Available on line www.jocpr.com

Journal of Chemical and Pharmaceutical Research

J. Chem. Pharm. Res., 2010, 2(2): 274-278

ISSN No: 0975-7384

Formulation and evaluation of floating drug delivery system of Metformin Hydrochloride

D. B. Raju, R. Sreenivas and M. M. Varma*

Shri Vishnu College of Pharmacy, Vishnupur, Bhimavaram, India

Abstract

Sustained release gastroretentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Gastroretentive floating drug delivery systems (GFDDS) of metformin hydrochloride, an antidiabetic drug with an oral bioavailability of only 50%(because of its poor absorption from lower gastrointestinal tract) have been designed and evaluated. Hydroxy propyl methyl cellulose(HPMC K4M) and carbopol 934P were used as polymers and sodium bicarbonate as gas generating agent to reduce floating lag time.Tablets were prepared by wet granulation method. Floating tablets were evaluated for hardness, friability, weight variation, drug content, floating properties and in vitro release pattern. The in vitro drug release followed first order kinetics and drug release was found to be diffusion controlled.

Key words: Metformin HCl, Floating drug delivery system, HPMC, Carbopol.

Introduction

During the last decade, many studies have been performed concerning the sustained release dosage forms of drugs, which have been aimed at the prologation of gastric emptying time (GET). The GET has been reported to range from 2 to 6 h, in humans in the fed state(1). Retention of drug delivery systems in the stomach prolongs the overall gastrointestinal transit time, thereby resulting in improved bioavailability. Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected

to basically two complications, that of short gastric residence time and unpredictable gastric emptying rate (2).

Depending on the mechanism of buoyancy, two distinctly different methods viz., effervescent and non effervescent systems have been used in the development of floating drug delivery systems (FDDS)(3). Effervescent drug delivery systems utilize matrices prepared with swellable polymers such as methocel(4) or polysaccharides and effervescent components e.g.,sodium bicarbonate and citric or tartaric acid. Floating drug delivery systems offer important advantages: as they are less prone to gastric emptying resulting in reduced intra and intersubject variability in plasma drug levels, effective for delivery of drugs with narrow absorption windows, reduced dosing and increased patient compliance ,reduced C_{max} and prolonged drug levels above the minimum effective concentration and improved safety profile for drugs with side effects associated with high $C_{max.}$

Metformin Hcl is a biguanide antihyperglycemic agent that improves glucose tolerance in patients with type II diabetes. Metformin Hcl is incompletely absorbed from gastrointestinal tract,it has absorption window confined to upper part of gastrointestinal tract .It has half life of 1.7 hours and its absolute bioavailability is reported to be about 45-50% of the administered dose, hence it is a suitable candidate for gastroretentive floating drug delivery system.

Materials and Methods

Metformin Hcl and HPMC K4M were received as gift samples from Monarch Labs., Hyderabad. Carbopol 934P and PVP K 30 were procured commercially from National Scientific Products, Mumbai. Citric acid was procured from S.D. Fine Chem. Ltd., Mumbai. Sodium bicarbonate, talc and magnesium stearate were procured from Loba Chemie, Mumbai.All other chemicals used were of analytical reagent grade.

Preparation of Floating tablets

Tablets were prepared by wet granulation method. Metformin Hcl (500 mg) was mixed with required amount of polymers and other excipients (Table 1). All the excipients were passed through sieve no. 60, mixed and granulated with 10% solution of PVP K-30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45^{o}C for 2h. Dried granules were passed through sieve no. 24 and mixed with magnesium stearate and talc. Granules were compressed into tablets using single station tablet compression machine (Cadmach).

Table1. Composition of floating tablets of Metformin Hcl. Ingredients (mg/tablet)

Formulations	Drug	HPMC K 100M	Carbopol 934P	Citric acid	Sodium bicarbonate	PVP k-30	Magnesium Stearate	Talc
F1	500	100	-	15	50	75	5	5
F2	500	150	-	15	50	75	5	5
F3	500	-	100	15	50	75	5	5
F4	500	-	150	15	50	75	5	5
F5	500	75	75	15	50	75	5	5

Table 2.Physicochemical Characteristics of Tablets
(All values are expressed as mean ± S.D.; n=3)

Batches	Hardness (Kg/cm^2)	Friability (%)	%Drug Content	Buoyancy Lag Time	Total Floating Time (hrs)
F1	4.8±0.6	0.42±0.04	98.9±0.5	3min 41 sec	>8
F2	4.5 **±0.2**	0.74±0.06	96.1±0.8	2min 56 sec	>8
F3	6±0.5	0.59±0.04	95.8±0.4	3min 09 sec	>12
F4	5.2±0.4	0.86±0.07	95.2±0.5	2min 34 sec	>12
F5	6.8±0.4	0.79±0.05	96.7±0.7	4min 17 sec	>12

Evaluation of Tablets

Weight Variation

Twenty tablets were selected randomly and the average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight.

Hardness and Friability

Hardness of tablets (n=3) was determined using Monsanto hardness tester. Friability of the tablets were checked using Roche friabilator. Preweighed sample of tablets(n=10) was placed in the friabilator, operated for 100 revolutions. Tablets were then dusted and reweighed. The experiment was repeated three times.

Table 3. Cumulative % drug release(*mean± S.D.;n=3*)from various formulations
Time (hr)

Formulations	1	2	4	6	8	10	12
F1	25.2±0.45	48.6±0.62	67.5±0.58	81.2±0.15	97.2±0.45	100±0.4	-
F2	21.6±0.53	40.3±0.62	62.5±0.46	76.8±0.51	95.8±0.73	100±0.3	-
F3	22.1±0.56	29.9±0.19	43.2±0.81	54.7±0.58	72.7±0.69	81.7±0.45	89.5±0.19
F4	19.4±0.51	23.8±0.43	48.9±0.62	64.4±0.69	76.1±0.32	82.1±0.19	91.2±0.6
F5	17.32±0.22	29.2±0.29	34.5±0.31	42.5±0.52	65.6±0.54	69.2±0.2	75.1±0.5
Marketed product	24.3±0.56	34.2±0.75	59.4±0.13	74.7±0.25	81.9±0.45	90.7±0.2	92.3±0.81

Table 4. Dissolution kinetics and dissolution parameters of Metformin Hcl floating tablets

Formulations	First order eqn.		Zero order eqn.		Higuchi eqn.	Peppas eqn.	
	r	k	r	k	r	r	n
F1	0.9915	0.147	0.9832	5.34	0.9913	0.9991	0.659
F2	0.9932	0.156	0.9882	6.73	0.9866	0.9938	0.659
F3	0.9803	0.164	0.9785	6.13	0.9804	0.9986	0.656
F4	0.9825	0.175	0.9757	6.09	0.9888	0.9984	0.67
F5	0.9882	0.182	0.9872	6.92	0.9814	0.9932	0.56

Estimation of Drug Content

Twenty tablets of each formulation were weighed and powdered. The quantity of powder equivalent to 100 mg of drug was transferred into 100 ml volumetric flask, it was shaken with 70 ml of distilled water and volume was adjusted to 100ml with water. The solution was filtered,

suitable dilutions were made and absorbance was recorded by using Elico U.V. spectrophotometer at 233nm.The experiment was repeated three times.

Floating or Buoyancy Test

The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT).The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37±0.5^{o}C in 900ml of simulated gastric fluid at pH 1.2.The time of duration of floatation was observed visually.

In Vitro Drug Release Study

In vitro release studies were carried out by using USP paddle dissolution test apparatus .900ml of 0.1 N HCl (pH1.2) was taken in the dissolution vessel and the temperature of the medium was maintained at 37±0.5^{o}C. 100rpm was maintained, 0.5 ml of sample was withdrawn at predetermined time intervals for 12 hours and the same volume of the fresh medium was replaced. The samples were analysed at 233nm by using a UV spectrophotometer(Elico).The dissolution data obtained were plotted as cumulative percentage drug release versus time as zero order, log cumulative percentage drug retained versus time as first order release kinetics, cumulative percentage drug release versus square root of time as higuchi equation and log of fraction of drug released versus log time as Korsemeyer –peppas equation.

Results and Discussion

Hydrodynamically balanced tablets of metformin Hcl (intra gastric buoyant tablets) were prepared and evaluated to increase its local action and bioavailability.In the present study five formulations with variable concentration of polymer were prepared and evaluated for physicochemical properties and in vitro drug release.

On immersion in 0.1 N Hcl solution at pH 1.2 at 37±0.5^{o}C tablets floats immediately and remain buoyant upto 8-12 hrs without disintegration. Floating property of the tablet is governed by both the swelling (hydration) of the polymer when it contacts with the gastric fluid, which in turn results in increase in the bulk volume, and the presence of internal voids in the dry centre of the tablet(porosity). These two factors are essential for the tablet to acquire bulk density < 1 and so remain buoyant on the gastric fluid (5).

Hardness of the tablets was in the range of 4.5 to 7 kg/cm^{2}.This ensures good handling characteristics of all the batches. Weight loss in the friability test was less than 1% in all the cases, ensuring that the tablets were mechanically stable. All the floating tablets prepared contained the drug within 100±5% of the label claim. All the formulated tablets (F1 to F5) passed the weight variation test as the % weight variation was within the pharmacopoeial limits of ± 5% of the average weight.Table2 shows the results of buoyancy study. From the results ,it is evident, that formulation F4 containing carbopol 934P showed least floating lag time (2min34sec) and good total floating time >12hrs,while the formulation F5 containing both carbopol 934P and HPMC K100M showed highest BLT(4min17 sec) and total floating time of >12hrs.This may be due to the different concentrations of polymer and gas generating agent. Release parameters of floating tablets are shown in table 3 and 4.The formulation F4 was

screened from the above formulations for comparing its in vitro release with the marketed formulation. This is because F4 exhibited least buoyancy lag time 2min.34 sec. Batch F4(carbopol 934P 150 mg, sodium bicarbonate 50 mg) demonstrated good sustained release (Table3). From the in vitro dissolution data it was found that formulation F1 and F2 containing HPMC K 100M released 97.2% and 95.8% of drug with in 8 hr of study, indicating that the polymer amount is not sufficient to control the drug release. F4 containing carbopol 934P(150 mg)alone released 91.23% of drug at the end of 12 hr. Hence, F4 showed better sustained release than the other formulations(F1,F2,F3 and F5).

When the release data was analyzed as per zero and first order kinetic models(Table 4),the best fit with higher correlation (r> 0.9803)was observed with first order model indicating that the drug release from all the batches followed first order kinetics. As the polymer concentration was increased, release rate was decreased(6).When the release data were analyzed as per peppas equation, the release exponent n was found in the range of 0.56 to 0.67 indicating non-fickian (anomalous) diffusion as the release mechanism from all the tablets prepared. Plots of percent released versus square root of time was found to be linear (r> 0.9804) with all the tablets, indicating that the drug release from the tablets was diffusion controlled. Based on cumulative % drug released at the end of 8hrs, the formulations can be arranged as F1>F2>F4>F3>F5. Metformin Hcl release from floating tablet F4 formulated employing 150 mg carbopol 934P was similar to that from Gluformin XL-500 mg, a commercial sustained release formulation of metformin Hcl.

Buoyant drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastroretentive time and a better control of fluctuations in the plasma drug concentrations.

Conclusion

Release of metformin HCl from the floating tablets formulated with HPMC and /carbopol was slow and spread over 12 h and depended on % of polymer in the tablet. Release was diffusion controlled and followed first order kinetics. All the formulated floating tablets exhibited non-fickian diffusion as the drug release mechanism. Formulation F4 showed better sustained release than the other formulations.

References

[1] P Tayade, *Express Pharma Pulse* **2003**; 14: 1-4.
[2] PV Swamy, UV Bhosale, SN Hiremath, SB Shirsand, SA Raju, *Indian Drugs* **2008**; 45; 293-300.
[3] AK Hilton, PB Deasy, *Int. J Pharm*. **1992**; 86: 79-88.
[4] R Garg , GD Gupta, *Asian Journal of Pharmaceutics*, **2007**; 1; 219-222.
[5] KPR Chowdary, MN Murali Krishna, *International Journal of Pharmaceutical Sciences and Nanotechnology*, **2008**; 1: 167-170.