wjpmr, 2018,4(10), 139-145

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

FORMULATION AND IN VITRO EVALUATION OF GASTRO RETENTIVE FLOATING TABLETS OF GLIPIZIDE

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Article Received on 13/08/2018 **Article Revised on 04/09/2018** **Article Accepted on 25/09/2018**

ABSTRACT

The purpose of present investigation was to develop and evaluate floating drug delivery system of an oral hypoglycemic agent. The floating tablets of Glipizide were prepared by using HPMC K4M, HRMCK100, Xanthan gum polymers. The pre compression and post compression parameters were performed as per pharmacopoeial standards. The tablets were prepared by direct compression method. Dissolution measurements were carried out in a (USP) dissolution testing apparatus the invitro buoyancy studies were performed and Compatibility study was performed by FTIR. The compatibility study of the prepared Glipizide floating tablets confirms that there is no interaction between the drug and polymers used.

KEYWORDS: Glipizide, Gastroretentive, floating drug delivery, sustained release, polymers.

INTRODUCTION

Glipizide is an oral rapid- and short-acting anti-diabetic medication from the sulfonylurea class and its IUPAC name is N-[2-[4 cyclohexylcarbamoylsulfamoyl) phenyl]ethyl]-5-methylpyrazine-2-carboxamide -(It is classified as a second-generation sulfonylurea.[1,2,3,4] Glipizide sensitizes the beta cells of pancreatic islets of Langerhans insulin response, meaning that more insulin is released in response to glucose than would be without glipizide ingestion.[5,6,7,8] Glipizide acts by partially blocking potassium channels among beta cells of pancreatic islets of Langerhans. By blocking potassium channels, the cell depolarizes, which results in the opening of voltage-gated calcium channels. The resulting calcium influx encourages insulin release from beta cells.[9,10] It may also be used with other diabetes medications. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems.

MATERIALS AND MRTHODS

Materials

Glipizide drug obtained from Natco pharma pvt Ltd .Kothur Shad nagar, Rangareddy, Hydroxy propyl methyl cellulose, Xanthan gum, Avicel, Sodium bicarbonate. Lactose, Mg-Stearate were purchased from S.D fine chemicals, Mumbai, Maha rastra.

Method

Preparation of Glipizide floating tablets By direct compression method, using drug and variable concentration of polymers (HPMC K4M, HPMCK100, Xanthan gum, Sodium Bicarbonate, MCC, Lactose, Mg-sterate, and Talc. The respective powders & optional additives were blended thoroughly with a mortar and pestle. The powder blended was then lubricated with Mg-stearate and purified talc and then compressed on a tablet punching machine.

Evaluation parameters

Pre-compression evaluation

Angle of Repose

Angle of repose was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula.

$$\emptyset = \tan^{-1}\frac{h}{r}$$

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

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (*Vb*) and weight of powder (*M*) was determined. The bulk density was calculated using the formula.

$$\rho b = \frac{m}{Vd}$$

Tapped Density

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (*Vt*) occupied in the cylinder and weight (M) of the blend was measured.

Carr's compressibility index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the granules was determined by Carr's compressibility index, which is calculated by using the following formula

$$I = \frac{Vo - Vt}{Vo} \times 100$$

Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula

$$\text{Haunser ratio} = \frac{pt}{pd}$$

Where ρt is tapped density and ρd is bulk density. Lower Hausner ratio (< 1.25)

indicates better flow properties than higher ones (>1.25).

Post-compression evaluation parameters for formulated tablets

Weight variation

Twenty tablets from each formulation were selected at random and average weight was determined. Then the individual tablets were weighed and were compared with average weight.

Hardness

The hardness of the tablet from each formulation was determined using Pfizer hardness tester.

Friability

Friability of the tablets was determined using Roche Friabilator. This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dedusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$\text{Friability (f)} = (1 - \frac{W_o}{W}) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablet after the test.

Thickness and diameter

The thickness and diameter of tablet was carried out using Digital caliper. Five tablets were used for the above test from each batch and results were expressed in millimeter.

***In-vitro* dissolution studies**

The release rate of Glipizide from floating tablet was determined using the United States Pharmacopoeia (USP) dissolution testing apparatus II. The dissolution test was performed using 900ml of 0.1 N HCL, at 37 ± 0.5^{0}C and 50 rpm. The samples were taken at pre-selected time intervals with replacement of equal volume of dissolution medium.

***In-vitro* buoyancy studies**

The in vitro floating behavior of the tablets was studied by placing them in 100 ml beaker 100 ml of 0.1 N HCl (pH 1.2, 37^{0}C). The time, tablet required for the emerge on the surface is floating lag time (FLT) or buoyancy lag time (BLT). And the time tablet constantly float on the surface of the medium is called total floating time (TFT).

Compatibility

Compatibility studies were performed through FTIR spectroscopy. The IR spectrum of pure drug and physical mixture of drug and polymer was studied. The characteristic absorption peaks of Glipizide obtained were obtained at 4000-500cm^{-1}. It has been observed that there is no chemical interaction between Glipizide and polymer's used. From the fig no 5.3, 5.4, 5.5, 5.6, & 5.7 it was observed that peak obtained in spectra drug an polymers. which show there were no interaction between drug and polymers

Composition of Glipizide floating tablet with FLT and TLT

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Drug	10	10	10	10	10	10
HPMC K100				25	30	35
HPMC K4M	25	30	45			
Xanthan gum	10	15	20	10	15	20
MCC	65	60	50	65	60	60
$NAHCO_3$	20	20	20	20	20	20
MG -STERATE	2	2	2	2	2	2

TALC	3	3	3	3	3	3
LACTOSE	65	60	50	65	60	50
TOTAL WEIGHT	200	200	200	200	200	200
FLT (Seconds)	92	109	133	41	67	87
TFT (h)	>12	>12	12	>12	>12	>12
Ingredients (mg)	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Drug	10	10	10	10	10	10
HPMC K100	20	20	20			
HPMC K4M				20	20	20
Xanthan gum	10	15	20	10	15	20
MCC	75	65	70	75	65	70
$NAHCO_3$	20	20	20	20	20	20
MG - STERATE	2	2	2	2	2	2
TALC	3	3	3	3	3	3
LACTOSE	60	65	65	60	65	55
TOTAL WEIGHT	200	200	200	200	200	200
FLT (Seconds)	144	162	187	64	95	107
TFT (h)	>12	>12	12	>12	>12	12

RESULTS

Pre-compression parameters of Glipizide floating tablets

Formulation code	Angle of repose (θ) ±SD	Bulk density $_3$(gm/cm) ±SD	Tapped density 3 (gm/cm) ±SD	Hausner ratio (HR)±SD	Carr index (Ic) ±SD
F1	22.43±0.726	0.220±0.010	0.260±0.010	1.180±0.010	15.397±0.594
F2	24.06±0.556	0.225±0.020	0.260±0.010	1.150±0.060	15.792±0.357
F3	22.46±0.471	0.234±0.015	0.270±0.026	1.190±0.010	16.016±0.640
F4	22.64±0.746	0.250±0.010	0.266±0.015	1.124±0.005	11.706±0.512
F5	23.64±0.312	0.230±0.011	0.300±0.010	1.199±0.009	16.676±0.560
F6	22.85±0.665	0.224±0.010	0.262±0.011	1.129±0.006	11.423±0.511
F7	22.21±0.825	0.210±0.010	0.260±0.010	1.180±0.010	15.398±0.594
F8	21.84±0.645	0.230±0.011	0.250±0.010	1.190±0.010	16.015±0.640
F9	21.54±0.346	0.220±0.005	0.282±0.011	1.207±0.004	17.676±0.732
F10	22.87±0.934	0.227±0.010	0.266±0.005	1.173±0.005	15.002±0328.
F11	22.96±0.471	0.230±0.010	0.270±0.010	1.173±0.010	14.827±0.550
F12	22.85±0.520	0.224±0.011	0.260±0.010	1.163±0.030	15.399±0.592

Post-compression evaluation of Glipizide floating tablets

Formulation code	Weight variation Average wt in (mg)±SD	Hardness (Kg/cm^2) ±SD	Diameter in (mm) ±SD	Thickness in (mm) ±SD	Friability (%)±SD	Drug content uniformity (%)±SD
F1	199.58± 0.934	4.355± 0.208	9.34± 0.577	2.245± 0.057	0.756± 0.057	99.672±0.612
F2	200.5± 0.885	4.943± 0.115	9.32± 0.577	2.144± 0.066	0.592± 0.055	97.564±0.407
F3	195.6± 0.824	4.856± 0.115	9.65± 0.577	2.126± 0.055	0.759± 0.015	99.044±0.817
F4	200.04± 0.889	5.062± 0.155	9.00± 0.000	2.250± 0.000	0.671± 0.010	99.486±0.147
F5	200.3±0.833	4.801± 0.200	8.65± 0.577	2.285± 0.057	0.764± 0.011	98.592±0.391
F6	200.2± 0.952	4.932± 0.115	8.67± 0.577	2.129± 0.010	0.766± 0.090	96.362±0.305
F7	199.97± 0.877	4.863± 0.115	9.00± 0.000	2.239± 0.049	0.745± 0.060	98.738±0.228
F8	200.2± 0.834	4.465± 0.115	8.67± 0.577	2.881± 0.052	0.769± 0.011	98.148±0.502
F9	200.15± 0.815	4.737± 0.115	8.65± 0.577	2.942± 0.057	0.663± 0.010	98.424±0.116
F10	200.1± 0.857	4.946± 0.115	8.65± 0.577	2.253± 0.000	0.779± 0.017	98.432±0.355
F11	200.14± 0.815	4.644± 0.115	9.00± 0.000	2.204± 0.100	0.663± 0.010	94.513±0.130
F12	200.12± 0.748	4.802± 0.200	8.67± 0.577	2.355± 0.100	0.782± 0.010	96.172±0.677

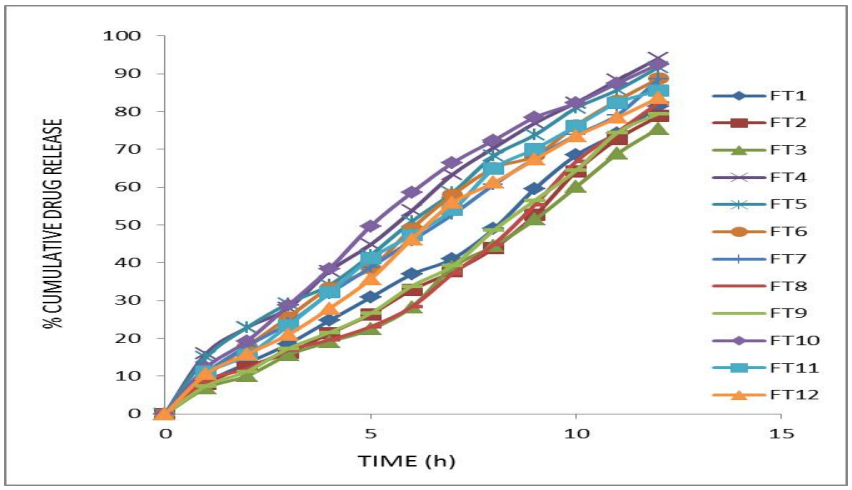
In-vitro drug release data of Glipizide floating tablets of batch F1 to F6

Time	% Cumulative release					
	FT1±SD	FT2±SD	FT3±SD	FT4±SD	FT5±SD	FT6±SD
1	9.276±0.438	8.000±0.150	7.899±0.88	16.985±0.219	15.052±0.207	10.043±0.174
2	15.478±0.305	15.606±0.306	13.138±0.262	26.900±0.182	24.953±0.218	18.912±0.328
3	18.530±0.133	17.210±0.393	17.629±0.349	29.057±0.304	27.274±0.393	26.637±0.262
4	26.754±0.219	22.358±0.307	16.124±0.231	35.836±0.264	35.117±0.315	36.466±0.267
5	33.838±0.217	26.395±0.353	25.419±0.267	48.825±0.134	44.039±0.353	38.545±0.282
6	35.962±0.278	35.857±0.413	29.327±0.364	53.772±0.349	52.943±0.348	49.082±0.200
7	47.114±0.218	38.709±0.354	35.877±0.308	66.424±0.305	59.637±0.307	59.034±0.307
8	48.987±0.267	45.925±0.365	46.513±0.354	74.421±0.258	68.269±0.309	67.108±0.393
9	59.648±0.183	52.638±0.395	57.518±0.355	75.991±0.524	74.878±0.352	68.340±0.307
10	68.467±0.218	65.236±0.350	62.096±0.269	87.379±0.200	83.945±0.396	77.404±0.256
11	75.267±182	73.736±0.174	69.861±0.267	85.351±0.534	87.733±0.262	83.953±0.958
12	82.346±0.182	78.812±0.135	75.624±0.219	96.083±0.457	91.542±0.782	88.812±0.314

***In-vitro* drug release data of Glipizide floating tablets of Batch F7 to F12**

Time	% Cumulative release					
	FT7±SD	FT8±SD	FT9±SD	FT10±SD	FT11±SD	FT12±SD
1	10.831±0.352	8.872±0.172	7.474±0.455	12.323±0.0.447	11.322±0.219	10.625±0.532
2	16.998±0.0.266	11.997±0.328	12.328±0.412	18.331±0.437	15.622±0.397	16.824±0.742
3	24.017±0.352	18.878±0.220	17.341±0.353	28.774±0.744	24.466±0.485	21.058±0.653
4	33.898±0.393	19.618±0.306	21.623±0.307	38.457±0.524	32.158±0.353	27.949±0.698
5	38.828±0.315	23.146±0.399	25.634±0.532	49.716±0.659	43.154±0.439	35.747±0.618
6	45.856±0.353	29.388±0.347	33.853±0.534	58.581±0.656	47.343±0.448	46.248±0.661
7	55.835±0.348	37.172±0.394	39.282±0.332	69.471±0.568	54.060±0.573	55.865±0.662
8	60.689±0.308	44.951±0.353	49.630±0.367	72.428±0.632	64.934±0.513	63.201±0.746
9	67.741±0.352	55.434±0.308	56.568±0.355	78.508±0.228	73.164±0.581	67.382±0.702
10	75.842±0.306	67.828±0.351	64.488±0.397	83.304±0.402	76.211±0.397	73.515±0.747
11	79.132±0.353	74.582±0.308	75.404±0.315	87.488±0.444	82.343±0.415	78.396±0.704
12	88.621±0.414	82.356±0.306	79.521±0.423	92.354±0.864	85.624±0.367	83.731±0.537

***In-vitro* drug release profile of Glipizide floating tablets of batches F1 to F12**



***In-vitro* buoyancy studies of the Glipizide floating tablet**

In-vitro buoyancy studies of the Glipizide floating tablet using

HPMC K4M

At (92 sec) After 12 hrs

***In-vitro buoyancy* studies of the Glipizide floating tablet using HPMC K100**

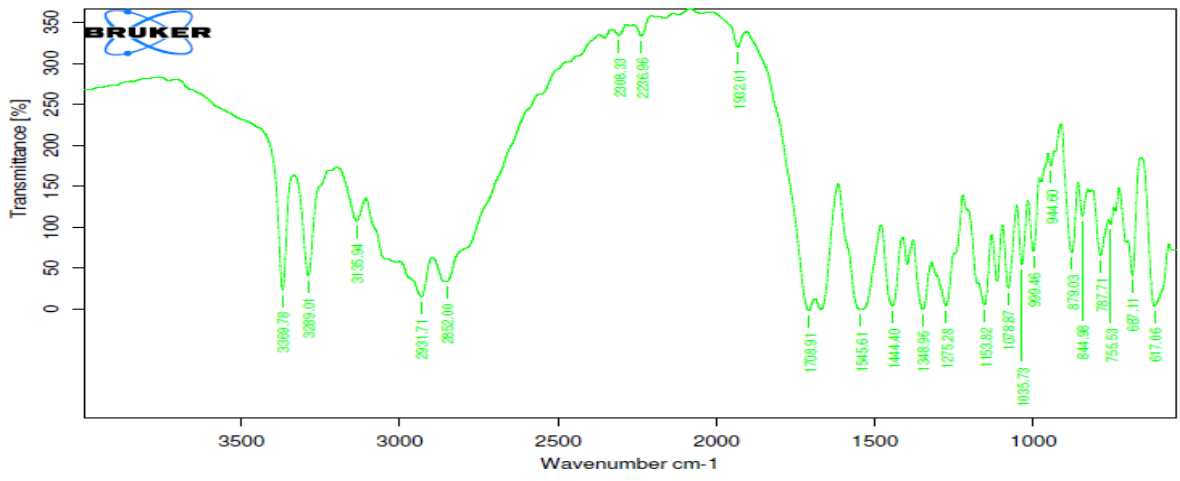
At (41 sec) After 12 hrs

Compatability studies

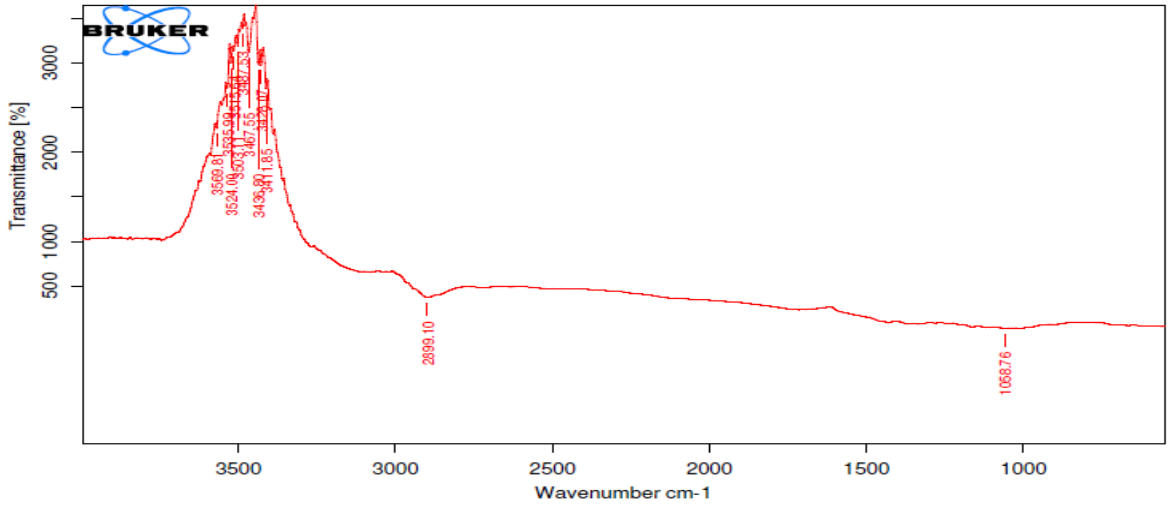
FTIR Spectroscopy

The IR spectrum of pure drug was found to be similar to the standard spectrum of Glipizide.

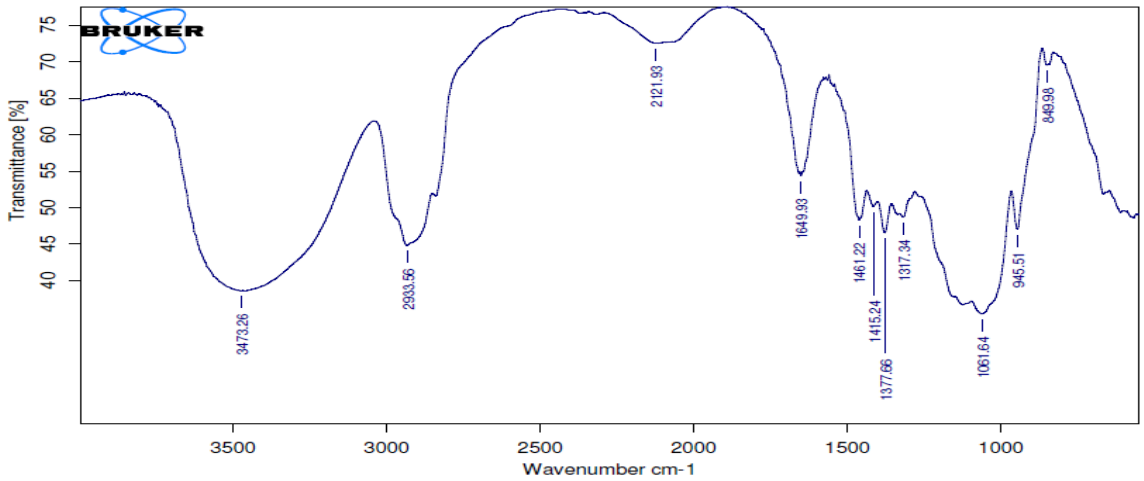
IR spectra of Glipizide



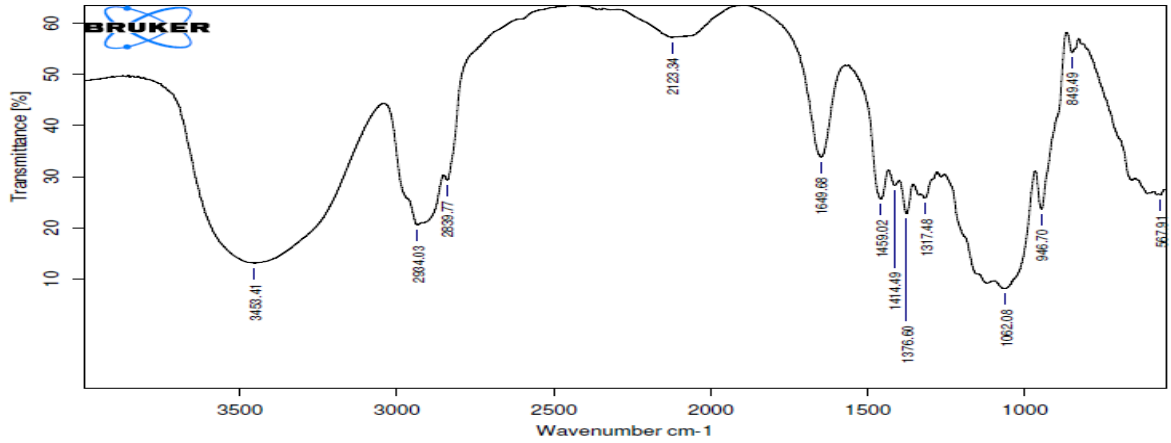
IR spectra of MCC



FT-IR Spectra of HPMC K4M



FT-IR Spectra of HPMC K100



DISCUSSION

In the present study, Gastroretentive drug delivery systems of Glipizide were prepared by using different viscosity grades of hydroxy propyl methyl cellulose (HPMC), viz., K4M and HPMCK100, and Xanthan gum at different drug to polymer ratios with gas generating agent like sodium bicarbonate FTIR drug-polymers interaction studies. It was found that Glipizide was compatible with HPMC K4M, HPMCK100, and Xanthan gum, used in the formulation, there were no extra peaks observed. Thus the chosen polymers for the

formulations were found to be compatible with Glipizide and have no physical interaction.

The angle of repose of the drug powder was in the range of 21.54 to 24.06, the Carr's index was found to be in the range of 11.42 to 17.67 indicating compressibility of the tablet. Haunser's ratio was found in the range of 1.12 to 1.20 is good .Prepared tablets were evaluated for weight variation and percentage deviations from the average weight are reported in table 5.5.and was found to be within the prescribed official limits. The friability of the formulations as found to be between 0.59 to 0.78 is reported in table 5.5 and as that of which was found to be within the official requirement (i.e. not more than 1%). The thickness of the tablet indicates that die fill was uniform. The thickness depends upon the size of the punch and the weight of the tablet (200 mg). The thickness of the batch from F1-F12 was found to be 2.12-2.94 mm and hardness was found to be 4.3-5.0 Kg/cm2 as reported in table 5.5 which had good mechanical strength. On immersion in 0.1 N HCL solution pH (1.2) at 37^0C, the tablets floated, and remained buoyant without disintegration. Fig 5.14 to 5.17 shows Buoyancy character of prepared tablet. From the results it can be concluded that the batch containing HPMC K4M polymer showed good floating lag time (FLT). Formulation containing HPMC K4M, HPMCK100 showed less FLT compare to formulation containing Xanthan gum.

In-vitro dissolution studies were performed for all the batches of tablets containing Glipizide using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. Formulations F1, F2 and F3 containing drug and HPMC K4M exhibited 82.356±0.182, 79.812±0.135 and 75.624±0.219 of drug release 12 hrs. Formulations F4, F5 and F6 containing drug polymer HPMCK100, exhibited 95.083±0.457, 91.542±0.782 and 88.812±0.314 of drug release in 12 hours. Formulations F7, F8 and F9 containing drug and polymers like HPMCK100 and Xanthan gum exhibited 88.621±0.414, 82.356±0.306 and 79.521±0.423 of drug release in 12 hours. Formulations F10, F11 and F12 containing drug and polymers like HPMC K4M and Xanthan gum exhibited 92.354±0.864, 85.624±0.367 and 83.731 ±0.537 of drug release in 12 hours respectively.

CONCLUSION

From the compatibility studies, it is concluded that, HPMC K4M, Xanthangum, HPMCK100, were compatible with drug Glipizide and thus suitable for the formulation of Glipizide floating tablets.

Glipizide tablets were fabricated by direct compression method.

In-vitro buoyancy studies were performed for all the formulations, F1 to F12 by using 0.1 N HCL solution at 37^0C. Tablet containing HPMC (F4) showed good buoyancy with very short lag time and long floatation time of more than 12 hrs in 0.1 N HCL. *In-Vitro* release study is performed for 12 hrs. Optimized formula containing HPMCK100 (F4) showed better release compare to other formulations and it followed zero order kinetics. The non-Fickian diffusion was confirmed as the drug release mechanism from this formulation.

From this study, it was concluded that HPMCK100 can be used in formulation of Glipizide sustained release gastro retentive floating drug delivery system. Overall, this study concludes that viscosity of the polymer is a major factor affecting the drug release and floating properties of FDDS.

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