AN EMULGEL PREPARATION: A TOPICAL FORMULATION USED TO TREAT COLD SORES CAUSED BY HERPES SIMPLEX VIRUS

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Abstract

Herpes simplex virus is the main cause of herpes labialis commonly known as cold sores which is highly established worldwide. This study was aimed to formulate and evaluate an emulgel of anti-viral drug valacyclovir for the treatment of cold sores. Using slow emulsification method, the emulgel was prepared and characterised for FTIR studies, pH analysis, spredability, swelling index, drug content, globules size, in-vitro drug release ,comparative in-vitro drug release studies, SEM studies and in-vitro drug release kinetics using zero order, first order, higuchi model and korsmeyer peppas model . FTIR studies provided no evidence of chemical interaction between valacyclovir and excipients used .The pH of the formulations was within an appropriate range for skin. The swelling index and spredability were optimum for the better patient compliance. The swelling behaviour was 98.84 % after 60 min. The drug content was found to be within the official pharmacopeial limit i.e, 100 ± 10%. The surface morphology revealed by scanning electron microscopy showed spherical oil globules with smooth surface morphology. The emulgel released 90.10 % of valacyclovir after 10 hours. Comparative in-vitro diffusion study was performed to compare the percentage drug release between the optimised formulation (F4) and that of the pure drug. In-vitro drug release kinetics revealed that the optimised formulation follows non-fickian diffusion as the correlation co-efficient (n) is less than 1. It is concluded that the valacyclovir emulgel defined all its physical properties and can be applied topically for the treatment of herpes labialis infection.

Keywords: - cold sores, emulgel, valacyclovir, non-fickian, diffusion, in-vitro, topical.

I. INTRODUCTION

Cold sores also known as herpes labialis, are commonly occurring ailments in individuals around the world, characterised by erythema and blisters followed and accompanied by burning pain, largely affecting the face, mouth, and throat. It causes pain, burning, tingling or itching sensation at the affected site which is generally followed by a cluster of blisters. It is usually mild and self-limiting, lasting 2–3 weeks, but can cause severe disease in those who are at risk such as the immunocompromised.[1] Herpes labialis is triggered by herpes simplex virus type 1 (HSV-1). After primary infection, the virus retreats via the sensory nerve into the particular ganglion (usually the trigeminal ganglion), where it lies concealed throughout the individual's lifetime. [2] Stimuli such as fever, menstruation, sunlight, and upper respiratory infections can resuscitate the virus, after which it returns to the epithelial cells via the sensory nerve. [3] The main use of an anti-viral treatment is to eradicate the viral growth of the herpes simplex virus upon the skin surrounding the lips on the facial area and its available formulations are only available in the form of solid dosage form which is the tablet form. [4, 5]

The disadvantages/ bio-availability problems patients are facing when taking these medications are burning and itching sensations with topical treatments and some experienced headache and nausea with anti-viral oral treatments along with decreased bioavailability.

Incorporating an anti-viral drug, valacyclovir into a novel topical drug delivery system such as the emulgel has more potential to exert its action in eradicating the effects caused by the virus. Valacyclovir is a guanine nucleoside antiviral used to treat various herps infections and a prodrug of acyclovir, approved by the FDA in 1995. It slows the growth and spread of the herpes virus to help the body fight infections. Valacyclovir is used to treat cold sores in children and also prevents cytomegalovirus following a kidney transplant in high-risk cases. [6, 7, 8]

Topical drug delivery system:

Topical delivery is the application of a drug-containing formulation to the skin directly to treat the cutaneous disorder. The topical delivery route for drug administration has many advantages over the other pathways including avoiding the hepatic first-pass metabolism effect, continuous drug delivery, fewer side effects and improved patient amenableness. [9] As skin is one of the principal and most superficial organs in the human body, pharmacists utilise it to deliver various drugs which cannot be delivered through other delivery routes.

Topical gels are defined as semisolid systems in which a liquid phase is constrained within a three-dimensional polymeric matrix of natural or synthetic gum in which a high degree of physical or chemical cross-linking has been formed. [10]

Emulgel is a type of topical drug delivery system in which gel and emulsion are combined, where the emulsion used, can be both w/o and o/w. It acts as a vehicle to deliver the selected drug to the skin. The water phase containing the gelling agent converts classic emulsion into an emulgel. Emulgels are seen as a better choice for class-II of drugs as per the BCS classification system, which shows poor solubility and high permeability. Emulgel possesses the properties such as thixotropic, greaseless, easily spreadable, and bio-friendly and increases patient acceptability. [11]

II. Materials and methods

Chemicals – Valacyclovir was obtained as a gift sample from Hetero labs, Hyderabad. Carbopol 934, span 80, tween 80, liquid paraffin, Potassium Dihydrogen Phthalate and Sodium Hydroxide were procured from SD Fine Chemicals Ltd.

Methods

Standard calibration curve of valacyclovir

The stock solution (1 mg/ml) was prepared by weighed accurately 10 mg of valacyclovir emulgel and transferred to a 50 ml volumetric flask then makeup the final volume with methanol. Different concentrations (2, 4, 6, 8, and10µg/ml) of solutions were prepared from the stock and measure the absorbance at 254 nm by using UV-Visible spectrophotometer and blank reagent. Graphs were plotted taking concentration on X-axis and absorption on Y-axis to give linear curve and the method obeyed Beer's law.

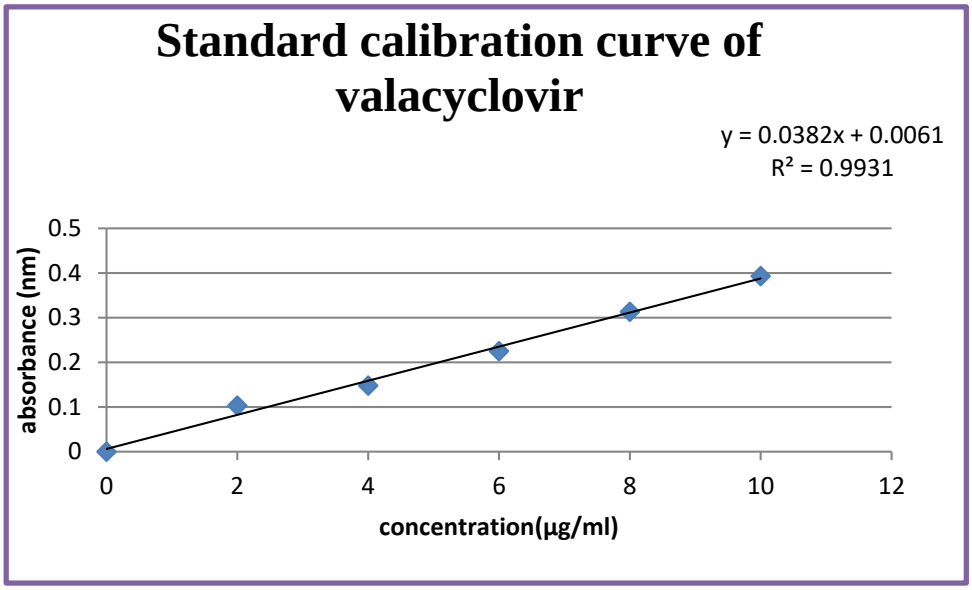

Fig. 1. Standard calibration curve of valacyclovir

Preparation of valacyclovir emulgel:

The gel was prepared by mixing Carbopol 934p and HPMC K100 in purified water separately with stirring. Next, the aqueous phase of emulsion is prepared by dissolving tween 80 in distilled water and the oil phase was prepared by mixing span80 in liquid paraffin. Both the oil phase and aqueous phases are heated separately at 70ºc. The drug i.e. valacyclovir was dispersed in oil phase. Then, the oil phase was added to aqueous phase with continuous stirring and was allowed to cool down until the formulation reached to the room temperature. The carbopol/HPMC gel base is added to the emulsion in a ratio of 1:1 by continuous stirring to produce a valacyclovir emulgel. Different formulation trails were prepared using different concentration polymers. They are assigned with formulation codes (F1, F2, F3, F4, F5, and F6).

Table no 1: formulation trials (composition) of valacyclovir emulgel

Ingredients	F1	F2	F3	F4	F5	F6
1.Drug (0.1gm)	0.1	0.1	0.1	0.1	0.1	0.1
2.HPMC(gm)	-	-	-	0.28	0.3	0.32
3.Carbopol (gm)	0.2	0.25	0.27	-	-	-
4.Tween-80 (ml)	0.05	0.05	0.05	0.05	0.05	0.05

Ingredients	F1	F2	F3	F4	F5	F6
1.Drug (0.1gm)	0.1	0.1	0.1	0.1	0.1	0.1
5.Span-80 (ml)	0.075	0.075	0.075	0.075	0.075	0.075
6.Liquid paraffin (ml)	2.5	2.5	2.5	2.5	2.5	2.5
7. Water(ml)	qs	qs	qs	qs	qs	qs

Evaluation parameters:

Pre-formulation evaluation tests:

1) FTIR analysis – The FTIR studies were conducted to check the drug excipient compatibility. Small amount of sample of drug and excipients were placed on the crystal of alpha bruker FTIR instrument and the spectra were obtained by opus software, which were later interpreted for its compatibility. [12]

Post-formulation evaluation tests:

1) Physical examination: The prepared formulations were inspected visually for their colour, homogeneity and consistency. [13]

2) Determination of pH: For pH determination, take 1gram of product and dissolve in 10ml of distilled water and pH measured with digital pH meter value should be in the range of 5-6 similar to skin ph. [14]

3) Spredability: It can be determined by using the slip and drag method, for this take the emulgel on the glass slide and cover it with another glass slide. Now the weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Time to cover 5cmdistance for the upper slide was recorded and used to calculate Spredability by using the following formula: [15]

$$\text{Spredability}(S) = M*L/T$$

Where M=Weight tied to the upper slide

L=Length of glass slides

T=Time taken to cover the distance by upper slide

4) Swelling index: 1gm of prepared emulgel is taken on a porous aluminium foil and then placed separately in a 50ml beaker containing 10ml of 0.1N NaOH. Then, samples were removed from beakers at different time intervals kept in a dry place for some time and reweighed. The swelling index is calculated as follows: [16]

$$\text{Swelling index (SW)}\ \% = (Wt - Wo)/Wo * 100$$

(SW)%=Equilibrium per cent swelling

Wt =Weight of swollen emulgel after time t

Wo =Original weight of emulgel at zero time

6) Drug content determination: 100mg of prepared emulgel samples were mixed with 50ml of methanol. This resultant solution is sonicated for 30 min. Drug content was analysed using the suitable analytical method from this solution and absorbance was checked with phosphate buffer as blank. [17]

7) Microbial assay: Ditch plate technique was used. It is a technique used for the evaluation of the bacteriostatic activity of a compound. Agar media was prepared and placed in Petri-plates to solidify. A ditch was made in the plate with the help of a sterile cup-borer and an emulgel was added and kept for incubation for 18-24Hrs. The microbial growth was observed far from the emulgel. This states that the emulgel has bacteriostatic activity. [18]

8) Globule size and its distribution in emulgel: 1gm of the emulgel samples was dissolved in purified water and agitated to get a homogeneous dispersion. Calibrate eyepiece micrometre by using stage micrometre and calculate the factor. Take emulgel on a slide and add 1-2 drops of amaranth dye to stain the oil globules and the oil globules size is noted. [19]

9) In-vitro drug release study- Franz diffusion cell was used for the drug release studies. Valacyclovir emulgel 100mg was applied onto the surface of the egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with a phosphate buffer solution with ph 6.8 to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer and the temperature was maintained at 37ºC. The samples were collected at a time interval of 1hr. Samples were analysed for drug content by UV visible spectrophotometer after appropriate dilutions. The amount of drug released across the egg membrane was determined as a function of time. [20]

10) Comparative in-vitro diffusion study – Franz diffusion cell was used for the comparative in-vitro drug release studies. Valacyclovir emulgel (100mg) and pure drug were applied onto the surface of the egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of the diffusion cell. The receptor chamber was filled with a phosphate buffer solution of ph 6.8 to solubilize the drug. The receptor chamber was stirred by a magnetic stirrer and the temperature was maintained at 37ºC. The samples of F4 and pure drug were collected at a time interval of 1hr. Samples were analysed for drug content by UV visible spectrophotometer after appropriate dilutions. The amount of drug released across the egg membrane was determined as a function of time.

11) Scanning electron microscopy-

Scanning electron microscopy is a test procedure that scans a sample with an electron beam to produce a magnified image for surface morphology analysis. The optimised formulation (F4) was visualized using SEM electron microscope with an accelerating voltage of 100 kV and magnification up to 20.00 kx approximately. Analysis of surface morphology and apparent shape of the optimised formulation (F4) was performed via scanning electron microscopy as reported in literature with slight modification. The samples for SEM were prepared by attaching the emulgels on metal stubs with the help of a double-sided adhesive

tape and dried in a vacuum chamber. Then, a 10 nm thick gold coating was applied with a sputter-coater and observed under high resolution SEM. [21]

12) In-Vitro Release kinetics:

The release data obtained was fitted into various mathematical models. The parameters 'n' and time component 'k', the release rate constant and 'R', the regression coefficient were determined by Korsemeyer-peppas equation to understand the release mechanism. [22]

III. Experiment and Result

Drug-excipients compatibility by FTIR

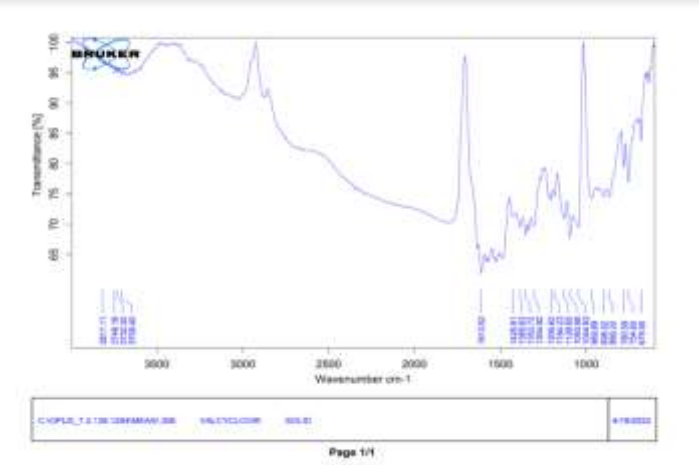

Fig. 2. FTIR graph of valacyclovir

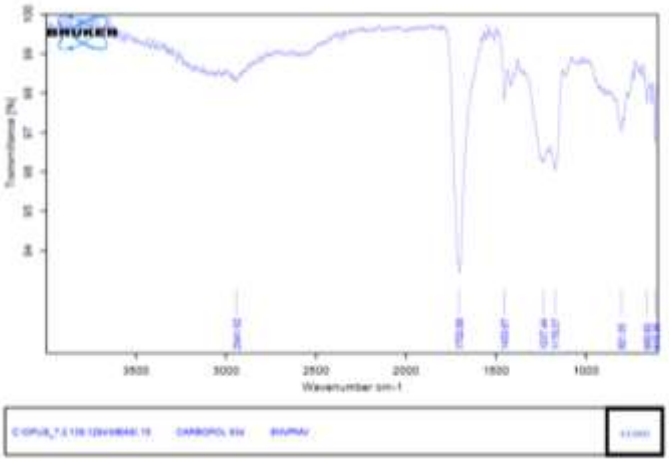

Fig.3. FTIR graph of carbopol

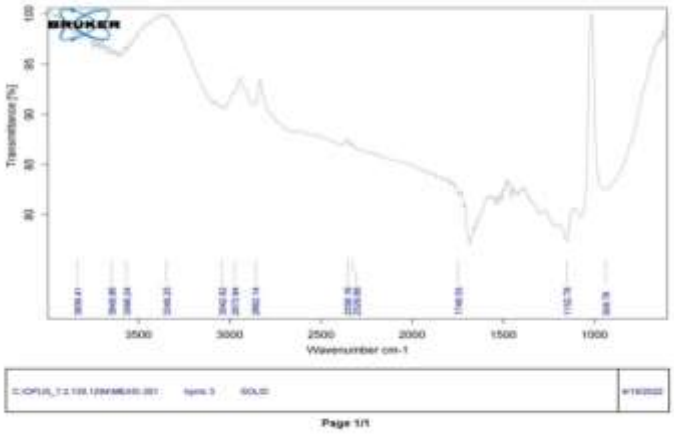

Fig.4. FTIR graph of HPMC

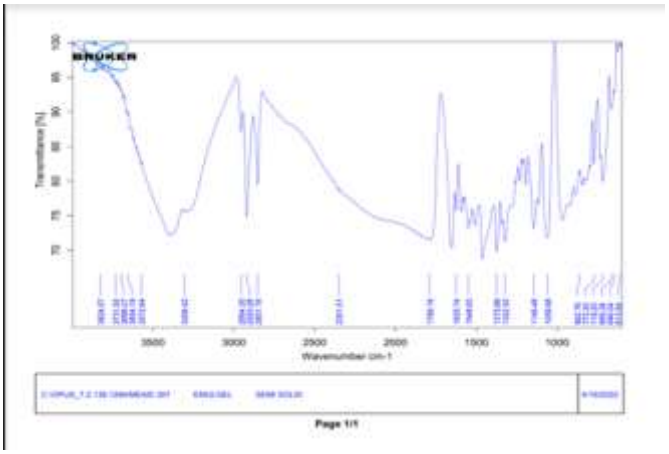

Fig.5. FTIR graph of formulation

FTIR Interpretation: FTIR study of pure drug (fig. 2),, carbopol 934 (fig.3) and HPMC (k100) (fig. 4) , and with formulation (fig. 5) were performed.

The experimental result shows there was no significant deviation between drug and polymers which confirm the compatibility. So these polymers and other excipients were selected for formulation. [23, 24, 25, 26, 27, 28]

Table no: 2 - Interpretation of FTIR analysis

Chemical	Wave number	Functional group
Drug	3817.11 cm^{-1}, 1613.52 cm^{-1}	(N-H stretching) (C=O stretching)
Carbopol	1703 cm^{-1} 2941 cm^{-1}	(C=O stretching bond), (OH stretching bond).
HPMC	2922.59 cm^{-1}, 3420.14 cm^{-1}	(C-H stretching vibration) N-H stretching bonds
Span 80	3359.78 cm^{-1} 1738.68 cm^{-1}	stretching vibration of the OH- group C=O stretching vibration
Tween 80	1092.46 cm^{-1} 1301.30 cm^{-1}	C=O stretching vibration C-O stretching vibration of ester group
Liquid paraffin	2920 $cm^{-1}$and 1461 cm^{-1},	C-H stretching and bending absorption bands
Formulation	3717.12 cm^{-1} 1513.25 cm^{-1}	(N-H stretching) (C=O stretching)

Post formulation studies

Physiochemical tests

Table no: 3 - Interpretation of physiochemical properties analysis

s.no	Formulation code	Colour	homogeneity	consistency	pH
1	F1	whitish	excellent	excellent	6.07
2	F2	whitish	excellent	excellent	6.28
3	F3	whitish	excellent	excellent	6.49
4	F4	whitish	excellent	excellent	6.98
5	F5	whitish	excellent	excellent	6.86
6	F6	whitish	excellent	excellent	6.76

Physical examination: The prepared valacyclovir emulgel formulations were examined for white viscous creamy characteristics with a smooth and homogeneous appearance. All of the

samples showed positive results, however F4 formulation was subjected to have excellent homogeneity and consistency. [29]

pH determination-according to literature , skin pH is said to be in the range 5.5-7. The ph was determined for all the 6 batches and the range was found to between 6.07-6.98. This analysis indicates that the compatibility of formulations matches with that of the skin pH and it can display good topical delivery. [30]

Post-formulation evaluation tests

Table no: 4 - Interpretation of physical characteristics evaluation

s.no	**Formulation no.**	**Drug content (%)**	**Swelling index (%)**	**Spredability(Sec)**	**Zone of inhibition(cm)**	**Globule size and its distribution(µm)**
1	F1	94.0	25.20	53.9	1.3	107.25
2	F2	93.0	45.83	54.3	1.2	178.75
3	F3	92.4	61.05	56.7	1.0	143.0
4	F4	98.9	94.84	64.4	0.5	71.5
5	F5	95.6	73.80	41.6	1.2	250.25
6	F6	96.7	85.47	51.7	1.1	214.5

Spredability-spredability of emulgel is a significant parameter. With decrease in viscosity, spredability increases. F4 showed highest spredability 64.4. It was easily spreadable because of low viscosity. [31]

Swelling index- Formulations with HPMC K 100 showed maximum swelling index in comparison with carbopol 934. Among all the formulation, F4 emulgel with HPMC K 100 showed the highest swelling index. Variation in swelling index value may be dependent on the water uptake nature and chain strength of the polymer. [32]

Drug content determination-The drug content of the formulations is determined by UV spectrophotometer at a wavelength of 254 nm, all the formulations shows the drug content in between the limit of 92% to 98%. [33]

Microbial assay – this evaluation test was carried to check the sterility if the batches as the emulgel formulation is more susceptible to a bacterial attack, commonly by E.coli. Among all the formulations, F4 formulation was found to have less microbial growth when compared with other formulations. [34]

Fig.9. (a) before incubation Fig .9. (b) after incubation

Fig.9. (a, b) microbial assay studies of optimized formulation (F4)

In -vitro drug release study-

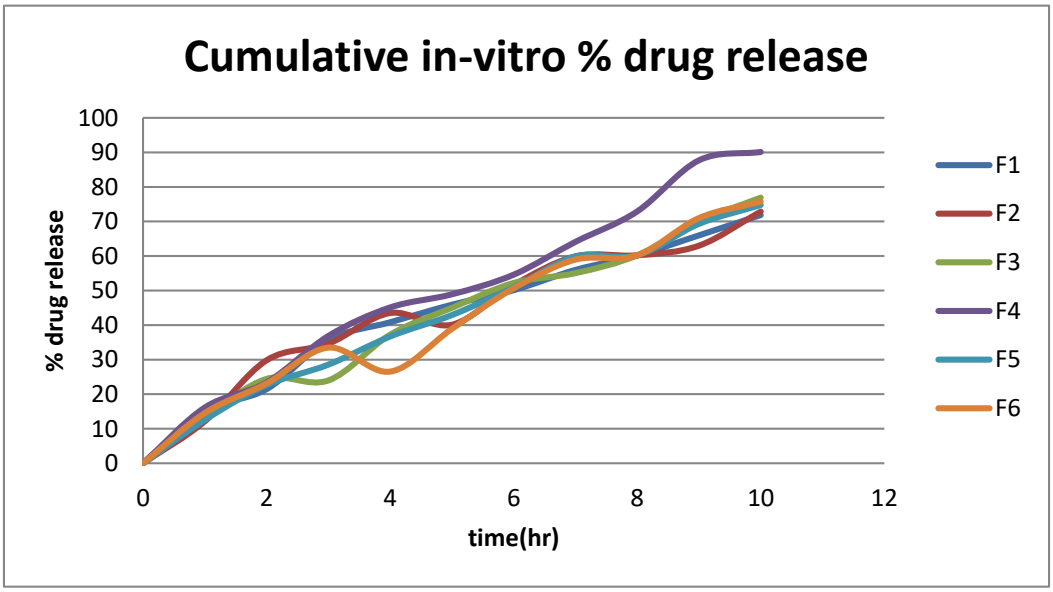

Fig.10. graphical representation of cumulative % in-vitro drug release

Release of drug from the formulation was depended on the nature and concentration of polymer. Formulations with carbopol 934 shows the drug release in descending order F3>F2>F1 where the amount of drug released after 10 h was 76.89%,72.68%, 71.86% respectively, and for the formulations with HPMC (K100) the drug release was recorded in descending order F4>F6>F5 where the amount of drug released after 10 h was 90.10%, 75.74%,74.76 % respectively. It has been concluded that the HPMC (K100) emulgel with low concentration of polymer, F4 shows maximum release. It shows that HPMC (K100) is better polymer than carbopol 934 for formulating emulgel. The cumulative % in-vitro drug release profile of all the formulation batches has been shown in fig.12. [35]

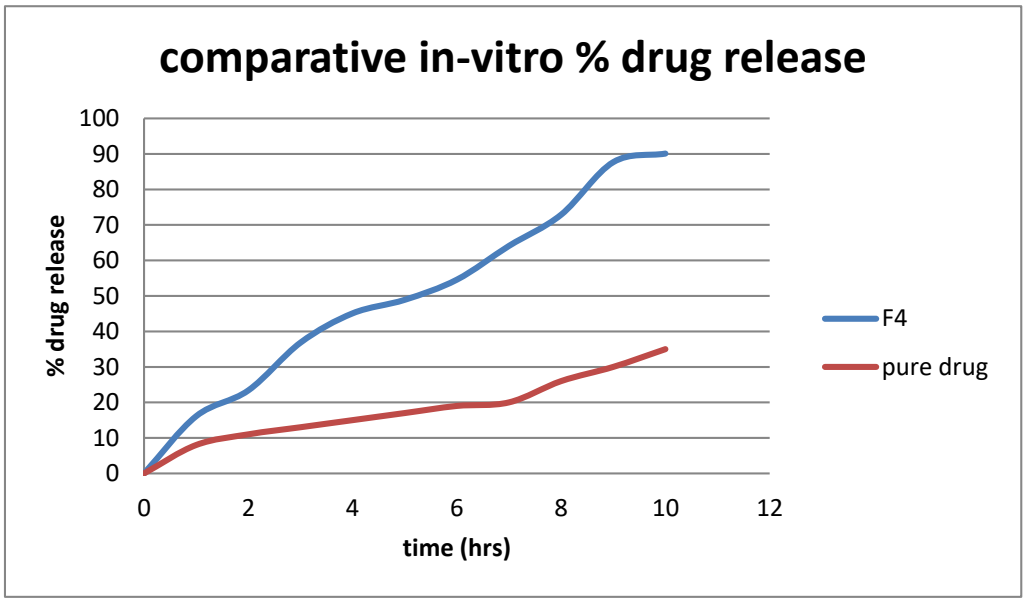

Fig.11. graphical representation of comparative in-vitro studies carried between optimized formulation (F4) and pure drug

This comparative in-vitro study was performed to compare the percentage drug release between the optimised formulation (F4) and that of the pure drug and it was found out that the drug release and diffusion rate of valacyclovir in emulgel was increased on comparison with pure drug.

Hence the objective of improving solubility and diffusion of drug through the skin by formulating into emulgel formulation has been achieved.

Scanning Electron Microscopy Studies

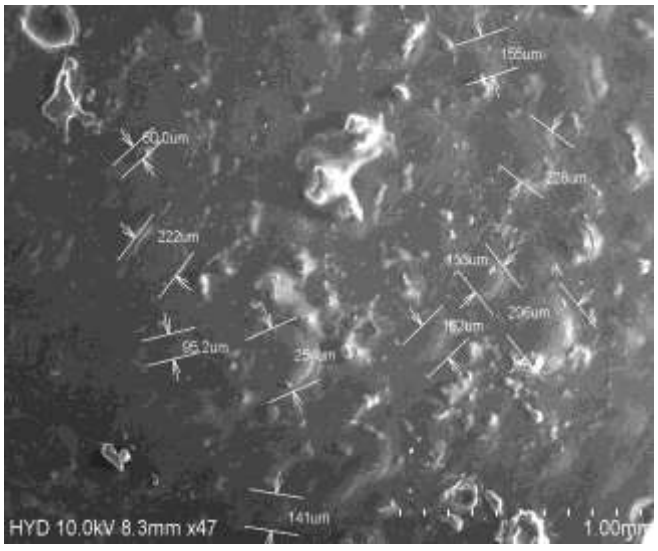

Fig.12. SEM photographs of optimised formulation (F4)

SEM studies interpretation-

The surface morphology of the optimized emulgel formulation examined by SEM is illustrated in Fig 12. The emulgel formulation appeared as spherical particles with smooth surface morphology with spherical oil globules. [36, 37]

IN-VITRO DRUG RELEASE KINETICS

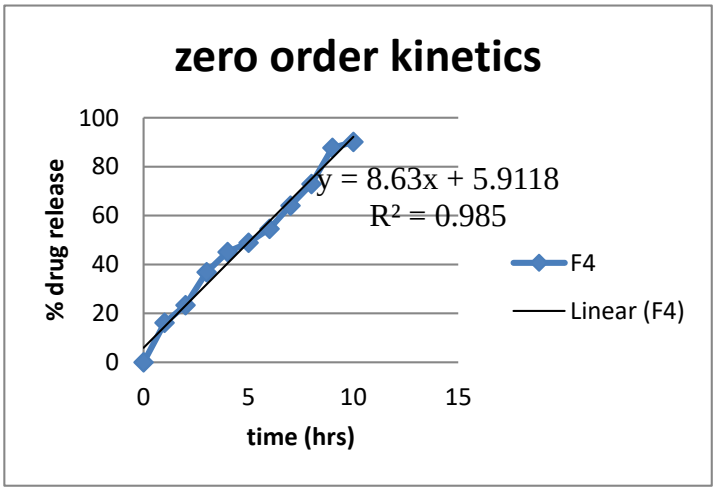

Fig.13. Zero-order plot for optimized formulation (F4)

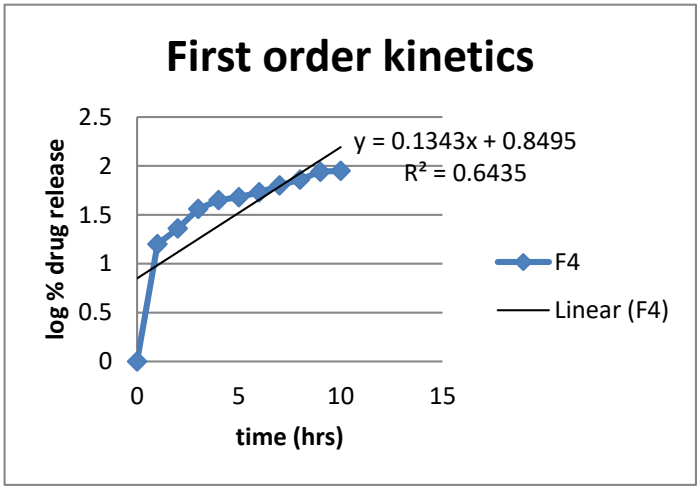

Fig.14. First-order plot for optimized formulation (F4)

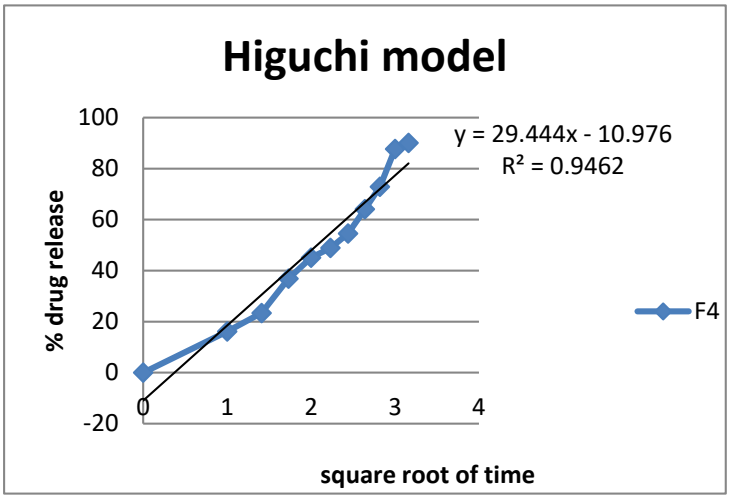

Fig.15. Higuchi plot of optimised formulation (F4)

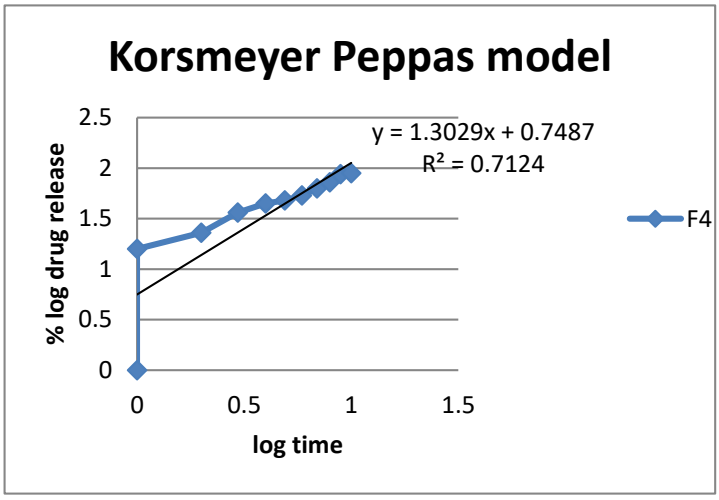

Fig.16. Korsmeyer-Peppas plot of optimised formulation (F4)

Table no- 5: release kinetics of optimized formulation of r^2value

Formula code	Zero order	First order	Higuchi	Korsemeyer peppas	
	$_R2$	$_R2$	$_R2$	$_R2$	n
F4	0.985	0.6435	0.9462	0.7124	0.82

From the above coefficient of determination and release exponent values collected from zero order kinetics, first order kinetics, higuchi model and korsmeyer peppas model, the n value is less than 1, indicating that the optimized formulation follows non-fickian diffusion model. [38, 39, 40, 41, 42]

IV. CONCLUSION

Topical drug delivery system, being a novel drug delivery will be used broadly for its uprising advantageous factors. This research was undertaken with an aim to formulate an anti-viral, valacyclovir emulgel due to its unavailability in the pharmaceutical market for the treatment of herpes labialis. Although, oral medications of the latter are widely available, it's not used to such an extent owing to first pass metabolism and decreased bio-availability. Loading valacyclovir drug into an emulgel base will give an edge over its absorptive properties, bio-availability and enhanced target-drug delivery. This study was initiated with drug-excipients studies by using FTIR, the results obtained from the FTIR analysis showed no possible chemical interactions between the drug (valacyclovir) and excipients(carbopol 934, HPMC, span 80, tween 80, liquid paraffin and formulation). Therefore, these excipients were selected for formulating the emulgel.

Eventually, 6 batches of emulgel with formulation codes (F1, F2, F3, F4, F5, and F6) were prepared and evaluated for their physiochemical parameters, physical characteristics such as colour, homogeneity, pH, drug content, spredability, swelling index, zone of inhibition and globule size along with in-vitro drug release studies. The best formulation from the 6 batches (F1 to F6), found to be efficient with whitish creamy consistency, ph(6.89),drug content (98.9% from UV analysis), swelling index of 94.84 %, spredability (64.4 sec), less microbial growth, globule size (71.5 µm) and in-vitro drug release was F4 with release of 90.10 %.The optimised formulation (F4) was now evaluated for comparative in-vitro studies, SEM studies and in-vitro release kinetics using zero-order, first-order, Higuchi and korsmeyer models. Comparative in-vitro study was performed to compare the % drug release between the optimised formulation (F4) and that of the pure drug and it was found out that the drug release and diffusion rate of valacyclovir in emulgel was increased on comparison with pure drug. From SEM studies, F4 was found to have smooth surface morphology with spherical oil globules evenly distributed. By in-vitro release kinetics, we can conclude that the optimised formulation (F4) follows non fickian diffusion as the n value is less than 1. Therefore, findings of our study indicate that a hydrophobic drug, valacyclovir can be delivered topically/ trans-dermally as an emulgel with improved solubility and diffusion of drug through the skin for the local treatment of herpes labialis with required physiochemical parameters and also can be made available to the young and old after technology transfer to pharmaceutical industries.

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