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ISSN: 0975-7538
Research Article

Formulation development and evaluation of floating drug delivery of Anti-diabetic drug

Saravanakumar K*[1], Mohan Kumar A[1], Nagaveni P[2], Jayachandra Reddy P[3], Gowri Y[4]

[1]Sree Vidyanikethan College of Pharmacy, A.Rangampet, Tirupati-517102, Chittoor District, Andhra Pradesh, India
[2]Gokula Krishna College of Pharmacy, Sullurpet 524121, Nellore District, Andhra Pradesh, India
[3]Krishna Teja Pharmacy College, Tirupati - 517506, Chittoor District, Andhra Pradesh, India
[4]Mahathi College of Pharmacy, Madanapalle 517319, Chittoor District, Andhra Pradesh, India

ABSTRACT

Polymer concentration and gas generating agents were effect on the floating drug release from floating tablets. To utilize the dissolution data and gain insight into the drug release mechanism from polymer floating tablet. The objective of the present research was to enhance sustained release floating tablets of Glibenclamide by wet granulation method by using synthetic and natural polymers like *tamarindus indica* seed powder extract and HPMC K_4, ethyl cellulose as floating agent, microcrystalline cellulose as super disintegrate, filler, talc, magnesium stearate as glidant and lubricant. The active pharmaceutical ingredient, excipient mixtures are subjected to pre-formulation studies such as Fourier transform infra-red spectroscopy and differential scanning colorometry shown that there was no interaction between drug and polymers. The floating tablets are subjected to physicochemical, *in-vitro* drug release and kinetic studies. The prepared formula tions of physicochemical properties were found within the limits. The optimized formulation of drug release was extended for a period of 8 hr. The release kinetics of formulated drug follows first order models.

Keywords: Glibenclamide; *In-vitro* buoyancy; Wet granulation; Kinetic models; Sustained release.

INTRODUCTION

The oral administration is the most accepted route because of its convenience of self-administration, but poor bioavailability of orally administered drugs are still challenging one, thus extensive improvements in drug discovery process are made (Singh BN *et al.,* 2000). To overcome this variability, these efforts have been made to enhance the retention time of the dosage form for extensive period (Arora S *et al., 2005)*.

Diabetes mellitus is a complex metabolic disorder resulting from insufficiency of insulin/pancreas dysfunction. The disease is classified into insulin-dependent diabetes mellitus (type 1 diabetes), Non-insulin dependent diabetes mellitus (type 2 diabetes), and Gestational diabetes mellitus (American Diabetes Association, 2010). Glibenclamide is used with diet to decrease blood glucose by increasing the insulin secretion from pancreas (Kamlesh J Wadhar *et al.,* 2001). Floating drug delivery systems having important advantages (Brahma N *et al.,* 2000) they are less prone to gastric emptying showing in lowered intra and inter subject variability in plasma levels, reduced dose frequency, improved patient compliance and improved safety profile for drugs with high C_{max}.

* Corresponding Author
Email: saravanakumar156@gmail.com
Contact: +91-9000090348
Received on: 18-06-2015
Revised on: 24-06-2015
Accepted on: 29-06-2015

MATERIALS & METHODS

Glibenclamide was received as a gift sample from A to Z pharmaceuticals pvt. Ltd. Chennai, India. *Tamarind seed* aqueous extract polymer was prepared in Sree Vidyanikethan College of Pharmacy, Tirupati, India. HPMC K_4M and MCC obtained from A to Z pharmaceuticals pvt, Ltd, Chennai, India.

Tamarind seed aqueous extract powder

The seeds of *tamarindus indica* (Manmohan S *et al.,* 2014) were washed neatly with plenty of water to r emove the adhering materials. Then, the reddish testa of the seeds were isolated by heating with sand in the ratio of 1:4 (Seed:Sand). The testa was removed and crushed lightly. The crushed testa of *tamarindus indica* seed was separated (Mishra MU *et al.,* 2011). The *tamarindus* seed extract powder was used as polymer and *tamarindus* seed polysaccharide was used as a binder. The polysaccharide was extracted by the following method.

Formulation of floating tablets

The floating tablets were prepared by wet granulation method (Chethan M *et al.,* 2012) by using *tamarindus indica* aqueous seed extract powder, HPMC K_4 and

tamarindus indica polysaccharide as binder, ethyl cellulose as floating agent, microcrystalline cellulose as di s-integrant and filler, talc, magnesium stearate as glidant and lubricant respectively. The drug is mixed with di s-integrant and triturates homogenously using mortar and pestle. To this mixture, slowly add the binder sol u-tion until get a wet cohesive mass. Pass this wet mass through sieve no.#22 to get uniform sized wet granules. To this granule, add talc, magnesium stearate by physical mixing and were pressed into tablets on a remiek mini press II rotary tablet punching machine. Formulation of Glibenclamide floating tablets were shown in table no.1.

PREFORMULATION STUDIES

Preformulation studies (Streubel A *et al.,* 2003) were conducted for individual and mixture of components, which are mainly involved in this work.

FT-IR

Pure drug Glibenclamide, *tamarindus indica* seed powder and mixture of drug, seed powder were subjected to FTIR spectroscopic study (Agilent Technologies). The spectra's were scanned over the wave number ranges from 4000 – 800 cm^{-1}. The obtained FT-IR spectra's were reported in figure no.1.

Differential Scanning Calorimetry

DSC thermo grams of API, *tamarindus indica* seed powder and mixture of drug, seed powder were analyzed. DSC was carried out under the nitrogen purge (20 ml/min). The samples are weighed into standard aluminium pans and empty pan was used as standard. The obtained DSC graphs were reported in figure no.2.

PRE AND POST COMPRESSION PARAMETERS

Pre and post compression parameters were characterized for the prepared granules and tablets.

Angle of repose

The fixed funnel method was performed that is s e-cured with its tip at a given height (h), which was kept 2 cm above graph paper that is placed on a flat horizontal surface. With r is the radius of base of pile, angle of repose can be determined by following equation

$$\theta = tan - 1\ (h/r)$$

Where, θ is the angle of repose, h is height of pile, r is radius of base of the pile.

Bulk and tapped density

A weighed amount of 2 g of prepared granules from each formulation was introduced into the 10 ml of measuring cylinder. The initial volume was observed, the cylinder was allowed to fall down its own weight from the hard surface from a height of 2.5 cm at 2 sec Intervals. The tapping was continued until no further change in the volume was noted LBD and TBD were calculated using the following formulas:

$$\textbf{Bulk Density} = \frac{\textbf{Weight of the powder}}{\textbf{Volume of the packing}}$$

$$\textbf{Tapped Density} = \frac{\textbf{Weight of the powder}}{\textbf{Tapped volume of the packing}}$$

Carr's index

The Carr's index is used as an indication of the flow ability of powder materials. The Carr's index greater than 25 indicates poor flow ability and below 15 good flow ability. The Carr's index is an indication of the powder compressibility. It is calculated by the following formula.

$$\mathbf{C} = \frac{\mathbf{100\ (Vb) - (Vt)}}{\mathbf{(Vb)}}$$

Where, V_b = free settled volume of a given mass of powder, V_t = tapped volume of the same mass of powder.

Hausner's ratio

It is used in industries as indication of the flow ability of a powder and measured by the ratio of tapped density to the bulk density.

$$\textbf{Hauser's ratio} = \frac{\textbf{tapped density}}{\textbf{bulk density}}$$

Hardness

The hardness of the tablet was determined by Monsanto harness tester, the crushing strength (kg/cm^2) in all the cases. The reading at the marked scale was recorded for the pressure, which is required to break the tablet.

Weight variation

The weight variation test was performed by the weighing 20 randomly selected tablets individually, calcula t-ing the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 10%.

Friability

The 20 tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 min. During friability the tablets were deducted, weighed again and observed value should not be more than 1%. Percentage friability was measured using the following formula,

$$\%\ \mathbf{F} = \frac{\textbf{Initial weight} - \textbf{Final weight}}{\textbf{Initial weight}} \mathbf{X100}$$

Drug content uniformity

Five tablets of each formulation (Ramesh Bomma *et al.,* 2009) were weighed and powdered. The equivalent weight of 10 mg of each formulation was transferred into 100 ml volumetric flask and diluted by using 0.1N

HCl as the solvent and samples were analyzed by using UV/Visible spectrophotometer at 265 nm.

***In-vitro* buoyancy**

The time for tablet to emerge on surface of the medium is called as floating lag time (FLT) and duration of time for the dosage form to constantly remain on surface of medium is called the total floating time (TFT). The *in-vitro* buoyancy (Streubel A *et al.,* 2003) was determined by the floating lag time, the tablets were placed in a 100-mL beaker containing 0.1N HCl.

Swelling Index

The swelling index (Anka Rao A *et al.,* 2010) was carried out for 8 hr. From this, it can indicate that uptake of 0.1N HCl into the tablet matrix, producing an increase in weight due to increase in concentration of the pol ymer. Decrease in polymer concentration leads to i ncrease the drug release but some extent it may leads to disruption of a tablet due to loss of hydration.

***In-vitro* drug release**

The *in-vitro* drug release (Sasa Baumgartner *et al.,* 2000) of floating tablets were determined by using USP-II paddle apparatus and 900 ml of 0.1N HCl as di ssolution medium and allowed to equilibrate the temp of 37°C±0.5°c. The floating tablets were placed in the vessel and the apparatus was operated for 8 hr in 0.1N HCl at 50 rpm. At defini te time intervals 5 ml of sample was withdrawn periodically and volume replaced with equivalent volume of the fresh medium. The samples were analyzed using UV spectrophotometer at 265 nm.

***Ex-vivo* permeation study**

Ex-vivo permeation (Jaimini M *et al.,* 2007) was carried out by using modified version of a diffusion cell. Sheep stomach membrane, glued with mucosal side facing upward at one end of the diffusion cell. The end containing membrane was dipped in a beaker containing 100 ml of 0.1N HCl. This beaker was placed on magnetic stirrer maintained temperature at 37±0.5°C and stirred with a magnetic bead. The tablet was stuck on the sheep stomach membrane which was previously moistened with a 2 ml of 0.1N HCl. Samples of 5 ml were withdrawn from the beaker at a predetermined time intervals and then analysed for Glibenclamide at 265 nm with suitable dilution by using UV-Visible spectrophotometer.

RESULTS AND DISCUSSION

FT-IR spectra and DSC thermograms indicated that there was no interaction between Glibenclamide and excipients and no changes in functional groups and melting points of drug and excipients. The comparative DSC thermogram of drug, polymers and physical mi xture showed that there was no any major difference in onset temperature and peak temperature, when compared with pure drug thermogram. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

The Pre-compression parameters of compressibility percentage were found to be less than 15% in all the formulations, which indicated very good flow properties. The angle of repose was found to be less than 30 indicate excellent flow properties. Tablet harnesses were found to be in the range of 3-4.4 kg/cm^2, with the weight variation found to be 118±1.29 to 121±2.47 the friability values were in between 0.22% and 0.47%. The Glibenclamide floating tablet's content was found to be within 95.2 ±0.32 of the labelled amount.

The swelling index was carried out for 8hr. From the figure No.4, which has indicated that uptake of 0.1N HCl into the tablet matrix, producing an increase in weight due to increase in concentration of the pol ymer. Decrease in polymer concentration leads to i ncrease in drug release but some extent it may lead to disruption of a tablet due to loss of hydration. Among the formulation's maximum, swelling was seen in formulation F1 which has high concentration of hydroxypropyl methylcellulose. Results indicate that as the concentration of hydroxypropyl methylcellulose increases the swelling index has increases.

In-vitro buoyancy time indicated that to extend the resident time at a specific area which can depend on nature of polymer. *In-vitro* buoyance study was represented like F7>F4>F6>F1, hence F1 formulation has more floating time compared to other formulations.

Seven formulations of varying concentrations of pol ymers were prepared. Among the 7 formul ations i.e. F1–F7, the order of drug release was found to be drug>F7>F6>F5>F4>F3> F2>F1. Among them, F1 is considered to be the best formulation for formulating into a floating tablet with optimum drug release rate of 69.62%.

Release kinetic study evidenced that the F1 formul ation followed the fist order release, indicating that di ffusion pattern of release, where the swelling of F1 releases Glibenclamide slowly. The correlation coefficient (r) and release rate constants (k) value of zero, first, matrix, peppas, and Hixson-Crowell plotted for the formulations. The drug release data were explored for the type of release mechanism followed. The correl ation coefficient (r) value for F7 formulation obtained is 0.9894 and it shows fist order release followed by zero order kinetics.

Ex-vivo studies were carried out which revealed that F1 formulation showed the drug present per surface area 4.338 %µg/cm^2 and the flux 0.686 µg/cm^{-2} h^{-1} of Glibenclamide into sheep stomach membrane. *Ex-vivo* permeation study of formulation F1 shows better drug release through selected mucosa and represents the data in table No.6. The result of percentage drug permeated through sheep mucosa was found to be 26.29%. The cumulative amount of drug (µg/cm^2) per

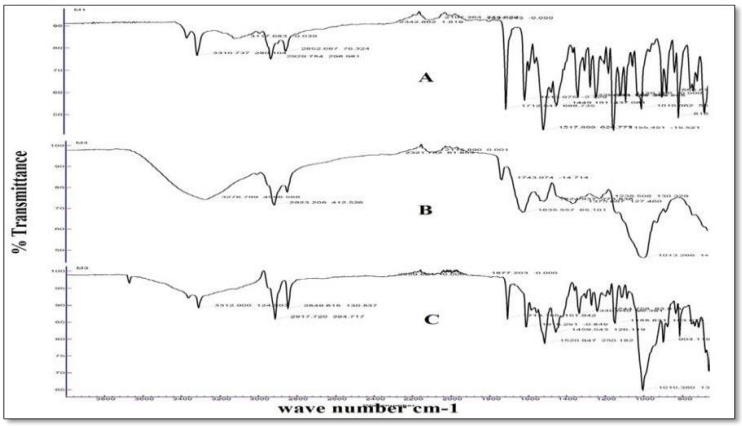

Figure 1: FTIR spectrum of sample A, B & C

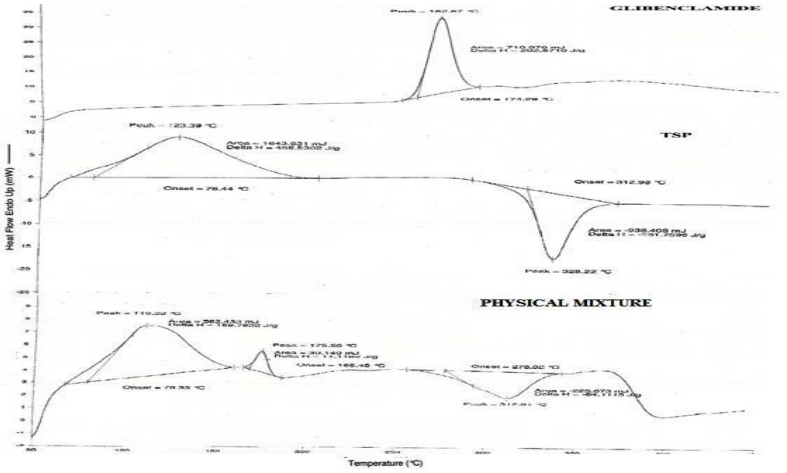

Figure 2: Comparative DSC Thermogram of sample A, B, C

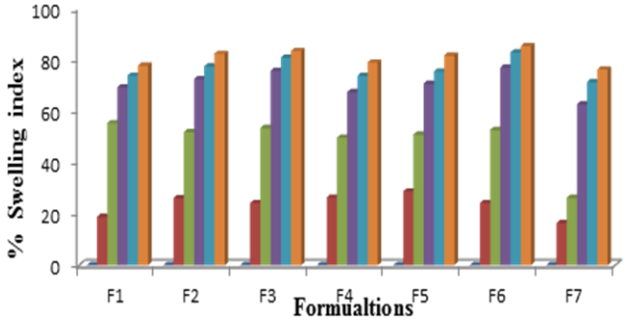

Figure 3: Swelling index of formulations (F1 – F7)

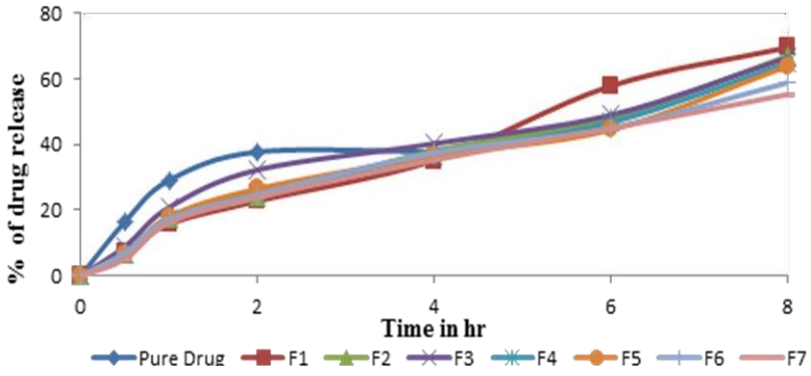

Figure 4: In-vitro drug release data for F1-F7 and pure drug

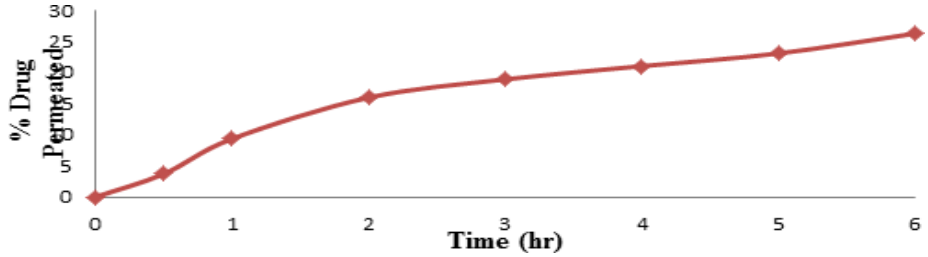

Figure 5: Ex-vivo permeation data of formulation F1

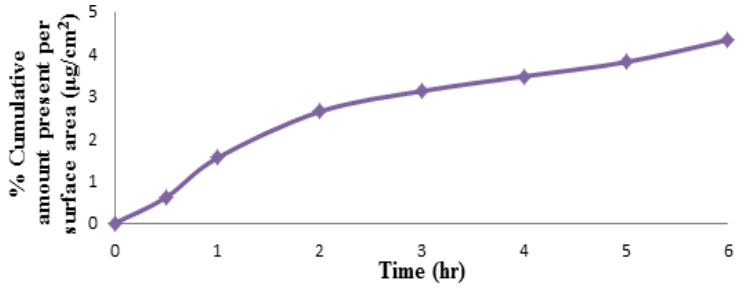

Figure 6: Percentage cumulative amount of drug present per surface area for Glibenclamide (F1)

Table 1: Formulation of Glibenclamide floating tablets

S.No	Ingredients (mg)	Formulations						
		F1	F2	F3	F4	F5	F6	F7
1	Glibenclamide	10	10	10	10	10	10	10
2	HPMC K_4	75	65	55	-	-	-	27.5
3	*Tamarindus indica* seed powder extract	-	-	-	75	65	55	27.5
4	Ethyl cellulose	15	25	35	15	25	35	35
5	Micro crystalline cellulose	12	12	12	12	12	12	12
6	Talc	4	4	4	4	4	4	4
7	Magnesium stearate	4	4	4	4	4	4	4

Table 2: Pre-compression parameters for Glibenclamide tablets

Formulation codes	Angle of re-pose (°)	Bulk density (g/cc)±SD	Tapped density (g/cc) ±SD	Hausner's ratio ±SD	Compressibility index (%) ±SD
F1	31.44±0.594	0.454±0.003	0.518±0.0017	1.136±0.011	13.58±1.861
F2	30.09±0.958	0.467±0.0025	0.524±0.0011	1.116±0.005	11.62±0.482
F3	32.07±0.073	0.472±0.0096	0.535±0.0174	1.130±0.017	13.14±1.710
F4	38.30±0.278	0.523±0.0015	0.611±0.0032	1.163±0.005	16.74±0.926
F5	29.36±0.324	0.534±0.0025	0.617±0.0011	1.150±0.010	15.53±0.746
F6	26.62±0.510	0.555±0.0037	0.656±0.0058	1.176±0.005	18.22±0.236
F7	25.41±0.310	0.564±0.0030	0.623±0.0069	1.096±0.005	10.39±0.694

Table 3: Post-compression parameters for Glibenclamide tablets

Formulation codes	Drug con-tent (mg/tab) ± SD	Hardness (kg/cm²) ± SD	Thickness ± SD	Weight variation (mg) ± SD	Friability (% weight loss) ± SD	Buoyancy	
						Lag Time (sec)	Floating Time (hrs)
F1	91.7± 0.45	3.7±0.200	3.3± 0.12	119±0.01	0.320±0.010	57	>11
F2	93.6± 0.32	4.0±0.100	3.4± 0.10	121±2.42	0.338±0.010	52	>12
F3	90.3± 0.25	4.3±0.513	3.1± 0.05	120±1.11	0.354±0.009	50	>12
F4	87.3± 0.56	3.5±0.503	2.8± 0.09	118±1.29	0.393±0.006	51	>12
F5	89.9± 0.37	3.2±0.404	2.9± 0.21	119±0.07	0.425±0.006	54	>11
F6	92.1± 0.41	3.0±0.400	3.2± 0.13	121±2.47	0.472±0.009	52	>12
F7	95.2± 0.32	4.4±0.503	3.1± 0.21	120±1 .01	0.220±0.017	50	>12

Table 4: Swelling index of formulation F1-F7

Time (hr)	Swelling index (%)						
	F1	F2	F3	F4	F5	F6	F7
1	18.8 ± 0.012	26.1 ± 0.047	24.2 ± 0.024	26.3 ± 0.264	28.7± 0.628	24.2±0.0568	16.4±0.082
2	55.2 ± 0.151	51.7 ± 0.038	53.4 ± 0.064	49.6 ± 0.824	50.8± 0.064	52.6±0.626	26.2±0.064
4	69.2 ± 0.064	72.4 ± 0.068	75.6 ± 0682	67.3 ± 0.248	70.6±0.0862	76.9±0.0864	62.5±0.062
6	73.7 ± 0.082	77.3 ± 0.036	80.7 ± 0.068	73.6 ± 0.826	75.3±0.0982	82.7±0.0684	71.2±0.048
8	77.6 ± 0.035	82.2 ± 0.658	83.3 ± 0.694	78.8± 0.0682	81.5±0.0686	85.2±0.002	76.1±0.068

Table 5: In-vitro drug release of pure drug & formulations (F1-F7) in 0.1N HCl

Time (hr)	Cumulative % drug release (S.D means n = 3)							
	Pure Drug	F1	F2	F3	F4	F5	F6	F7
0.5	16.5 ± 0.21	7.40 ± 0.19	6.55 ± 1.41	8.98 ± 0.93	6.55 ± 1.19	6.84 ±0.71	7.04 ±1.31	5.14 ± 0.65
1	29.12 ±0.95	15.80 ±0.12	17.35 ± .53	20.90 ±1.26	17.63 ±1.13	18.06±1.98	17.36±2.09	16.21 ±0.25
2	37.76 ± .46	22.82 ±1.08	23.82 ±0.30	32.35 ±1.32	25.38 ±2.19	26.51±1.68	24.81±1.71	23.95 ±0.94
4	37.72 ± .65	35.27 ±1.78	38.11 ±1.52	40.31 ±1.07	36.85 ±1.85	36.57±1.20	37.55±1.18	35.37 ±1.40
6	-	57.98 ±0.60	48.09 ±2.19	49.17 ±0.86	46.82 ±0.46	44.56±1.03	45.41±1.76	45.37 ±0.86
8	-	69.62 ±1.26	67.47±3.50	66.58 ±1.56	64.92 ±2.82	64.06±3.58	58.97±1.63	55.39 ±1.80

Table 6: Ex-vivo permeation data of formulation F1

Time (hr)	% drug permeated
0.5	3.71±0.068
1	9.35±0.084
2	15.98±0.328
3	18.92±0.928
4	21.040.0312
5	23.09±0.0686
6	26.29±0.0462

Table 7: Percentage cumulative amount of drug present per surface area for Glibenclamide floating tablet [F1]

Time (hr)	% Cumulative amount of drug present per surface area (µg/cm^2)
0.5	0.612
1	1.542
2	2.636
3	3.122
4	3.471
5	3.810
6	4.338

Table 8: Release kinetics of Glibenclamide floating tablets

F.Code	r&k values	Zero order	First order	Matrix	Peppa's release	Hixcrow
F1	r	0.9880	0.9904	0.9601	0.9934	0.9940
	k	9.1641	0.1419	21.52	21.520	0.0404
F2	r	0.9775	0.9850	0.9701	0.9839	0.9881
	k	8.6523	0.1287	20.4912	13.4987	0.0372
F3	r	0.9298	0.9747	0.9851	0.9749	0.9667
	k	8.8995	0.1316	21.5075	17.2822	0.0382
F4	r	0.9689	0.9851	0.9750	0.9796	0.9850
	k	8.4073	0.1223	20.0087	13.68.80	0.0357
F5	r	0.9617	0.9834	0.9776	0.9775	0.9815
	k	0.3400	0.1205	19.9289	14.1327	0.0352
F6	r	0.9543	0.9872	0.9865	0.9855	0.9802
	k	7.9600	0.1109	19.100	14.27	0.0329
F7	r	0.9947	0.9894	0.9834	0.9704	0.9820
	k	7.6185	0.1038	18.24	11.93	0.0311

meated through the surface area with permeation time of the drug was found to be 4.338 µg/cm^2. From the slope of plots, flux (J_s) and the permeability coefficient were obtained by dividing flux with the total amount of drug. Formulation F1 showed flux of 0.686 µg cm^{-2} h^{-1} and permeability coefficient of 0.0057 cm h^{-1}. *Ex-vivo* Permeation study shows optimum drug permeation for F1 formulation.

CONCLUSION

It is a promising area for systematic delivery of orally inefficient drugs as well as an attractive alternative for non-invasive delivery. Glibenclamide tablets prepared by wet granulation method shows good acceptable hardness for the prepared tablets. Among all the formulations F1 was selected as an optimized formulation which shows optimum release of drug and maintains the therapeutic efficacy of drug in plasma concentration.

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