CHARACTERISATION AND FORMULATION OF TOPICAL METHYL SALICYLATE PATCHES: EFFECT OF SOLVENTS ON ADHESION AND DRUG PERMEATION

YEOH SOO CHIN

UNIVERSITI SAINS MALAYSIA

2023

CHARACTERISATION AND FORMULATION OF TOPICAL METHYL SALICYLATE PATCHES: EFFECT OF SOLVENTS ON ADHESION AND DRUG PERMEATION

by

YEOH SOO CHIN

Thesis submitted in the fulfilment of the requirements
for the degree of
Master of Science

January 2023

ACKNOWLEDGEMENT

It is always a pleasure to remind the friends in Universiti Sains Malaysia for their suggestions and guidance to uphold my practical skills.

In the journey of my postgraduate study, I would like to express my sincere gratitude to Dr Goh Choon Fu as my supervisor for providing me the opportunity to take this industrial collaboration project. His patience and helpfulness enable me to grow as a research scientist by sharing his immense knowledge. The support from him helps me go through the hard time during research and thesis writing.

My thanks also extended to Ministry of High Education and THP Medical Sdn Bhd for their financial support. I would like to express my appreciation to Ms Loh Poh Lee and the staffs in THP Medical Sdn Bhd for their sharing assistance and experience. Without their cooperation, the research work cannot be done smoothly and successfully.

A warm appreciation given to Professor Dr Vikneswaran A/L Murugaiyah for giving suggestions and recommendations on this study. Also, a special thanks to Ms Wong Li Ching for being a good lab mate and friend. I feel grateful for her helps throughout the research. I am thankful to the Skin Lab members making a pleasure environment to work.

Last but not least, words are insufficient to express my warm gratitude to my family members for their financial and moral support. Their encouragement always keeps me up to go through the hard time. I would like to thanks my little sister for always cheering me up.

TABLE OF CONTENTS

LIST OF TABLES

Page

LIST OF FIGURES

Page

LIST OF SYMBOLS

R^2	Correlation coefficient
J_{max}	Maximum flux
P	Octanol/water partition coefficient
n	Release exponent
J_{ss}	Steady-state flux
σ	Surface tension
T_{max}	Time to maximum flux

LIST OF ABBREVIATIONS

ANOVA	Analysis of Variance
ATR-FTIR	Attenuated total reflectance-Fourier transform infrared
CMC	Carboxymethyl cellulose
DIA	Drug-in-adhesive
Durabond	Durabond PC 1879A
HPLC	High-performance liquid chromatography
IPM	Isopropyl myristate
LA	Labrasol®
LOD	Limit of detection
LOQ	Limit of quantification
MAI	Maisine® CC
MS	Methyl salicylate
Nikasol	Nikasol TS-6520
PBS	Phosphate buffered saline
PLU	Plurol® oleique CC 497
PVP	Polyvinyl pyrrolidone
PSA	Pressure-sensitive adhesives
PG	Propylene glycol
SC	Stratum corneum
TRC	Transcutol®

LIST OF APPENDICES

PENCIRIAN DAN FORMULASI TAMPAL TOPIKAL METIL SALISILAT: KESAN PELARUT PADA PELEKATAN DAN PENELAPAN DRUG

ABSTRAK

Tampalan topikal metil salisilat (MS) adalah popular untuk pengendalian kesakitan. Profil penelapan kulit daripada MS adalah penting untuk reka bentuk formulasi tetapi kajian yang sediakan adalah terhad. Projek ini bertujuan untuk menyiasat pengaruh pelarut terhadap pencirian tampalan, pelepasan ubat dan penelapan MS. Dalam projek ini, pelarut yang sesuai telah dipilih untuk formulasi tampalan. Spectroskopi transformasi Fourier Infra Merah dengan Pantulan Penuh Pengecilan (ATR-FTIR) telah digunakan untuk mengimbas helaian stratum korneum (SC) yang dirawat dengan pelarut dan MS. Seterusnya, kajian penelapan *in vitro* telah dijalankan dengan 10%v/v MS dalam pelarut. Selepas itu, tampalan yang mengandungi 5% w/w pelarut dan/atau 10% w/w MS telah disediakan dengan Durabond PC 1879A (8%w/w), Nikasol TS-620 (7%w/w), selulosa karboksimetil (3.5% w/ w) dan polivinil pirolidon (3% w/w). Seterusnya, tampalan yang terbentuk tertakluk kepada ujian pencirian fisiokimia, termasuk spektroskopi ATR-FTIR, kajian kelekitan menggunakan kuar keluli tahan karat, kajian kekuatan kupasan dengan kulit telinga khinzir, kajian pengembungan, kajian pelepasan ubat dan kajian resapan kulit *in vitro*. Dalam kajian penelapan *in vitro*, propilena glikol (PG) dalam larutan ubat menunjukkan penelapan kulit terhadap MS yang tertinggi dan diikuti oleh Plurol® oleique (PLU), Labrasol® (LA), Transcutol® (TRC), Maisine® (MAI)

dan isopropil miristat (IPM) pada jam 24. Dalam analisis ATR-FTIR, MS, PLU, LA dan IPM menunjukkan gangguan pada lipid SC, manakala perubahan konformasi protein SC telah ditunjukkan oleh PG, PLU, LA, TRC dan MAI. Fenomena ini mungkin menunjukkan bahawa perubahan konformasi protein SC memberikan peningkatan penelapan kulit yang lebih banyak terhadap MS. Penggabungan pelarut meningkatkan kelekitan tampalan tetapi mengurangkan kekuatan kupasan tampalan dengan MAI dan IPM. Kelekitan dan kekuatan kupasan berkurangan dengan MS dalam tampalan, kecuali tampalan MAI. Interaksi pelekat dengan pelarut boleh mempengaruhi kelekitan tampalan pada substrat akibat tindakan pengplastikan atau anti-pengplastikan. Manakala hidrofobisiti pelarut boleh mengurangkan kekuatan kupasan kerana sentuhan dengan kulit yang berkurangan. Tambahan pula, formulasi tampalan mengurangkan kemeruapan MS dengan perolehan MS yang lebih tinggi berbanding dengan larutan ubat. Tampalan MAI mempamerkan penelapan kulit terhadap MS yang tertinggi pada jam 24. Pelepasan ubat yang lebih tinggi dalam tampalan dapat membantu menghasilkan kepekatan MS yang tinggi pada permukaan kulit. Selain itu, interaksi SC dengan pelarut juga memainkan peranan utama dalam meningkatkan penelapan MS. Kesimpulannya, pelarut dapat mempengaruhi ciri-ciri tampalan dan resapan kulit MS. Oleh yang demikian, pelarut dapat mempengaruhi ciri-ciri tampalan dan resapan kulit MS. Keseluruhannya, PG menghasilkan resapan kulit MS yang tertinggi dalam sistem pelarut tunggal (~90 μg/cm^2) selama 24 jam dan kekuatan pelekatan tetapi dengan jumlah kumulatif MS resapan kulit yang lebih rendah (~80 μg/cm^2) antara semua pelarut untuk formulasi tampalan. Walaupun resapan MS yang lebih tinggi

telah dicapai dengan MAI dan TRC dalam fomulasi tampalan (~110 – 150 µg/cm^2), mereka mempunyai kekuatan pelekatan tampalan yang lebih rendah. Oleh itu, formulasi tampalan dengan PG dianggap sebagai formulasi yang unggul dengan kekuatan pelekatan tampalan yang baik secara relatifnya dan jumlah kumulatif MS resapan yang lebih tinggi daripada tampalan komersial untuk tujuan pengurangan kesakitan.

CHARACTERISATION AND FORMULATION OF TOPICAL METHYL SALICYLATE PATCHES: EFFECT OF SOLVENTS ON ADHESION AND DRUG PERMEATION

ABSTRACT

Topical methyl salicylate (MS) patch is popular for pain management. The skin permeation profile of MS is important for formulation design but limited studies were conducted. This project aims to investigate the effect of solvents on the characteristics of patches, drug release and permeation of MS. In this project, suitable solvents were first selected for the patch formulation. Attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectroscopy was utilised to scan the stratum corneum (SC) sheets treated with solvents and MS. Next, *in vitro* permeation studies were carried out with 10%v/v of MS in solvents. After that, patches containing 5%w/w of solvents and/or 10%w/w of MS were prepared with Durabond PC 1879A (8%w/w), Nikasol TS-620 (7%w/w), carboxymethyl cellulose (3.5%w/w) and polyvinyl pyrrolidone (3%w/w). Next, the patches formed were subjected to physiochemical characterisation tests, including ATR-FTIR spectroscopy, tackiness test using stainless-steel probe, peel strength test with porcine ear skin, swelling test, *in vitro* drug release and skin permeation studies. In *in vitro* permeation studies, MS in propylene glycol (PG) in drug solution displayed the highest skin permeation of MS and followed by Plurol® oleique (PLU), Labrasol® (LA), Transcutol® (TRC), Maisine® (MAI) and isopropyl myristate (IPM) at 24 h. In the ATR-FTIR analysis, MS, PLU, LA and IPM

showed disordering of the SC lipids, while the change of the SC protein conformation was exhibited by PG, PLU, LA, TRC and MAI. This may indicate that the SC protein conformation change provides a greater skin permeation enhancement effect on MS. The inclusion of solvents enhanced the tackiness of patches but decreased the peel strength of patches with only MAI and IPM. The tackiness and peel strength decreased with MS in the patch, except for MAI patches. The interaction of adhesives with solvents may influence the tackiness of patches to the substrates due to plasticisation or anti-plasticisation actions. While the hydrophobicity of solvents may decrease the peel strength because of a reduced skin contact. Furthermore, the patch formulation reduced the volatility of MS with a higher recovery of MS as compared with drug solutions. MAI patches exhibited the highest skin permeation of MS at 24 h. A higher drug release in patches may help to create a high concentration of MS on the skin surface. Also, the interaction of the SC with solvents plays a major role in enhancing the permeation of MS. Hence, solvents can strongly affect the characteristics of patches and skin permeation of MS. Overall, PG promoted the highest MS permeation in the neat solvent system (~90 µg/cm^2) over 24 h and patch adhesion but with a lower cumulative amount of MS permeated (~80 µg/cm^2) among all solvents for patch formulation. Despite a higher MS permeation were found with MAI and TRC in the patch formulation (~110 – 150 µg/cm^2), they have a lower patch adhesion. Patch formulation with PG was thus considered an ideal formulation with relatively good patch adhesion and better permeation profile than a commercial patch for pain relief purpose.

CHAPTER 1

INTRODUCTION

1.1. Human skin

Skin is the largest organ of the body, which offers a convenient site for medication administration (Alkilani et al., 2015). Understanding the skin structure is vital to comprehend the mechanism of drug permeation. The skin comprises three layers: epidermis, dermis and hypodermis, as described in Figure 1.

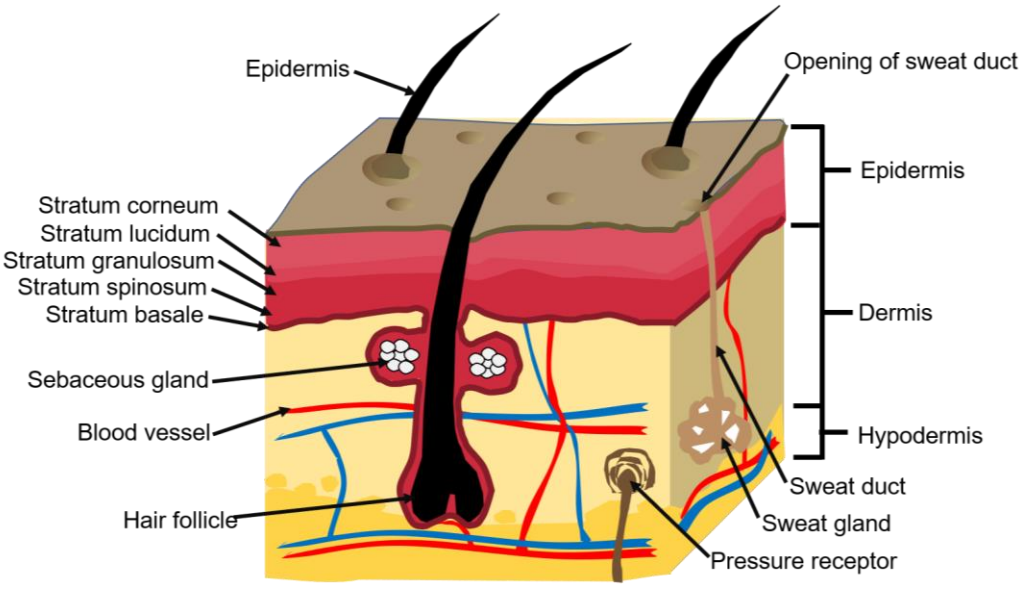


Figure 1 Human skin structure. Adapted from Ng and Lau (2015).

Rein (1924) suggested that the outermost layer of the epidermis, stratum corneum (SC), possessed the highest resistance to the transport of drugs through the skin. The remaining viable epidermis can be further subdivided into stratum lucidum, stratum granulosum, stratum spinosum and

stratum basale (Ng and Lau, 2015). The hydrophilicity of the skin increases with the depth of the skin. Figure 2 describes the structure of the SC. The SC with a thickness of 10 – 20 µm consists of non-living corneocytes embedded in the intercellular lipid matrix (Elias, 1983; Michaels et al., 1975; Pan et al., 2020).

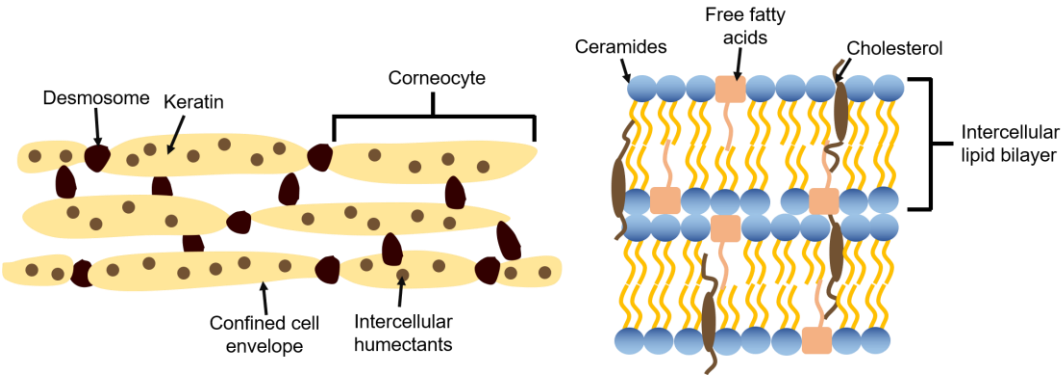


Figure 2 Structure of the SC. Adapted from Abdo et al. (2020).

The intercellular lipid matrix of the SC composes of predominantly ceramides (41%), fatty acids (9%), cholesterol (27%) and cholesterol sulphates (10%) (Bouwstra et al., 2000; Suhonen et al., 1999). Desmosomes connect corneocytes to maintain the structural stability of the SC (Suhonen et al., 1999). The free fatty acids in the SC lipid bilayers are responsible for the hydrophobic properties of the SC. The hydrophobic chains of fatty acids contribute to a non-planar gap between the crystalline lipid lamellae of the cell wall and the neighbouring cells (Yu et al., 2021). The mobility of SC is promoted by cholesterols in the SC (Rawlings, 2003). Cholesterol sulphate provides a stabilising effect by inhibiting the enzymatic degradation of desmosomes (Benson and Watkinson, 2012; Sato et al., 1998). The highly organised and lipophilic SC restricts the permeation of drug molecules.

The skin layer that lies underneath of epidermis is the dermis. The dermis functions to provide elasticity and strength because it contains collagen and elastin (Walters and Roberts, 2002). This layer of skin also delivers oxygen and nutrients to the skin through an extensive vascular network embedded (Benson and Watkinson, 2012). Nerve endings, hair follicles, subcutaneous and sweat glands are also present in the dermis. The hypodermis layer locates in the innermost of the skin, consisting mainly of subcutaneous fats. The hypodermis serves as a storage of energy, protects the skin from shock and allows the mobility of the skin (Gilaberte et al., 2016). Nerves and blood vessels are embedded in this skin layer.

1.2. Percutaneous drug delivery

Percutaneous drug delivery has become one of the popular routes to deliver drugs thereby attracting attentions of scientists to investigate the formulation and delivery of actives through the skin (Abd et al., 2018; Al-Akayleh et al., 2021; Chadha et al., 2011; Geevarghese and Shirolkar, 2020). Drugs delivered through the skin avoid hepatic first-pass metabolism and this provides an alternative route for drugs with a low oral bioavailability and severe systematic side effects (Karande and Mitragotri, 2009). The topical administration is also easy and possible to withdraw immediately. Percutaneous drug delivery can allow the application for more than 24 h and reduce dose frequency.

Drugs can be delivered transdermally to the systemic circulation system to treat systemic diseases such as hypertension (Kshirsagar et al.,

2012; Zafar et al., 2010), Alzheimer's disease (Ameen and Michniak-Kohn, 2017), cardiovascular and cerebrovascular disorders (Shen et al., 2013). In contrast, topical drug delivery is useful for the treatment of local dermatologic disorders (Goyanes et al., 2016; Gupta et al., 2012), skin inflammation (Barone et al., 2020), skin cancer (Jain et al., 2020) and pain management (Jorge et al., 2011; Stanos and Galluzzi, 2013). This is because drugs are only retained in the skin with a lower systemic side effect (Cilurzo et al., 2012).

There are two major pathways for molecules to penetrate through the SC (Hsu et al., 2004). Figure 3 shows the two possible drug transportat routes through the SC, transepidermal (intracellular and intercellular) and transappendageal pathways (Alkilani et al., 2015).

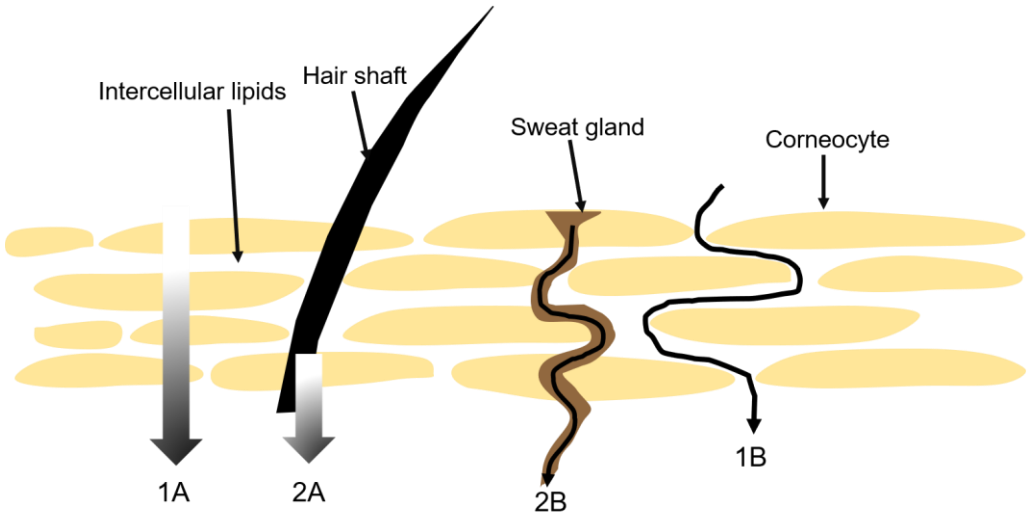


Figure 3 Penetration routes of drugs through the SC: Transepidermal route through (1A) transcellular keratinised cells and (1B) intercellular lipids; Transappendageal via (2A) hair follicle and (2B) sweat gland. Adapted from Hadgraft and Lane (2011).

Transepidermal penetration is sub-divided into intracellular and intercellular routes (Schuetz et al., 2005). Drugs diffuse through the intracellular route by travelling between the corneocytes (Albery and Hadgraft, 1979). This pathway allows the direct transport of hydrophilic or polar drugs through the skin. While, the intercellular pathway occurs by diffusion through the intercellular lipids matrix in the SC (Illel, 1997). The intercellular lipids matrix occupying 5 – 30% of the SC provides a predominant permeability barrier to most molecules (Dayan, 2005). Most lipophilic and amphiphilic drug molecules travel through this pathway (Benson and Watkinson, 2012).

The transappendageal pathway involves the penetration of molecules across sebaceous glands, eccrine (sweat) glands and hair follicles (Benson and Watkinson, 2012). The skin appendages are only available for 0.1 – 1% of the total skin area. However, this route is essential for highly lipophilic drugs such as testosterone (Wierckx et al., 2014) and osthole (Lan et al., 2016).

The rate-limiting step for percutaneous drug delivery depends on the partitioning and diffusion of drugs through the SC (DamgaliI et al., 2022; Subedi et al., 2010b). The drugs then partition into the hydrophilic epidermis and finally the dermis. Drug molecules readily delivered through the skin have the following properties: log *P* between 1 – 3, molecular weight less than 500 Da, daily dosage ≤ 20 mg and melting point less than 200°C. (Brown et al., 2006; Carpentieri-Rodrigues et al., 2007; Karande and Mitragotri, 2009).

1.2.1. Principles of percutaneous drug delivery

Fick's diffusion law is commonly adopted to describe the rate of the transfer of compounds between two compartments across the membrane at a given time (Dayan, 2005; Enderle, 2012). The equation is defined as follows:

$$\frac{dq}{dt} = -DA\,\frac{dc}{dx} \qquad \text{Equation 1}$$

where

q = quantity of compounds

t = time

A = surface area of membrane

c = concentration

D = diffusion coefficient

dx = membrane thickness

$\frac{dc}{dx}$ = concentration gradient

There are two types of dosing to observe the permeation kinetics of permeants, including infinite and finite dosing. The permeation study that evaluates the steady-state flux (J_{ss}) profile should be carried out under infinite dose conditions. Without the influence of dose, a steady-state concentration gradient of the permeant across the membrane can be obtained (Lau and Ng, 2017). The J_{ss} equation is expressed by:

$$J_{SS} = \frac{K_Q D}{\delta} \Delta C_S$$ Equation 2

where

C = concentration

D = diffusion constant

K_Q = partition coefficient

δ = thickness of the SC

Infinite dosing is often utilised to define the properties of permeant but fails to mimic the actual life situation. In contrast, finite dosing uses a small amount of actives that is same as the amount of drugs incorporated in the formulation (Lau and Ng, 2017). The permeation profile with finite dosing can be obtained by plotting a curve between time (t) versus cumulative amount per unit area (Q). The finite dosing is commonly reported as maximum flux (J_{max}) and the time to maximum flux (T_{max}). The J_{max} is acquired from the gradient ($\frac{dQ}{dt}$) of the near-linear portion of the curve. The equations of J_{max} and T_{max} are represented by (Kasting, 2001; Scheuplein and Ross, 1974):

$$J_{max} = \frac{1.85 D C_0 \delta}{h^2}$$ Equation 3

$$T_{max} = \frac{\delta^2 - h^2}{6D}$$ Equation 4

where

D = diffusion coefficient

C_0 = concentration of permeants in the first layer of the SC

h = thickness of the SC

δ = thickness of finite dose layer on the skin surface

1.3. *In vitro* skin permeation studies

In vitro studies are preferred over than *in vivo* studies to observe the skin absorption of formulation because of a low cost and ethical considerations. *In vitro* studies are often conducted using Franz diffusion cells based on the Organisation of Economic Cooperation and Development (OECD) guidelines (OECD, 2004b). The vertical Franz diffusion cells are frequently utilised, consisting of a sampling port, donor and receptor chambers as shown in Figure 4.

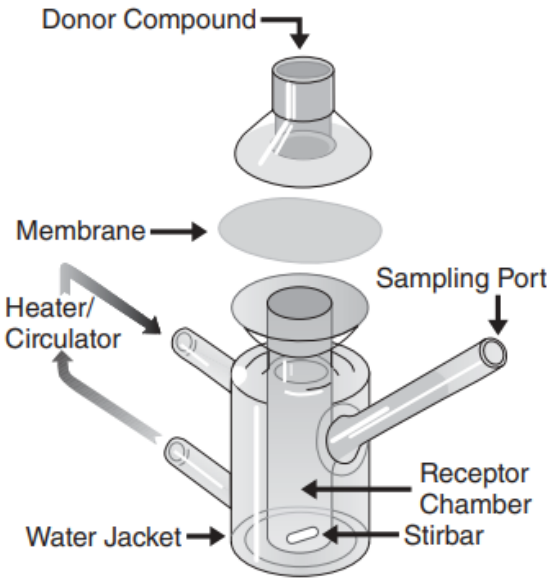


Figure 4 Vertical Franz diffusion cells. Adapted from Finnin et al. (2012).

A piece of membrane is sandwiched between donor and receptor chambers. A good seal between two chambers and mixing is necessary during the permeation study. The donor chamber allows occlusion or unoccluded dosage forms. Besides, the receptor fluid must not be the rate-limiting step for skin absorption and allow a sufficient solubilisation of drugs in

the receptor fluid. The receptor fluid needs to maintain a ‘sink condition’ for continuous drug penetration through the membrane (Finnin et al., 2012). A solubilising agent may be required if the solubility of drugs in the receptor fluid is less than 10 mg/L (Bronaugh and Stewart, 1984).

In vitro studies can be categorised into *in vitro* drug release and *in vitro* permeation tests. *In vitro* drug release tests monitor the amount of dissolved drug to be released from a semi-solid or solid formulation over a period of time. The membrane used for the drug release test must be inert such as nylon, polyethylene and cellulose membranes (Morales et al., 2004; Schulz et al., 2010; Suksaeree et al., 2015).

On the other hand, *in vitro* permeation study is carried out to investigate the activity of excipients or formulation over a period of time and monitor the effectiveness of actives in the formulation. The selection of skin membrane is critical to mimic the *in vivo* studies. Human skin is considered as the gold standard for *in vitro* permeation studies. However, the difficulty in obtaining human skin and ethical issues have become the problems affecting the feasibility of the analysis. Human skin can only be stored at −20°C for 12 months (Bronaugh et al., 1986). A long storage time may weaken the barrier integrity of the skin. Thus, porcine ear skin is the preferred choice because of its similar structure to human skin (Neupane et al., 2020).

Porcine ear skin has compact layers which are similar to human skin (Greve et al., 2008; Jacobi et al., 2007). Keratinocytes are present in the viable epidermis of porcine ear skin. The hair follicles of porcine ear skin have inner and outer root sheath like human skin. The sebaceous glands

with hair follicles and sweat glands with a duct are also present in the porcine ear skin. Table 1 summarises the similarities of porcine ear skin as compared with human skin.

Table 1 Similarities of porcine ear skin and human skin. Adapted from Jacobi et al. (2007).

Description	Human skin	Porcine ear skin
SC thickness (μm)	6 – 19	17 – 28
Thickness of viable epidermis (μm)	70 (shoulder) 82 (buttock)	60 – 85
Thickness of dermis (mm)	1.8 – 1.9 (back) 1 (other body regions)	1.86
Average number of hairs at 1 cm^2	14 – 32	20
Diameter of hairs (μm)	57 – 68 (terminal hairs)	58 – 97
Depth of hairs extended into the dermis (mm)	> 3 mm (terminal hairs) < 1 (vellus hairs)	0.96 – 1.38

1.4. Patch formulation

Many dosage forms are available for transdermal and topical delivery, such as gel, lotion, cream and patches. Patches are more user-friendly than other dosage forms due to their good stability, comfortable to apply, ease to carry and available for a prolonged application without the concern of being washed off. Patches are flexible and single-dose adhesive bandages containing active ingredients to be delivered through the skin (Audett et al., 2013).

The adhesion of the patch is essential to ensure proper dosing for patients and reduce the dose frequency (Wokovich et al., 2006). A patch lacking adhesion may result in the patch falling off, thereby causing the

therapeutic failure. In addition, the patch that quickly falls off may cause high costs to patients.

The adhesion of the patch can be affected by the adhesive materials. The complex combination between the adhesives and patch formulation can be found in different patch designs. Generally, two types of patches are available, reservoir and matrix patches, as shown in Figure 5 (Benson and Watkinson, 2012).

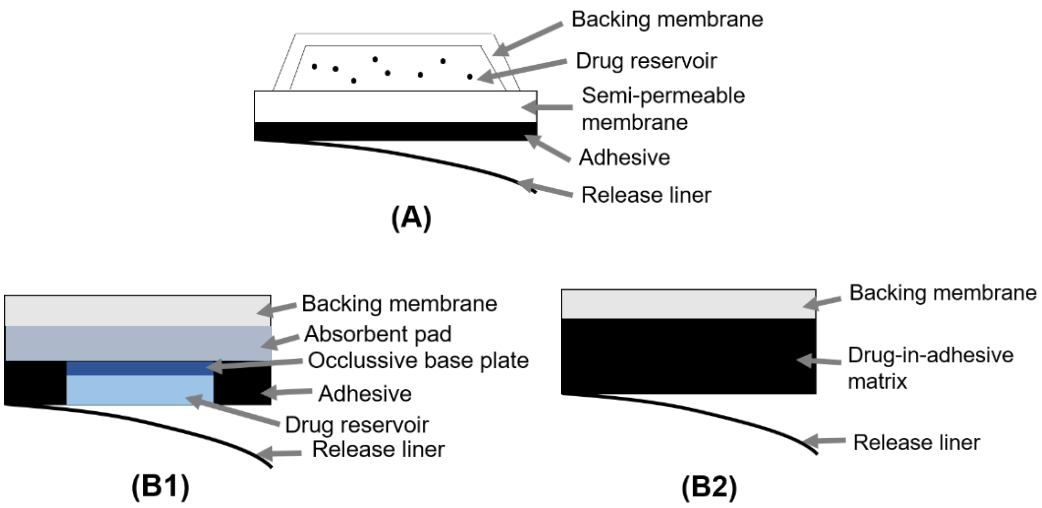


Figure 5 (A) Reservoir and (B) matrix type patches: (B1) matrix-dispersion patch and (B2) DIA patch. Adapted from Dhiman et al. (2011) and Sharma (2018).

A reservoir patch (Figure 5A) consists of a drug reservoir in solution, semi-solid or suspension form that is enclosed between a backing liner and semi-permeable membrane with an adhesive layer and a release liner (Benson and Watkinson, 2012). The drying step can be avoided during preparation of patches. Therefore, the evaporation of the volatile solvents, such as alcohol, can be reduced. The rate-limiting membrane may decrease

the release of solvents from the reservoir to avoid direct contact of the solvents with the skin and skin irritation (Bose et al., 2021). The disadvantages of the reservoir patch design are the risk of leakage and the bulkiness of the patch (Dhiman et al., 2011). The drugs may diffuse into and saturate the membrane pores and in-line adhesive layer during storage, resulting in a burst initial delivery rate (Pastore et al., 2015).

In 2008, Alza Pharmaceuticals and Sandoz issued a recall for a fentanyl patch (Duragesic®, dose of 12.5 – 100 µg/h of fentanyl) (Lane, 2013b; Patel et al., 2012a). The reservoir patch was prepared by dissolving fentanyl in ethanol and gelled with hydroxyethyl cellulose. An ethylene-vinyl acetate copolymer film was used as a rate-limiting membrane. The reservoir design of fentanyl patch showed leakage from the medication pouch. The leaking may cause overdose or fatal to users. Afterwards, matrix design was used to manufacture the fentanyl patch.

On the other hand, matrix patches can be categorised into two basic systems, matrix-dispersion and drug-in-adhesive (DIA) systems. In a matrix-dispersion system (Figure 5B1), the drug is dispersed in a polymer matrix and fixed onto an occlusive base plate with the same material as the backing liner (Dhiman et al., 2011; Sharma, 2018). The adhesive layer is then spread around the drug layer by partially overlaying it to form an adhesive rim. The matrix-dispersion patch involves multiple manufacturing steps and an extra occlusive base plate. The patch adhesion may be poor because the drug layer does not contain any adhesiveness.

While, DIA system (Figure 5B2) is much easier to be produced by mixing drugs in the adhesive layer and spread on the backing liner (Sharma, 2018). The adhesive matrix of the patch is dried by solvent casting or hot-melt adhesive method to enable the curing of the adhesive matrix before attaching it to a release liner for storage (Otterbach and Lamprecht, 2021). The simple design of DIA patch reduces the cost of manufacturing and is lighter, thinner and more flexible (Lane, 2013b). This patch is more comfortable to wear. Therefore, DIA patch allows for a long period of application with a better consumer acceptability. The patch storage may prolong without the worry of leakage like a reservoir patch. In 2013 – 2014, the market was dominated by the DIA patch design with over 50 brands available due to a low production cost and the fact that it can overcome most problems faced by reservoir and matrix-dispersion patches (Pastore et al., 2015).

1.4.1. Polymer carrier

During the preparation of patches, polymers act as a carrier in the composition to build up the matrix layer to hold the drugs and adhesives. This is because polymers can provide better mechanical properties, controlled drug release from patches and texture of the formulation (Latif et al., 2022). Polymers can be divided into hydrophobic and hydrophilic polymers. Hydrophobic polymers, including polyethylene, polypropylene and polystyrene, have a low affinity to water and are usually used as coating materials and blood-contacting medical applications, such as artificial kidneys

and prosthetic heart valves (Ahmad et al., 2018; Brash, 1979). The disadvantage is the need for organic solvents to dissolve the polymers. In contrast, hydrophilic polymers are water soluble, such as poly(acrylamide) and polyvinyl pyrrolidone (PVP), or water-swellable, like poly(2-hydroxyethyl methacrylate) and carboxymethyl cellulose (CMC) (Schmidt, 2019). The properties of swelling, flexibility, biocompatibility and self-assembly make hydrophilic polymers popular in drug delivery (Schmidt, 2019; Willersinn et al., 2017).

CMC and PVP offer a good enhancement on the skin delivery of drugs and the texture of patches (Latif et al., 2022; Michele et al., 2022; Ullah et al., 2021; Zare et al., 2021). CMC is a polysaccharide of cellulose ether, which consists of glucose derivatives joined by β-(1,4)-glycosidic linkages as shown in Figure 6A (Kontogiorgos, 2022). CMC is commonly used as a rheology modifier by absorbing and holding water and is resistant to bacterial decomposition that increases the shelf life of formulations (Aravamudhan et al., 2014; BeMiller, 2019). The good binding ability of CMC provides stable water retention within the crosslinking networks between CMC and water during storage and makes CMC efficient to be a thickening agent in cold and hot water (Adden et al., 2021).

PVP (polyvidone or povidone) (Figure 6B) is a hygroscopic synthetic polymer composed of monomers of N-vinylpyrrolidone groups (Hiremath et al., 2019; Kariduraganavar et al., 2014). PVP can absorb water up to 40% of its weight and ready to form films (Kariduraganavar et al., 2014). PVP has an excellent wetting property to provide adhesion on the solid surface and

binding ability to gel the formulation. Therefore, PVP is usually used as a binder and thickening agent.

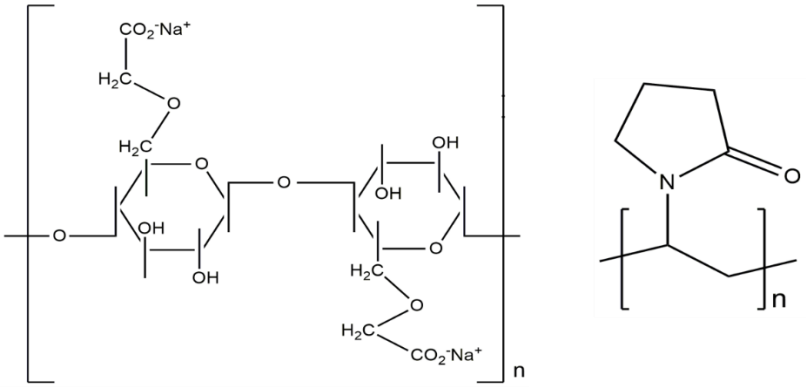


Figure 6 Structures of (A) CMC and (B) PVP

The concentration of CMC and PVP used in the formulation is mostly around 2 – 5%. Cheng et al. (2008) suggested that 2.1%w/v of CMC was able to stabilise the emulsion film of palm olein by providing a better mechanical strength via interaction with deacetylated konjac glucomannan. Taghizadeh et al. (2009) observed that 5% of PVP increased the tackiness of acrylic DIA patches (Gelva 737 contained copolymer of vinyl acetate-2-ethylhexyl acrylate, hydroxyethylacrylate and glycidyl methacrylate). Methotrexate was loaded in 5% of CMC and 1% of hydroxypropylmethylcellulose to form a patch with a better tensile strength (12.33 ± 0.72 kg/cm^2) as compared with a control (1:1 of CMC: hydroxypropylmethylcellulose) (9.62 ± 0.43 kg/cm^2) (Latif et al., 2022). The patch also demonstrated controlled drug release up to 92.87% over 24 h as compared with the control (~60%). The CMC/PVP-based (3:0.1%w/w) β-

glycyrrhetinic acid patch with Solupus® (copolymer of polyvinyl caprolactame-polyvinyl acetate-polyethylene glycol graft) and bentonites showed a better mechanical property, self-adhesion to the skin and controlled release of drugs (Michele et al., 2022).

1.4.2. Pressure-sensitive adhesives (PSA)

The choice of adhesives is essential to avoid skin irritation and achieve the desired adhesion. The commonly used pressure-sensitive adhesive (PSA) are natural rubber, synthetic rubber, polyisobutylene, silicone and acrylic polymers (Pastore et al., 2015). Many marketed patches still use natural rubber latex as PSA due to good adhesion, biocompatibility and high mechanical resistance (Suksaeree et al., 2014). However, natural rubber latex may cause skin irritation due to latex allergy (Deval et al., 2008). A total of 30 allergic reactions was reported from January 2015 to September 2017 related to the use of cosmetic products containing natural rubber latex, such as hair bonding and eyelash adhesives (FDA, 2018). Frequent exposure to natural rubber latex also may cause skin sensitivity. This is due to the immune response to allergic reactions triggered by the antigenic proteins, cis-1,4-polyisoprene polymer and plant proteins from the natural rubber latex (Suksaeree et al., 2014). Extra procedures are needed to remove the protein from the natural rubber latex such as enzyme treatment, centrifugation, creaming and chlorination. Therefore, other adhesive polymers are worth exploring as a substitution for natural rubber latex.

On the other hand, acrylic PSA exhibits low allergenicity, a good physiochemical stability and an acceptable miscibility with most drugs (Liu et al., 2017; Pemberton et al., 2014) such as indomethacin, isosorbide dinitrate, 5-fluorouracil (Yasunori et al., 1992) and sibutramine (Subedi et al., 2010a). Many studies have explored the potential of acrylic adhesive in forming patches (Parhi and Padilam, 2018; Patel et al., 2012b; Pinto et al., 2009; Sadeghi et al., 2016). Acrylic PSA provides benefits of excellent clarity, and better resistance to aging as compared to natural rubber (Bae et al., 2013; Lee et al., 2019). Therefore, acrylic PSA has a wide application in pharmaceutical and manufacturing industries, such as splicing tape, protective foils and medical tape.

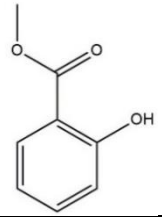
The blending of acrylic adhesive with silicone or different types of acrylic PSA can strengthen the adhesion properties and sustain the drug release profile (Taghizadeh et al., 2010; Tanojo et al., 1994). Metha-acrylic alkyl ester copolymer aqueous emulsion (Nikasol TS-6520) and aqueous acrylic polymer dispersion (Durabond PC 1879A) are aqueous polymer dispersion emulsion acrylic PSA with ester functional group. The copolymers of both acrylic PSA are ethyl acrylate and acrylic acid. Wu et al. (2014) prepared sumatriptan succinate with Nikasol ((2-propenoic acid, 2-ethylhexyl ester polymer with methyl 2-propenoate) and hydrophilic acrylic adhesive (HGA 64: the content was not mentioned). This Nikasol patch exhibited a better peel adhesion (756.7 ± 10.5 g with the 2.5 cm of patch length) and tackiness (372.2 ± 13.2 g) as compared with the HGA 64 patch (peel adhesion: 676.7 ± 44.8 g/2.5 cm; tackiness: 288.3 ± 54.7 g). Nikasol was also used in patch formulation for some patents (Tsurushima et al., 2016;

Tsurushima et al., 2020). The glycol salicylate gel patch fabricated with Nikasol (6 – 7.5%w/w), polyacrylic acid, gelatin, polyvinyl alcohol and glycerine showed adhesion on the elbow of 15 volunteers up to 20 h (Tsurushima et al., 2016). Tsurushima et al. (2020) carried out a tackiness test by rolling a steel ball on the inclined stage with the patches fixed on the stage. The distance at which the steel ball stopped was measured as tackiness. The patches involved in the test were made up of 0.4 – 12%w/w of Nikasol, gelatin and polyvinyl alcohol. The tackiness was shown in an acceptable range of 21 – 38 mm, which may not cause pain during removal (tackiness was not calculated).

1.5. Methyl salicylate (MS) as a model drug

MS is one of the most popular salicylates used in pain management commercial products, especially for musculoskeletal pain. MS is a colourless and light pale liquid methyl ester of salicylic acid (synthetic oil of wintergreen) (Lapczynski et al., 2007). MS can be obtained from synthesis or extraction of *Gaultheria procumbens* (Ericaceae) leaves and bark of *Betula lenta* (Betulaceae). MS fulfils the basic requirements as a suitable candidate for delivery to the skin based on the properties of MS outlined in Table 2 (Hadgraft, 2004).

Table 2 Physiochemical properties of MS

Physiochemical properties	Methyl salicylate
Structure	
IUPAC name	Methyl 2-hydroxybenzoate
Molecular weight (g/mol)	152.1[a]
Melting point (°C)	-8[b]
Boiling point (°C)	220 – 224[c]
Aqueous solubility (mg/L)	1875 at 25°C[d]
Solubility parameter (cal/cm^3)$^{1/2}$	10.61[e]
Log *P*	2.36[f]
***pK*$_a$**	9.8[a]
Vapour pressure, Pa	5.3[g]
Density (g/m^3)	1.174[h]

[a] Calculated from ChemDraw software; [b] obtained from Yalkowsky et al. (2016); [c] obtained from Seskar et al. (1998); [d] obtained from Johnson and Jinqiu (2019); [e] obtained from Ma et al. (2014); [f] obtained from Liyana-Arachchi et al. (2013); [g] obtained from Spiandore et al. (2014); [h] obtained from Guard (1999)

Topical MS is usually used at 10 – 30% (Anderson et al., 2017; Martin et al., 2004a; Parker et al., 2004). MS may be used as a flavouring agent at a very low concentration (0.0001 – 0.6%) but this is uncommon due to the possible toxicity such as salicylism (CIREP, 2003; Martin et al., 2004b). Some mouthwashes and breath fresheners contained 0.08 – 0.2% of MS because MS gives a sweet and mint-like odour (Anderson et al., 2017).

MS is a lipophilic drug that readily penetrates the skin. The analgesic and anti-inflammatory actions to relieve pain are achieved by hydrolysis of MS into active SA rapidly by esterase in the epidermis and dermis of the skin (Anderson et al., 2017). Counterirritancy of MS is achieved by a stinging sensation counteracting the burning of pain nerve endings in muscles and

joints to relieve the underlying pain (Green and Flammer, 1989; Wand-Tetley, 1956). The retention of MS in the skin can be up to 20% after 10 h of application (Roberts et al., 1982). Menthol and camphor are often added into MS formulation as skin penetration enhancers (Martin et al., 2004a; Patel et al., 2007a). The inhibition of esterase by menthol and camphor can achieve a sustained efficacy in the skin to slow down the hydrolysis of MS and allow MS to travel into the deeper skin (Martin et al., 2004a; Yano et al., 1991). Table 3 shows some MS DIA patches available in the market and they are commonly incorporated with camphor (1.5 – 3.1%w/w) and menthol (3.95 – 6%w/w).

Table 3 Pharmaceutical products of MS available over the counter. Adapted from Yeoh and Goh (2021).

Formulation	Concentration of MS (%w/w, otherwise specified)	Composition
AsperFlex™ Pain Relieving Patch (NJ, US)	10	Camphor (3.1%w/w), menthol (6%w/w), aluminium glycinate, propylene glycol, sodium acrylate-sodium acryloyldimethyl taurate copolymer, tartaric acid, 2,4-Imidazolidinedione, disodium EDTA, water, glycerin
DG™ health medicated relief patch (Korea)	10	Camphor (3.1%w/w), menthol (6%w/w), hydrogenated polydecene, pentaerythritol tetrakis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate), liquid petroleum, styrene-acrylamide copolymer
Firstdoc® Cold & Hot Pain Relief Patch (China)	4	Lidocaine (4%w/w), menthol (5%w/w), acrylic acid, aluminium hydroxide, carmellose sodium, 2-ethylhexyl acrylate, glycerin, isopropyl myristate, methyl acrylate, nonoxy-nol-30, polyacrylic acid, polysorbate 80, sodium polyacrylate, sorbitan sesquioleate, starch, talc, tartaric acid, titanium dioxide, water
Salonpas® Pain Relieving Patch (Japan)	10	Camphor (3.1%w/w), menthol (6 %w/w), mineral oil, perfume, polyisobutylene, styrene-isoprene-styrene block copolymer, aluminium silicate, terpene resin, titanium dioxide
Satogesic® Medicated Adhesive Pads (Japan)	0.8	Camphor (1.48%w/w), menthol (3.95%w/w), Capsaicin (0.0056%w/w), peppermint oil, zinc oxide, butylated hydroxytoluene, calcium carbonate, glyceryl rosinate, natural rubber, polybutene, polyisobutylene, terpene resin

In 2008, the US Food and Drug Administration approved the occlusive patch formulation (Salonpas® pain relief patch) as the first over-the-counter topical patch for MS (FDA, 2008). A clinical study involving 208 adult patients

was carried out to highlight the pain relief action of the patch (10% of MS) up to 12 h after the application for only 8 h (Higashi et al., 2010).

MS still attracts the interest of scientists in understanding the physiochemical properties of MS, thereby improving the efficacy of MS with different formulations for better pain treatment (Yeoh and Goh, 2021). The flux of MS was improved by forming patches with styrene-isoprene-styrene copolymer (D1113) as PSA ($flux_{10\text{-}24h}$: 1.97 ± 0.15 µg/cm^2/h) as compared with the rubber patch ($flux_{10\text{-}24h}$: 0.88 ± 0.11 µg/cm^2/h) (Wang et al., 2014). MS in styrene-isoprene-styrene copolymer patch also showed a higher MS accumulation in the skin and muscle of Kunming mice during *in vivo* study as compared with the rubber patch. Besides, a chitosan-based film was prepared by encapsulating MS into nanoemulsion to increase drug loading capacity in the film and this successfully controlled the *in vitro* release of MS (Silva et al., 2020).

1.6. Solvents as chemical penetration enhancers

The SC barrier is the main obstacle to the drug absorption through the skin. Drug penetration through the skin is governed by a passive kinetic process involving a concentration gradient (Lane, 2013a). Solvents are added as a drug carrier which can also help to improve the percutaneous absorption of drugs to circumvent the SC barrier. Thus, they can be referred to as chemical penetration enhancers, sorption promoters or accelerants (Pan et al., 2020). The solvents can interact with the component of the SC to

reduce the barrier resistance temporarily and reversibly (Ahmed and Sushma, 2015; Kar et al., 2019).

An ideal solvent should be non-toxic, pharmacologically inert, compatible with drugs and excipients, does not cause any adverse pharmacology effects on the skin and inexpensive (Ahmed and Sushma, 2015; Roy et al., 2017). Extensive literature has been conducted on the investigation of skin penetration enhancers in the formulation (Ameen and Michniak-Kohn, 2017; Luo et al., 2021; Montenegro et al., 2021; Quinones et al., 2014; Shen et al., 2018). This is due to the flexibility for translational application, being inexpensive and easy incorporation of solvents in the formulation (Dragicevic et al., 2015). However, the concentration of solvents used must be considered to avoid skin irritation.

1.6.1. Mechanisms of action

Solvents can improve drug permeation through the skin by increasing solubilisation of the drug and the thermodynamic activity of formulation (Dragicevic et al., 2015; Williams and Barry, 2012). Apart from that, solvents can interact with the skin to overcome the SC barrier. There are three main mechanisms of solvents suggested to act on the SC components for drug transport through the skin as follows (Kováčik et al., 2020; Williams and Barry, 2012):

i. Disruption of lipids in the SC (lipid modification)
ii. Interaction with the intercellular protein junction (protein modification)
iii. Enhancement of partition coefficient between formulations and the SC (partitioning enhancement)

Figure 7 depicts the mechanism of actions for solvents interacting with the intercellular lipid bilayers of the SC.