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DEVELOPMENT AND EVALUATION OF TRANSDERMAL GEL OF FEMCYCLOVIR USING PENETRATION ENHANCER AND ALOE-VERA

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ABSTRACT

Gel Formulations of famciclovir were prepared by simple mixing using stirrer with carbopol 940, HPMC K100M and *aloe vera* powder swelled in water intended for topical application. Famciclovir is an antiviral drug having higher protein binding, hepatic metabolism low bioavailability and low penetration power in skin. For preparation of gel formulations penetration enhancer (di sodium EDTA) was selected by solubility saturation method. Three trial batches were optimized on visual characters formulations CF-4, CF-5, HF-4, HF-5 and CHF-1 to CHF-5 were qualified. These qualified gel batches were further evaluated on ground of gel properties e.g. pH, Viscosity, Spreadability and % drug content, Formulations CF-4, CF-5, HF-4 and HF-5 showed % Drug content less than 90% hence removed from study. Formulation batches CHF-1 to CHF-5 were subjected for *in-vitro* drug release study, CHF-1(81.23%), CHF-2 (79.70%), CHF-3 (90.9%), CHF-4 (94.39%) and CHF-5 (92.82%). Though, all tested formulations showed good drug release profile but Regression value $R^2 = 0.946$ of CHF-4 revealed the CHF- 4 possessed excellent drug release. Different parameters were calculated for comparisons and finally the enhancement ratio was calculated that was 2.034. *In-vitro* drug release data of Gel batch CHF-4 was further expended for kinetic modeling.

KEYWORDS: Transdermal Gel, Femcyclovir, Penetration Enhancer, *Aloe-Vera*.

INTRODUCTION

Transdermal drug delivery system is convenient route for the delivery of drugs having short biological half life.[1,2,3] Transdermal gels are delivered the drug through the skin in controlled and predetermined manner in order to increase the therapeutic efficacy of drug and

reduced side effect of drug.[4,5] Famciclovir is used to treat infections caused by viruses especially herpes simplex that cause cold sores around the mouth and anus.[6,7,8] Femciclovir is sparingly soluble in water,[9] hence require developing a transdermal gel formulation to provide pain free administration, control release and local delivery.[10,11] Penetration enhancer was also used to allow the drug to penetrate in to the skin.[12,13] *Aloe-vera* was help to reduce the irritation caused by femciclovir.[14]

MATERIAL AND METHODS

Femciclovir was obtained from Ipca Laboratories, *Aloe vera* powder, Carbopol 940 and HPMC K100M was purchased from HiMedia Laboratories Pvt Ltd., Mumbai, Thiourea, Urea and Poly ethylene glycol was purchased from Finar Chemical (India) Pvt Ltd Ahmedabad. All used solvents and chemicals were laboratory grade.

Preformulation studies

(a) Organoleptic properties: The drug (famciclovir) powder was examined for its organoleptic properties like color, odour and taste it was observed.

(b) Determination of solubility: A fixed amount of drug was taken and then solvent was added and observes the solubility visually. Solubility study should be performed for famciclovir to determine solubility in various solvents like water, methanol, 0.1N NaOH, 0.1N HCl, Ethanol & 7.4pH buffer.

(c) Melting point determination: The Melting point was determined by the capillary method using Digital Melting point apparatus.

(d) Analytical estimation by U V-spectrophotometer

(i) Determination of wavelength of maximum absorbance (λ_{max})

10 µg/ml solution of was scanned in UV-spectrophotometer range from 200-400nm using double beam visible spectrophotometer.

(ii) Preparation of calibration curve

(ii) a Preparation of stock solution: Weigh accurately 10mg of famciclovir was dissolved in about 1ml of solvent, and volume was made upto 10 ml using same solvent the prepared solution was 1mg/ml or 1000µg/ml.

(ii) b Preparation of dilutions from stock solution: From this stock solution 1ml solution was pipette out in 10 ml calibrated volumetric flask filled upto 10ml prepared solution was 100 µg/ml and dilutions of 10, 20, 30, 40 &50 µg/ml was obtained from 100µg/ml solution. The absorbance of these solutions was taken on double beam U V spectrophotometer using

λmax at 306 nm. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve. Same procedure was fallowed for every solvent.

(e) Partition coefficient

In the pharmaceutical sciences, a partition (P) (also called distribution coefficient (D)) is the ratio of concentrations of a drug in the two immiscible phase mixture at equilibrium. Normally one of the solvents chosen is water (hydrophilic) while the second is hydrophobic such as n-Octenol.

(f) FT-IR spectra analysis

FT-IR Spectroscopy used to investigate and predict any physicochemical interactions between different components, in a formulation and therefore it applied to selection of suitable chemically compatible excipient. While selecting the ingredients, we would choose those which are stable, compatible and therapeutically acceptable. The aim of compatibility study was to test, whether there is any interaction between the excipients and the drug and compatibility between the drug and excipients.

Formulation development

(a) Selection of penetration enhancers: on the basis of saturation solubility of drug in the known concentration of penetration enhancer, we selected the penetration enhancer for gel formulations. 2 ml of penetration enhancer solution was taken in a test tube and dissolved the drug with stirring at ambient temperature until saturation. Drug concentration in saturated penetration enhancer solution was measured by UV visible spectroscopy at 306 nm.

(b) Method of preparation of transdermal gel

Accurately, weighed amount of polymers (Carbopol 940, HPMC K100M, *aloe vera* powder) according to formula were dispersed in purified water and allowed to swell overnight. Drug dissolved in solutions of selected penetration enhancers (Di sodium EDTA). After swelling polymers mix the solution with magnetic stirrer and drug-penetration enhancer solution was added in it with string and preservatives solution were also added. Final volume was made up and prepared gels were subjected for further characterization.

Characterization of famciclovir loaded transdermal gels

(a) Visual observation: Those properties of formulations which were observed visually e.g. color, consistency, homogeneity, clearance and phase separation.

(b) Determination of pH: The pH of formulated gel was determined by using digital pH meter at ambient (room) temperature. Prepared gels were accurately weighed and dispersed in 50ml purified water to make 10% solution. The calibration of pH meter was done with buffered solution before each use.

(c) Viscosity: A cone and plate viscometer with spindle C75-2 (Brookfield) at 100rpm was used to determine viscosity of different formulated gels.

(d) Spreadability study: Spreadability of prepared gel was determined by placing 0.5 g of gel within a circle of 1 cm diameter pre-marked on a glass plate. The slides were pressed upon each other so as to displace any air present and the adhering gel was wiped off. The two slides were placed onto a stand such that only the lower slide is held firm by the opposite fangs of the clamp allowing the upper slide to slip off freely by the force of weight tied to it. 20 gm weight was tied to the upper slide carefully. The time taken by the upper slide to completely detach from the lower slide was noted. The spreadability was calculated by using the following formula.

$$S = m \frac{l}{t}$$

Value "s" is Spreadability, "m" is the weight tied to the upper slides, "l" is the length of glass slide, and "t" is the time taken.

(e) % Drug content determination

The % drug content of prepared Gel was determined by dissolving of gel equivalent to 10 mg famciclovir in 10 ml methanol, sonicated in bath sonicator then filtered by filter paper. After preparation of suitable dilutions with pH 7.4 phosphate buffer, absorbance was determined using double beam UV-spectrophotometer with pH 7.4 phosphate buffer as blank at wavelength 306nm.

(f) Diffusion study

The diffusion of famciclovir from gel formulations was studied through and cellophane membrane using the Franz diffusion apparatus. The donor cell was filled with gel formulation equivalent to 4 mg of drug. The receptor compartment was filled with phosphate buffer of pH 7.4. The temperature of the receptor compartment was maintained at 37 ± 0.5 ^{o}C by circulating hot water through the jacket of Franz diffusion cell. Orifice size of Franz diffusion cell was 11.28 mm diameter and surface area was calculated as 1.00 cm^2 and receptor

compartment volume was 8ml. The samples were removed at predetermined intervals of time and replaced immediately with equal volume of receptor solution to maintain sink conditions. The aliquots were analyzed at 306 nm by UV spectrophotometer.

(g) Stability study

Stability study is performed for F5 as the formulation shows greatest drug release and hence can be termed as 'best formulation' from within those that are developed. Stability study was carried out for 1 month, the formulation was kept in stability chamber at 40oC and at 75% relative humidity. After one month the formulation was checked for following parameters.

Kinetics models of drug release

There are several models to represent the drug dissolution profiles where f (t) is a function of time related to the amount of drug dissolved from the pharmaceutical dosage form.

(a) Zero order kinetics: This model represents an ideal release profile in order to achieve the pharmacological prolonged action. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (that is, a constant release rate). The following equation is used to express the model:

$$\mathbf{Q_t = Q_o + K_{ot}}$$

Where,

Q_t is the amount of drug dissolved in time t,

Q_o is the initial amount of drug in the solution,

K_o is the zero order release constant

For practical purposes the equation is rearranged: **Percent drug released = Kt**

This is applicable to dosage forms like transdermal systems, coated dosage forms, osmotic systems as well as matrix tablets with low soluble drugs.

(b) First order kinetics: First order release constitutes drug release in a way that is proportional to the amount of drug remaining in its interior, in such a way that amount of drug released by unit time diminish. The following equation is used to express the model:

$$\mathbf{\log Q_t = \log Q_o + K_t/2.303}$$

Where,

Q_t is the amount of drug dissolved in time t,

Q_o is the initial amount of drug in the solution

K_t is the first order release constant

For practical purposes the equation is rearranged: **Log % of drug unreleased = K_t/2.303**

This model is applicable to dosage forms such as those containing watersoluble drugs in porous matrices.

(c) Higuchi model: Higuchi describes drug release as a diffusion process based in Fick's law, square root dependent. The following equation is used to express the model**:**

$$Q_t = K_h t^{1/2}$$

Where,

Q_t is the amount of drug dissolved in time t,

K_h is the first order release constant

For practical purposes the equation is rearranged: **Percent drug released = $Kt^{1/2}$**

This model is applicable to systems with drug dispersed in uniform swellable polymer matrix as in case of matrix tablets with water soluble drugs

(d) Peppas-Korsmeyer model: This model is widely used when the release mechanism is not well known or when more than one type of release phenomenon could be involved. The following equation is used to express the model

$$Q_t/Q_\infty = Kt^n$$

Where, Q_t is the amount of drug dissolved in time t, Q_∞ is the amount of drug dissolved in infinite time, n is the release exponent indicative of drug release mechanism, K is the kinetic constant.

RESULTS

Preformulation studies

(a) Organoleptic properties of famciclovir

Table no. 1: Organoleptic properties of pure drug famciclovir.

Test	Specification	Observations
Color	White	Complies
Taste	Characteristic	Complies
Odor	Odorless	Complies
Physical state	Solid pellets	Solid amorphous powder

(b) Determination melting point

Table no. 2: Melting point of drug famciclovir.

Sr. no	Material	Specification	Melting point
1.	Famciclovir	102 - 104 ^{0}C	102 ^{0}C

(c) Solubility study

Table no. 3: Solubility profile of famciclovir in different solvent.

S. no.	Solvents	Solubility
1.	Distilled water	Sparingly Soluble
2.	Ethanol	Slightly Soluble
3.	Methanol	Freely Soluble
4.	Ethyl acetate	Sparingly soluble
5.	pH 7.4 Phosphate Buffer	Soluble, dispersible

(d) Determination of Wavelenth of Maximum Absorbance (λ_{max})

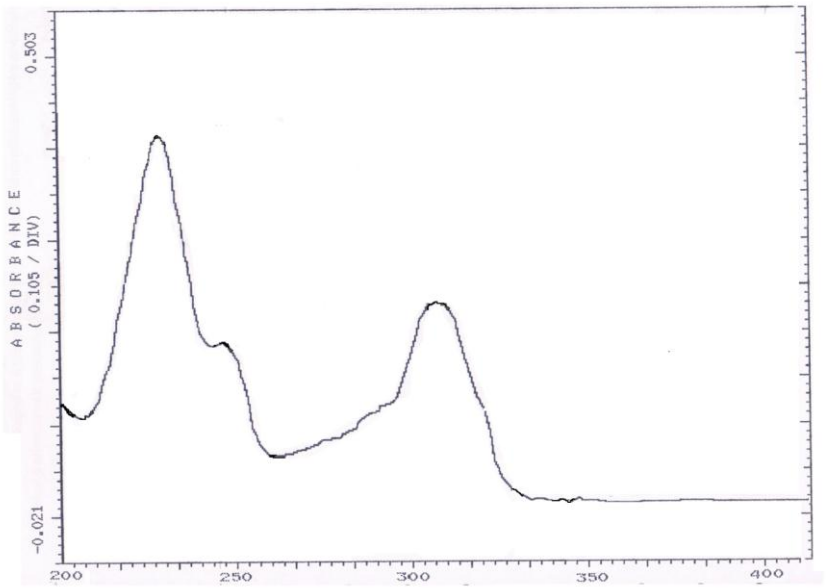

Figure no. 1: Scanning of wavelenth of famciclovir.

Table no. 4: Wavelength of maximum absorbance (λ_{max}).

Conc. (µg/mL)	Scanning range (nm)	Peaks observed (nm)	Selected λ_{max}
10	200-400	224, 244, 306	**306 nm**

(e) Preparation of the calibration curves of famciclovir

Table no. 5: Linearity of famciclovir 7.4 pH buffer.

Conc. (µg/ml)	0	10	20	30	40	50
Absorbance	0	0.109	0.228	0.352	0.472	0.605

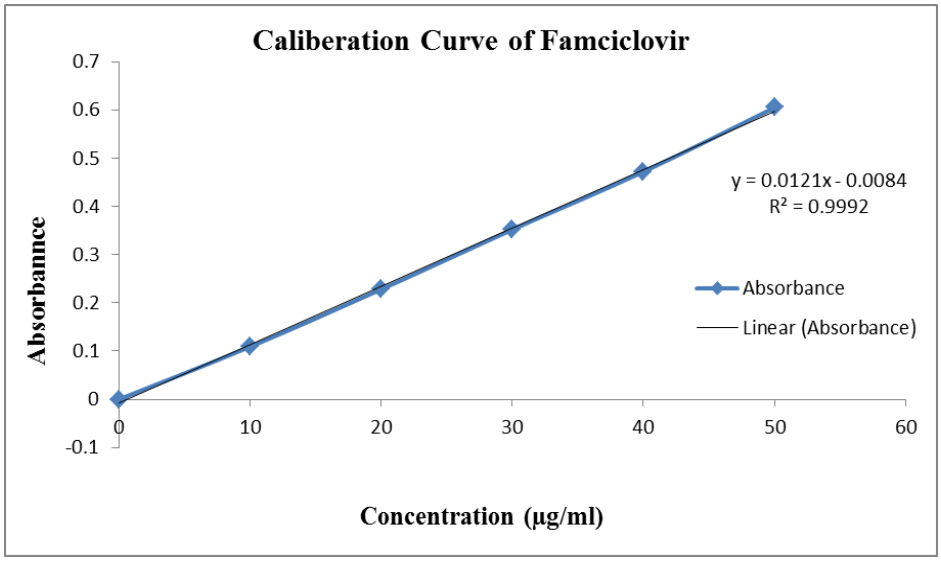

Fig. no. 2: Calibration curve of famciclovir in 7.4 pH buffer.

Linearity equation: y = mx + c,

y = 0.012x – 0.008

y = abs. of unknown sample

m= slope = 0.012

x = Conc. (µg/ml)

c= Intercept = 0.008

r^2= 0.999

(f) Partition Co-efficient

Table no. 6: Partition Co-efficient.

Sr. no.	Solvents	Absorbance
1.	Water	0.754
2.	n- Octanol	1.363

Partition coefficient = concentration of n- Octanol / concentration in water

Concentrtion in n-Octanol

y = 0.012x – 0.008

1.363 =0.012x – 0.008

x = 1.355/0.012

x = 112.92 ppm

Concentrtion in water

y = 0.012x – 0.008

0.754 = 0.012x – 0.008

x = 0.746/0.012

x = 62.167 ppm

Partition coefficient = 112.92/62.167 = 1.82

(g) Compatibility study

(g)(i) Physical compatibility study

Table no. 7: Physical compatibility study of famciclovir with polymer.

S. no.	Material	Storage at room temperature	Storage at 45^0C -50^0C	Storage at 2^0C -8^0C
1	Pure Drug (10mg)	Stable	Stable	Stable
2	Famciclovir + Di sodium EDTA	Stable	Stable	Stable
3	Famciclovir + propylene glycol	Stable	Stable	Stable
3	Famciclovir + Di sodium EDTA + *aloe vera* powder + propylene glycol	Stable	Stable	Stable

(g)(ii) Chemical compatibility study by FT-IR

Table no. 8: FT-IR Peaks of famciclovir.

Standarded Peaks(Cm^{-1})	Observed Peaks(Cm^{-1})	Peak Assigned
3000-3500	3441	N-H_2 str, sharp
3200-3000	3184	N-H str, sharp
3000-2840	2858	CH_3 str
1750-1710	1714	C-O str. (Ester)
1650-1600	1634	C=C str
1210-1163	1181	C-O str (Ester)

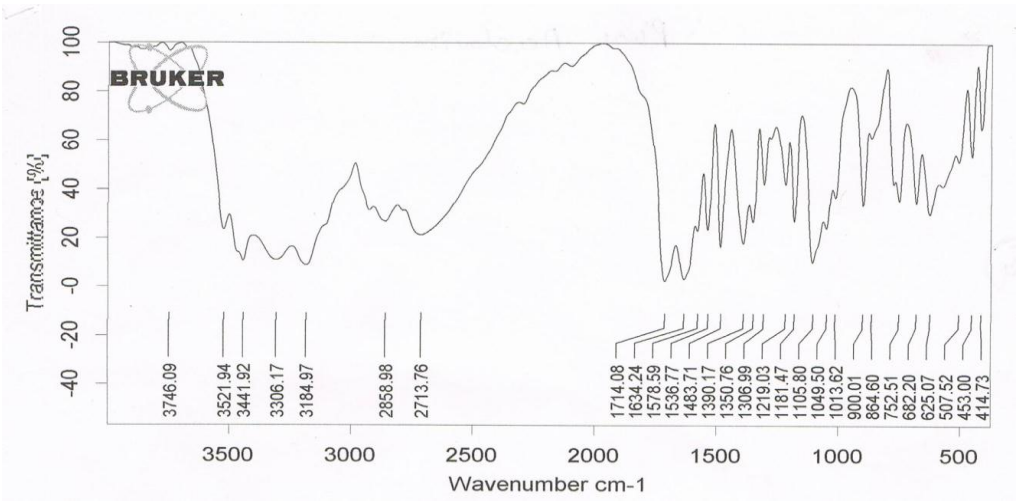

Figure no. 3: FT-IR spectrum of famciclovir pure.

Formulation development

(a) Selection of penetration by saturation solubility

Table no. 8: Solubility of famciclovir in different oils at 25 ^{o}C.

S. no.	Oil	Drug solubility (mg/ml)
01	0.02 % Sodium EDTA	14.0
02	Propylene glycol	11.0
03	Poly ethylene glycol	10.8
04	Urea	10.5
05	Thiourea	09.3
06	Nerolidol	07.0

Di Sodium EDTA 0.02 % was selected as penetration enhancer for further procedure to development of gel formulation.

Optimization of formulation

Different trial formulations were prepared and studied for their physicochemical characterization and visual observation and finally got the optimized formulations. The trial formulations of gel were prepared in three batches, formulations prepared according to following formulae:

(a) Trial batch- 01: In first trial batch, drug famciclovir and penetration enhancer percentage remains constant and the percentage of polymer(s) was gradually increased.

Table no. 9: Formulations of trial batch- 01.

S. no.	Ingredients	CF-1	CF-2	CF-3	CF-4	CF-5
1	Famciclovir (mg)	100	100	100	100	100
2	Carbopol 940 (%w/v)	0.2	0.4	0.6	0.8	1.0
3	*Aloe vera* powder (%w/v)	0.5	0.5	0.5	0.5	0.5
4	Disodium EDTA solution (%w/v)	0.02	0.02	0.02	0.02	0.02
5	Methyl paraben (%w/v)	0.02	0.02	0.02	0.02	0.02
6	Propyl paraben(%w/v)	0.1	0.1	0.1	0.1	0.1
7	Purified Water q.s. to produce 100ml	100	100	100	100	100

(b) Trial batch 02: In second trial batch, drug famciclovir and oil concentration percentage remains constant and the percentage of Smix (1:1) will gradually increase.

Table no. 10: Formulations of trial batch- 02.

S. no.	Ingredients	HF-1	HF-2	HF-3	HF-4	HF-5
1	Famciclovir (mg)	100	100	100	100	100
2	HPMC K100M (%w/v)	0.2	0.4	0.6	0.8	1.0
3	*Aloe vera* powder (%w/v)	0.5	0.5	0.5	0.5	0.5
4	Disodium EDTA solution (%w/v)	0.02	0.02	0.02	0.02	0.02

5	Methyl paraben (%w/v)	0.02	0.02	0.02	0.02	0.02
6	Propyl paraben(%w/v)	0.1	0.1	0.1	0.1	0.1
7	Purified Water q.s. to produce 100ml	100	100	100	100	100

(c) Trial batch- 03: In second trial batch, drug famciclovir and oil concentration percentage remains constant and the percentage of Smix (1:1) will gradually increase.

Table no. 11: Formulations of trial batch- 03.

S. no.	Ingredients	CHF-1	CHF-2	CHF-3	CHF-4	CHF-5	CHF-0
1	Famciclovir (mg)	100	100	100	100	100	100
2	Carbopol 940 (%w/v)	0.2	0.4	0.6	0.8	1.0	0.8
3	HPMC K100M (%w/v)	0.8	0.6	0.4	0.2	0.0	0.2
4	*Aloe vera* powder (%w/v)	0.5	0.5	0.5	0.5	0.5	0.5
5	Disodium EDTA solution (%w/v)	0.02	0.02	0.02	0.02	0.02	0.00
6	Methyl paraben (%w/v)	0.02	0.02	0.02	0.02	0.02	0.02
7	Propyl paraben(%w/v)	0.1	0.1	0.1	0.1	0.1	0.1
5	Purified Water q.s. to produce 100ml	100	100	100	100	100	100

(d) Optimization results of all prepared formulation

Table no. 12: Optimization of all prepared formulation.

S. no.	Code of formulation	Visual observation	Thermo dynamic Stability
1	CF-1	Yellowish, Coludy	Phase separation
2	CF-2	Yellowish, Coludy	Phase separation
3	CF-3	White, Coludy	Phase separation
4	CF-4	Clear	Stable
5	CF-5	Clear	Stable
6	HF-1	Light yellow, Clear	Phase separation
7	HF-2	Light yellow, Clear	Phase separation
8	HF-3	Light yellow, Clear	Phase separation
9	HF-4	Clear	Stable
10	HF-5	Clear	Stable
11	CHF-1	Yellowish, Clear	Stable
12	CHF-2	Yellowish, Clear	Stable
13	CHF-3	Clear	Stable
14	CHF-4	Clear	Stable
15	CHF-5	Clear	Stable

From the study reported in above tables, formulations **CF-4, CF-5, HF-4, HF-5 and CHF-1** to **CHF-5** were selected for further studies. Rests of formulations were discarded because they were thermodynamically unstable and phase separation occurred within 7 days.

It was also observed during this study that as the concentration of polymer increased stability and clearness of formulations was improved.

Evaluation of prepared gel formulations

(a) Physical Observation and Properties of prepared gel formulations

Table no. 13: Physical Observation, pH, Viscosity and Spreadability of prepared gels.

Gel formulation Code	Physical Observation	pH	Viscosity (cp)	Spreadability gm.cm/sec	% Drug content
CF-4	Clear	6.2	4718	9.334	86.32
CF-5	Clear	6.8	5543	10.334	89.53
HF-4	Clear	7.1	5455	9.341	87.44
HF-5	Clear	6.6	5531	10.326	87.98
CHF-1	Yellowish, Clear	6.9	4548	7.265	90.21
CHF-2	Yellowish, Clear	6.5	4623	8.331	94.53
CHF-3	Clear	6.6	5342	9.314	93.31
CHF-4	Clear	7.3	6832	12.722	98.42
CHF-5	Clear	6.7	7638	11.421	96.81

Formulations CF-4, CF-5, HF-4 and HF-5 showed % Drug content less than 90% that's why these were not considered for further study.

(b) *In-vitro* cumulative %drug release (permeation) study of formulated gel preparations

Table no. 14: *In-vitro* cumulative %drug release of gel preparations.

Time (hrs)	Cumulative %drug release of gels				
	CHF-1	CHF-2	CHF-3	CHF-4	CHF-5
0	0	0	0	0	0
1	14.14	14.49	19.77	17.12	18.45
2	29.33	29.44	39.02	34.23	36.99
4	51.69	51.57	67.61	57.20	67.25
6	66.76	65.57	87.82	75.97	87.10
8	75.50	73.34	88.99	84.83	89.71
10	81.23	79.79	90.90	94.39	92.82

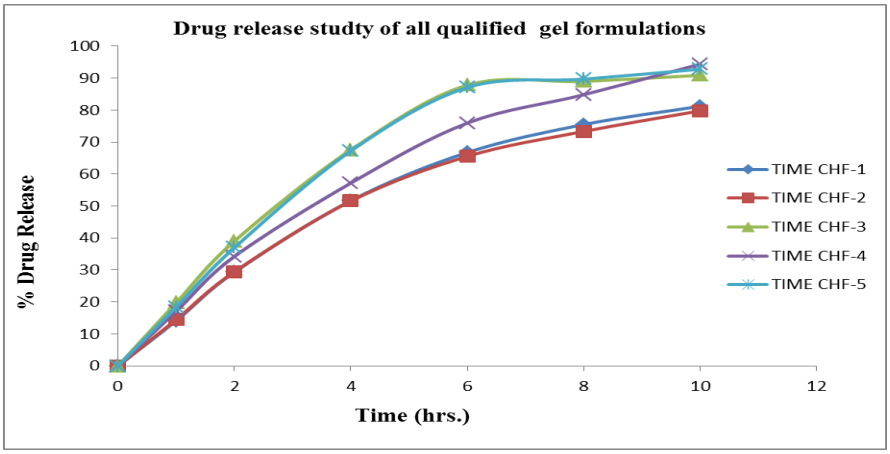

Figure no. 4: *In-vitro* cumulative % drug release of gel preparations.

Table no. 15: R^2 values of all microcapsules of vitamin-E formulations.

Model	Equation	R^2
CHF-1	y = 8.185x + 9.270	R² = 0.937
CHF-2	y = 7.958x + 9.641	R² = 0.933
CHF-3	y = 9.206x + 15.52	R² = 0.866
CHF-4	y = 9.34x + 10.6	R² = 0.946
CHF-5	y = 9.466x + 14.12	R² = 0.883

On the basis of % drug release study, regression (R^2) values of all gel formulations showed that formulation CHF-4 possessed excellent release profile.

Optimization of effect of penetration enhancer

(a) Preparation of blank formulation

Formulation **CHF-0** was the blank formulation which was same as the CHF- 4 without penetration enhancer intended for comparison in permeability.

Table no.16: Stability of blank formulation.

S. no.	Code of formulation	Visual observation	Thermo dynamic Stability
1	CHF-4	Clear	Stable
2	CHF-0	Clear	Stable

(b) Comparative permeation study between gel batch CHF-4 and blank gel batch CHF-0

Equivalent to 4 mg of famciclovir gel batch **CHF-4** and **CHF-0** were filled into the donor compartment of Franz Diffusion cell and 8ml of phosphate buffer pH 7.4 filled in receptor compartment for each experiment separately.

Table no.17: I*n-vitro* drug release profile of optimized gel formulation (CHF-4).

Time (hr.)	S.R.T.	Log T.	Abs.	Conc (µg/ml)	Amt. in 1ml (mg)	Amt. in 8ml (mg)	Correction factor	% C.R	Log % C.R	% Drug remaining	Log% drug remaining
0	0	0	0	0	0	0	0	0	0	100	2
1	1	0	0.120	10.7	0.0107	0.0856	-	17.12	1.234	82.88	1.918
2	1.141	0.301	0.265	22.7	0.0227	0.1819	0.0107	34.23	1.534	65.77	1.818
4	2	0.602	0.455	38.6	0.0386	0.3087	0.0227	57.20	1.757	42.80	1.631
6	2.449	0.777	0.620	52.3	0.0523	0.4185	0.0386	75.97	1.881	24.03	1.381
8	2.828	0.903	0.707	59.6	0.0596	0.4765	0.0523	84.83	1.929	15.17	1.181
10	3.162	1.000	0.789	66.41	0.0665	0.5316	0.0596	94.39	1.975	05.61	0.749

Table no. 18: I*n-vitro* drug release profile of Blank gel formulation (CHF-0).

Time (hr.)	S. R. T.	Log T.	Abs.	Conc. (µg/ml)	Amt. in 1ml (mg)	Amt. in 8ml (mg)	Correction factor	% C.R	Log % C.R	% Drug remaining	Log% drug remaining
0	0	0	0	0	0	0	0	0	0	100	2
1	1	0	0.032	3.34	0.0034	0.0267	-	05.34	0.728	94.66	1.976
2	1.141	0.301	0.127	11.25	0.0113	0.0900	0.0034	17.32	1.239	82.68	1.917
4	2	0.602	0.223	19.25	0.0192	0.1539	0.0113	28.53	1.455	71.47	1.854
6	2.449	0.777	0.317	27.08	0.0271	0.2165	0.0192	39.46	1.596	60.54	1.782
8	2.828	0.903	0.358	30.50	0.0305	0.2437	0.0271	43.32	1.637	56.68	1.734
10	3.162	1.000	0.385	32.80	0.0328	0.2626	0.0305	46.42	1.667	53.58	1.729

(c) Comparison of drug permeation on different parameters

Table no. 19: Results of drug permeation parameters across membrane.

Formulation code	Q_{10} (mg/cm^2)	Jss (mg/cm^2)/hr	Kp(x 10^{-3})	ER
CHF-0	1.8568	0.18568	46.42	-
CHF-4	3.776	0.3776	94.40	2.034

Where,

Q_{10} = Cumulative amount of drug released per unit surface area

Jss = Steady state flux

Kp = Permeability coefficient (Jss/C) where, C is initial amount of drug in donor compartment

ER = Enhancement ratio, is ratio of Kp with pretreatment and Kp without pretreatment

Kinetics modeling for optimized gel batch CHF-4

(a) Zero order model

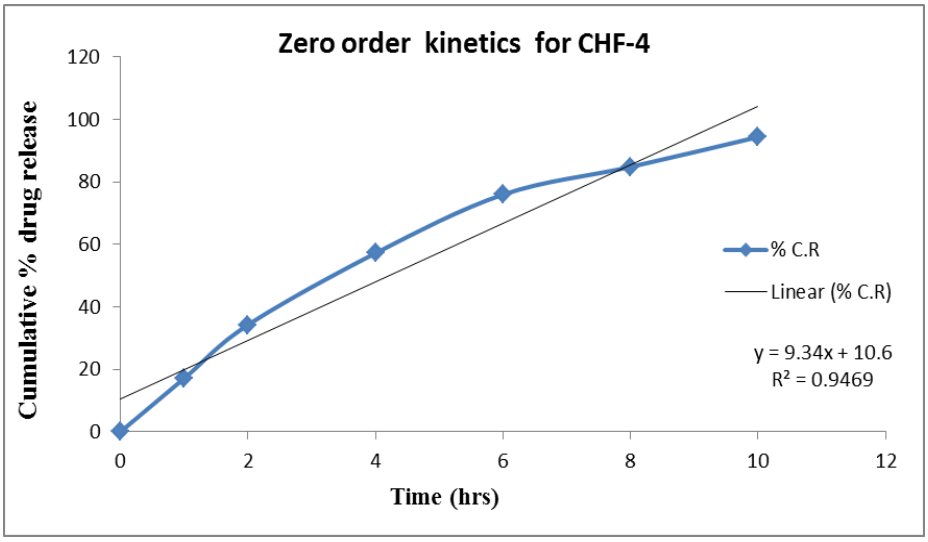

Fig. no. 5: Zero order for model for CHF-4.

(b) First order model

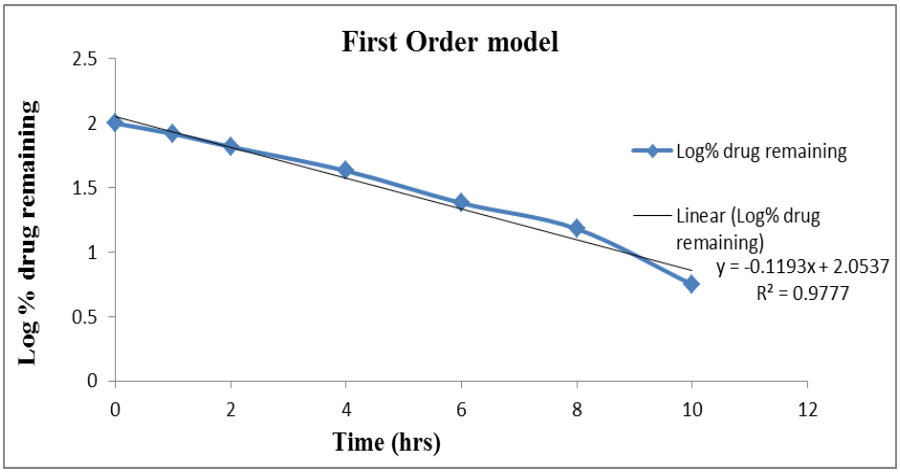

Fig. no. 6: First order model for CHF-4.

(c) Higuchi model

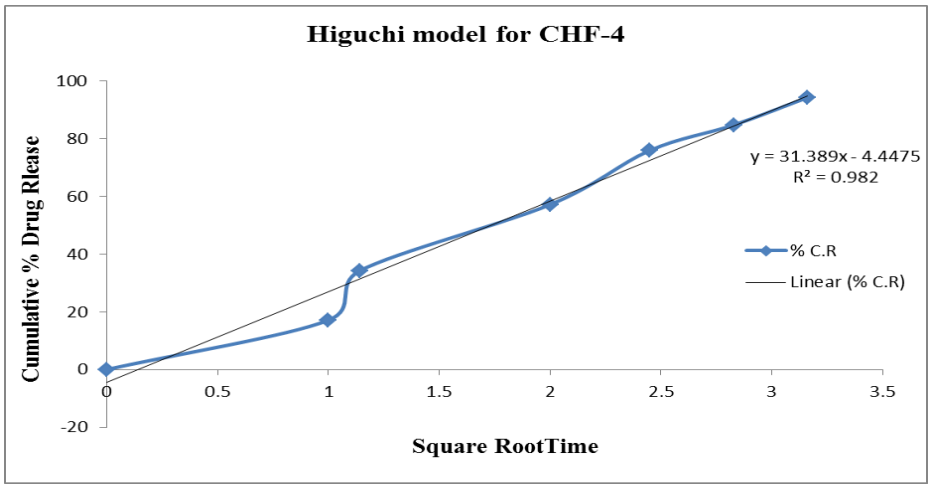

Fig. no. 7: Higuchi model for CHF-4.

(d) Korsmeyer-Peppas model

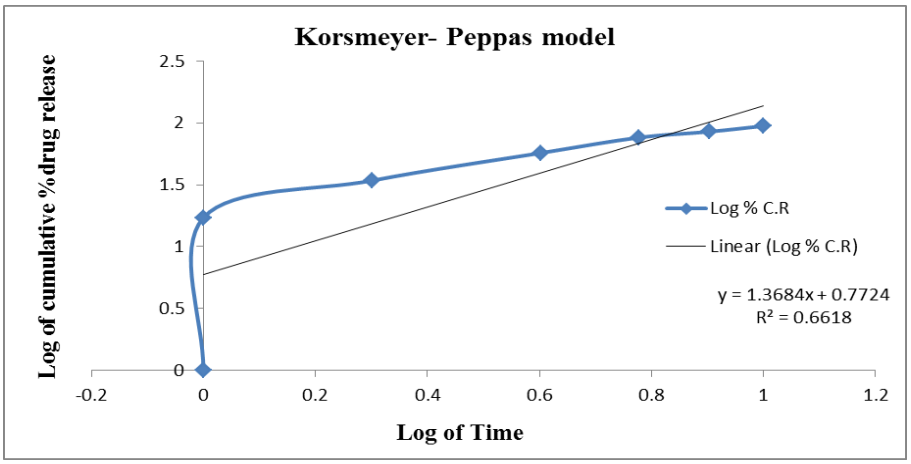

Fig. no. 8: Korsmeyer- Peppas model forCHF-4.

Table no. 20: I*n-vitro* curve fits for various release systems for optimized gel CHF-4.

Model	Equation	R^2
Zero order	y = 9.34x + 10.6	R² = 0.946
First order	y = -0.119x + 2.053	R² = 0.977
Higuchi	y = 31.38x - 4.447	R² = 0.982
Korsmeyer –Peppas	y = 1.368x + 0.772	R² = 0.661

Stability Studies

Table no. 21: Stability studies of optimized gel batch CHF-4.

Time (Days)	% Drug release		
	4 °C	25 °C	40 °C
0	94.39	94.39	94.39
15	92.41	91.31	91.32
30	90.02	91.14	91.06

DISCUSSION

During the Preformulation studies it is found that the organoleptic properties of famciclovir comply as reported. White, characterstic, odorless, solid pellets of famciclovir was sparingly soluble in water and ethyl acetate, soluble in Phosphate buffer (pH 7.4) also dispersible, freely soluble in methanol. Melting point of Famciclovir was complies with reported and was found at 102 ^{0}C. λ_{max} was determined in phosphate buffer pH7.4 solvent at 306 nm. Standard calibration curve was prepared using concentration range 10 - 50 µg/ml and linearity equation as y = 0.012x - 0.008 with R^2 = 0.999. Partition coefficient of famciclovir was found 1.82. Drug famciclovir was also compatible with used excipients, physically stable and chemically stable as observed in FT-IR spectra.

For preparation of gel formulations penetration enhancer (di sodium EDTA) was selected by solubility saturation mrthod for particular drug famciclovir among six different penetration enhancers. Total sixteen different formulations were prepared using different concentrations of polymers carbopol 940, HPMC K100M and *aloe vera* powder by mixing in purified water. Where, amount of carbopol 940m and HPMC K100M were very and amount of aloe vera and drug fixed. Three trial batches were optimized on visual characters formulations CF-4, CF-5, HF-4, HF-5 and CHF-1 to CHF-5 were qualified. These qualified gel batches were further evaluated on ground of gel properties e.g. pH, Viscosity, Spreadability and % drug content, Formulations CF-4, CF-5, HF-4 and HF-5 showed % Drug content less than 90% hence removed from study. Formulation batches CHF-1 to CHF-5 were subjected for *in-vitro* drug release study, CHF-1(81.23%), CHF-2 (79.70%), CHF-3 (90.9%), CHF-4 (94.39%) and CHF-5 (92.82%). Though, all tested formulations showed good drug release profile but Regression value R^2 = 0.946 of CHF-4 revealed the CHF- 4 possessed excellent drug release. Hence, formulation **CHF-4** was selected for further study and blank formulation **CHF- 0** same as CHF- 4 without penetration enhancer was prepared for comparison of effect of penetration enhancer. Different parameters were calculated for comparisons and finally the enhancement ratio was calculated that was 2.034. *In-vitro* drug release data of Gel batch CHF-4 was further expended for kinetic modeling. Kinetic modeling revealed that optimized Gel batch CHF- 4 was followed Higuchi model with regression value (R^2 = 0.982).

Accelerated Stability studies for 30 days was conducted with optimized Gel batch CHF-4 on three different temperatures (4, 25 & 40^{o}C) and found that no significant variation in % drug release during whole study.

CONCLUSION

Gel Formulations of famciclovir were prepared by simple mixing using stirrer with carbopol 940, HPMC K100M and *aloe vera* powder swelled in water intended for topical application. Famciclovir is an antiviral drug having higher protein binding, hepatic metabolism low bioavailability and low penetration power in skin. The drug requires a drug delivery system that provides a bypass for these problems and improves absorption through skin by enhancing penetration. Prepared gels were characterized for compatibility study, visual observations pH, Viscosity, Spreadability, % drug content, *in-vitro* drug release. Due to selection of appropriate polymer ratio this drug delivery systems showed good penetration and helped to protect from described biological problems, also provide the famciclovir for 10 hrs continuously on specific site of action. Major advantages of the system include ease of preparation, high % drug cntent and long drug release over 10 hours. From this study, it was concluded that Gel of famciclovir offers bettder and improved penetration thus enhanced bioavailability, protection of drug from biological systems and continuous release of the medicament over 10 hrs and subsequent efficacy is improved.

CONFLICTS OF INTEREST

There are no conflicts of interests.

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