorpromazine hydrochloride complied with the criteria of the USP (1995:354).

2.3.2.2 Assay of doxylamine succinate

According to the USP (1995:559) doxylamine succinate may not contain less than 98.0 percent and not more than 101.0 percent of $C_{17}H_{22}N_2O$ $C_4H_6O_4$, calculated on the dried basis. The assay of doxylamine succinate was done titrimetrically with 0.1 N perchloric acid. The difference between the blank and the test value was used to determine the assay The assay of the raw material was done in duplicate and found to be 100.61 % and 99.73 % respectively. The average assay of doxylamine succinate was 100,2 %. The doxylamine succinate complied with the criteria of the USP (1995:559).

2.3.3 High performance liquid chromatography (HPLC) system

The HPLC-system consisted of a Spectraseries P100 isocratic pump (Spectra Physics Analytical, Fremont,) with a Rheodine injection system (Cotati, California, USA) and a Spectra System UV-1000 - variable wavelength UV-detector (Spectra Physics Analytical, Fremont). Data was registered and integrated with a EZChrom Chromatographic datasystem (Version 6.2) (Scientific Software Inc., San Ramon). For chlorpromazine hydrochloride a Lichrospher® 100RP-18 (250 x 4 mm) column (Merck, Darmstadt) was used. The injection volume was 100 µl and the samples were analysed at a fixed wavelength of 254 nm. The mobile phase consisted of acetonitrile

- tetrahydrofuran - water (60:30:10) with a flow rate of 2 ml.min^{-1}. The mobile phase was filtered through a 0,45 µm HV filter (Millipore, Milford, USA). An internal standard was not used, since the samples were analysed without undergoing any further extrations or adaptations. For doxylamine succinate a Nova-Pak® CN HP 60 Å 4 µm (3.9 x 150 mm) column (Waters, Milford, Massachusetts) was used, with a mobile phase (2 ml.min^{-1}) of acetonitrile - methanol - 5 mM potassium dihydrogen orthophosphate buffer containing 0.72 mM triethylamine and adjusted to pH 5.30 with glacial acetic acid (70:10:20). The injection volume was 100 µl and the samples were analysed at a fixed wavelength of 262 nm. The mobile phase was filtered through a 0,45 µm HV filter (Millipore, Milford, USA). The samples were analysed without any adaptations and no internal standard was used. All analysis were conducted at room temperature.

2.3.3.1 Preparation of standard solutions

Chlorpromazine hydrochloride and doxylamine succinate stock solutions (n = 2) were prepared daily in saline solution and used for the establishment of calibration curves. The required amounts of the chlorpromazine hydrochloride and doxylamine succinate stock solutions were diluted with saline. The chlorpromazine hydrochloride standard solutions were prepared by weighing 10 mg chlorpromazine hydrochloride and dissolving it in 10 ml saline to produce a 1 mg.ml^{-1} solution. 100 µl of this solution was diluted to 10 ml with saline to produce a 10 µg.ml^{-1} solution. 200, 100, 50, 10, 5 and 1 µl of the 10 µg.ml^{-1} solution were diluted with saline to produce 200, 100, 50, 10, 5 and 1 ng.ml^{-1} solutions. The doxylamine succinate standard solutions were prepared by weighing 10 mg doxylamine succinate and dissolving it in 10 ml saline to produce a 1 mg.ml^{-1} solution. 100 µl of this solution was diluted to 10 ml with saline to produce a 10 µg.ml^{-1} solution. 500, 300, 200, 100, 50 and 5 µl of the 10 µg.ml^{-1} solution were diluted with saline to produce 500, 300, 200, 100, 50, and 5 ng.ml^{-1} solutions.

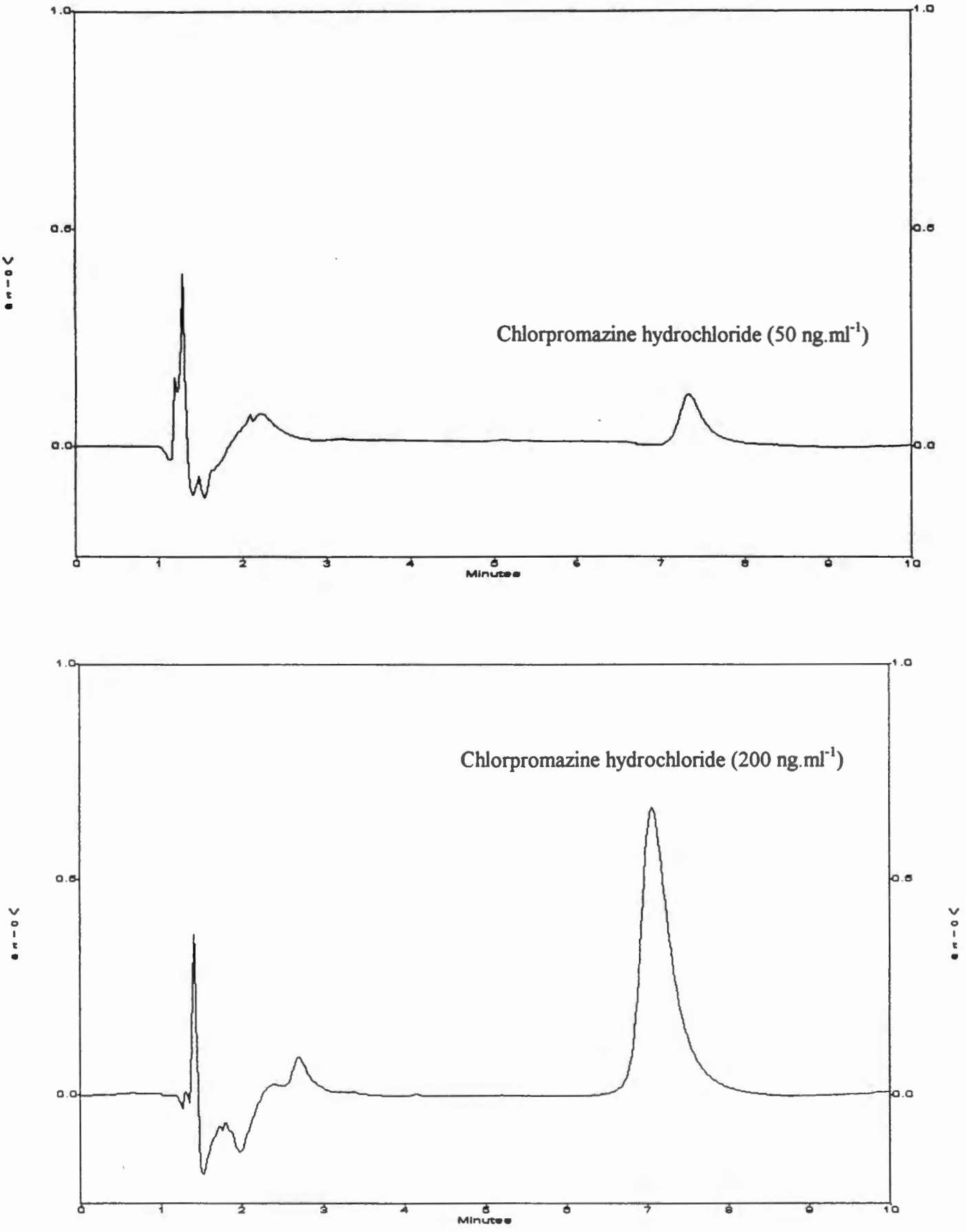


FIGURE 2.1: HPLC-chromatograms obtained for chlorpromazine hydrochloride.

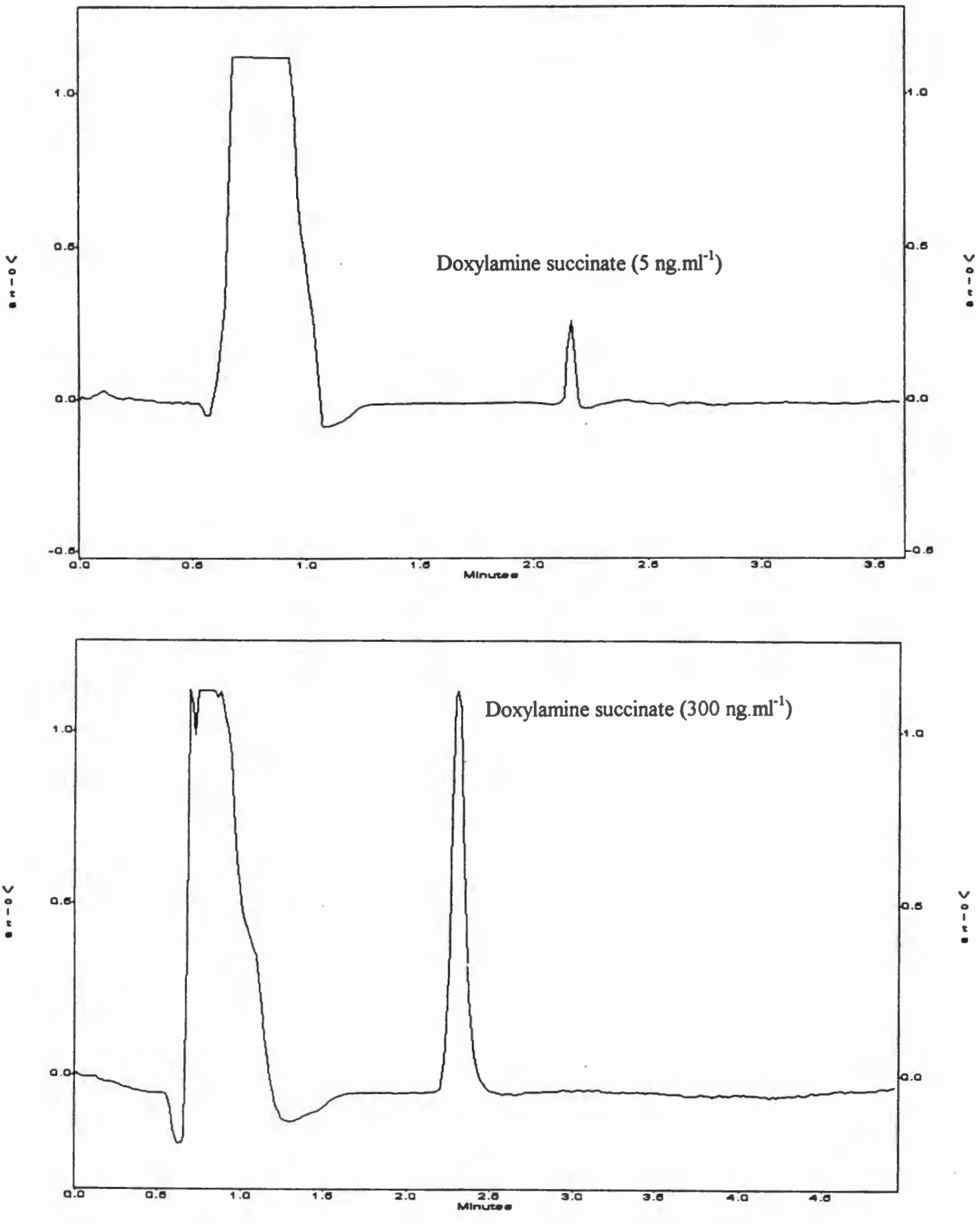


FIGURE 2.2: HPLC-chromatograms obtained for doxylamine succinate.

2.3.3.2 Validation of the HPLC analytical method

2.3.3.2.1 Calibration curves

Calibration curves were established, using standard solutions (n = 2) of chlorpromazine hydrochloride with concentrations of 1, 5, 10, 50, 100 and 200 $ng.ml^{-1}$. For the establishment of a calibration curve for doxylamine succinate concentrations of 5, 50, 100, 200, 300 and 500 $ng.ml^{-1}$ were used. Standards were analysed three times and the calibration curves were established using the average value for each concentration.

2.3.3.2.2 Selectivity

Selectivity is the ability of the analytical method to detect and analyse a component in the presence of other components such as decomposition products. This methods seems to be selective since there are no endogenous interfering peaks at the retention time of chlorpromazine hydrochloride (7 to 9 min) and doxylamine succinate (2 to 4 min).

2.3.3.2.3 Linearity

The assay linearity for chlorpromazine hydrochloride and doxylamine succinate were determined by performing linear regression analysis on the plot of the peak area versus concentration. For chlorpromazine hydrochloride a range of 1 - 200 $ng.ml^{-1}$ was used and for doxylamine succinate a range of 5 - 500 $ng.ml^{-1}$ was used. Daily standard curves were constructed using the appropriate analytical procedure. The data are best described by a linear equation $y = mx + c$ where:

y = peak area of the drug
m = slope
x = concentration of the drug in $ng.ml^{-1}$
c = y-intercept

TABLE 2.1: *Regression values obtained for chlorpromazine hydrochloride for three standard curves constructed on different days.*

Number	R^2	Slope	y-intecept
1	0.99995	225742	0
2	0.99707	217372	0
3	0.99887	246291	0
Average	0.99863	229802	
SD	0.00145	14880	
% RSD	0.14569	6.47549	

SD - Standard deviation % RSD - Percentage relative standard deviation

TABLE 2.2: *Regression values obtained for doxylamine succinate for three standard curves constructed on different days.*

Number	R^2	Slope	y-intecept
1	0.99954	26844	4×10^{-6}
2	0.99658	28015	5×10^{-6}
3	0.99912	24220	4×10^{-6}
Average	0.99841	26360	
SD	0.00160	1943	
% RSD	0.16041	7.37227	

SD - Standard deviation % RSD - Percentage relative standard deviation

For chlorpromazine hydrochloride a mean correlation coefficient (n=3) of 0.99730 ± 0.00430, and for doxylamine succinate a mean correlation coefficient (n=3) of 0.99841 ± 0.00160 was obtained, indicating a high degree of linearity and demonstrating the good stability of the analytical system.

2.3.3.2.4 Precision

The precision of the method was investigated in terms of intra-day (repeatability) variations. Standard solutions were freshly prepared each day, implying that investigation of inter-day variation would not be necessary.

2.3.3.2.5 Repeatability

The repeatability of a method is given by the comparison of values following replicate measurements.

The intra-day variability was determined by performing HPLC analysis (n=6) of three samples containing known amounts of chlorpromazine hydrochloride (5, 100 and 200 $ng.ml^{-1}$). The variation in the response (% RSD) of the measuring system, when 6 measurements were made on the same sample on the same day and under the same conditions, did not exceed 7.87 %.

Three doxylamine succinate samples containing known amounts (5, 100 and 300 $ng.ml^{-1}$) were also determined by HPLC analysis. The variation in response (% RSD) when 6 measurements were made on the same sample on the same day, did not exceed 6.46 %.

2.3.3.2.6 Sensitivity

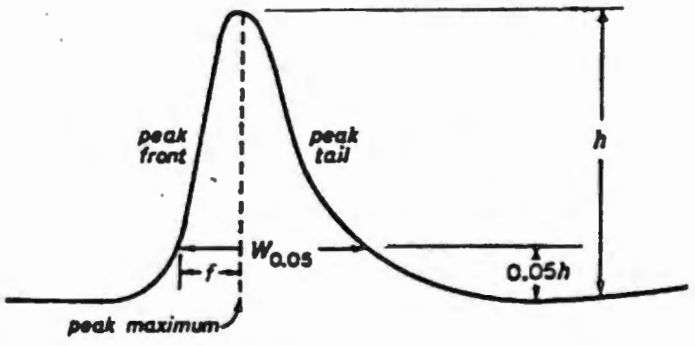
Based on a 100 µl sample volume, the limit of quantification (the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy) for chlorpromazine hydrochloride was 0.5 $ng.ml^{-1}$ (% RSD < 15 %). The limit of detection (the lowest concentration of analyte in a sample that can be detected, but not necessarily quantitated) for chlorpromazine hydrochloride for the proposed method for all saline samples was 0.25 $ng.ml^{-1}$. The lowest quantable concentration for doxylamine succinate was 5 $ng.ml^{-1}$ (% RSD < 15 %) and the limit of detection for doxylamine succinate was 1.25 $ng.ml^{-1}$.

2.3.3.3 System suitability

System suitability is used to verify that the resolution and reproducibility of the chromatographic system are adequate for the analysis to be done.

2.3.3.3.1 Peak symmetry

The tailing factor, T, a measure of peak symmetry, is unity for perfectly symmetrical peaks and its value increases as tailing becomes more pronounced. As peak symmetry increases, integration and hence precision becomes less reliable. A degree of tail or head formation is calculated by using the equation in figure 2.3.



$$T = \frac{W0,05}{2f}$$

Where:

T = tailing factor

$W_{0,05}$ = width of peak at 5 % height

f = the leading edge of the peak, the distance being measured at a point 5 % of the peak height from the baseline.

***FIGURE 2.3**: Formula used to calculate tailing (USP, 1995:1776).*

Chlorpromazine T = 1.72

Doxylamine T = 1.14

As shown from the tailing factors determined (n = 3) chlorpromazine hydrochloride and doxylamine succinate did not show appreciable tailing.

2.3.3.3.2 Theoretical plate number (N)

The theoretical plate number takes into account the width of the peak (bandspreading) and can therefore be used to measure the efficiency of a system. The formula used to calculate N appears in equation 2.1 below. It must be remembered that this term is relative and the number generated is unit-less.

$$N = 16\left(\frac{t}{W}\right)^2 \qquad (2.1)$$

Where:

N = Theoretical plate number

t = Retention time of peak

W = Width of peak

The number of theoretical plates for the column that was used to determine chlorpromazine hydrochloride in saline solution was 1075.84 and doxylamine succinate was 4871.71 and therefore the columns were efficient.

2.4 TRANSDERMAL DIFFUSION STUDIES

2.4.1 Laboratory animals

Hairless mouse skin was chosen as the model for this study. According to Vollmer *et al.* (1993:242), data from animals are not transferable to man, but are useful for investigating the optimal vehicle to use and for the study of penetration enhancers.

2.4.2 Criteria for inclusion of laboratory animals

The laboratory animals used for this study fulfill to the following criteria:

Specie:	Hairless mouse
Sex:	Male and female (see 2.5)
Age:	16 - 18 weeks
Mass:	20 -25 g

In order to obtain statistically meaningful results Statistical Services (PU for CHE) suggested that the number of animals used per formulation must be 6.

2.4.3 Anaesthesia of the animal

For the duration of the experiment, the animal was anaesthetised with Fluothane® (halothane). An initial dose of 4 % and a maintenance dose of 2 % Fluothane® was used. Initially, the animal was placed in a glass container. Fluothane® was sprayed onto a paper towel inside the container to establish a 4 % halothane-air mixture. As soon as the animal lost the righting reflex (a state where the animal has no control of its own balance, and stays on its side or back when turned over), which varied between 40 seconds and one minute, the animal was coupled onto an anaesthesia apparatus. The anaesthesia apparatus consisted of a 1,19 liter plastic bag and a 5 liter plastic bag, connected to a three way valve. Sodium lime was placed in the bags to absorb the exhaled carbon dioxide. The two plastic bags were connected to two exits of the three way valve and the mouse was connected to the third exit. Before the mouse was connected, the plastic bags were filled with oxygen and halothane, 4 % for

induction and 2 % for maintenance. This method made it possible to regulate the level of anaesthesia. The three way valve was used to direct the 2 % or 4 % halothane-air mixture to the mouse. The apparatus needed to perform the anaesthesia is shown in figure 2.4. Figure 2.5 shows the valve used to regulate the level of anaesthesia. The diffusion cell used in transdermal absorption studies is shown in figure 2.6 and figure 2.7 shows the halothane filled plastic bags and the regulating valve connected to the animal while under anaesthesia. (Marais, 1992:47).

A: Sealing tape

B: Surgical clamp

C: Sodium lime

D: Plastic bags

E: Latex rubber

F: Regulating valve

***FIGURE 2.4:** Apparatus needed to perform the anaesthesia.*

FIGURE 2.5: *The three way regulating valve used to regulate the level of anaesthesia.*

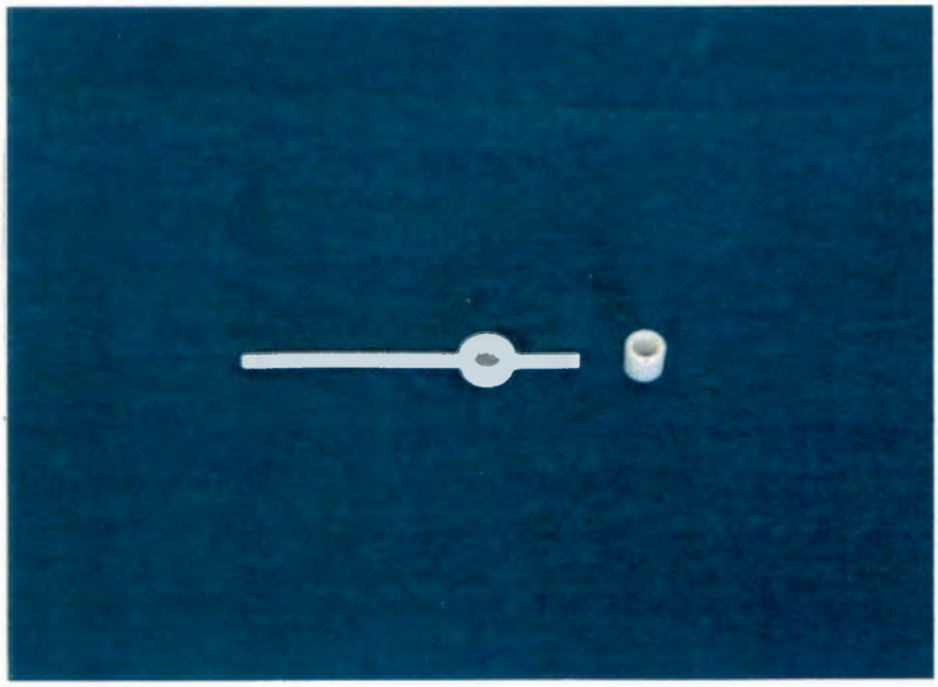


FIGURE 2.6: *Diffusion cell used in the transdermal absorption studies.*

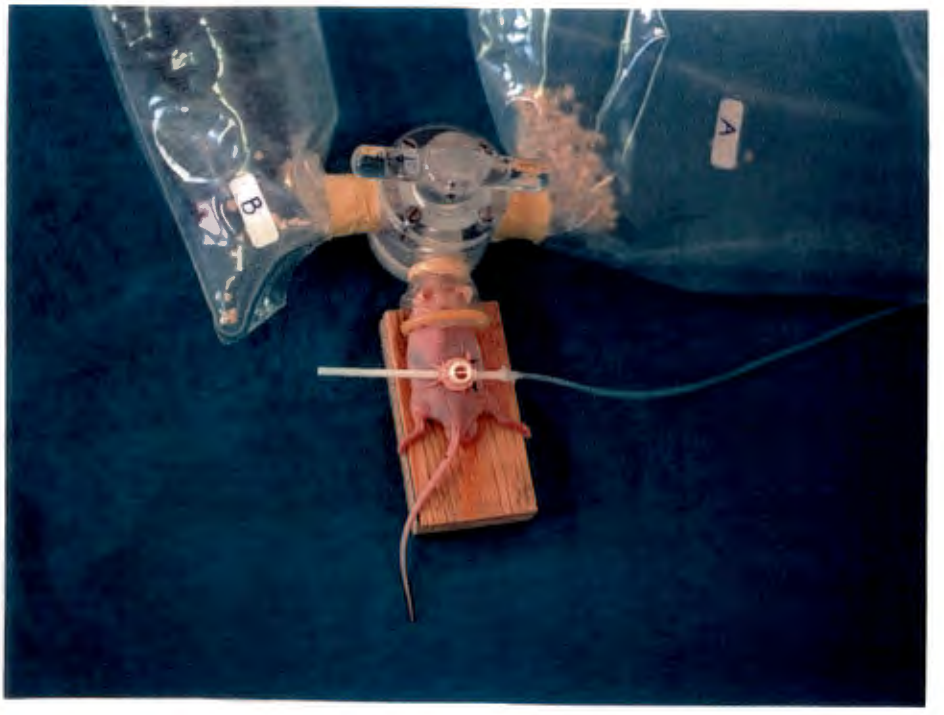


FIGURE 2.7: *Halothane filled plastic bags and the regulating valve connected to the animal while under anaesthesia.*

2.4.4 General procedures

In this study an adapted receptor diffusion cell was used. The animal would be kept alive for the duration of the experiment, and the skin would not start to deteriorate and loose it's barrier properties due to a lack of blood supply to the skin. After the mice were anaesthetised as described in 2.4.3, a cut was made on the dorsal skin without stretching or damaging the skin, and a blunt cut was made to separate the skin from the body. Usually no bleeding occurred during the surgery, suggesting no alteration to the blood supply to the specific skin area. An adapted receptor diffusion cell was then implanted under the dorsal skin of the animal. The diffusion cell consisted of a receptor chamber, with a volume of 0,13 cm^3, that was implanted under the skin, and a donor cell which was placed on top of the receiver cell on the outside of the skin. The donor cell was tied to the in- and outlets of the receiver cell to ensure the correct position on top of the receiver cell, and to prevent leakage of the fluid from the donor cell. The donor cell which exposed 0,32 cm^2 of skin to the applied drug, had a height

cell. The donor cell which exposed 0,32 cm^2 of skin to the applied drug, had a height of 4,5 mm and a radius of 7 mm. A schematic drawing of the diffusion cell is shown in figure 2.8 (Marais, 1992:46).

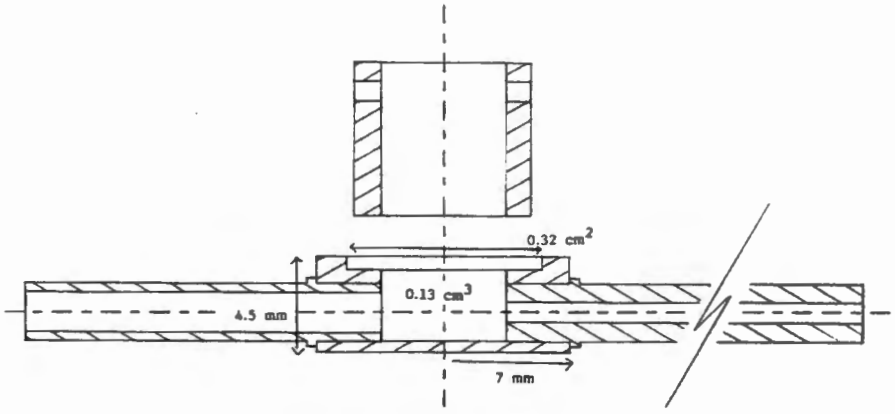


***FIGURE 2.8**: Schematic drawing of the diffusion cell.*

To prevent a drop in body temperature, the experiments were performed in an incubator with a temperature ranging from 29 - 30°C, and a relative humidity of 36 - 40 %. The selected drugs were applied as a liquid in the donor cell, a volume of 150 µl chlorpromazine hydrochloride dissolved in ethanol (5 $mg.ml^{-1}$), together with 5 % of appropriate penetration enhancers (oleic acid and phosphatidylcholine) were applied to the dorsal skin of the hairless mice respectively. Two solvents known for their penetration enhancing effect, namely Transcutol® and Labrafil M 1944 CS® were also tested. Saline solution (0,9 % NaCl) was send through the receptor cell at a rate of 10 $ml.h^{-1}$. Samples from the outlet of the receptor cell were collected in glass containers at intervals of 30 minutes over a period of 12 hours. All samples were protected from light due to the fact that chlorpromazine hydrochloride and doxylamine succinate are both light sensitive drugs. These samples were then analysed. After completion of the experiment, the animals were sacrificed by means of a 40 mg sodium pentobarbitone intraperitoneal injection.

2.4.5 Sampling

Samples were taken every 30 minutes over a period of 12 hours after application of the drugs. All samples were protected from light.

2.5 EFFECT OF GENDER OF LABORATORY ANIMALS ON TRANSDERMAL DRUG DELIVERY

Research on transdermal delivery of drugs - both *in vitro* and *in vivo* - has been done on a wide range of animals. Male hairless mice are often used, and the use of female mice is reported in some publications (Loftsson *et al.*, 1997:465).

Gender-related differences in drug pharmacokinetics are well known and are found in both laboratory animals and humans (Kato in Huang *et al.*, 1995:1647). Huang *et al.* (1995:1649) did a study on Sprague-Dawley rats to determine the effect of gender on plasma concentrations of zidovudine following intavenous administration. No significant differences were found in terminal half-life ($t_{½}$), mean residence time, total clearance, renal clearance, or steady-state volume of distribution between the male and female rats. However, the non-renal clearance was significantly lower in the female rats than in the male rats while the fraction excreted unchanged in the urine was greater in the female rats. No data on the the effect of gender on transdermal drug delivery could be found.

As part of this study, a correlation was made between the use of male and female hairless mice skin in *in vivo* transdermal drug delivery studies. Table 2.3 shows the flux and AUC values obtained using male and female mice respectively.

TABLE 2.3: *Pharmacokinetic parameters of chlorpromazine determined after transdermal application of 150 µl of a 5 mg.ml^{-1} solution of chlorpromazine hydrochloride in ethanol together with oleic acid (5 %). (n=3)*

	Flux ($\mu g.cm^{-2}.h^{-1}$)	AUC ($\mu g.ml^{-1}.h^{-1}$)
Male	60.20 ± 0.86	755.84 ± 39.02
Female	56.87 ± 5.15	782.74 ± 49.15

The AUC values for the two groups were calculated from the mean chlorpromazine concentrations using the trapeziodal rule. The determination of statistically

significant differences in the areas under the concentration-time curves (AUC values) between the two groups were based on Dunnett's T-test. No statistically significant differences ($p < 0.05$) with a confidence interval of 95 % were indicated for the parameter AUC between the male and female mice.

2.6 CONCLUSION

The HPLC methods have been validated and proven to be simple, specific and sensitive enough for the determination of the concentrations of chlorpromazine hydrochloride and doxylamine succinate in saline solution after the application of the drug on the skin of hairless mice. The retention time for chlorpromazine hydrochloride and doxylamine succinate was less than 9 and 4 minutes respectively. The reproducibility, accuracy and sensitivity were good. Thus, these methods were efficient for the quantitative determination of chlorpromazine hydrochloride and doxylamine succinate in saline solution following transdermal drug delivery. The experimental animal method used in this study seems to be an easy and effective method to determine transdermal absorption of drugs after topical application, with the advantage that alive, in tact skin is used for the duration of the experiment. A disadvantage of this method may be that some of the drug permeating through the skin may be swept away by systemic circulation and , therefore, would not be quantified in the permeation receptor fluid.

CHAPTER 3

TRANSDERMAL DELIVERY OF CHLORPROMAZINE HYDROCHLORIDE AND DOXYLAMINE SUCCINATE

3.1 INTRODUCTION

Peroral administration is the principal route of administration for chlorpromazine hydrochloride and doxylamine succinate. These drugs are used for the treatment of nausea and vomiting associated with pregnancy during all stages of gestation, including labour, and have been proven to be safe and effective for these indications (Briggs *et al.*, 1986:85; Pray, 1994:26). Chlorpromazine is readily absorbed from the gastro-intestinal tract but is subjected to considerable metabolism in the gut wall and first-pass effect. There is some evidence of enterohepatic recycling. Owing to the first-pass effect, plasma concentrations following peroral administration are much lower than those following intramuscular administration. Chlorpromazine has a large volume of distribution and a high metabolic clearance resulting in low blood concentrations particularly when the oral route is used (Reynolds, 1993:578-579). Doxylamine succinate is well absorbed after peroral or parenteral administration, but is also subjected to hepatic biotransformation (USP DI, 1994:299). The physicochemical characteristics of chlorpromazine hydrochloride and doxylamine succinate e.g. high potency, low molecular weight and low melting point made them the drugs of choice for transdermal drug delivery studies (see 1.4.1).

Transdermal drug delivery offers an attractive alternative to conventional oral therapy as a means of achieving a constant therapeutic level of drug in the biophase. The main advantages of transdermal drug delivery comparted to peroral dosage regimens are that pharmacokinetic variability associated with the gastro-intestinal tract (effect of pH, motility, transit time of food intake) and metabolism within the gastro-intestinal tract and first-pass effect in the liver are avoided with the transdermal route (Ridout *et al.*, 1988:115). Although these advantages are similar to those associated

with intravenous infusion, transdermal drug delivery offers a safer and more convenient method of drug administration.

The aim of this part of the study was to determine the *in vivo* transdermal absorption of chlorpromazine hydrochloride and doxylamine succinate as a function of time after application of the respective drugs to hairless mice skin.

3.2 MATERIALS AND METHODS

3.2.1 Reagents, raw materials and HPLC system

Reagents and materials as mentioned previously in 2.3.1.1 and 2.3.1.2 were used. Transcutol and Labrafil M 1944 CS® were supplied by Gattefossé, France. Oleic acid and 68% ethanol were supplied by SAARCHEM (Muldersdrift, South Africa), and phosphatidylcholine was supplied by Sigma (St. Louis, USA). The amount of chlorpromazine hydrochloride and doxylamine succinate that penetrated the skin after topical application were determined by the HPLC method described in 2.3.3.

3.2.2 Application of the drug

3.2.2.1 Calculation of the applied dose

The required dose size (DM) for the controlled release drug delivery device can be calculated using equation 3.1 (Ritschel, 1988:67).

$$DM = \frac{C_{ss}.Cl.\tau}{f} \qquad (3.1)$$

where

DM = dose size

C_{ss} = steady state

Cl = clearance

τ = dosing intervals

f = bioavailability

Table 3.1 provides the pharmacokinetic parameters necessary for the calculation of dose size.

TABLE 3.1: *Pharmacokinetic parameters of chlorpromazine hydrochloride and doxylamine succinate that are necessary for the calculation of the dose size for controlled release drug delivery devices.*

	Chlorpromazine hydrochloride	**Doxylamine succinate**
Steady state (C_{SS})	10.5 - 99.2 $mg.ml^{-1}$ [1]	0.96 $mg.ml^{-1}$ [1]
Clearance (Cl)	0.84 $l.h^{-1}$ [2]	13.02 $l.h^{-1}$ [5]
Bioavailability (f)	0.32 [3]	1 [6]
Half life ($t_{½}$)	10.9 h [4]	10.1 h [7]
Volume of distribution (V_d)	21 $l.kg^{-1}$ [3]	2.83 $l.kg^{-1}$ [7]

1. Calculated from $C_{SS} = R^O/Cl$ and $R^O = D/\tau$ thus $C_{SS} = D/\tau \cdot 1/Cl$ (Ritschel, 1988:65-66)

   R^O = delivery rate

   D = dose

   Cl = clearance

   τ = dosing intervals (taken as 12h)

2. Dorson and Crimson (1988:777)
3. Ritschel (1992:356)
4. Yeung *et al.* (1987:807)
5. Freedman and Greenblatt (1985:450)
6. Not available (taken as 1)
7. Freedman *et al.* (1989:312)

Dose for chlorpromazine hydrochloride

$$DM = \frac{C_{SS}.Cl.\tau}{f} \qquad (3.1)$$

$$DM = \frac{10.5 \cdot 0.84 \cdot 12}{0.32} \quad \text{to} \quad DM = \frac{99.2 \cdot 0.84 \cdot 12}{0.32}$$

$$= 330.75 \text{ mg (for a 70 kg human)} \qquad = 3124.8 \text{ mg}$$

$$= 0.118 \text{ mg (for a 25 g mouse)} \qquad = 1.116 \text{ mg}$$

Dose for doxylamine succinate

$$DM = \frac{0.96 \cdot 13.02 \cdot 12}{0.32}$$

= 149.99 mg (for a 70 kg human)

= 0.054 mg (for a 25 g mouse)

Since the concentration of the drug is the driving force behind the movement of the drug into the first layers of the skin (Cairncross, 1993:55), higher concentrations than those calculated for controlled release drug delivery devices were used for the *in vivo* study. In order to assure that an excess of the drug is present after application, 0.75 mg of the drug was applied (150 µl of a 5 $mg.ml^{-1}$ solution) (see 3.2.2.2).

3.2.2.2 Vehicles used in this in vivo study

The rate of percutaneous absorption of a drug greatly depends upon the nature of the vehicle in which it is presented. A drug administered at a potentially effective concentration may, after all, be rendered ineffective by an inappropriate vehicle. The vehicle might exert an influence either indirectly by affecting the partition coefficient of the drug or directly by altering the physical properties of the skin, perhaps, by promoting hydration (Parikh *et al.*, 1984:292). Numerous transdermal absorption studies, both *in vitro* and *in vivo* were conducted using ethanol/water (70:30) as donor medium (Hadgraft *et al.*, 1995:285; Calpena *et al.*, 1994:29; Mak *et al.*, 1990:67 and Naik *et al.*, 1995:299). In this study ethanol/water (68:32) was used as donor medium for the various formulations tested.

Ethanol and the various penetration enhancers, solvents with enhancing properties and solubilising agents were used as vehicles for chlorpromazine hydrochloride and doxylamine succinate respectively.

Oleic acid is often used as a penetration enhancer alone or in combination with solvents with enhancing properties such as alcohols (Baker and Santus, 1993:12).

The fact that oleic acid is an endogenous component of skin lipids (Lampe in Tanojo, 1996:110) increases their potential to be used as penetration enhancers because they are not irritating to the skin (Baker and Santus, 1993:13-14), and the fetus would not be in danger, due to exposure to foreign particles. The mode of action of oleic acid as penetration enhancer is still under investigation, but it has been postulated that penetration enhancement can be achieved by increasing drug solubility in the vehicle (Goodman in Tanojo, 1996:100) or by fluidising of the skin lipid structure in a manner analogous to enhanced membrane permeability resulting from thermally induced stratum corneum lipid disordering (Naik *et al.*, 1995:300). Mak *et al.* (1990:73) did a study to determine the concentration of oleic acid necessary for maximal penetration enhancing. They found that there was an increase in stratum corneum lipid disorder up to a concentration of 1 %, a further increase in concentration (from 1 % to 10 %) did not cause additional disordering and thus could be considered to be harmless (Tanojo, 1996:119).

Phosphatidylcholine and other phospholipids act by reducing the skin's resistance to drug permeation and not by increasing drug solubility (Mahjour *et al.*, 1990:251). A percutaneous penetration study conducted by Yokomizo (1996:225) showed that treatment with 5 % phospholipids was superior to penetration with 1 % phospholipids.

Transcutol® may enhance drug penetration by diffusing into the stratum corneum and altering the solubility parameter, but does not appear to have a fluidising effect on structured lipids (Harrison *et al.*, 1996:545). Panchagnula and Ritschel (1991:610) found that 50 % Transcutol® was the optimum concentration to be used.

Labrafil M 1944 CS® is a non ionic amphiphilic excipient used as a solubilising agent (Product information, Gattefossé Co.). Bonina *et al.* (1993:45 - 55) demonstrated the ability of Labrafil® to facilitate the flux and the diffusivity of caffeine across the stratum corneum. They concluded that the potential of a vehicle to increase the affinity between stratum corneum and drug should be considered with regard to transdermal and topical drug delivery. Paulesu *et al.* (1988:200) found that Labrafil® did not significantly improve the absorption of interferon administered by oral route, but it modified the pattern of the areas under curve. The peak was delayed when

Labrafil® was present and remained fairly constant until the end of the experiment. Labrafil M 1944 CS® is a composition of palmitic acid, stearic acid, oleic acid, linoleic acid and other mono-, di- and triglycerides and polyethylene glycol mono- and diesters. The mode of action of Labrafil M 1944 CS® is not clear, but it might be similar to that of the fatty acid and fatty acid ester enhancers - increasing drug solubility or fluidising the skin lipid structure (Goodman in Tanojo, 1996:100 and Tanojo, 1996:100). No information concerning the optimum concentration to be used could be obtained from the literature.

Table 3.2 shows the concentrations and amounts of the drugs and vehicles applied to the dorsal skin of the hairless mice as previously described in 2.4.4.

TABLE 3.2: *Concentrations and amounts of chlorpromazine hydrochloride, doxylamine succinate, penetration enhancers, solvents and solubilising agents applied to the dorsal skin of the laboratory animals, after the application of 150 µl (0.75 mg) of the various formulations.*

Formula applied	Drug (mg) CP[1] or DS[2]	Ethanol % (v/v)	Oleic acid % (v/v)	PC[3] % (m/v)	Transcutol® % (v/v)	Labrafil M 1944 CS® % (v/v)
1	0.75	100				
2	0.75	95	5			
3	0.75	95		5		
4	0.75	50			50	
5	0.75	50				50

1 Chlorpromazine hydrochloride

2. Doxylamine succinate

3 Phosphatidylcholine

3.2.3 Lipid/water partition coefficient (log P)

The lipid/water partition coefficient of a drug is one of the basic determinants for specific drug permeability through the stratum corneum. Substances with either too low or too high lipophilicity will have low rates of diffusion through the stratum corneum (Parikh *et al.*, 1984:291). Once a drug has crossed the stratum corneum, it

corneum into the living cells of the epidermis, which will largely be aqueous in nature and which is essentially buffered at pH 7.4 (Smith, 1990:25). The log P value of chlorpromazine hydrochloride was experimentally determined to be 3.71 (HyperChem™, Hypercube, Inc., Canada), while the value obtained from the literature is 3.4 (Lund, 1994:800). Doxylamine succinate's log P value was determined to be 2.56 (HyperChem™, Hypercube, Inc., Canada), while no value could be found in the literature.

3.2.4 Sample collection

Samples were collected as described in 2.4.5. All samples were protected from light due to the fact that chlorpromazine hydrochloride and doxylamine succinate are both light sensitive drugs. Samples were stored at room temperature and analysed within 24 hours after collection.

3.2.5 Calibration curve

Calibration curves for the analysis of chlorpromazine hydrochloride and doxylamine succinate in saline solution were made using saline solution containing a known amount of chlorpromazine hydrochloride and doxylamine succinate respectively. Concentrations and preparation of the calibration curves are indicated in 2.3.3.2.1.

3.3 RESULTS

3.3.1 Chlorpromazine

The mean chlorpromazine concentrations together with the standard deviations (SD) for the five formulations tested are shown in table 3.3.

The mean chlorpromazine concentrations as function of time for the five formulations are shown in figure 3.1 and the mass/unit area-time profiles for the five formulations of chlorpromazine are shown in figure 3.2.

TABLE 3.3: *Mean chlorpromazine concentrations (n=6) that penetrated the skin after topical application of chlorpromazine hydrochloride in ethanol and in combination with the penetrations enhancing and solubilizing agents. (150 µl of a 5 mg.ml^{-1} chlorpromazine hydrochloride solution equivalent to 0.75 mg chlorpromazine hydrochloride were applied).*

	Concentration chlorpromazine (ng.ml^{-1}) following topical application of 5 mg.ml^{-1} of the drug				
Formulation	**Ethanol**	**Oleic acid**	**Phosphatidylcholine**	**Transcutol®**	**Labrafil M 1944 CS®**
Time (h)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
0.0	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000
0.5	10.34 ± 2.4999	23.41 ± 19.0699	7.03 ± 8.6471	9.68 ± 6.2476	16.43 ± 13.1898
1.0	11.28 ± 3.2322	18.53 ± 18.1498	5.72 ± 8.2330	8.16 ± 4.1053	10.78 ± 8.7344
1.5	9.57 ± 3.4372	15.50 ± 15.1787	1.88 ± 1.5624	6.37 ± 3.3439	3.11 ± 1.4108
2.0	7.86 ± 3.1533	10.32 ± 9.5040	2.31 ± 1.7141	5.44 ± 2.5016	2.82 ± 0.8461
2.5	5.77 ± 2.1111	8.62 ± 6.6356	1.85 ± 1.0540	5.23 ± 1.8183	7.23 ± 7.3225
3.0	5.29 ± 2.0081	7.63 ± 5.2362	2.14 ± 1.7098	5.49 ± 1.6063	9.10 ± 6.7820
3.5	5.10 ± 2.0646	10.86 ± 11.4344	3.11 ± 1.7605	3.89 ± 1.4852	6.71 ± 1.5643
4.0	4.54 ± 1.7619	22.14 ± 15.9894	3.26 ± 1.7628	4.28 ± 1.6943	8.51 ± 7.0985
4.5	4.33 ± 1.5704	46.75 ± 21.3547	3.29 ± 1.6916	3.27 ± 0.8284	4.79 ± 1.7076
5.0	4.23 ± 1.3383	61.67 ± 24.4364	2.93 ± 1.4899	2.93 ± 0.9514	4.41 ± 2.2673
5.5	4.50 ± 1.3882	82.30 ± 35.3273	4.13 ± 3.8113	2.34 ± 1.0662	4.53 ± 2.7617
6.0	4.38 ± 1.7951	97.79 ± 40.7535	3.79 ± 1.2709	2.15 ± 1.2635	3.72 ± 1.9998

TABLE 3.3: (continued)

	Concentration chlorpromazine ($ng.ml^{-1}$) following topical application of 5 $mg.ml^{-1}$ of the drug				
Formulation	**Ethanol**	**Oleic acid**	**Phosphatidylcholine**	**Transcutol®**	**Labrafil M 1944 CS®**
Time (h)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
6.5	4.30 ± 1.7955	111.16 ± 49.2953	4.12 ± 1.3121	2.21 ± 1.0307	4.23 ± 1.0976
7.0	4.47 ± 1.5193	121.81 ± 50.3055	3.85 ± 1.9199	2.11 ± 0.9043	5.21 ± 2.2384
7.5	4.23 ± 1.4827	126.11 ± 57.5525	4.61 ± 3.1000	1.92 ± 0.8317	4.77 ± 1.8291
8.0	4.22 ± 1.2907	136.23 ± 56.8480	3.70 ± 1.9140	1.84 ± 0.6497	4.80 ± 1.6694
8.5	4.11 ± 1.5673	130.55 ± 60.5704	3.36 ± 1.6358	1.67 ± 0.7522	4.50 ± 1.0294
9.0	3.76 ± 1.6269	123.61 ± 57.9658	3.15 ± 1.7271	1.35 ± 0.6507	4.66 ± 1.2904
9.5	3.73 ± 1.3247	104.87 ± 46.9124	2.90 ± 1.5230	1.50 ± 0.6554	4.86 ± 1.9963
10.0	3.35 ± 1.4308	90.16 ± 35.7268	2.34 ± 1.2781	1.38 ± 0.5628	4.28 ± 1.2451
10.5	3.05 ± 1.1943	78.69 ± 26.6557	2.19 ± 1.6260	1.30 ± 0.5133	4.10 ± 1.2733
11.0	2.98 ± 1.1403	63.45 ± 12.9294	2.02 ± 1.2030	1.19 ± 0.5273	3.75 ± 0.5889
11.5	2.71 ± 0.8096	47.83 ± 6.3196	1.73 ± 1.3726	1.07 ± 0.3429	3.48 ± 0.7476
12.0	2.28 ± 0.9769	37.00 ± 2.2303	1.21 ± 1.3245	0.96 ± 0.2261	3.66 ± 0.8061

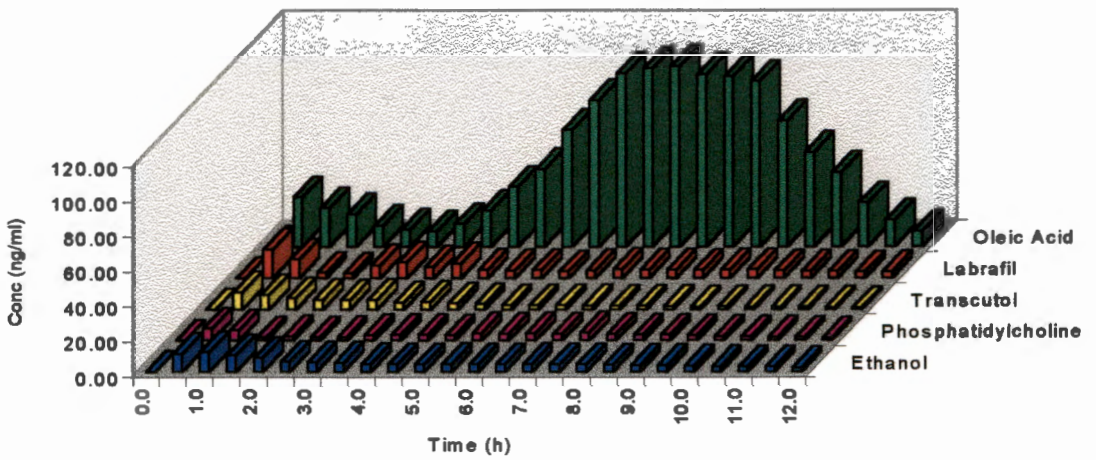


FIGURE 3.1: *Mean concentration-time profile for all five formulations of chlorpromazine (n = 6), after the dorsal application of 150 µl of a 5 mg.ml^{-1} solution of chlorpromazine hydrochloride together with the various penetration enhancers, solvents and solubilising agents*

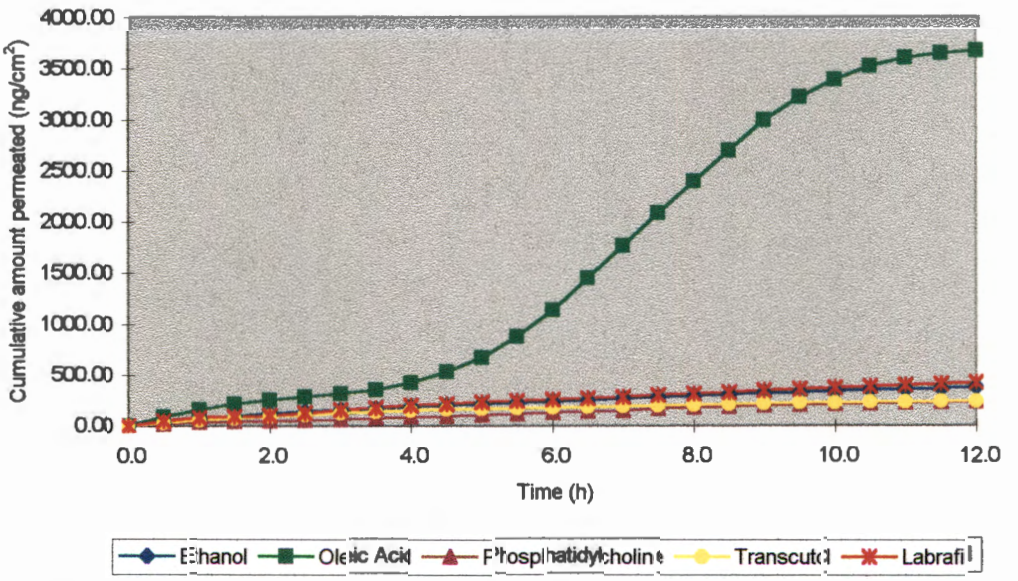


FIGURE 3.2: *Mass/unit area-time profile for all five formulations of chlorpromazine (n = 6), after the dorsal application of 150 µl of a 5 mg.ml^{-1} solution of chlorpromazine hydrochloride together with the various penetration enhancers, solvents and solubilising agents*

The pharmacokinetic parameters (n = 6) calculated for the five different formulations are summarised in table 3.4.

TABLE 3.4: *Pharmacokinetic parameters of chlorpromazine determined after transdermal application of 150 µl of a 5 mg.ml^{-1} solution of chlorpromazine hydrochloride in ethanol together with the various penetration enhancers, solvents and solubilising agents (n = 6).*

FORMULATION	Flux ($\mu g.cm^{-2}.h^{-1}$)	$AUC_{(0-12h)}$ ($ng.ml^{-1}.h$)	C_{max} ($ng.ml^{-1}$)	T_{max} (h)	Lag time (T_o) (h)
Ethanol	3.51 ± 1.22	59.59 ± 18.37	11.66 ± 2.91	0.83 ± .026	0.48 ± 0.25
Oleic acid	45.49 ± 22.70	586.83 ± 298.57	118.64 ± 51.21	8.08 ± 0.66	1.44 ± 0.12
Phosphatidylcholine	2.71 ± 0.94	38.01 ± 10.86	9.52 ± 7.91	3.67 ± 3.39	0.88 ± 0.33
Transcutol®	2.07 ± 0.38	38.61 ± 8.74	9.68 ± 6.25	0.50 ± 0.00	0.34 ± 0.19
Labrafil M 1944 CS®	3.66 ± 0.87	66.35 ± 15.74	20.78 ± 11.16	2.17 ± 2.96	0.73 ± 0.46

3.3.1.1 Statistical comparison of the applied formulations of chlorpromazine hydrochloride

The AUC values for the different formulations were calculated from the mean chlorpromazine concentrations using the trapezoidal rule. The determination of statistically significant differences in the areas under the concentration-time curves (AUC values) between the five formulations were based on Dunnett's T-test. Table 3.4 lists the AUC values of the different formulations of chlorpromazine hydrochloride.

Statistically significant differences ($p < 0.05$) with a confidence interval of 95 % were indicated for the parameter AUC between chlorpromazine in ethanol (as solvent) and chlorpromazine with oleic acid as enhancer. The other formulations with chlorpromazine did not show any statistically significant differences ($p < 0.05$). In this case it was found that oleic acid was able to enhance the transdermal absorption

of chlorpromazine to such an extent (10 times more compared to ethanol) that therapeutic equivalent levels were obtained.

3.3.2 Doxylamine

The mean doxylamine concentrations together with the standard deviations (SD) for the five formulations tested are shown in table 3.5.

The mean doxylamine concentrations as function of time for the five formulations are shown in figure 3.3 and the mass/unit area-time profiles for the five formulations of doxylamine are shown in figure 3.4.

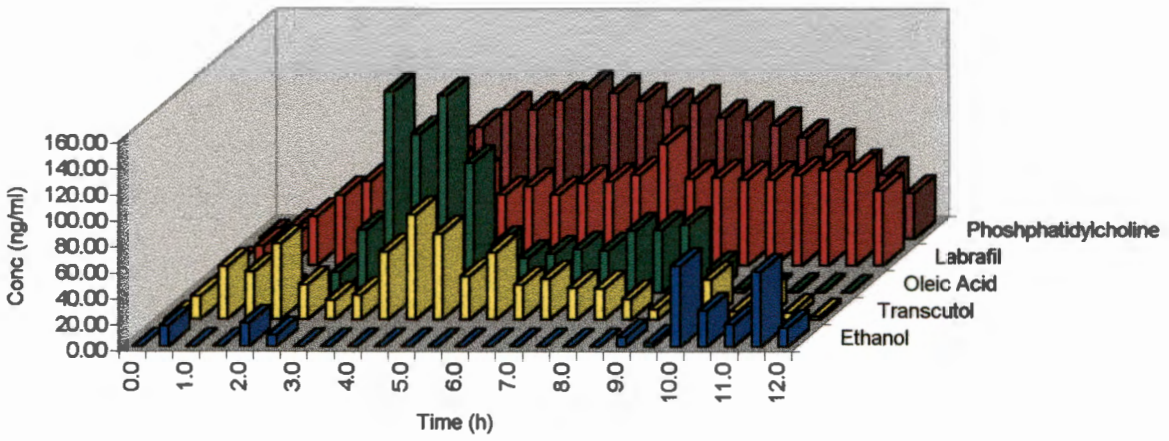


FIGURE 3.3: *Mean concentration-time profile for all five formulations of doxylamine (n = 6), after the dorsal application of 150 µl of a 5 mg.ml^{-1} solution of doxylamine succinate together with the various penetration enhancers, solvents and solubilising agents*

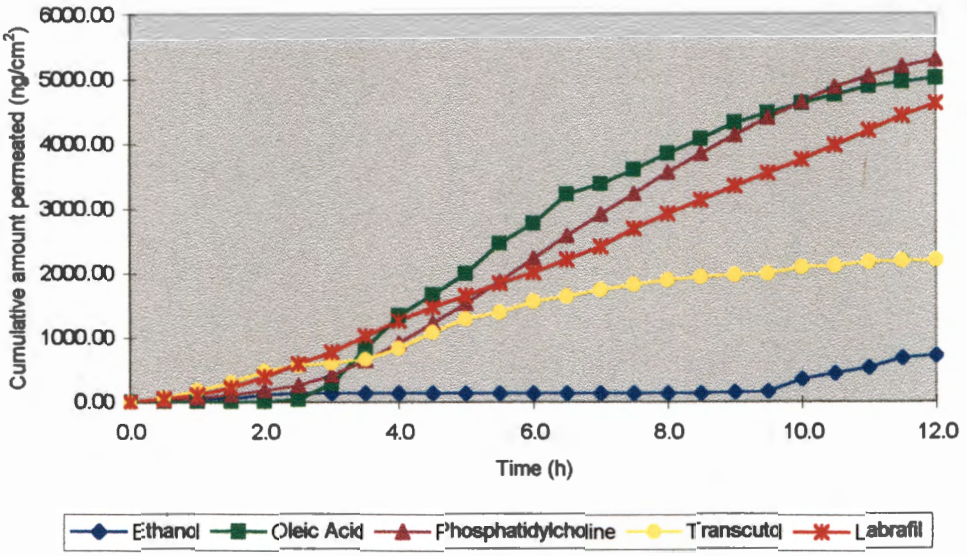


FIGURE 3.4: *Mass/unit area-time profile for all five formulations of doxylamine (n = 6), after the dorsal application of 150 µl of a 5 mg.ml^{-1} solution of doxylamine succinate together with the various penetration enhancers, solvents and solubilising agents*

TABLE 3.5: *Mean doxylamine concentrations (n=6) that penetrated the skin after topical application of doxylamine succinate in ethanol and in combination with the penetrations enhancing and solubilising agents. (150 µl of a 5 mg.ml^{-1} doxylamine succinate solution equivalent to 0.75 mg doxylamine succinate were applied).*

	Concentration doxylamine (ng.ml^{-1}) following topical application of 5 mg.ml^{-1} of the drug				
Formulation	**Ethanol**	**Oleic acid**	**Phosphatidylcholine**	**Transcutol®**	**Labrafil M 1944 CS®**
Time (h)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
0.0	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000	0.00 ± 0.0000
0.5	16.22 ± 23.8376	< LOQ	8.08 ± 13.0014	17.92 ± 19.7465	14.88 ± 10.0747
1.0	< LOQ	< LOQ	11.93 ± 13.7656	40.82 ± 76.7525	19.07 ± 9.1581
1.5	< LOQ	< LOQ	16.13 ± 18.1982	36.72 ± 50.6032	37.59 ± 18.7883
2.0	18.09 ± 26.5851	< LOQ	20.60 ± 24.1634	58.66 ± 43.1640	54.35 ± 27.9197
2.5	9.01 ± 13.2436	15.54 ± 14.7601	27.66 ± 23.1376	27.08 ± 33.1400	65.15 ± 35.0219
3.0	< LOQ	48.48 ± 23.0491	51.37 ± 27.1083	15.23 ± 28.5946	56.74 ± 59.2605
3.5	< LOQ	154.78 ± 71.8875	73.05 ± 25.2722	18.93 ± 31.7058	79.69 ± 47.9661
4.0	< LOQ	122.33 ± 99.7511	85.73 ± 34.3944	52.09 ± 77.9856	77.36 ± 45.5536
4.5	< LOQ	152.11 ± 124.3868	99.35 ± 27.8200	81.23 ± 84.8290	69.49 ± 33.5823
5.0	< LOQ	100.02 ± 72.2334	99.37 ± 18.4528	66.33 ± 71.5481	54.80 ± 33.3575
5.5	< LOQ	37.21 ± 25.5990	106.53 ± 19.3759	33.44 ± 33.9983	61.18 ± 44.3249
6.0	< LOQ	26.37 ± 18.4357	115.51 ± 21.5948	52.00 ± 55.8637	54.45 ± 43.7221

TABLE 3.5: (continued)

	Concentration doxylamine ($ng.ml^{-1}$) following topical application of 5 $mg.ml^{-1}$ of the drug				
Formulation	**Ethanol**	**Oleic acid**	**Phosphatidylcholine**	**Transcutol®**	**Labrafil M 1944 CS®**
Time (h)	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
6.5	< LOQ	29.89 ± 19.6619	112.00 ± 27.0386	26.96 ± 50.3078	63.74 ± 65.5423
7.0	< LOQ	33.43 ± 6.2527	106.37 ± 27.3653	31.22 ± 45.2380	64.95 ± 58.2222
7.5	< LOQ	32.32 ± 26.0941	101.75 ± 28.3419	24.66 ± 30.1920	69.88 ± 50.3140
8.0	< LOQ	47.90 ± 31.1735	104.66 ± 27.6287	23.77 ± 44.9403	93.97 ± 66.4249
8.5	< LOQ	48.49 ± 32.7459	93.23 ± 25.2403	16.27 ± 31.2885	66.92 ± 53.7600
9.0	7.66 ± 11.2636	52.30 ± 40.6254	91.86 ± 25.8558	8.26 ± 20.2246	67.98 ± 50.5920
9.5	< LOQ	17.73 ± 11.3563	87.37 ± 26.5012	7.54 ± 18.4692	66.66 ± 57.0396
10.0	62.23 ± 91.4599	< LOQ	77.68 ± 21.9977	30.73 ± 56.3770	66.60 ± 47.8433
10.5	28.09 ± 41.2780	< LOQ	70.87 ± 32.7287	6.71 ± 16.4320	70.20 ± 31.2585
11.0	17.56± 25.8095	< LOQ	55.04 ± 31.0988	19.91 ± 48.7693	74.01 ± 15.3075
11.5	57.89± 85.0749	< LOQ	48.88 ± 29.3551	5.85 ± 0.14.3377	73.19 ± 18.8512
12.0	14.45 ± 21.2412	< LOQ	35.18 ± 25.1761	< LOQ	57.93 ± 20.5275

< LOQ : Below the limit of quantification

The pharmacokinetic parameters (n = 6) calculated for the five different formulations are summarised in table 3.6.

TABLE 3.6: *Pharmacokinetic parameters of doxylamine determined after transdermal application of 150 µl of a 5 mg.ml^{-1} solution of doxylamine succinate in ethanol together with the various penetration enhancers, solvents and solubilising agents (n = 6).*

FORMULATION	Flux ($\mu g.cm^{-2}.h^{-1}$)	$AUC_{(0-12h)}$ ($ng.ml^{-1}.h$)	C_{max} ($ng.ml^{-1}$)	T_{max} (h)	Lag time (T_o) (h)
Ethanol	2.22 ± 5.44	68.15 ± 166.92	62.23 ± 91.46	10.00 ± 0.00	0.21 ± 0.50
Oleic acid	40.46 ± 14.77	462.66 ± 116.60	198.76 ± 90.84	5.20 ± 2.17	1.00 ± 0.48
Phosphatidylcholine	67.77 ± 12.70	841.29 ± 159.09	122.19 ± 24.68	5.58 ± 1.69	1.37 ± 0.11
Transcutol®	27.83 ± 19.38	351.78 ± 241.70	174.29 ± 32.09	6.33 ± 3.21	1.24 ± 0.63
Labrafil M 1944 SC®	52.96 ± 26.65	725.90 ± 342.21	131.58 ± 39.25	7.25 ± 3.36	1.24 ± 0.18

3.3.2.1 Statistical comparison of the applied formulations of doxylamine succinate

The AUC values for the different formulations were calculated from the mean doxylamine concentrations using the trapezoidal rule. The determination of statistically significant differences in the areas under the concentration-time curves (AUC values) between the five formulations were based on Dunnett's T-test. Table 3.6 lists the AUC values of the different formulations of doxylamine.

Statistically significant differences ($p < 0.05$) with a confidence interval of 95 % were indicated for the parameter AUC between doxylamine in ethanol and doxylamine with oleic acid as enhancer, doxylamine in ethanol and doxylamine together with phosphatidylcholine, between doxylamine in ethanol and doxylamine in combination with Transcutol® and between doxylamine in ethanol and doxylamine with Labrafil M 1944 CS®.

3.4 DISCUSSION

3.4.1 Chlorpromazine

The transdermal absorption of chlorpromazine in combination with oleic acid produced promising results (figure 3.1). As seen from the pharmacokinetic parameters after application of the five formulations of chlorpromazine in table 3.5, it was only oleic acid which produced concentration, and a flux, high enough to be of therapeutic value. The concentrations obtained fell within the therapeutic index of chlorpromazine hydrochloride (30 - 350 $ng.ml^{-1}$) (Reynolds, 1993:1669), and were maintained for a period of 7.5 h (4.5 to 12.0 h after application). The maximum concentration (C_{max}) reached was 118.64 ± 51.21 $ng.ml^{-1}$ at a time of 8.08 ± 0.66 h, with flux and $AUC_{(0 - 12h)}$ values of 45.49 ± 22.70 $\mu g.cm^{-2}.h^{-1}$ and 586.83 ± 298.57 $ng.ml^{-1}.h$ respectively.

Chlorpromazine in ethanol did not show any significant absorption. The use of phosphatidylcholine, Transcutol® and Labrafil M 1944 CS® as penetration enhancers and solubilising agents did not improve the transdermal delivery of chlorpromazine to such an extend that it could be of any therapeutic importance.

3.4.2 Doxylamine

Figure 3.2 clearly shows that all the formulations of doxylamine succinate, except for doxylamine in ethanol reached concentrations comparable to therapeutic levels. The concentration-time profiles of the different formulations showed that doxylamine in combination with phosphatidylcholine provided the most promising results.

The pharmacokinetic parameters after application of the five formulations of doxylamine (table 3.6) showed that the highest $AUC_{(0 - 12h)}$ - 841.29 ± 159.09 $ng.ml^{-1}.h$ - and flux - 67.77 ± 12.70 $\mu g.cm^{-2}h^{-1}$ - were obtained with phosphatidylcholine as enhancer.

Concentrations which fell within the therapeutic index of doxylamine succinate (5 - 300 $ng.ml^{-1}$) were reached with oleic acid (2.5 to 12.0 h after application),

phosphatidylcholine (1.0 to 12.0 h), Transcutol® (0.5 to 8.5 h) and Labrafil M 1944 CS® (0.5 to 12.0 h) as enhancers. Therapeutic levels were maintained for periods of 9.5; 11; 8 and 11.5 h respectively. The maximum concentration (C_{max}) was reached with oleic acid (198.76 ± 90.84 $ng.ml^{-1}$) at a time of 5.30 ± 2.17 h.

Commercially available nitroglycerin as a model drug for transdermal absorption show fluxes of 10 - 20 $\mu g.cm^{-2}.h^{-1}$ and $AUC_{(0-24\ h)}$ values ranging from 1661 ± 419 to 2094 ± 315 $ng.ml^{-1}.h$ (Ridout *et al.*, 1988:124). Chlorpromazine hydrochloride in combination with oleic acid showed similar trends as nitroglycerin when comparing the flux and the AUC. Doxylamine in combination with oleic acid, phosphatidylcholine, Transcutol® and Labrafil M 1944 CS® respectively also compared well with values obtained from commercially available nitroglycerin.

3.5 CONCLUSION

Chlorpromazine hydrochloride and doxylamine succinate are both anti-emetic drugs that are proven safe and effective for use against nausea and vomiting associated with pregnancy. Considering the physicochemical as well as the pharmacokinetic properties of these two drugs and the characteristics that are necessary for transdermal absorption, it became apparent that doxylamine would be the drugs of choice to study transdermal absorption.

Results obtained with chlorpromazine hydrochloride in combination with oleic acid showed promising results. The mode of action of oleic acid is not clear, but it might be speculated that oleic acid act by fluidising the skin lipids. Another explanation for the good results obtained with oleic acid as penetration enhancer, may be due to the fact that it is used in combination with ethanol. Not one of the other formulations of chlorpromazine hydrochloride showed concentrations comparable to therapeutic levels. One of the reasons for the poor absorption of chlorpromazine may be that the lipid/water partition coefficient (log P) of chlorpromazine (3.71) is too high for transdermal absorption. Chlorpromazine hydrochloride would therefore not be recommended as a suitable drug for transdermal drug delivery.

Results obtained with doxylamine succinate in combination with the different penetration enhancers showed that this drug is an excellent candidate for inclusion into a transdermal drug delivery system (TTS). The data obtained compared well with data obtained from commercially available nitroglycerin - used as a model drug for transdermal drug delivery. With a lipid/water partition coefficient of 2.56 it once again became apparent that the log P value is a useful parameter in predicting the transdermal delivery of drugs. According to Guy (1996:1766) compounds with a log P value between 1 and 3, with relatively low molecular weight and modest melting points, are likely to have good transdermal absorption. Guy and Hadgraft (1989:70-71) stated that a drug with a log P value of < 2 can be considered to be a potential candidate for transdermal delivery.

From this study followed that:

- chlorpromazine hydrochloride with oleic acid as penetration enhancer showed excellent transdermal absorption ($AUC_{(0 - 12\ h)}$ = 586.83 ± 298.57 $ng.ml^{-1}.h$ and flux = 45.49 ± 22.70 $\mu g.cm^{-2}.h^{-1}$);

- chlorpromazine hydrochloride in ethanol did not show any significant absorption. Using phosphatidylcholine, Transcutol® and Labrafil M 1944 CS® as enhancers, solvents and solubilising agents, did not improve transdermal absorption to such an extend that it was of therapeutic importance;

- doxylamine succinate in ethanol in combination with oleic acid showed good transdermal absorption ($AUC_{(0 - 12\ h)}$ = 462.66 ± 116.60 $ng.ml^{-1}.h$ and flux = 40.46 ± 14.77 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate combined with phosphatidylcholine had the ideal concentration-time profile for transdermal drug delivery, with concentrations comparable to therapeutic levels obtained for 11 hours ($AUC_{(0 - 12\ h)}$ = 841.29 ± 59.09 $ng.ml^{-1}.h$ and flux = 67.77 ± 12.70 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate together with Transcutol® also showed good transdermal absorption ($AUC_{(0 - 12\ h)}$ = 351.78 ± 241.70 $ng.ml^{-1}.h$ and flux = 27.83 ± 19.38 $\mu g.cm^{-2}.h^{-1}$);

- doxylamine succinate and Labrafil M 1944 CS® showed good transdermal absorption ($AUC_{(0 - 12\ h)}$ = 725.90 ± 342.21 $ng.ml^{-1}.h$ and flux = 52.96 ± 26.65 $\mu g.cm^{-2}.h^{-1}$) and concentrations comparable to therapeutic levels were maintained for 11.5 hours and

- doxylamine succinate in ethanol did not show any significant transdermal drug delivery.

In continuation of this study the following should be investigated:

- the transdermal delivery of chlorpromazine hydrochloride in combination with other penetration enhancers;

- formulation of transdermal drug delivery systems (TTS) with doxylamine succinate in combination with oleic acid, phoshpatidylcholine, Transcutol® and Labrafil M 1944 CS® respectively;

- transdermal delivery of doxylamine succinate in combination with other penetration enhancers and

- other routes of drug delivery e.g. intranasal administration, could be investigated as alternative to peroral administration of anti-emetic drugs.

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