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RESEARCH ARTICLE

EFFECT OF PERMEATION ENHANCERS ON THE PENETRATION MECHANISM OF TRANSDERMAL GEL OF NIFEDIPINE

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ABSTRACT

The objective of the present research work was to formulate transdermal carbopol gel and compare five different permeation enhancer (polyethylene glycol400, olive oil, oleic acid, limonene and dimethyl sulfoxide), using a model drug (Nifedipine) to evaluate the antihypertensive activity of gel and compared for in vitro and in vivo drug release. The formulated gel were evaluated for physical appearance, drug content, viscosity, spreadability, pH determination, clarity, extrudability and also for antihypertensive activity are suggestive of good characteristic properties of best batch. Permeation enhancers show maximum effect in the concentration between 3 to 9 %, above this concentration the effect of permeation enhancer stabilized i.e. don't show significant effect. Formulation F12 showed maximum drug release of 78.518% in 8hr which contained 9% permeation enhancer concentration i.e(oleic acid). Thus it concluded from the data that oleic acid is having maximum penetration power among olive oil, limonene, PEG400 and DMSO. From the optimized batch F12 showed zero order kinetic model of drug release. All Formulation Shows Good Results, Do Not Cause Any Kind of Skin Irritation. The transdermal delivery of Nifedipine shows good results avoiding side effects of first pass metabolism and G.I.T irritation.

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INTRODUCTION

Nifedipine is a antihypertensive BCS class II drug, which decreases arterial smooth muscle contractility and subsequent vasoconstriction by inhibiting the influx of calcium ion through L-type calcium channels. It acts primarily on vascular smooth muscle cells by stabilizing voltage-gated L-type calcium channels in their inactive conformation. By inhibiting the influx of calcium in smooth muscle cells, nefidipine prevents calcium-dependent myocyte contraction and vasoconstriction (Dollery, 1999). Transdermal delivery systems (TDS) were introduced onto the US market in the late 1970s, but transdermal delivery of drug had been around for a very long time. The systems can greatly improve patient compliance through avoidance of first-pass metabolism, improved bioavailability, reduction of systemic side effects and dosing schedule (Kalinin et al., 2002). Emergence of novel techniques for skin permeation enhancement and development of methods to lessen skin irritation would widen the transdermal market for hydrophilic compounds, macromolecules and conventional drugs for new therapeutic indications. As evident from the ongoing clinical trials of a wide variety of drugs for various clinical conditions, there is a great future for transdermal delivery of drugs (Allan 8th edition). Transdermal gel can provide sustained plasma concentration profile for long periods of time. The drug is absorbed continuously through the skin and enters the bloodstream. Mainly trandermal drug delivery system is used for their local action. Drug delivery through trasdermal route provide less chance of an overdose or underdose and permit both local and systemic effects. Gels are generally more effective than creams or sprays. The aim of our present work was to develop carbopol gel using different permeation enhancers for transdermal drug delivery system for Nifedipine and to evaluate it in vitro. The advantages of transdermal delivery over other delivery systems are as follows-Easy elimination of drug delivery in case of toxicity, Reduction of dosing frequency an enhancement of patient compliance, Transdermal medications deliver a steady infusion of drug over an extended periods of time and The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.

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MATERIALS AND METHODS

Nifedipine (EURO pharmaceutical Ltd., Mumbai), carbopo l940 (loba chemie pvt ltd., Mumbai), Ethanol (S.D.fine-chem ltd., Mumbai), glycerin (loba chemie pvt ltd., mumbai), PEG400 (S.D.fine-chem ltd., Mumbai), propylene glycol (central drug house ltd., New Delhi), triethanolamine (S.D.fine-chem ltd., Mumbai), disodium hydrogen orthophosphate (S.D.fine-chem ltd., Mumbai), potassium dihydrogen orthophosphate(S.D.fine-chem ltd., Mumbai), sodium chloride (S.D.fine-chem ltd., Mumbai), olive oil (S.D.fine-chem ltd., Mumbai), oleic acid (S.D.fine-chem ltd., Mumbai), dimethyl sulfoxide (S.D.fine-chem ltd., Mumbai), limonene (S.D.fine-chem ltd., Mumbai)

Preformulation studies

Preformulation study is the preliminary step in the development of any drug delivery system. The objective of preformulation studies is to develop a portfolio of information about the drug substance to serve as a set of parameters against which detailed information design can be carried out. Melting point of the drug was analyzed using digital melting point apparatus and observed value was compared with reported melting point. FT-IR spectral studies of (drug and excipents) was performed to analyze compatibility of drug and excipents. drug-polymer purity and melting point were analyzed. A solution of nifedipine was prepared in the phosphate buffer (pH7.4). λmax was determined by scanning the above solution between 200-400nm,using Shimadzu UV spectrophotometer.

Standard plot of Nifedipine in phosphate buffer pH 7.4

Preparation of phosphate buffer solution (7.4): Dissolve 0.19gm of potassium dihydrogen phosphate, 2.38gm of disodium hydrogen phosphate and 8.0gm of sodium chloride in sufficient distilled water to produce 1000ml.Adjust the pH if necessary.

Preparation of stock solution (100µg/ml): 10 mg of pure drug was taken in 10ml volumetric flask, volume was made up to marks with phosphate buffer (pH7.4) (stock solution A). 5ml of the stock solution A was taken in another volumetric flask and volume was made up to 50ml with phosphate buffer 7.4(stock solution B i.e. 100µg/ml solution was obtained). From this solution, aliquots of 1.0ml, 2.0ml, 3.0ml, 4.0ml and 5.0ml were taken and diluted up to 10ml in order to get the concentration ranging from 10-50µg/ml. These concentration were used to determine absorbance at λmax 350nm against blank using UV-VIS spectrophotometer.

Formulation studies

Permeation enhancers: permeation enhancers were used in three different concentrations i.e 3%,6%,9%. Permeation enhancers used were oleic acid, olive oil, limonene, PEG 400, DMSO.

Procedure: About 0.1gm of NP was weighed and dissolved in 10gm of ethanol, to this solution, specified quantity of glycerin and propylene glycol was added and dissolved (solution A). Weighed quantity of carbopol 940 was added to distilled water, added permeation enhancer and stirred to dissolve the same. The solution was then neutralized and made viscous by addition of triethanolamine (solution B).Solution was then added dropwise in solution A with constant stirring and weight was made up to 100gm to get the final gel preparation.

Characterization method for nifedipine gel

The prepare carbopol gel, having different permeation enhancer were characterized by in-vitro dissolution studies (release rate).

In-vitro dissolution studies: Dissolution study was carried out across egg membranes by using USP apparatus –II, paddle type for 8hr.phosphate buffer pH 7.4 was used as medium (900ml) and was maintained at 37±0.5ºC. Samples (5ml) were collected periodically at 0.5,1,2,3,4,5,6,7 and 8hr and assayed for dissolution spectroscopically at 350nm. After dissolution study the gel which has best drug release is selected for further studies. In our study carbopol gel shows best release.

Physical appearance and homogeneity: They were tested for their appearance and presence of any aggregates.

Clarity: The clarity of various formulation was determined by visual inspection under black and white background and it was graded as follows; turbid:+,clear:++,very clear(glassy):+++.

Measurement of pH: The pH of various gel formulation was determined by using digital pH meter. 1gm of gel was dissolved in 100ml distilled water and store for two hours. The measurement of pH of each formulation as done in triplicate and average values are calculated.

Spreadability:0.5gm gel was placed within a circle of 1cm diameter premarked on a glass plate over which a second glass plate was placed. A weight of 500gm was allowed to rest on the upper glass plate for 5 min. The increase in the diameter due to spreading of the gel was noted.

Extrudability: The formulation were filled in to collapsible aluminium tubes. The tubes were pressed to extrude the 0.5 cm ribbon of the gel in 10 second and the extrudability of formulations was checked.

Drug content: A specific quantity(100mg) of gel was taken and dissolved in 100ml of phosphate buffer of pH 7.4.the volumetric flask containing gel solution was shaken for 2hr on mechanical shaker in order to get complete solubility of drug. This solution was filtered and estimated.

Skin irritation test

The primary skin irritation test was performed on healthy test was performed on healthy rats weighing between 150 to 200gm. The control gel was applied on the left dorsal surface of each rat, where as the test gel was applied on the right dorsal surface of rat. The gel was removed after a period of 24 hrs with the help of alcohol swab and the skin was be examined for erythema/redness.

Formulation of carbopol gel of Nifedipine

Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
Formulation																
Carbopol (gm)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Ethanol (gm)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Glycerine (gm)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Propylene Gylcol (gm)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Triethanolamine (gm)	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Oleic Acid (%)	----	3	----	----	----	----	6	----	----	----	----	9	----	----	----	----
Olive Oil (5)	----	----	3	----	----	----	----	6	----	----	----	----	9	----	----	----
Limonene (%)	----	----	----	3	----	----	----	----	6	----	----	----	----	9	----	----
PEG 400 (%)	----	----	----	----	3	----	----	----	----	6	----	----	----	----	9	----
DMSO (%)	----	----	----	----	----	3	----	----	----	----	6	----	----	----	----	9
Water	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm	Up to 100 gm

STABILITY STUDIES

Accelerated stability studies: The stability studies were conducted according to ICH guidelines by storing the formulation at 40±2ºC/30% RH in stability chamber for three months. The formulation was analyzed for the change in appearance, pH or drug content by procedure stated earlier spectrophotometrically at 350 nm using phosphate buffer (pH 7.4) as blank (6).

RESULTS AND DISCUSSION

a) Preformulation studies

Identity and purity of sample of nifedipine was found to be yellow and crystalline powder.melting was analyzed using digital melting point apparatus and found to be 171ºC.λmax scanning helps in identifying the drug's purity. DSC of drug shows drug is 99.22%pure, melting point is 171.17ºC and molecular weight is 346.3g/mol. Thus DSC analysis shows that drug sample analyzed was nifedipine.

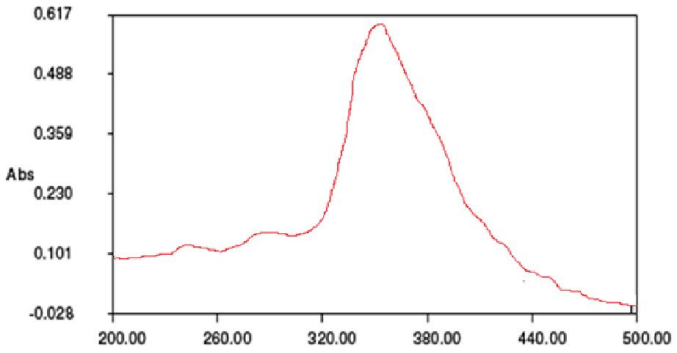

Fig. 1. λmax scan of Nifedipine

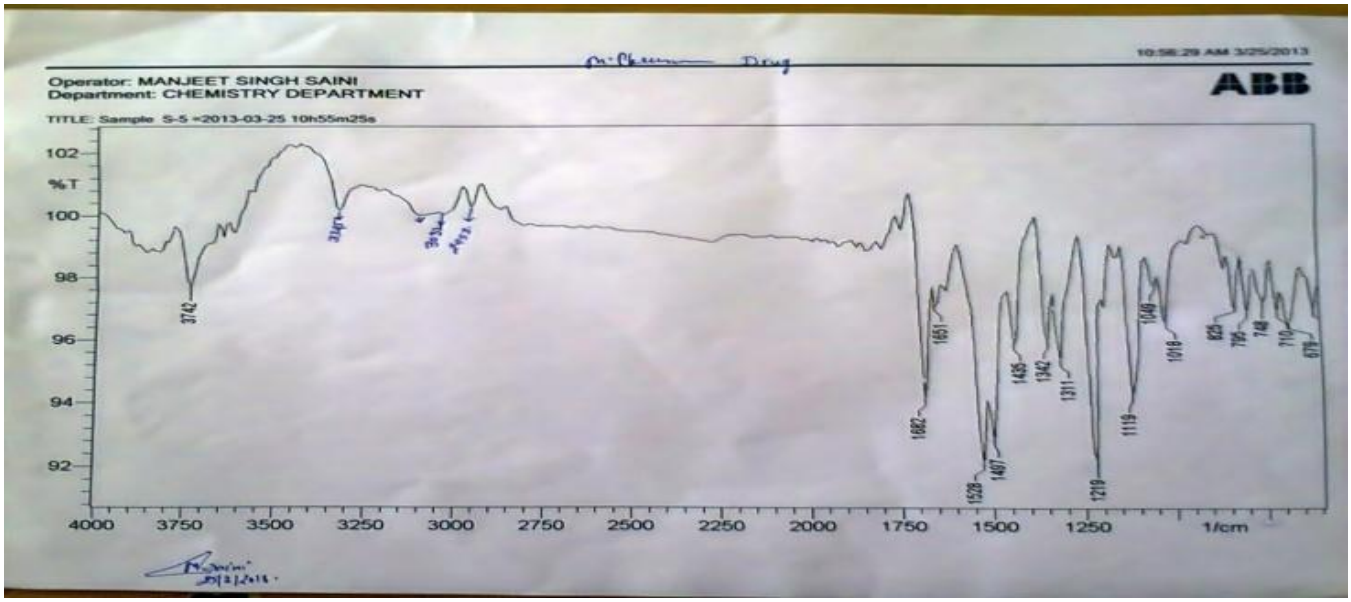

Fig.2. The spectra of pure drug Nifedipine

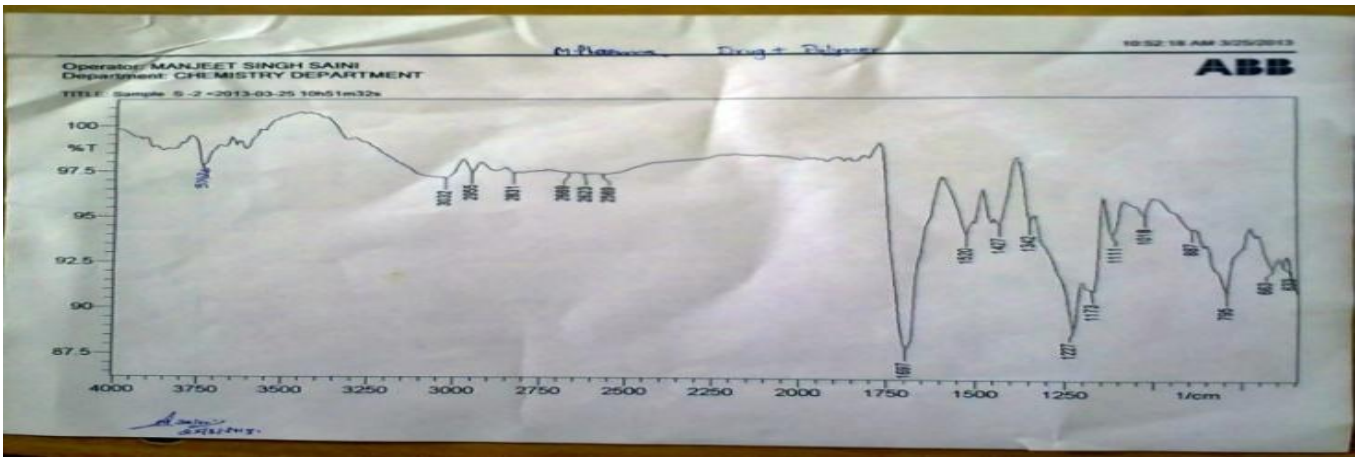

Fig.3. The spectra of drug+polymer(carbopol)

b) Caliberation curve of Nifedipine in phosphate buffer (7.4)

The obtained R^2 value is high (0.985), close to 1. From this study, it was concluded that there was a good correlation between the experimental and theoretical values.

Table 2. Caliberation data of nifedipine in phosphate buffer (7.4)

S. No.	Concentration (µg/ml)	Absorbance
1	1	0.02
2	2	0.031
3	4	0.048
4	6	0.069
5	8	0.092
6	10	0.11
7	12	0.13

c) Characterization of gel: In-vitro dissolution study was carried out for carbopol gel, having different permeation enhancers in phosphate buffer pH 7.4. the %CDR from the different formulation is given in Table (3-5).

Table 3. Dissolution profile of Carbopol gels having 3% permeation enhancer in phosphate buffer (pH 7.4)

S.No.	Time (hr)	% Drug Release					
		Without enhancer (F1)	F2	F3	F4	F5	F6
1	0.5	0.818	15.955	10.636	8.591	6.955	5.727
2	1	3.277	18.498	13.150	12.730	10.675	9.032
3	2	5.341	35.373	25.495	15.664	14.007	11.945
4	3	8.234	36.795	29.727	19.023	16.948	14.057
5	4	12.780	37.816	31.936	21.173	20.314	16.180
6	5	20.214	40.477	34.157	33.970	21.652	17.905
7	6	21.961	46.016	37.207	37.020	26.270	21.684
8	7	27.961	60.091	40.902	38.659	30.383	24.800
9	8	32.866	64.502	55.570	46.793	39.630	36.632

Table 4. Dissolution profile of Carbopol gels having 6% permeation enhancer in phosphate buffer (pH 7.4)

S.No.	Time (hr)	% Drug Release				
		F7	F8	F9	F10	F11
1	0.5	18.409	5.727	6.545	16.364	9.409
2	1	20.148	11.077	8.218	21.364	12.734
3	2	25.577	16.457	9.491	25.164	17.305
4	3	32.673	21.048	16.089	26.120	19.855
5	4	34.898	28.527	16.995	28.718	22.009
6	5	41.225	33.184	29.770	30.102	29.902
7	6	66.405	37.866	35.661	32.311	37.020
8	7	71.245	54.323	41.400	40.889	46.064
9	8	78.098	71.473	62.636	57.980	50.511

The release rate of carbopol gel F2(64.502%) was highest in comparison to the other formulations. So according to the data obtained from the release pattern, carbopol gel was used for further studies. Results shows that the following order of release(F2>F3>F4>F5>F6>F1). The release rate of carbopol gel F7 (78.09%) was highest in comparison to the other formulations. Result shows the following order of release(F12>F13>F14>F15>F16). Thus it is conclude from the data oleic acid is having maximum penetration power among oleic acid, olive oil, limonene, PEG400 and DMSO gel were successfully prepared formulated gels were subjected to various characterization parameters for their evaluation.

Table 5. Dissolution profile of Carbopol gels having 9% permeation enhancer in phosphate buffer (pH 7.4)

S.No.	Time (hr)	% Drug Release				
		F12	F13	F14	F15	F16
1	0.5	19.227	15.955	9.000	10.227	10.636
2	1	20.561	20.543	20.505	16.420	15.605
3	2	25.993	30.066	25.936	22.648	19.782
4	3	33.091	40.050	29.352	25.227	21.936
5	4	34.500	45.589	35.650	27.411	25.330
6	5	40.825	58.930	38.709	30.016	32.014
7	6	66.411	66.616	45.875	33.043	37.916
8	7	72.898	69.811	55.425	40.807	50.259
9	8	78.518	71.768	62.739	57.932	51.427

Table 6. Evaluation of the prepared formulations of carbopol gel

Formula-tion Code	Clarity	Homogeneity	pH	Spreadi-bility (cm)	Drug Content analysis	Extrud-ability
F1	++	Homogenous	6.5	3.9	98.591	+
F2	++	Homogenous	6.4	2.5	97.364	+
F3	+++	Homogenous	6.2	3.4	99.000	+
F4	++	Homogenous	6.4	2.8	99.409	+
F5	+++	Homogenous	6.8	3.5	97.773	+
F6	++	Homogenous	6.7	2.9	97.364	+
F7	++	Homogenous	6.3	2.5	99.000	+
F8	++	Homogenous	6.5	3.4	97.364	++
F9	+++	Homogenous	6.7	2.7	98.182	++
F10	++	Homogenous	6.6	2.8	98.591	+
F11	+++	Homogenous	6.6	2.6	98.591	++
F12	++	Homogenous	6.4	3.1	99.000	++
F13	++	Homogenous	6.8	2.5	101.045	++
F14	+++	Homogenous	6.5	2.6	98.591	++
F15	++	Homogenous	6.6	3.1	97.773	++
F16	++	Homogenous	6.4	2.5	98.591	++

In-vitro dissolution studies: In-vitro dissolution studies of 16 formulation were performed using pH 7.4 phosphate buffer as medium and measuring drug concentration spectrophotometrically at 350 nm. The cumulative percent of drug release (%CDR) at different time interval are shown in table (7-10). Formulation F12 showed maximum drug release of 78.518% in 8 hr which contained 9% permeation enhancer concentration i.e (oleic acid).

Table 7. % Cumulative Drug Release of formulationsF_1-F_{16}(in-vitro study)

S. No.	Formulation Code	% CDR (in 8hr)
1	F_1	78.09
2	F_2	71.47
3	F_3	62.63
4	F_4	57.98
5	F_5	50.51
6	F_6	32.86
7	F_7	64.50
8	F_8	55.57
9	F_9	46.79
10	F_{10}	39.63
11	F_{11}	36.63
12	F_{12}	78.51
13	F_{13}	71.76
14	F_{14}	62.73
15	F_{15}	57.93
16	F_{16}	51.42

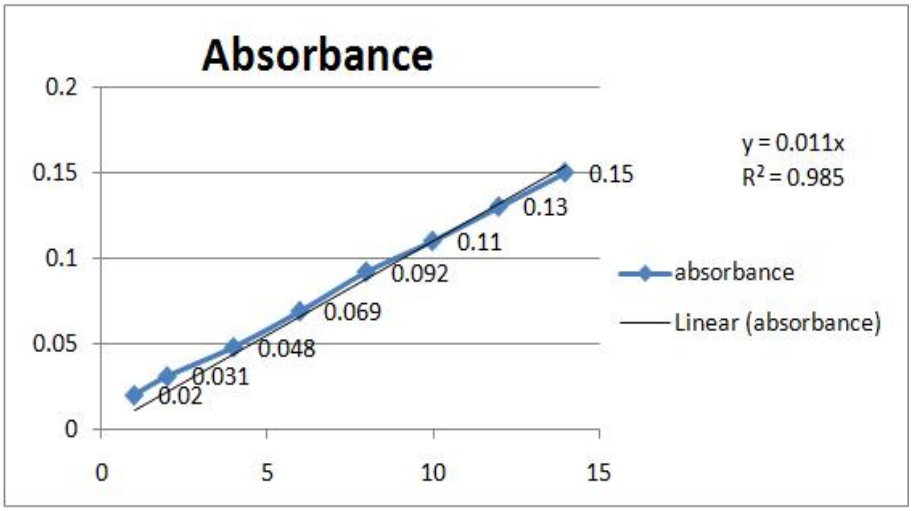

Fig. 5. Caliberation data of nifedipine in phosphate buffer (7.4)

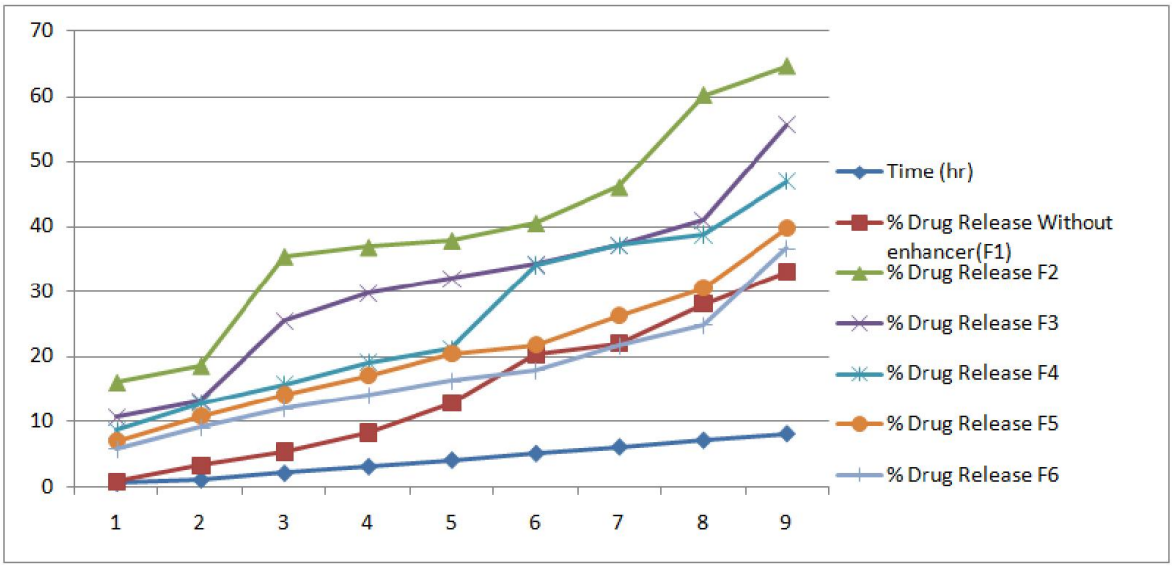

Fig.6. Graphical representation of dissolution profile of carbopol gel having 3% concentration of permeation enhancer

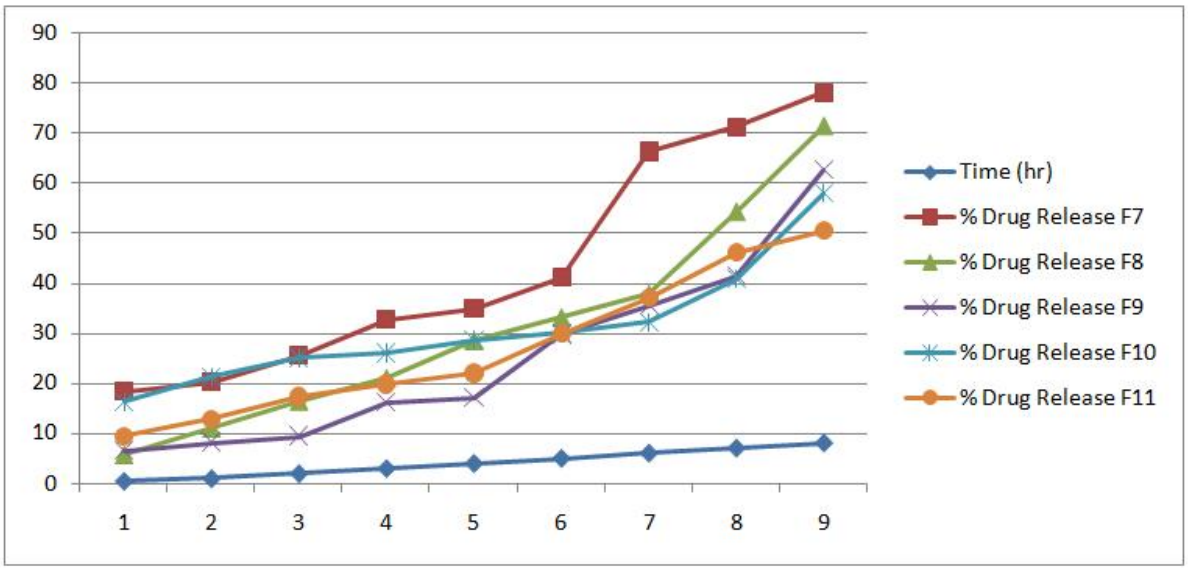

Fig.7. Graphical representation of dissolution profile of carbopolgel having 6% concentration of permeation enhancer

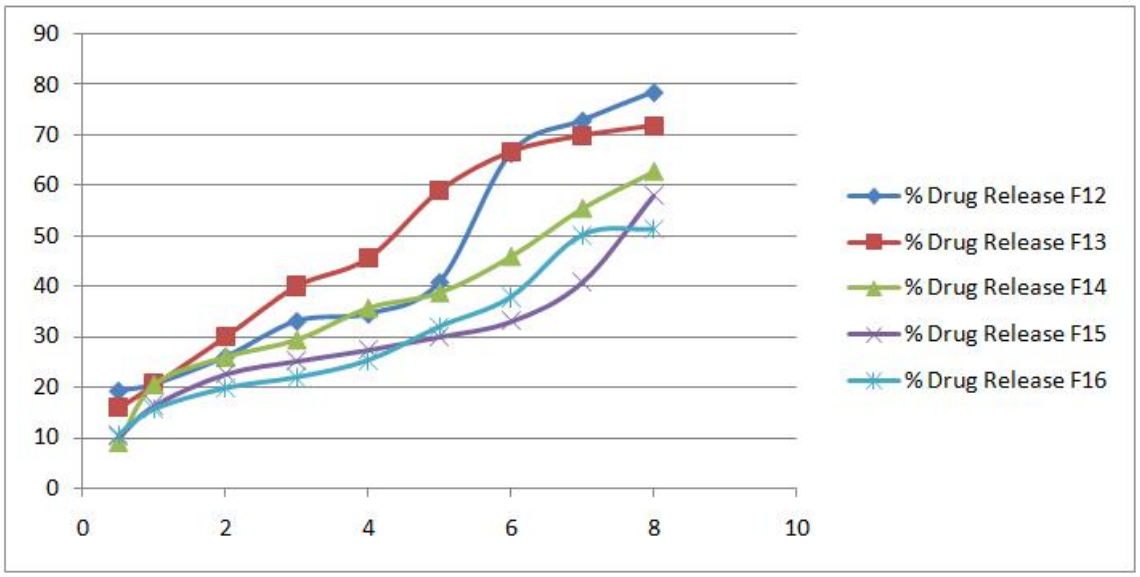

Fig.8. Graphical representation of dissolution profile of carbopol gel having 9% concentration of permeation enhancer

Table 8. % Cumulative Drug Release from formulation batches F_1–F_6

Time (hr)	% Cumulative drug release (% CDR)					
	F1	F2	F3	F4	F5	F6
0.5	0.818	15.955	10.636	8.591	6.955	5.727
1	3.277	18.498	13.150	12.730	10.675	9.032
2	5.341	35.373	25.495	15.664	14.007	11.945
3	8.234	36.795	29.727	19.023	16.948	14.057
4	12.780	37.816	31.936	21.173	20.314	16.180
5	20.214	40.477	34.157	33.970	21.652	17.905
6	21.961	46.016	37.207	37.020	26.270	21.684
7	27.961	60.091	40.902	38.659	30.383	24.800
8	32.866	64.502	55.570	46.793	39.630	36.632

Table 9. % Cumulative Drug Release from formulation batches F_7– F_{11}

Time (hr)	% Cumulative drug release (% CDR)				
	F7	F8	F9	F10	F11
0.5	18.409	5.727	6.545	16.364	9.409
1	20.148	11.077	8.218	21.364	12.734
2	25.577	16.457	9.491	25.164	17.305
3	32.673	21.048	16.089	26.120	19.855
4	34.898	28.527	16.995	28.718	22.009
5	41.225	33.184	29.770	30.102	29.902
6	66.405	37.866	35.661	32.311	37.020
7	71.245	54.323	41.400	40.889	46.064
8	78.098	71.473	62.636	57.980	50.511

Table 10. % Cumulative Drug Releasefrom formulation batches F_{12}-F_{16}

Time (hr)	% Cumulative drug release (% CDR)				
	F12	F13	F14	F15	F16
0.5	19.227	15.955	9.000	10.227	10.636
1	20.561	20.543	20.505	16.420	15.605
2	25.993	30.066	25.936	22.648	19.782
3	33.091	40.050	29.352	25.227	21.936
4	34.500	45.589	35.650	27.411	25.330
5	40.825	58.930	38.709	30.016	32.014
6	66.411	66.616	45.875	33.043	37.916
7	72.898	69.811	55.425	40.807	50.259
8	78.518	71.768	62.739	57.932	51.427

Skin irritation studies

Table 11. Irritation studies result

S. No.	Formulation Code	Erythema/Rednees
1	F_1	+
2	F_2	+
3	F_3	+
4	F_4	+
5	F_5	+
6	F_6	+
7	F_7	+
8	F_8	+
9	F_9	+
10	F_{10}	+
11	F_{11}	+
12	F_{12}	+
13	F_{13}	+
14	F_{14}	++
15	F_{15}	+
16	F_{16}	+

+means no irritation, no redness
++ means slight redness,

Thus All Formulation Shows Good Results, Do Not Cause Any Kind of Skin Irritation.

Accelerated stability studies of best batch (F12)

During the accelerated stability studies the appearance was clear and drug content is as written in table (Table 12).

Table 12. Stability study of optimized batch of gel

Formulation	Months	Appearance	Drug content
	0	Clear	99.00
	1	Clear	97.67
F12	2	Clear	95.56

Accelerated study showed that our formulation is stable and does not show any remarkable change in appearance and their drug content.

***In-vitro* release data of optimized formulation F12: Zero order kinetics**

Table 13. % Cumulative Drug Release of optimized formulation F_{12}

Time (hr)	% CDR
0.5	19.227
1	20.561
2	25.993
3	33.091
4	34.500
5	40.825
6	66.411
7	72.898
8	78.518

Mathematical modeling to study the Invitro permeation kinetics of optimized batch: To establish the order and mechanism of drug release, permeation data of the optimized batch was fitted to four different kinetic model and korsmeyerpeppas model. The model for best fit was predicted from the value of R^2 was 1. Hence, the model which gives the R^2 value nearest to 1 describes the order of drug permeation. From the results of data fitting to various models, it was found that the optimized batch F12 showed zero order kinetic model of drug release.

***In-vitro* release data of optimized formulationF12: First order kinetics**

Table 14. Log % Cumulative Drug retainedof optimized formulation F12

Time (hr)	Log % Cumulative drug retained
0.5	1.922395
1	1.895623
2	1.874113
3	1.868524
4	1.852979
5	1.844463
6	1.8305161.
7	771671
8	1.623461

F_{12}: First order kinetics

***In-vitro* release data of optimized formulationF_{12}: Higuchi model**

Table 15. % Cumulative Drug Release of optimized formulation F12

Time (hr)	Log % Cumulative drug release
0.5	1.21388
1	1.329675
2	1.400773
3	1.416981
4	1.458157
5	1.478599
6	1.509355
7	1.611603
8	1.763275

***In-vitro* release data of optimized formulationF_{12}: Korsmeyerpeppas model**

Table 16. Log % Cumulative Drug Release of optimized formulationF_{12}

Time (minutes)	Log of time (minutes)	Log % CDR
30	1.477121	1.21388
60	1.778151	1.329675
120	2.079181	1.400773
180	2.255272	1.416981
240	2.380211	1.458157
300	2.477121	1.478599
360	2.556303	1.509355
420	2.623249	1.611603
480	2.681241	1.763275

Table 17. Value of R^2 obtained from different kinetic models

Formulation Code	R^2			
	Zero order	First order	Higuchi model	Korsmeyer Peppas model
F12	0.930	0.752	0.851	0.816

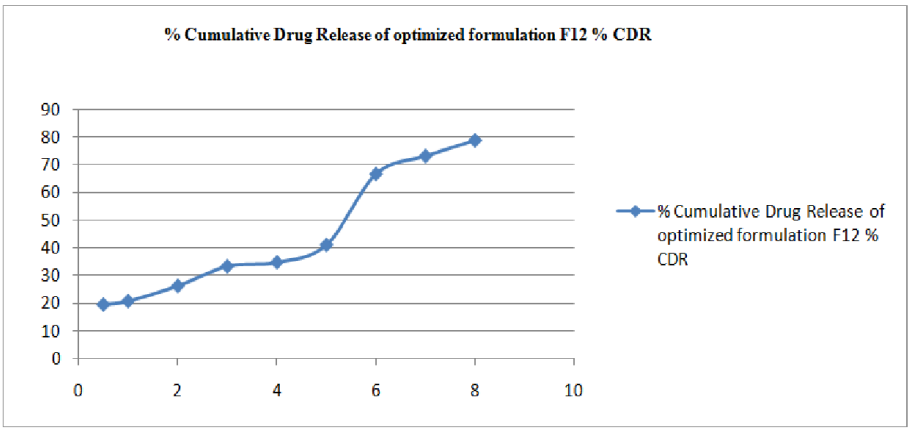

Fig. 13. Graphical representation of *In-vitro* release data of optimized formulationF_{12}: Zero order kinetics

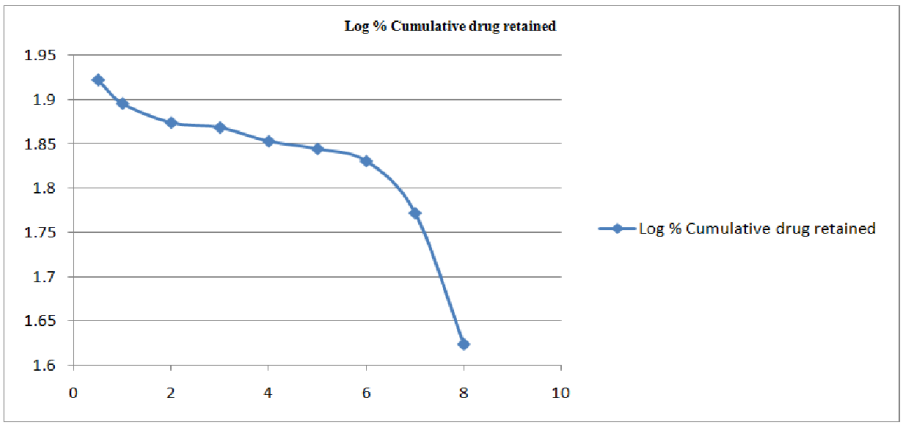

Fig. 14. Graphical representation of *In-vitro* release data of optimized formulation F_{12}: First order kinetics

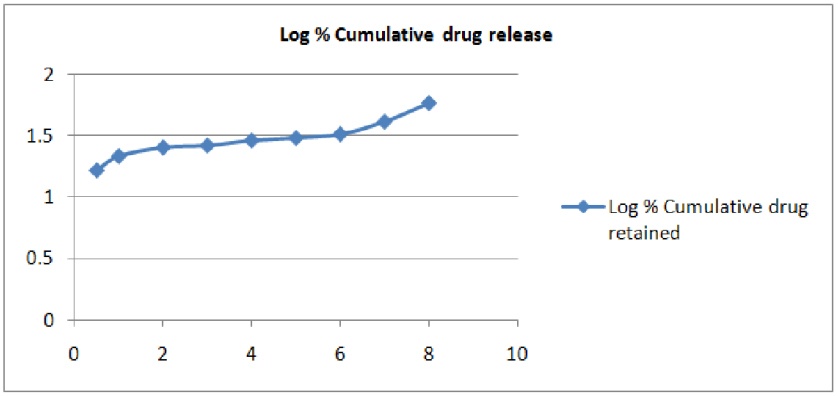

Fig. 15. Graphical representation of *In-vitro* release data of optimized formulationF_{12}: Higuchi model

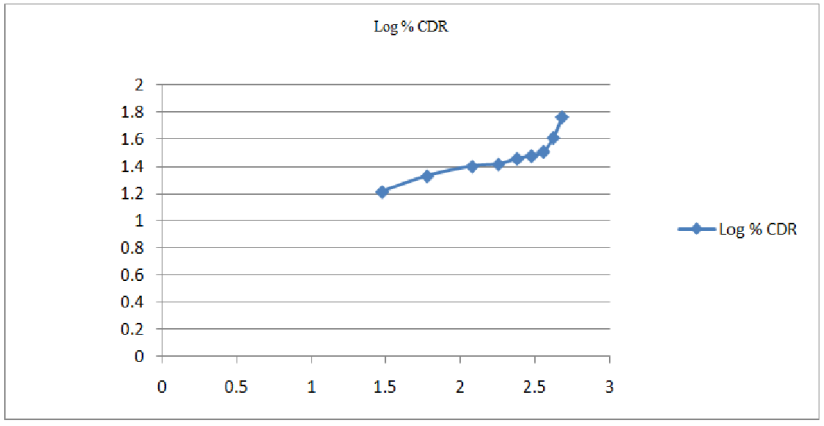

Fig. 16. Graphical representation of *In-vitro* release data of optimized formulation F12: KorsmeyerPeppas model

Conclusion

Transdermal delivery of Nifedipine shows good results avoiding side effects of first pass metabolism and g.i.t. irritation. From the experimental work we can say that an increase in concentration of permeation enhancer increases release rate. Permeation enhancers show maximum effect in the concentration between 3 to 9%, above this concentration the effect of permeation enhancer concentration i.e. (oleic acid). All other evaluation parameters like clarity, pH, viscosity, drug content, spreadibility and extrubility are suggestive of good characteristic properties of best batch. The experiment work results shows that concentration of permeation enhancer between 3-9% shows maximum increase in drug permeation through the skin.

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