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FORMULATION AND EVALUATION OF VERAPAMIL HYDROCHLORIDE EMULGEL FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Topical drug delivery offers an alternative to oral and intravenous administration, often providing better patient compliance and localized action. This study aims to formulate a Verapamil Hydrochloride emulgel, a calcium channel blocker primarily used to treat hypertension, and evaluate its effectiveness for diffusion through the skin. Emulgels combine the benefits of gels and emulsions, creating an ideal vehicle for poorly water-soluble drugs. Various parameters, including pH, drug content, in vitro drug release, and swelling index, were evaluated to determine the optimal formulation for transdermal delivery.

KEYWORDS: Emulgel, Verapamil Hydrochloride, Transdermal Delivery, Topical Gel, Calcium Channel Blockers, Skin Permeability, Drug Release.

INTRODUCTION

The skin, the body's largest organ, serves as a protective barrier, regulating temperature, preventing water loss, and shielding against pathogens and chemicals. Its two main layers, the epidermis and dermis, contribute to the skin's barrier function. The outermost layer, the stratum corneum (SC), plays a crucial role in limiting transdermal penetration of substances. Structurally, the SC resembles a "brick and mortar" model, where keratin-rich cells, or corneocytes, are embedded within a lipid matrix. This arrangement restricts transepidermal water loss (TEWL) and hinders chemical penetration. For transdermal drug delivery, understanding this barrier is essential.[1]

Transdermal drug delivery offers a promising alternative to oral administration, particularly for drugs requiring controlled release and enhanced patient compliance. This approach bypasses the first-pass metabolism, which can

reduce drug efficacy and increase side effects. To penetrate the skin effectively, drugs can take the transepidermal route through the SC or the transappendageal route via hair follicles and sweat glands. The choice of drug vehicle significantly impacts diffusion, with factors like the vehicle's solubility and pH influencing permeability.[2]

In this study, we explore the formulation of Verapamil Hydrochloride as an emulgel, combining gel and emulsion properties to enhance drug stability and skin penetration. Emulgels stabilize hydrophobic molecules and improve drug release through the skin, making them an ideal system for delivering calcium channel blockers like Verapamil. With the potential for greater stability, ease of application, and controlled release, emulgels represent a promising approach for topical drug delivery. This study evaluates the formulation's physical properties, drug release profile, and skin permeation, with a focus on enhancing transdermal absorption for effective hypertension treatment.[3]

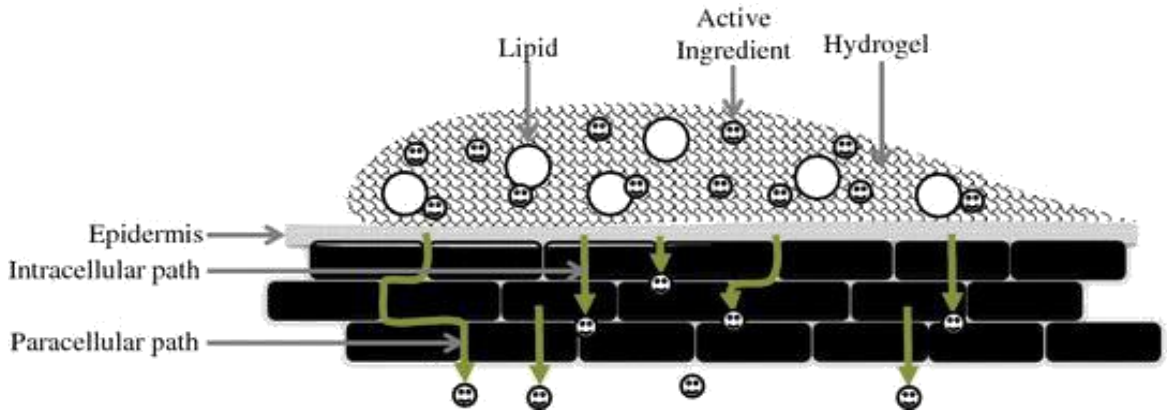


Fig: Schematic representation of an emulgel system.

MATERIALS AND METHODS

Verapamil Hydrochloride, Carbopol 934, liquid paraffin, Tween 20 and Sodium Lauryl Sulfate (SLS), Methyl Paraben, Propylene Glycol, Polyethylene Glycol (PEG) 400, Polyethylene Glycol (PEG) 600, Oleic Acid and Ethanol.

Method of preparation of emulgel

Emulgel was prepared using carbopol 934, as gelling agents. The gels in formulations were prepared by dispersing carbopol in purified water with constant stirring at a moderate speed. The oil phase of the emulsion was prepared by dissolving span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving tween 20 in purified water. Methyl and penetration enhancers were dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions were mixed with the aqueous phase. Then the oily phase were added to the aqueous phase with continuous stirring. Finally the emulgel was prepared by mixing the both gel and emulsion in 1:1 ratio.[5]

Formulation of gel (%W/W)

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Carbopol 934	1	1	1	1	1	1	1	1
Propylene glycol	2	2	2	2	2	2	2	2
Methyl paraben	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Formulation of emulsion (%W/W)

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
Verapamil	40	40	40	40	40	40	40	40
SLS	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Liquid paraffin	10	10	10	10	10	10	10	10
Tween 20	1	1	1	1	1	1	1	1
Propylene glycol	5	10	-	-	-	-	-	-
PEG 400	-	-	5	10	-	-	-	-
PEG 600	-	-	-	-	5	10	-	-
Oleic acid	-	-	-	-	-	-	5	10
ethanol	2	2	2	2	2	2	2	2
Distilled water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Fig: Formulation of emulgel using mechanical stirrer.

Method of evaluation of emulgels

Physical appearance: The prepared emulgels were inspected for the colour, homogeneity, consistency.[6]

pH: The pH values of 1% aqueous solutions of the prepared emulgels were measured by a digital pH meter.

Fig: 1% aqueous solutions of the prepared emulgels.

Swelling Index: For determination of swelling index of formulated emulgel following procedure was adopted, 1 gm of the gel is taken on porous aluminum foil and then placed separately in petriplates containing10 ml 0.1 N NaOH. Then samples were taken from petriplates at different time points and put it on a dry place for some time after it reweighed.[6]

Swelling index is calculated as follows:

$$SW\ \% = (w_t - w_o / w_o) \times 100$$

Where,

Wo = Initial weight of emulgel at zero time

Wt = Weight of swollen emulgel after time t

(SW) % = Percent swelling Index

Drug Content Determination: Gel formulation (1 gram) was dissolved in 7.4 ph phosphate buffer. Filtered it to obtain clear solution. The resulting solution absorbance was noted using UV Visible spectrophotometer at 273 nm. Drug content was determined from calibration curve for drug.[7]

***In-vitro* drug release studies:** *In-vitro* release behaviour of the drug from emulgel formulations were investigated using egg shell membrane. An interesting investigation used egg membrane which, like human stratum corneum, consists mainly of keratin. By using 0.5M hydrochloric outer shell of the whole egg was dissolved which resulting in a membrane. The franz diffusion cell was used for release and permeation study. One gram of gel was applied on the surface of egg membrane tied to the lower end of donor compartment. The volume of the receptor fluid was reserved 15ml.[8]

The temperature condition of the receptor fluid maintained at 37˚ C and stirred continuously at 300 rpm on a magnetic stirrer. Aliquots of 5.0 ml were withdrawn and analyzed for the drug content after suitable dilutions by spectrophotometric method. The volume of fluid which was withdrawn for analysis be replaced with the same volume of the fresh 7.4 ph phosphate buffer after each sampling. The cumulative amount released across the egg membrane was calculated and plotted against time.[9]

Fig: Preparation of egg membrane and in vitro diffusion study using Franz diffusion cell.

FTIR STUDIES

FTIR stands for furrier transform infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation s passed through a sample; some of the infrared radiations absorbed by the sample and some of it passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample like a finger no two unique molecular structures produces the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis.[10]

- It can identify unknown materials
- It can determine the quality ir consistency of a sample
- It can determine the interactions between samples
- It can determine the amount of components in the mixture.

RESULTS AND DISCUSSION

Physical evaluation of formulations

Formulation	Colour	Homogenicity	Consistency	Phase separation
F1	White	Good	Excellent	No
F2	White	Good	Excellent	No
F3	White	Good	Excellent	No
F4	White	Good	Excellent	No
F5	White	Excellent	Excellent	No
F6	White	Excellent	Excellent	No
F7	Yellowish white	Poor	Poor	Yes
F8	Yellowish white	Poor	Poor	Yes

pH determination of formulations

Formulations	F1	F2	F3	F4	F5	F6	F7	F8
pH	4.40	4.55	5.19	5.65	5.23	5.72	4.20	4.44

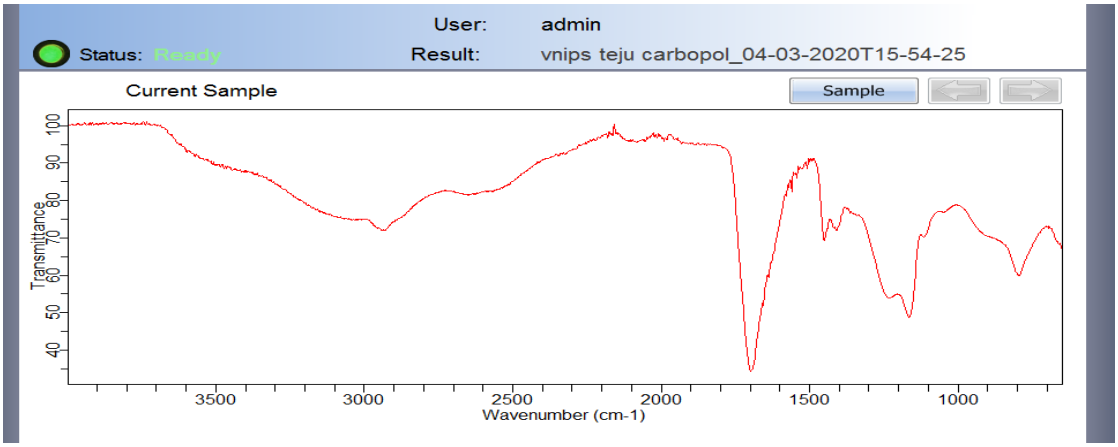
In vitro cumulative %drug release data of formulations F1 to F8

Formulations TIME (min)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)
0 min	0	0	0	0	0	0	0	0
15 min	7.4	6.23	11	12	9	14	7	8
30 min	11.8	10.30	14	18	13	21.65	8	12
60 min	24	27.23	20	24	28	32.42	23	22
90 min	39	26.25	29	36	32	44.8	24	27
120 min	41	30.60	40	46	43	51.3	29	30
180 min	51	44.8	45	53	46	55.01	38	40

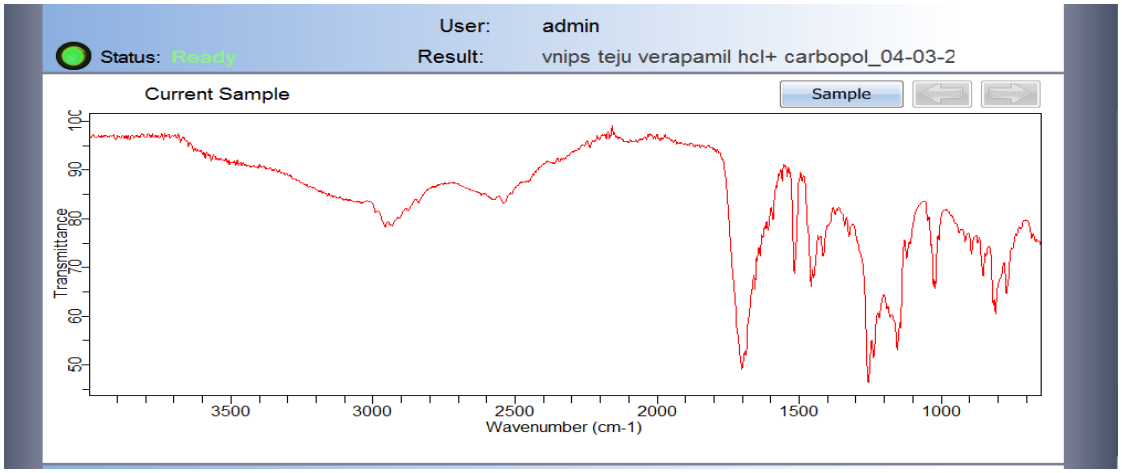
Swelling index of the formulations F1 to F8

Time Formulations	A (%) 1hr	B(%) 2hr	C(%) 3hr
F1	1	4	7
F2	3	9	11
F3	8	12	18
F4	11	17	23
F5	18	29	36
F6	25	41	54
F7	9	15	22
F8	14	23	31

FTIR spectrum of carbopol



FTIR spectrum of both verapamil hydrochloride and carbopol



DISCUSSION

The emulgel formulations (F1–F6) displayed a white, viscous, creamy consistency with a smooth, homogeneous texture and a glossy appearance, indicating good formulation stability and aesthetic appeal. Formulations F7 and F8, however, did not meet the same standards, suggesting less stable formulations.

The pH of the prepared emulgels was measured using a pH meter, and all formulations fell within the range of 5.61–6.23. This range is suitable for skin application, as it minimizes the risk of skin irritation by aligning closely with the natural skin pH.

Drug content analysis was conducted using a UV spectrophotometer at 273 nm, revealing drug content levels in the formulations as follows: 68.1%, 83.2%, 77.9%, 81.7%, 91.8%, 95.2%, 48.6%, and 56.2% for formulations F1–F8, respectively. The high drug content in formulation F6 (95.2%) reflects the effective incorporation and uniform distribution of Verapamil Hydrochloride within the emulgel matrix.

In the in vitro release study, drug release rates from the emulgel formulations followed the descending order of F6 > F4 > F2 > F5 > F3 > F1 > F8 > F7. Specifically, the amount of drug released after 120 minutes was observed as 55.01%, 53.21%, 51.36%, 46.41%, 45.83%, 44.23%, 40.71%, and 38.92% for each formulation, respectively. Formulation F6

demonstrated the highest drug release, underscoring its suitability for transdermal application by ensuring effective drug availability.

The swelling index, calculated over a period of three hours, indicated that F6 also had the highest swelling index at 54%, which suggests an optimal balance of water absorption and gel stability, contributing to its prolonged release capabilities.

Fourier-transform infrared (FTIR) studies were conducted to evaluate potential interactions between Verapamil Hydrochloride and Carbopol 934. The FTIR spectrum for Verapamil Hydrochloride showed characteristic peaks at 2800–2300 cm^{-1} (N-H stretch), 3030–2840 cm^{-1} (C-H stretch), 1262 cm^{-1} (C=O stretch), and 2236 cm^{-1} (C=N stretch). The mixture of Verapamil Hydrochloride with Carbopol 934 exhibited these characteristic peaks without significant shifts, indicating no notable chemical interactions between the drug and polymer. This stability is critical as it ensures that the drug's efficacy remains intact within the emulgel formulation.

CONCLUSION

Verapamil Hydrochloride emulgel exhibits promising characteristics for effective transdermal delivery. Formulation F6 achieved the highest drug release and stability, warranting further in vivo studies. Emulgels offer a stable, effective vehicle for enhancing the bioavailability of hydrophobic drugs, potentially improving patient compliance and therapeutic outcomes in hypertension management.

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