DRUG DISCOVERY

Effect of receptor and donor phase composition on permeation of pharmaceutical compound through model membrane

Muhmmad Abid Mustafa[1*], **Mahnoor Rashid**[1], **Shakeel Ahmad**[1], **Hamza Farooq**[2], **Asad Majeed Khan**[1], **Saba Naeem**[1], **Barira Amin**[1], **Fahad Ahmed**[3], **Qandeel Rafi**[1], **Nurhan Tariq**[1]

To Cite:
Mustafa MA, Rashid M, Ahmad S, Farooq H, Khan AM, Naeem S, Amin B, Ahmed F, Rafi Q, Tariq N. Effect of receptor and donor phase composition on permeation of pharmaceutical compound through model membrane. *Drug Discovery* 2023; 17: e27dd1943 doi: https://doi.org/10.54905/disssi.v17i40.e27dd1943

Author Affiliation:
[1]Department of Pharmaceutics, Lahore Pharmacy College, Lahore Medical & Dental College, University of Health Sciences, Lahore, Pakistan
[2]Research Student, Lahore Pharmacy College, Lahore Medical & Dental College, University of Health Sciences, Lahore, Pakistan
[3]Faculty of Pharmacy, University of Sargodha, Sargodha, Pakistan

[*]**Corresponding author**
Department of Pharmaceutics, Lahore Pharmacy College, Lahore Medical & Dental College, University of Health Sciences, Lahore, Pakistan
Email: abidbhatti222@gmail.com

Contact List

Muhmmad Abid Mustafa	abidbhatti222@gmail.com
Mahnoor Rashid	mahnoorrashid68@gmail.com
Shakeel Ahmed	shakeelkhokhar555@gmail.com
Hamza Farooq	hamzafarooq213@gmail.com
Asad Majeed Khan	asad.majeed@lmdc.edu.pk
Saba Naeem	saba.naeem@lmdc.edu.pk
Barira Amin	dr.barirah@gmail.com
Fahad Ahmed	mefahadahmed92@gmail.com
Qandeel Rafi	Qandeel.rafi@lmdc.edu.pk
Nurhan Tariq	nurhan.tariq@lmdc.edu.pk

Peer-Review History
Received: 02 May 2023
Reviewed & Revised: 05/May/2023 to 27/June/2023
Accepted: 01 July 2023
Published: 07 July 2023

Peer-Review Model
External peer-review was done through double-blind method.

Drug Discovery
pISSN 2278–540X; eISSN 2278–5396

DISCOVERY SCIENTIFIC SOCIETY

ABSTRACT

Background: Emerging interest in the development of nanotechnology liposomes to encapsulate, protect and deliver lipophilic components i.e., nutraceuticals, drugs, flavors, antioxidants and antimicrobial agents has revolutionized food, pharmaceuticals, agrochemicals and other industries. *Method:* Permeation of salicylic acid through a silicon membrane (the model membrane) was examined by using different compositions of buffer and propylene glycol. Franz cells were used to study the penetration of salicylic acid through a silicon membrane. The two buffer solutions of 7.5 and 6.8 pH were prepared. Afterwards, utilizing pH 7.5 buffers, four combinations of concentrations were prepared: 100% buffer, 75% buffer with 25% propylene glycol (3:1), 25% buffer with 75% PG (1:3) and 50% buffer with 50% PG (1:1). Similarly, four different concentrations were prepared with a buffer of 6.8 pH (same as above). Absorption of drugs in the receptor cell medium was investigated by measuring absorbances using a UV/vis spectrophotometer. *Result:* A total of eight results were obtained and compared to investigate the concentration at which salicylic acid absorbs most effectively. At pH 6.8, the absorbance was 31.1%; at (3:1) buffer: PG, 69.9%; at (1:1), 77.2%; and at (1:3), 58.8%. At pH 7.5, the absorbance was 24.5%; at (3:1) buffer: PG, 46.5%; at (1:1), 53.4%; and at (1:3), 22.2%, measured at a final test time of 75 minutes. Out of these four concentrations, salicylic acid showed maximum absorption at (1:1) buffer: PG combination. In pH 6.8 buffer, the salicylic acid showed more absorption and release through the membrane as compared to pH 7.5 buffer. The results were compared and discussed accordingly. *Conclusion:* A permeation study of salicylic acid through a silicon membrane indicates that both buffer and propylene glycol play a crucial role in absorption. The ratio of combination and pH has an essential influence upon absorption. From the results, it was inferred that salicylic acid showed maximum absorption, permeation and release through

the membrane at an acidic pH of 6.8. It means that if in transdermal drug delivery the pH of the skin is lower, salicylic acid will present enhanced permeation.

Keywords: Salicylic acid, Propylene glycol, Phosphate Buffer, Silicon membrane, Franz cell, FTIR, diffusion, absorbance, in-vivo, ex-vivo, permeation.

1. INTRODUCTION

A disease is a clinical condition in which various body processes presents abnormalities. These pathological conditions exhibit multiple deformaties in body functions (Porter and Moneta, 1995). In the present era, four types of diseases are most widely prevalent: Infectious, genetic, non-genetic and physiological disease. Normally, in infectious diseases viruses, bacteria and microorganisms are involved (Cohen and Williamson, 1991). Oral dosage form of medicines present a major drawback of non-compliance in paediatrics and geriatrics (Eraga et al., 2023; Rajput & Sailaja, 2023). To overcome this problem, a transdermal drug delivery system is used (Selvam et al., 2010; John & Sailaja, 2023).

The drug is released through transdermal drug delivery system upon contact with the skin. The drug is absorbed through the skin and is passed into the blood (Arunachalam et al., 2010). To observe release study of the drug through skin, Franz dispersion cells were used (Kumar et al., 2023). Franz diffusion cell is mainly used to determine the ex-vivo skin permeation and in-vitro drug release pattern of pharmaceutical preparations applied over the skin such as gels, creams, microemulsion, transdermal patches and creams (Ng et al., 2010).

A Franz-type diffusion cell is made up of two compartments named donor chamber and receptor chamber (Kumar et al., 2023; Salamanca et al., 2018). The receptor chamber has a fixed volume in which receptor media is placed (buffer media); it is basically attached with a sampling port through which receptor media is added. Surrounded by a heated magnetic stirrer chamber that is water jacketed. The water supply is connected to a water bath that thermostatically controls the temperature. The donor compartment is placed above the receptor cell. Between them, human skin or any model membrane is placed for studying the permeation process. The donor compartment contains the drug whose permeation is to be determined. It has various limits for the recipient chamber i.e., 4, 7 and 12 ml (Goebel et al., 2013).

The dissemination layer was the model membrane like skin. The skin should be absorbed with the saline arrangement or distilled water at any rate from 20 to 24 hours before permeation (Fujii et al., 2001). The settings required for this trial of these saturation contemplates are incorporated and a receptor containing medium must be kept up in steady mixing at a consistent temperature of 37°C. A blend of phosphorous saline with pH 7.4 and alcohol was utilized in the acceptor-containing chamber. The estimated measure of the test was pulled back from the receptor containing chamber and a similar quantity of the new arrangements ought to supplant the receptor-containing chamber to keep the quantity steady (Padula et al., 2018). The Franz diffusion cell is represented in (Figure 1) (Kumar et al., 2023).

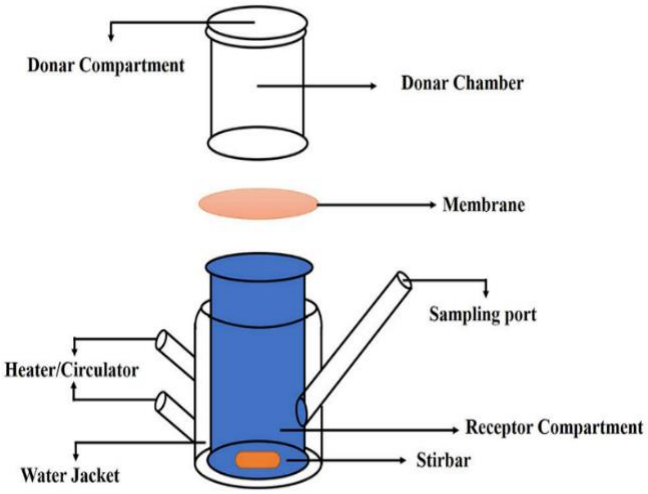

Figure 1 Franz diffusion cell

Drug release from the formulation and its permeation ability through layers of skin depend upon the intimate interaction between the drug, vehicle and skin. This procedure consists of the following steps: (a) Release of the drug from the formulation; (b) partitioning of the drug into the stratum corneum layer; (c) diffusion of the drug into the stratum corneum layer; (d) partitioning of drug into viable epidermis layers from the stratum corneum layer; (e) diffusion of drug across viable epidermis layers (Kalia and Guy, 2001). The objective of this study was to determine the effect of receptor medium on the drug release profile. A buffer solution with two different pH values (6.8 & 7.5) were used. Each of these buffers is made in different ratios of phosphate buffers (PB) and propylene glycol (PG).

2. MATERIALS AND METHOD

Materials

The materials used in this study were purchased from SIGMA-ALDRACH and were of pharmaceutical grade. These materials are the following:

Table 1 List of materials used in the study

Chemicals	PubChem ID	Chemical Name	Physical Appearence	Solubility	MP	BP
PG	1030	Propane 1,2 diol	Colorless liquid	Miscible	-59°C	188.2°C
Salicylic Acid	77085	2-Hydroxybenzoic acid	White crystaline powder	Not soluble in water	158.2°C	211°C
Buffer	-	-	-	-	-	-

Table 2 Instruments used in the study

Sr. No.	Instrument	Model	Use
1	Franz cell	57-6M Hanson Research Institute, California, USA	Determine whether skin is permeable
2	Weigthing balance	Ab 135-S, Mettler-Toledo Limited Bangkok, Thailand	Weighing
3	Magnetic Stirrer	Mr 3000D, Heidolph, Schwa Bach, Germany	To mix up
4	Silicon membrane	_	As skin membrane
5	UV Spectrophotometer	Halo DB 20 Dynamica	calibration curves
6	pH meter	Mettler, Toledo, Greifensee, Switzerland	To check PH
7	Water Distillation apparatus	Carelab	For distilled water

Formulation of 6.8 pH buffer

Dissolve 28.20 g of disodium hydrogen phosphate and 11.45 g of Potassium dihydrogen phosphate in suffient quantity of water to produce 1000 ml. Adjust the pH accordingly using 1M HCl solution.

Formulation of 7.5 pH buffer

Dissolve 6.8 g of Potassium dihydrogen orthophosphate and 1.56 g of Sodium hydroxide in 900ml of distilled water. Adjust the pH 7.5 with Sodium hydroxide and add sufficient water to produce 1000ml. Store the Buffer solution in suitable environment.

Standard calibration curve

Prepare the standard stock solution of salicylic acid by accurately weighing 10mg of it and adding it to 100ml of methanol. Use heat when needed because salicylic acid is sparingly soluble in cold water (1 part in 550 parts of water). Now take 1, 2, 3, 4, 5, 6, 7, 8, 9 ml from stock solution prepared and add 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 ml of methanol respectively. These dilutions are 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml, 60µg/ml, 70µg/ml, 80µg/ml, 90µg/ml and 100µg/ml respectively. Now measure the absorbance in UV/Vis Spectrophotometer at 358 nm. Note the aborbance values for each dilution.

Plot the absorbance versus concentration of salicylic acid. Apply the least square method to calculate the slope and intercept. Use the straight-line equation to calculate y. Calculate the R^2 value. The calibration curve is given (Figure 2). Calibration of salicylic acid in the buffer showed 0.9996 regression value shows a good linear relationship in between absorbance and cocentration.

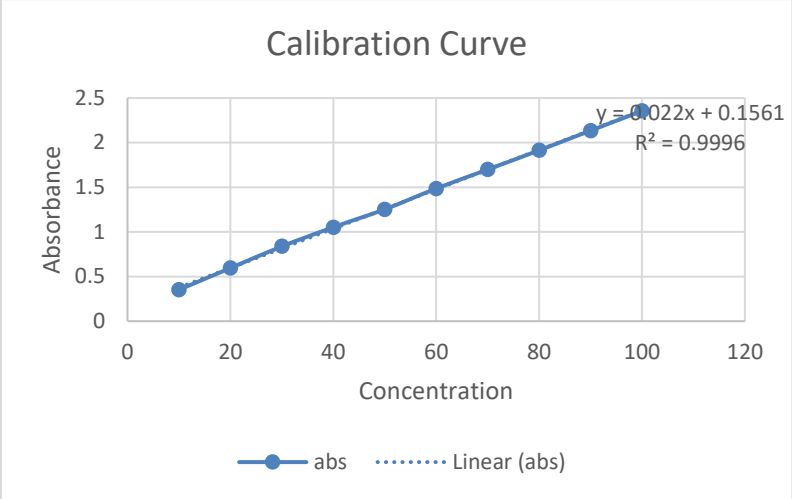

Figure 2 Calibration Curve

Composition

In the present study, 10mg drug is disolved in 2ml buffer. Concentration of the drug is 5mg/ml. This sample is taken into donor compartment. In receptor compartment, there are different concentrations and ratios of buffer and PG. A total of 8 samples of buffer solutions were used, whose composition is given (Table 3).

Table 3 Percentage composition of buffer and PG with their ratios in the sample

Sample	PG	PB
6.8 pH buffer		
S1	0%	100%
S2	75%	25%
S3	50%	50%
S4	25%	75%
7.5 pH buffer		
S5	0%	100%
S6	75%	25%
S7	50%	50%
S8	25%	75%

Procedure

The procedure performed was slightly different with the donor solution. As described earlier, there were 8 samples of buffer solutions with different concentration of buffer and PG. 4ml of this buffer solution in receptor compatment and constant drug 5mg/ml into the donor compartment was taken. To perform this procedure, 0.5ml solution from each sample was extracted after 0, 5, 15, 30, 60 and 75 minutes. After that, each sample was replenished with 0.5 ml of fresh receptor solution. Afterwards, UV spectrophotometry at 236nm for salicylic acid was performed.

By measuring this absorbance, we can find out the permeation of drugs through membranes and the differences between them. The results of UV spectrophotometry were analysed to determine the permeation of drugs through the silicon membrane. Moreover, the difference in permeation utilizing different concentration solutions was also observed.

3. RESULT AND DISCUSSION

Pre-formulation studies; Characterization of drug

Molar mass

The molar mass of salicylic acid is 138.122g/mol.

Melting Point

The melting point of salicylic acid is 158.6 °C.

Boiling point

The boiling point of salicylic acid is 200 °C.

Appearance

Appearance of salicylic acid is colorless to white fine-needle like crystals

Fourier Transform Infrared Spectroscopy (FTIR)

The FT-IR spectrum of biofield treated salicylic acid showed the characteristic IR absorption peaks at 3233 and 2837-3004 cm-1 that were due to OH and C-H stretching, respectively. The FT-IR data of treated salicylic acid exhibited the shifting in wave number of some bonds with respect to control sample (Trivedi et al., 2015).

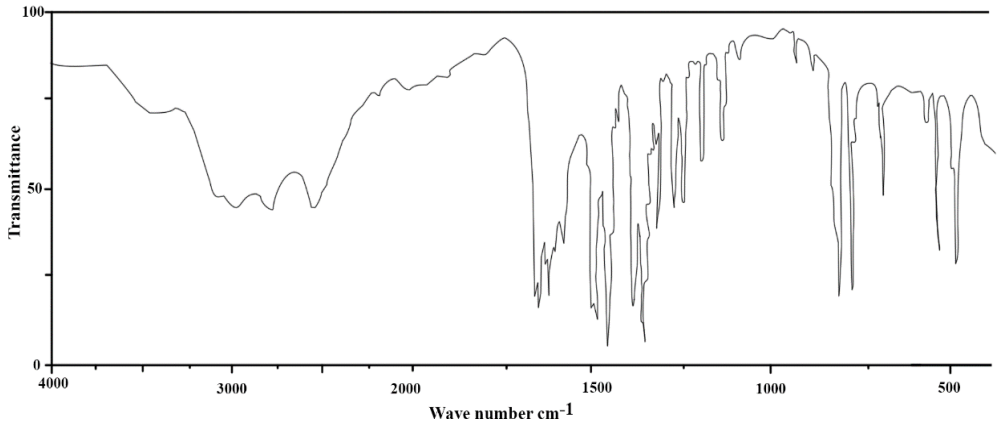

Figure 3 FTIR of salicylic acid

Results of 6.8 pH buffers

100% buffer in receptor compartment

Absorbance of salicylic acid in 100% buffer solution in receptor is in (Figure 4). At 75 minutes, 31.1 abs was maximum by finding absorbance in UV studies. It showed that there was some absorbance through the membrane in 100% buffer (Sheshala et al., 2019).

Absorbance in 75% buffer and 25% PG in receptor compartment

Absorbance of salicylic acid in 75% buffer and 25% PG in receptor is in (Figure 5). At 75 minutes, 69.9 abs was maximum by finding absorbance in UV studies. The (3:1) Buffer: PG solution showed greater absorbance as compared to the absorbance in 100% buffer solution.

Absorbance in 50% buffer and 50% PG in receptor compartment

Absorbance of salicylic acid in 50% buffer and 50% PG in receptor is in (Figure 6). At 75 minutes, 77.2 abs was maximum by finding absorbance in UV studies. At (1:1) Buffer and PG solution the drug showed maximum absorbance. Therefore, the drug release is increased with the change in buffer and PG concentration.

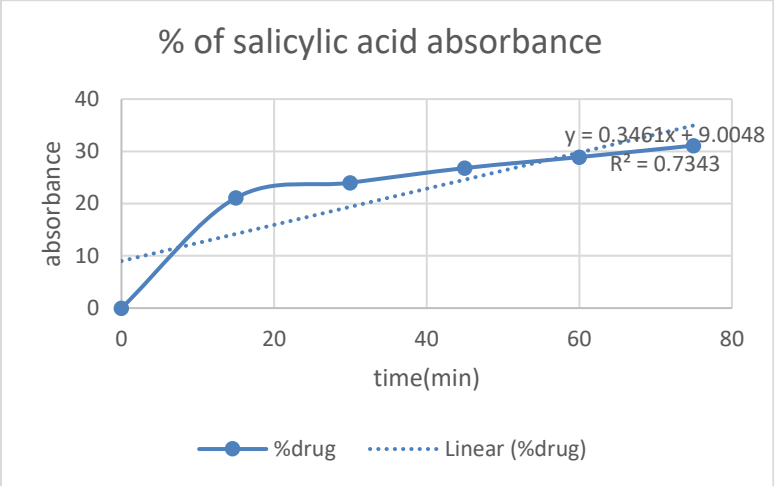

Figure 4 Absorbance of salicylic acid in 100% buffer in receptor

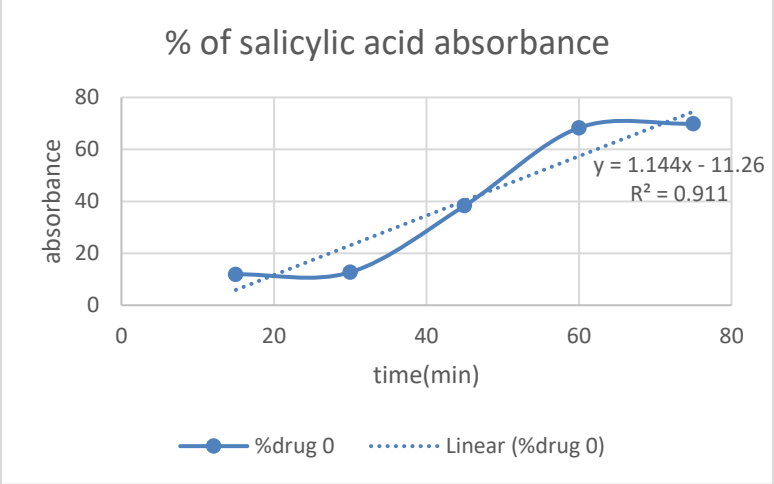

Figure 5 Absorbance of salicylic acid in 75% buffer aand 25% PG in receptor

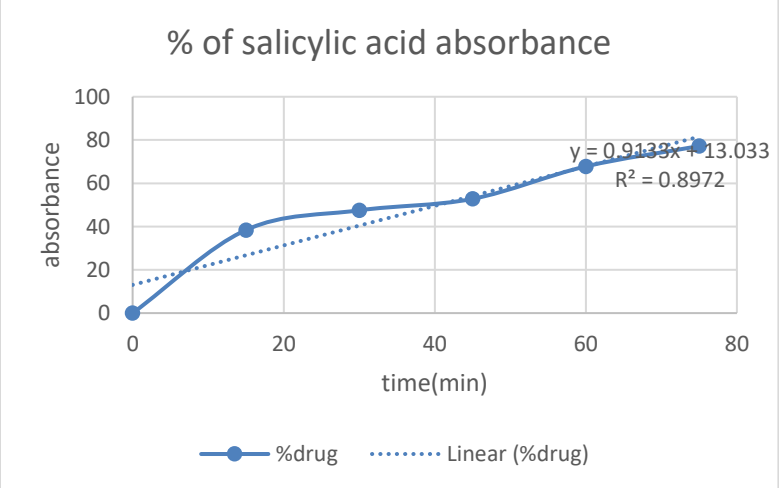

Figure 6 Absorbance of salicylic acid in 50% buffer and 50% PG in receptor

Absorbance in 25% buffer and 75% PG in receptor compartment

Absorbance of salicylic acid in 25% buffer and 75% PG in the receptor is in (Figure 7). At 75 minutes, 58.8 abs was maximum by finding absorbance in UV studies. The (1:3) solution of Buffer: PG showed that release of the drug is decreased with increase in PG concentration comparative to the (3:1) solution in which buffer is in greater concentration.

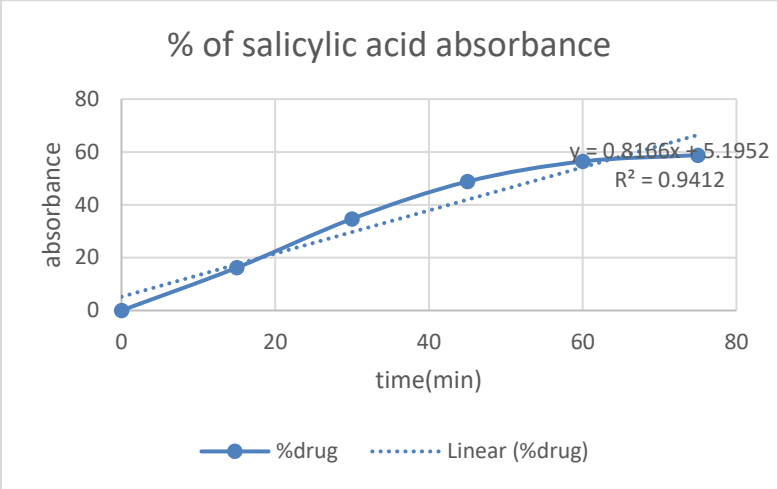

Figure 7 Absorbance of salicylic acid in 25% buffer and 75% PG in the receptor

Results of 7.5 pH buffers

Absorbance in 100% buffer in receptor compartment

Absorbance of salicylic acid in 100% buffer in the receptor is in (Figure 8). At 75 minutes, 24.5 abs was maximum by finding absorbance in UV studies. The drug showed comparatively less absorbance in basic 7.5 pH buffer comparitive to the same concentration of the buffer in acidic 6.8 pH buffer.

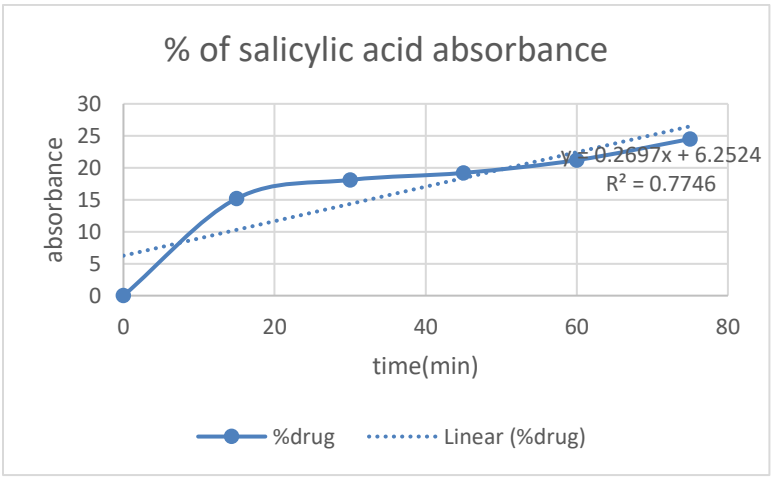

Figure 8 Absorbance of salicylic acid in 100% buffer in the receptor

Absorbance in 75% buffer and 25% PG in receptor compartment

Absorbance of salicylic acid in 75% buffer and 25% PG in the receptor is in (Figure 9). At 75 minutes, 46.5 abs was maximum by finding absorbance in UV studies.

Absorbance in 50% buffer and 50% PG in receptor compartment

Absorbance of salicylic acid in 50% buffer and 50% PG in the receptor is in (Figure 10). At 75 minutes, 53.4 abs was maximum by finding absorbance in UV studies.

Absorbance in 25% buffer and 75% PG in receptor compartment

Absorbance of salicylic acid in 25% buffer and 75% PG in receptor is in (Figure 11). At 75 minutes, 22.2 abs was maximum by finding absorbance in the UV studies (Shahzad et al., 2014).

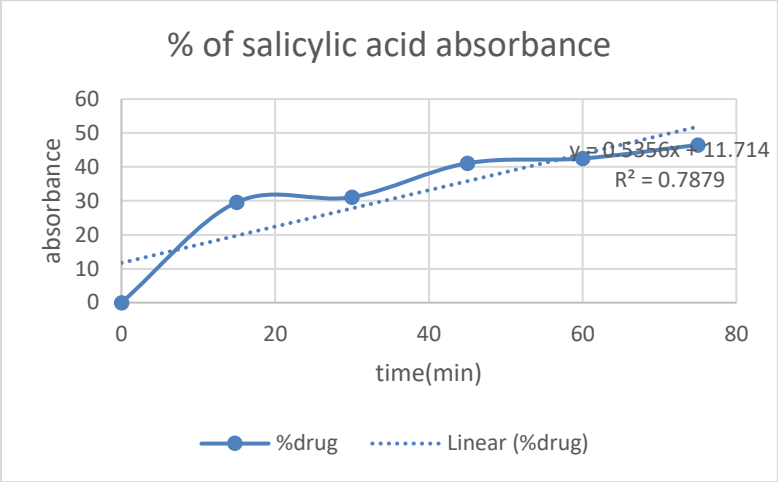

Figure 9 Absorbance of salicylic acid in 75% buffer and 25% PG in the receptor

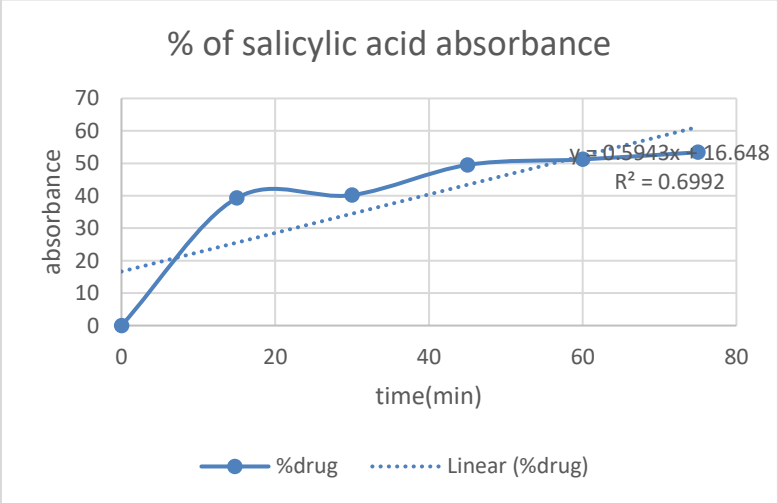

Figure 10 Absorbance of salicylic acid in 50% buffer and 50% PG in the receptor

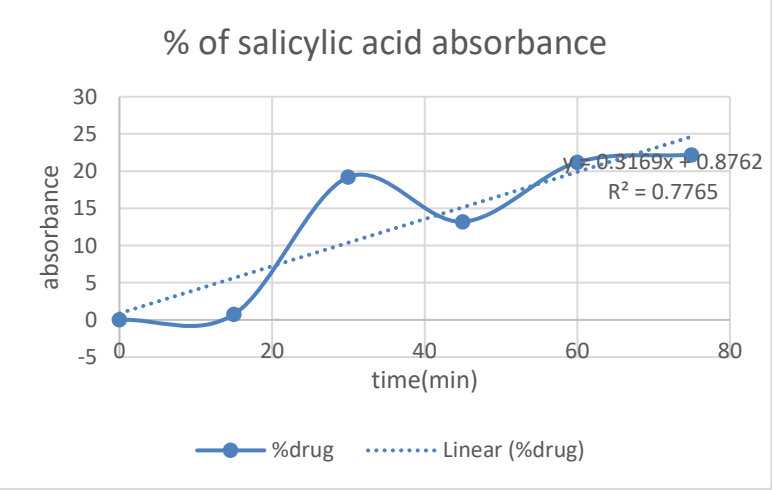

Figure 11 Absorbance of salicylic acid in 25% buffer and 75% PG in receptor

Discussion

Formulation of Buffers

For evaluation of the effect of pH on the permeation of salicylic acid through a silicon membrane (model membrane), two different buffers were prepared, one of which was acidic (6.8 pH) and the other was basic (7.5 pH). The reason behind preparing two

different buffer solutions was to prepare eight different combinations of different concentrations of buffer and propylene glycol solutions.

Role of buffer and propylene glycol concentration

A permeation study of salicylic acid using different receptor solution concentrations indicated that both buffer and propylene glycol play an essential role in its absorption and permeation. Different concentrations of buffer solution at pH 6.8 and 7.5 were used to find out the permeation. Buffer concentration and propylene glycol concentration varied from 100%: 0%, 75%: 25%, 50%: 50% and 25%: 75%, respectively. The study showed that at (1:1) or 50%: 50% concentrations of buffer and PG, salicylic acid presented maximum absorption.

Effect of pH change on permeation of drugs

Propylene glycol acts as a permeation enhancer for transdermal drug delivery. As well as, buffer as a better solvent for the drug. The study showed that pH has a significant impact on the permeation of the drug. The total flux of salicylic acid is greater at 6.8 pH. Thus, we studied buffers at two different pH values of 6.8 and 7.5 that were also compared later on. The results of this study explained that salicylic acid is better absorbed in 6.8 pH buffer as compared to a buffer of 7.5 pH.

The absorbance study showed that the release of drugs through the membrane is higher at 6.8 pH. It means that in transdermal drug delivery, the reduction in pH of the skin or organ will enhance the permeation process. Moreover, if we discuss the permeation studies and our concerns about results, the drug delivery percentage and the selection of receptor concentration play a key role. Therefore, if we use acidic pH buffers in the transdermal drug delivery system, the permeation of drug would be significantly enhanced as compared to the basic pH buffers.

4. CONCLUSION

This study accessed the effect of receptor and donor phase composition on the permeation of salicylic acid through a silicon (model) membrane. The study concludes that the desired permeation profile can be achieved with an alteration in the buffer and PG concentrations. The drug showed maximum permeation with 1:1 combination of buffer and PG respectively. This indicates that permeability is dependent on pH. In an acidic environment, drug release is higher as compared to the basic environment.

Informed consent

Not applicable.

Ethical approval

Not applicable.

Conflicts of interests

The authors declare that there are no conflicts of interests.

Funding

The study has not received any external funding.

Data and materials availability

All data associated with this study are present in the paper.

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