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Design and Evaluation of Mucoadhesive Gel of Glimepiride for Nasal Delivery

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ABSTRACT

Nasal Mucoadhesive gel of Glimepiride was prepared for Controlled release. Carbopol 934p was used as a key ingredient which gives mucoadhesion property to the gel formulations. Different formulations were prepared by varying the concentrations of Carbopol 934p and Hydroxyl Propyl Methyl Cellulose K4M (HPMC K4M). These formulations were evaluated for parameters like pH, Drug content, Viscosity, Mucoadhesive strength, Gel strength, In-vitro drug release, In-vitro permeation and Drug excipient compatibility. In this formulation the release profile depend on the concentration of Carbopol 934p and HPMC K4M. A 3^2 factorial design was applied to see the effect of variables Carbopol 934p (X1) and HPMC K4M (X2) on the response percentage drug release as a dependent variable. In vitro release data were fitted to various models to ascertain kinetic of drug release. Regression analysis and analysis of variance were performed for dependent variables. The results of the F-statistics were used to select the most appropriate model. Formulation containing Carbopol 934p(1.0%) and HPMC K4M(1.0%) was found to be optimum. The studies indicate that the formulation was effective in providing In-vitro release of drug and the mucoadhesive formulation

Keywords: Nasal Mucoadhesive gel, Gel strength, In-vitro drug release, In-vitro permeation

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INTRODUCTION

To overcome the limitations of oral and parenteral routes of administration, attempts have been made to employ partial therapy through nasal route. Nasal route offer many advantages mainly avoidance of first pass metabolism, direct transport into systemic circulation and CNS, rapid absorption etc.

Glimepiride is a Oral hypoglycaemic agent and is completely absorbed after oral administration but it is subjected to liver metabolism which contributes to its efficacy with single oral administration. To increase the patient compliance and to have convenience of administration, nasal gel of Glimepiride was prepared using Mucoadhesive polymers which may increases its residence time there by subsequent bioavailability.

Nasal formulation with the controlled action of drug is a good alternative. Challenges in the development of nasal formulation include low residence time. Mucociliary clearance can be overcome by developing a mucoadhesive formulation. Various systems are available for nasal drug delivery such as: nasal spray, nasal pumps, gels, microemulsion, suspensions, powders and mucoadhesive gels have been studied.[1]

The inability to administer these drugs by route other than parenteral route interest scientists to explore other possibilities such as nasal administration. The initial interest was soon confronted with disappointing in vivo results showing negligible bioavailability, typically in order of <5-10% for large molecules. On other hand , very good results were obtained with small organic molecules , which led to the successful formulation of a number of products currently on market.[2,3]

MATERIALS AND METHODS

Glimepiride was gifted by Glenmark Pharmaceuticals Ltd. Nashik. Carbopol 934P was obtained from Loba Chemie Pvt. Ltd. Sodium carboxymethylcellulose was obtained from Reliance cellulose and Hydroxy propyl methyl cellulose K4M was obtained from Research-Lab Fine Chem. Industry - Mumbai. All other materials and chemicals used was of laboratory reagent grade.

Methods

Different formulae of gels were prepared by considering all above parameters by taking appropriate quantities of ingredients into formulation. In these formulae, the concentration of Carboxymethylcellulose sodium was fixed at 4.5%, concentration of Carbopol 934P was kept from 1.0%-2.0% and Hydroxypropylmethylcellulose K4M was varied from 1.0%-2.0% (Table 1)

Table 1: Compositions of formulations

Formulation	Glimepiride (w/v)	HPMCbK4M (w/v)	Carbopol 934P(w/v)	Sodium CMC (w/v)	Benzalkonium Chloride(v/v)
F1	5	1.0	2.0	4.5	0.01
F2	5	2.0	1.5	4.5	0.01
F3	5	1.5	1.0	4.5	0.01
F4	5	2.0	1.0	4.5	0.01
F5	5	1.5	2.0	4.5	0.01
F6	5	1.0	1.5	4.5	0.01
F7	5	1.0	1.0	4.5	0.01
F8	5	2.0	2.0	4.5	0.01
F9	5	1.5	1.5	4.5	0.01

Each formulation was prepared by dissolving the drug in sufficient quantity of 0.1 N NaoH . Carbopol 934P, Hydroxypropylmethylcellulose K4M and carboxymethylcellulose sodium was dissolved in above drug solution by dispersion method and Benzalkonium chloride was finally added. The volume was make up by remaining drug solution and resultant solution is hydrated for 24 hr.

EVALUATION STUDIES

Determination of visual appearance, pH, and drug content[4,5,6]

The appearance was determined visually. The pH of each formulation was determined by using Digital pH meter (Systronics Digital pH meter 335). The drug content was determined by taking 0.3gm of gel in 20 ml beaker, 1 ml quantity from this solution was again diluted up to 10ml with o.1 N NaoH to get the final concentration of 25 µg/ml. Finally the absorbance of prepared solution was measured at 227.5nm by using UV visible spectrophotometer.

Compatibility Study[8]

Compatibility study was carried out by using Fourier transform infrared spectrophotometer (8400 s Shimadzu). FTIR study was carried on pure drug and physical mixture of drug and polymers. Physical mixtures samples kept for 1 month at 40^0C. The infrared absorption spectrum of Glimepiride and physical mixture of drug and polymers was recorded with a KBr disc over the wave number 4000 to 400 cm^{-1}.

Rheological study[5,6,7]

The rheological properties of mucoadhesive gels were determined by the Brookfield viscometer; type DV-II + PRO using spindle no. 62 and 63.Viscosity of the formulations were taken at two different temperature that is at room temperature and the 37^0C with varying shear rate.

Gel strength[5,6,7]

A sample of 50 g of the nasal gel was put in a 50 ml graduated cylinder. A weight of 14.33 g was placed onto the gel surface. The gel strength, which is an indication for the nasal gel at physiological temperature, was determined by the time in seconds required by the weight to penetrate 5 cm into the gel. All measurements was performed in triplicate (n=3). The apparatus use for measuring gel strength is shown in Figure 1.

Figure 1 Gel strength measuring device (A)weights (B)device (C) graduated cylinder (D)gel

Detachment Stress[5,6,7]

"Detachment Stress is the force required to detach the two surfaces of mucosa when a formulation/gel is placed in between them". The detachment stress was measured by using a modified analytical balance. A fresh goat nasal mucosa was obtained from local slaughter house. A section of fresh nasal mucosa was cut from the goat nasal tissue and washed with Simulated Nasal Electrolyte Solution. A piece of mucosa was fixed with mucosal side upward on a flat surface of object (such as bottom of vial) which was moistened with Simulated Nasal Electrolyte Solution. Another object which is having flat surface at bottom (such as vial) was used to which other section of nasal mucosa was attached with mucosal surface outside. This was attached to the one side of pan (with mucosa attached to flat surface in downward position). Formulations were placed onto a mucosal surface of object which was fixed in position. Then height of second object was adjusted so that mucosa surface of both objects came in intimate contact. Two minute contact time was given to ensure intimate contact between tissues and formulation. Then weight was kept rising in the pan until the adjustable object get detached. The weight required to detach the mucosal surfaces gave the mucoadhesive strength assessed in terms of weight (gm). The mucoadhesive strength was measured in terms of force of adhesion in Newton's by using following equation. All measurements was performed in triplicate (n=3).

Detachment Stress (dyne /Cm^2) = m×g/A

Where **m**= weight required for detachment of two vials in gms,

g= Accelerations due to gravity (980 cm/s^2)

A= Surface area exposed.

The apparatus for measuring mucoadhesive strength is shown in Figure 2.

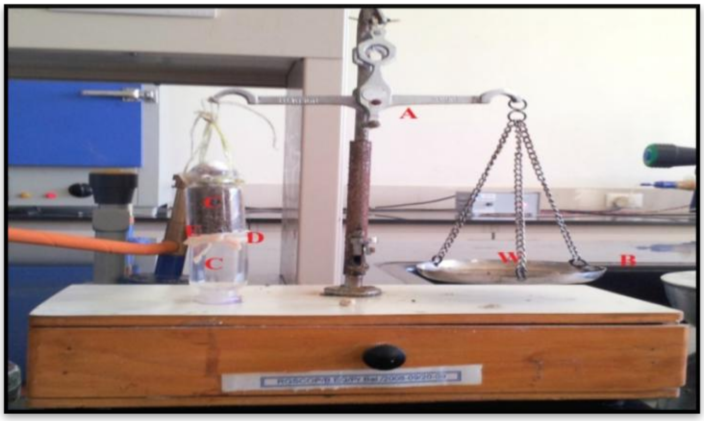

Figure 2. Modified balance for mucoadhesion study

A:Modified balance, **B**: Weighing pan, **W**: Weight , **C**: Glass Vial, **D**: Gel, **E**: Nasal Mucosa.

In-Vitro Drug release study [5,6,7]

In vitro release study of the formulated mucoadhesive gel was carried out in two-chamber diffusion cell through egg membrane. Diffusion cell with internal diameter 1.4 cm was used for the study. 0.3 gm formulation were placed in donor compartment and freshly prepared 100 ml Simulated Nasal Electrolyte Solution(Sodium chloride 0.745gm, Potassium chloride 0129gm, Calcium chloride dihydrated 0.005gm, Distilled water q.s 100ml) in receptor compartment. Egg membranes were mounted between donor and receptor compartment. The temperature of receiver compartment was maintained at the $37^0C \pm 0.5^0C$ during experiment and the content of the receiver compartment was stirred using magnetic stirrer. The position of the donor compartment was adjusted so that egg membrane just touches the diffusion medium. An aliquot of 2 ml was withdrawn from receiver compartment after 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 360, 420 & 480mins and same volume of fresh medium was replaced. Aliquot so withdrawn were suitably diluted and analyzed using UV spectrophotometer at 227.5nm.

In-vitro permeation study [5,6,7]

The drug permeation characteristics from formulation must be determined by using natural membranes so that similar pattern of release can obtain as that of In-Vivo permeation. For this purpose goat nasal mucosa was chosen because it is easy to get from slaughterhouse. The area of respiratory mucosa of goat's nose is relatively large, easier to handle and by ethical view no need to sacrifice a special animal for membrane. Fresh nasal tissue was removed from nasal cavity of goat. The tissue was placed on the diffusion cell with permeation area of 1.53 cm^2. The acceptor chamber of the diffusion cell (with volume capacity about 100 ml) was filled with Simulated

Nasal Electrolyte Solution (Sodium chloride 0.745gm, Potassium chloride 0129gm, Calcium chloride dihydrated 0.005gm, Distilled water q.s 100ml). Formulation containing drug equivalent to 5 mg was placed in donor compartment. At predetermined time point of 10 minute 2 ml of sample was withdrawn from acceptor compartment replacing the sample removed with Simulated Nasal Electrolyte Solution after each sampling for period of 8 hrs. Then sample were sufficiently diluted and measured with spectrophotometrically at 227.5 nm.

Accelerated stability studies[9]

The formulations were stored at room temperature & 40± 2°C with RH 60± 5% & 75± 5% respectively. The formulations were evaluated mainly for their physical characteristics at the predetermined intervals of 3 months and after 6 months like appearance/clarity, pH, viscosity and drug content.

RESULTS AND DISCUSSION

Visual appearance, pH, and drug content

All the Formulations were found to be white transparent gel, which indicates stability of drug and excipient in gel formulation. This also indicates no leaching from container material. pH of formulation was found to be in range i.e. 4.5-6.5. The pH of value of all the formulation is shown in Table 2. The percentage drug content of all prepared nasal formulations were found to be in the range of 98-101%. Therefore uniformity of content is maintained in all formulation.

Table 2: Evaluation Parameters

Formula	Observed pH (±S.D.)	Gel strength (sec) (±S.D.)		Detachment stress (dyne/cm^2) (±S.D.)	Drug content (%) (±S.D.)	Cumulative Drug Release (%) (±S.D.) after 8hrs
		at RT	at 37^{0}C			
F1	4.51±0.0100	11.69±2.1740	10.56±0.6379	1374.18±74.18	99.20±2.6457	18.68±0.03
F2	4.69±0.0230	10.06 ±0.1234	9.10 ±1.0950	1374.18± 74.18	98.30±1.5275	21.47±0.01
F3	4.87±0.0057	7.22±0.2926	6.26±0.4725	1147.91±147.0	99.50±1.000	65.34±0.02
F4	5.24±0.0057	7.67±0.1750	7.36±0.5507	1232.49±132.4	98.60±0.8544	55.68±0.00
F5	4.53±0.0200	25.14±0.6000	23.23±0.9865	1504.01±104.0	98.00±1.000	17.96±0.01
F6	5.07±0.0300	24.4 ±0.1000	20.76 ±0.6506	1500.89±200.0	98.76±0.5507	47.93±0.05
F7	5.37±0.0152	3.46±0.3417	1.9±0.2000	950.66±150.00	101.16±1.040	82.32±0.02
F8	4.74±0.0152	30.18±0.1903	26.13±0.5859	1700.95±99.99	98.63±.9609	11.66±0.02
F9	4.67±0.0351	26.83±1.1452	21.97±1.1849	1581.42±181.4	98.30±0.8544	24.27±0.01

Compatibility Study[8]

Infra-red spectra of drug and polymers showed matching peaks with the drug spectra. The characteristic peaks of drug were also present in the spectra of all drug- polymer combinations. It is shown in Fig 3.

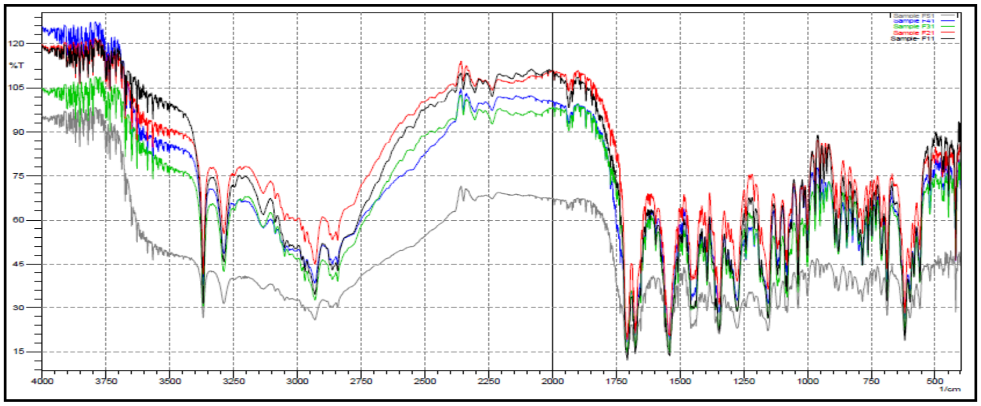

Figure.3: FTIR overlay of drug with individual polymerbrheological study

Table 3: Viscosity of formulations at 37^{0}C

RPM	**Viscosity (cp) at 37^{0}C**								
	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	69585	94060	72704	84702	121894	115895	20396	463101	101378
1.0	55988	65506	54948	65026	78463	79183	19196	307734	88781
1.5	46190	53269	45750	54708	53149	63346	18146	242348	79983
2.0	41271	45950	41871	47990	4371	53209	17596	203657	74384

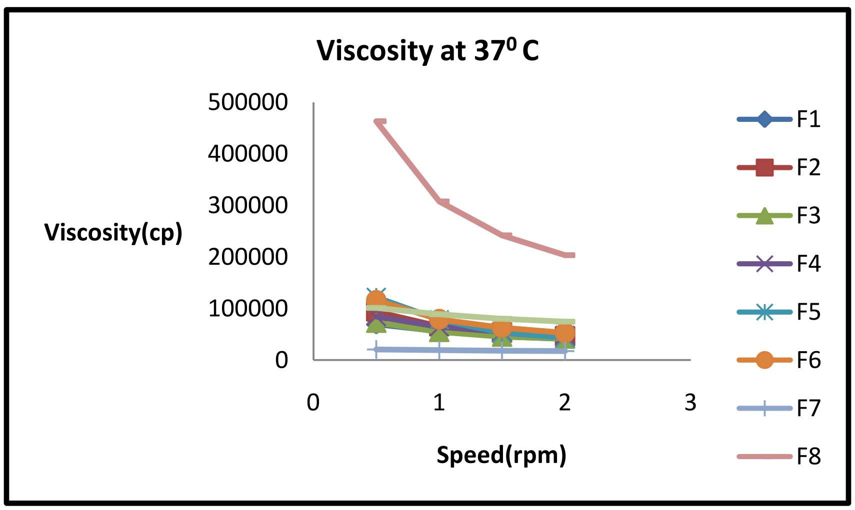

Figure 4: Viscosity of formulation at 37^0 C

Viscosity v/s rpm plots for all formulations shows decrease in viscosity as shear rate(rpm) was increased. As temperature was increased the decrease in viscosity was observed. Which indicate that gel has the pseudoplastic flow Figure 4.

Gel Strength

In the development of nasal mucoadhesive gel, the gel strength is important in finding the condition, which can delay the post nasal drip or anterior leakage. The gel strength was found to be affected by concentrations of gelling and mucoadhesive polymers. Optimal mucoadhesive gel must have suitable gel strength so as to be administered easily and can be retained at nasal mucosa without leakage after administration. Gel strength of all formulations showed comparable results as that of viscosity results and it is shown in Table 2.

Detachment Stress

Mucoadhesive force means the force with which gels bind to nasal mucosa. Greater mucoadhesion is indicative of a prolonged residence time of a gel and thus prevents its drainage from the nasal cavity. The Detachment Stress was determined for nasal gels. Results of this test indicate that the variable Carbopol 934 P and Hydroxypropylmethylcellulose K4M both are having effect on mucoadhesive strength. It shows that mucoadhesive force was increased with the increasing concentration of the carbopol 934P i.e. 2% and optimal concentration i.e. 2.0% Hydroxypropylmethylcellulose K4M. The detachment stress of all the formulations are shown in Table 2.

In-vitro Drug Release Study

The result shows that with increase in concentration of Carbopol 934P and Hydroxypropylmethylcellulose K4M the release rates were found to decrease gradually. The results showed that the gels had the ability to extend the release of Glimepiride for the duration of about 480 minutes (Table 2).

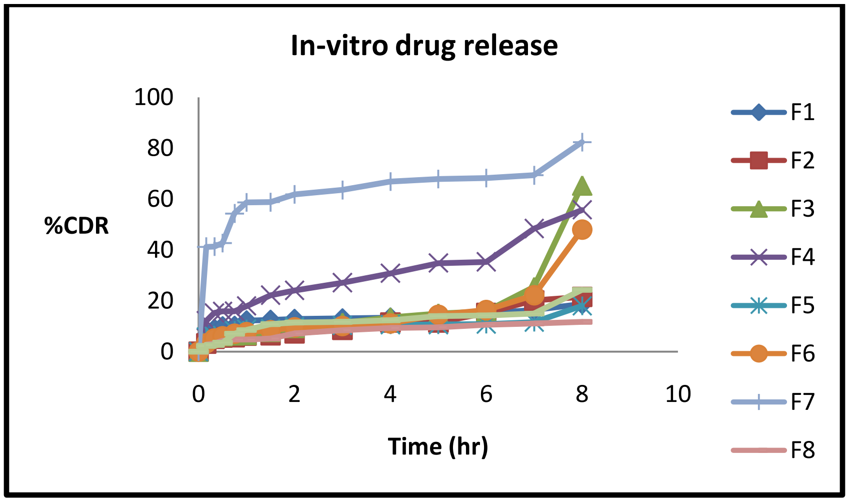

Figure 5: In-vitro release of all formulation

On the basis of Gel strength, Viscosity, Mucoadhesive strength, percent drug content and In-vitro drug release profile the optimum mucoadhesive gel formulation of Carbopol 934P 1% and Hydroxypropylmethylcellulose K4M 1% was selected. The **F7** batch was selected as optimized and subjected for permeation study. In-vitro drug release profile of all the formulations are shown in Figure 5.

Optimization

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentage of Hydroxypropylmethylcellulose K4M (X1) and Carbopol 934P (X2) were selected as independent variables and the dependent variable was % drug release. The data obtained were treated using Design expert version 8.0.4.1 software and analyzed statistically using analysis of variance (ANOVA). The data were also subjected to 3-D response surface methodology to study the interaction of Hydroxypropylmethylcellulose K4M (X1) and Carbopol 934P (X2) on dependent variable. The values of X_1 and X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of both the variables on the selected responses. From this data optimum concentration of Hydroxypropylmethylcellulose K4M (1.0 %) and Carbopol 934P (1.0 %) was found.(Figure 6).

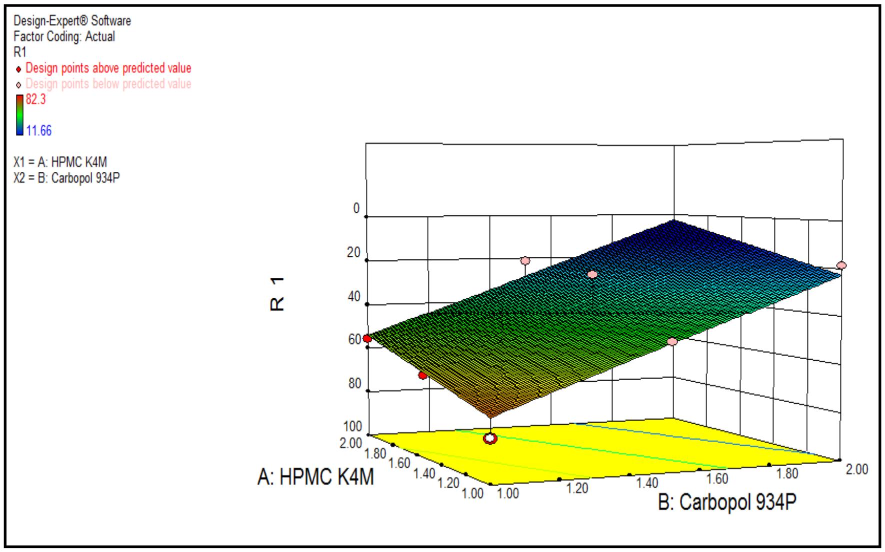

Figure 6: Surface Response plot showing effect of Hydroxypropylmethylcellulose K4M and Carbopol934P on release

$$Y1\ (\%\ CDR) = +145.92556 - 20.0333*(A) - 51.67333*(B)$$

From design expert version 8.0.4.1 five solutions were found in which optimum batch Hydroxypropylmethylcellulose K4M 1% and Carbopol934P 1% with desirability 0.886 was found to be optimum. From this data F7 batch was selected as optimum formulation.

In-Vitro permeation study

The In-vitro permeation study of formulation F7 is shown in Table 4.

The formulation F7 shows 32.66% release in 1 hr and 78.41 % release in 8 hr i .e. 3.92 mg drug which is sufficient for Antidiabetic activity . This suggest that this formulation can act as controlled release for treating type II diabetes mellitus(Figure 7).

Table 4. In-vitro permeation study of formulation F7

Sr.No.	Time(hrs)	Drug Permeation rate(mg/cm/hr) (±S.D.)	% Cumulative drug permeation(±S.D.)
1	0.16	0.88±0.01	22.22±0.0200
2	0.33	0.92±0.0057	22.46 ±0.5000
3	0.5	0.88±0.03	27.03±1.0300
4	0.75	1.50±0.2	28.29 ±0.9950
5	1.00	0.73±0.01	32.66±0.0550
6	1.50	1.38±0.02	34.98 ±0.0057
7	2.00	1.48±0.4850	42.26 ±0.0200
8	3.00	1.13±0.0057	42.54±0.0057
9	4.00	1.37±0.01	45.55±0.0100
10	5.00	1.13±0.0057	46.38±0.0351
11	6.00	1.98±0.02	60.78±0.2000
12	7.00	2.18±0.0057	66.84±0.0500
13	8.00	2.56±0.04	78.41±0.0550

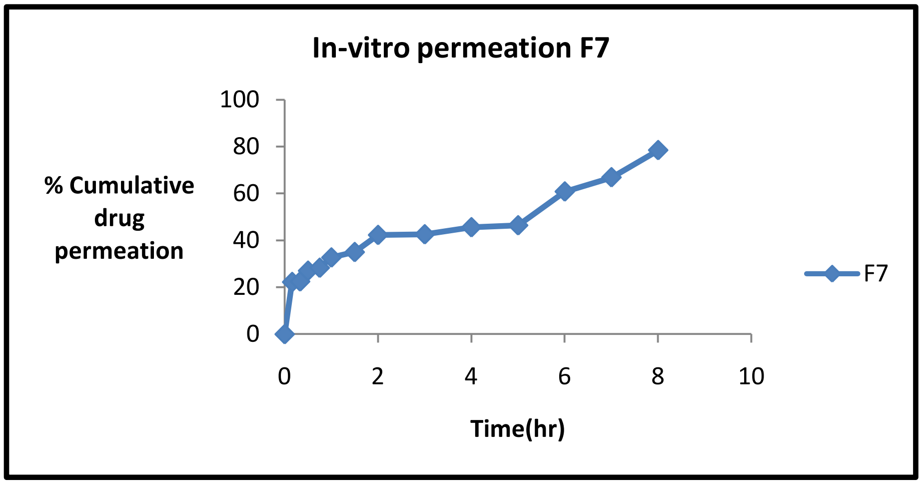

Figure 7:In-vitro permeation of optimized batch

Release Kinetics[10,11]

In the present study, the drug release was analyzed by PCP Disso version v3 software to study the kinetics of drug release mechanism. The factorial design batches followed korsmeyer peppas model kinetics. The R^2 value of korsmeyer peppas model was found close to one. The drug release was occurred by fickian diffusion mechanism as reflected by its n value 0.1797 (n<0.5).

Accelerated stability study

Formulations at room temperature were found to be stable up to 6 months. There is no change in drug content, visual appearance, pH and viscosity. All formulations stored at elevated temperature found to be unchanged.

CONCLUSION

Permeation study suggested that such formulation can be a alternative route to the conventional therapy of glimepiride and it can also be a part replacement/supportive therapy to the conventional oral administration of glimepiride. This formulation can also be effective against, the patient suffering from type II diabetes mellitus and unable to take oral medication.

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