INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

FORMULATION AND EVAUTION OF FOATING TABETS OF METFORMIN HYDROCHORIDE

M. Parvathi

Raghavendra Institute of Pharmaceutical Sciences and Research, Anantapur, Andhra Pradesh, India.

ABSTRACT

The purpose of this research was to prepare a floating drug delivery system of Metformin hydrochloride in order to increase the gastric residence time (GRT) and comparison of natural and synthetic polymer for better sustained effect. The tablets were prepared by wet granuation compression. The hardness of all formulations was found to be in the range of 3.4±0.2 – 5.5±0.1 kg/cm2. All formulations (F1 to F12) prepared by wet granulation method, batch F2 was best formulation and showed very slow release i.e. 96.52% in 12 h. The release behavior of the natural and synthetic polymers were compared according to obtained data. The release data were subjected to different models zero order, first order Higuchi and Pappas in order to evaluate their release kinetics and mechanisms. The drug release was observed by fickian diffusion mechanism. A combination of HMC K 100 and gellan gum shows better sustained release when compared with remaining polymers.The developed floating tablets of Metformin Hydrochoride may be used in clinic for prolonged drug release for at least 12hrs, thereby improving the bioavailability and patient compliance.

Key words: Metformin hydrochloride, floating drug delivery, gastroretentive, sustained release.

INTRODUCTION

oral route is the preferred route of administration of drugs because of low cost of therapy and ease of administration more of patient compliance. But the poor bioavailability (BA) of orally administered drugs is still a challenging one, though extensive advancements in drug discovery process are made[1]. The floating drug delivery system of drug is predominant method for sustained release of Metformin hydrochloride. Depending on the mechanisms of buoyancy, two different methods viz., effervescent and non-effervescent systems have been used in the development of floating drug delivery system. Effervescent methods utilize polymer metrics like HPMC K100, HPMC K15, Gellan gum, Xanthum gum and gas generating agent like sodium bicarbonate. Proper optimization of polymer and gas generating agent is important in improvement of sustained drug release and floating lag time respectively.

Metformin is an antihyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of metformin when given orally is 45–60%. Biological half-life of metformin is 1.5–1.6 h and the main site of its absorption is proximal small intestines[3,4]. This would lead to improvement in the bioavailability of the drug. In this way it stands an advantage over conventional dosage form, [5,6] which needs to be administered twice or thrice a day5-7.

Materials and Methods

Metformin hydrochloride and HPMC K 100, HMC K 15 were received as gift sample from Aurobindo pharmaceuticals Pvt. Ltd., Hyderabad. Sodium bicarbonate and remaining chemicals are of laboratory grade.

Preparation of floating tablet-effervescent technology

Composition of 12 different formulations of Metformin floating tablets is shown in table 1. All ingredients were passed through sieve no 120 and then weighed accurately, mixed thoroughly except talc .Tablets were prepared by wet granulation method using pvpk30 as a binder and solution of pvpk30 was made in isopropyl alcohol (40% of total wt of solid mass). Granules were prepared by passing the wet mass through sieve no 40. Prepared granules were dried in hot air oven at 50˚c for 30min. Dried granules were passed through sieve no 40 , lubricated with talc .Tablets were made by multi tooling lab scale punching machine.

CONCENTRATION (µg/mL)	ABSORBANCE
4	0.28
8	0.46
12	0.68
16	0.85
20	0.95

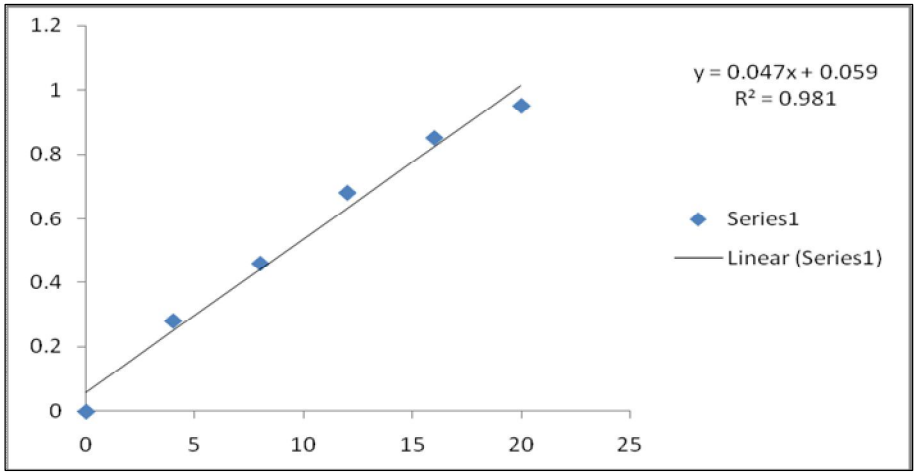


Fig. 1: Standard curve for Metformin hydrochloride at 234nm

Table 1: Composition of tablet

Ingredient (mg per tabet)	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)	F10 (mg)	F11 (mg)	F12 (mg)
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500	500	500	500
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
HPMC K100	50	100	150									
HPMC K15				10	20	30						
GELLAN GUM	5	10	15				5	10	15			
XANTHUM GUM										5	10	15
SODIUM BICARBONATE	50	50	50	50	50	50	50	50	50	50	50	50
TALC	7	7	7	7	7	7	7	7	7	7	7	7
Floating lag time(min)	2	5	60	Burst immediately	Burst immediately	Burst immediately	Burst immediately	Burst immediately	Burst immediately	Burst immediately	Burst immediately	Burst immediately

EVALUATION OF POWDER BLENDS [7-11]

ANGLE OF REPOSE

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\mathbf{Tan\theta = h/r}$$

Where, h and r are the height and radius of the powder cone.

BULK DENSITY

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD = Weight of powder blend/Untapped volume of packing

TDB = Weight of powder blend/Tapped volume of packing

COMPRESSIBILITY INDEX

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's index = TBD-LBD/TBD X 100

FLOATING PROPERTIES OF THE TABLET (FLOATING LAG TIME)

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time.

IN VITRO DISSOLUTION STUDIES

The release rate of Metformin hydrochloride from floating tablets was determined using United States Pharmacopeia (USP). Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of simulated gastric fuid(pH 1.2) at 37 ±0.5°C and 50 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples were filtered and diluted to a simulated gastric fuid. Absorbance of these solutions was measured at 234 nm using a UV/Vis double-beam spectrophotometer . Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

RESULTS

DRUG POLYMER INTERACTION STUDY

FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between Metformin hydrochloride and the polymers used.

PRE-COMPRESSION EVALUATION

The granules of various formulations containing drug and polymer were evaluated for the angle of repose, loose bulk density(LBD), tapped bulk density(TBD) , void volume, bulkiness, total porosity and Compressibility(Carr's) index given in Table 2. The angle of repose for all formulations were found to be in the range of 25-30 indicating excellent flow properties. The values for LBD and TBD were found to be in the range of 0.61 to 0.76 g/cm and 0.77 to 0.89 g/cm3 indicating good packing capacity. Carr's indexes for all formulations were found to be in the range of 16 to 24% indicating excellent flow properties, cohesiveness.

POST-COMPRESSION EVALUATION

Tablets of each formulation type (F1 to F12) were evaluated for parameters such as thickness, hardness and friability given in Table 3. The weight of all formulation tablets were within the range according to IP. The hardness was in range of 3.4-5.5 kg/cm2. Friability was found to be 0.73 – 0.84%. As friability was below 1% tablets in each formulation can withstand the mechanical shocks.

FLOATING BEHAVIOR OF THE TABLETS

The floating tablets of Metformin hydrochloride with the synthetic polymer (HPMC) shows better floating lag time (F2 5min) and it was floated up to 12 hrs and the floating lag time for remaining formulations are shown in the table No.1.

RUG RELEASE KINETICS

The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination r^2 coefficients was shown by both the zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration. Higuchi square root kinetic model describes, release drug from the insoluble matrix as square root of time dependent process. It describes release of drug by simple diffusion mechanism. The value of *n* with regression coefficient for all the formulations is shown in Table 3. The values of *n* were in the range of 0.4907 to 0.5312 (n is more than 0.5) indicating Nonfickian release governed by the drug diffusion. However as indicated by the values of r both of the models (Higuchi and Peppas) were found to be efficient in describe the release of Metformin hydrochoride from the floating tablets. All the parameters were run 3 times (n=3).

Table 2: Pre-compression Evaluation of Metformin floating tablets

FORMULATION CODE	Angle of Repose* (°)±SD	Loose Bulk Density* (g/cm3) ± SD	Tapped Bulk Density* (g/cm3) ± SD	Carr's Index* (%)±SD
F1	27.00±0.47	0.61±0.02	0.78±0.14	16.00±0.20
F2	26.15±0.67	0.69±0.04	0.79±0.12	24.00±0.30
F3	29.00±0.37	0.72±0.03	0.82±011	21.00±0.20
F4	28.00±0.57	0.77±0.06	0.89±0.13	19.00±0.50
F5	25.00±0.27	0.63±0.03	0.78±0.15	18.00±0.30
F6	26.15±0.57	0.66±0.05	0.77±0.16	24.00±0.40
F7	28.00±0.47	0.74±0.04	0.85±0.14	22.00±0.20
F8	27.00±0.47	0.76±0.05	0.86±0.14	19.00±0.50
F9	26.00±0.27	0.63±0.04	0.77±0.15	17.00±0.30
F10	25.15±0.57	0.68±0.06	0.78±0.13	24.00±0.30
F11	28.00±0.47	0.73±0.04	0.83±0.11	23.00±0.10
F12	27.00±0.55	0.76±0.05	0.88±0.12	18.00±0.40

Table 3: Post-compression evaluation of Metformin hydrochloride floating tablets

Formulation code	Thickness* (mm)±SD	Hardness* (kg/cm2) ±SD	Friability* (%)±SD
F1	4 ± 0.5	4.0±0. 3	0.82±0.04
F2	4 ± 0.5	4.0±0. 3	0.84±0.05
F3	4 ± 0.5	4.0±0. 3	0.83±0.02
F4	4 ± 0.5	4.1±0. 3	0.83±0.02
F5	4 ± 0.5	4.0±0. 3	0.84±0.04
F6	4 ± 0.5	4.0±0. 3	0.82±0.03
F7	4 ± 0.5	4.2±0. 2	0.82±0.05
F8	4 ± 0.5	3.4±0. 2	0.82±0.04
F9	4 ± 0.5	5.2±0. 4	0.77±0.05
F10	4 ± 0.5	5.4±0. 2	0.78±0.03
F11	4 ± 0.5	3.5.±0. 3	0.84±0.02
F12	4 ± 0.5	5.5±0.4	0.73±0.02

All the values are expressed as mean ± SD= standard deviation (n=3).

Table 4: % Cumulative release profile of F1-F12

Time in hours	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0.5	25.98	5.27	3.98	25.67	43.92	33.49	60.94	72.34	61.09	70.93	50.43	67.59
1	45.76	15.76	5.26	33.78	59.02	47.89	94.51	88.95	77.90	89.36	78.27	76.07
2	53.47	23.69	10.57	60.97	62.31	59.75	-	96.72	83.61	-	93.69	88.94
3	66.54	31.92	13.44	80.45	79.36	63.25	-	-	95.75	-	-	94.02
4	76.23	38.90	15.13	95.28	87.57	79.62	-	-	-	-	-	-
5	89.27	44.72	20.27	-	96.73	84.95	-	-	-	-	-	-
6	96.72	49.99	24.52	-	-	95.19	-	-	-		-	-
7	-	55.90	28.48	-	-	-	-	-	-	-	-	-
8	-	60.96	30.76	-	-	-	-	-		-	-	
9	-	75.95	32.88	-	-	-	-		-	-	-	-
10	-	83.92	43.46	-	-	-	-	-	-	-	-	-
11	-	89.34	53.67	-	-	-	-	-	-	-	-	-
12	-	96.52	66.84	-	-	-	-	-	-	-	-	-

Table 5: *In Vitro* drug release Kinetics of floating tablets of Metformin hydrochloride

Formulation Code	Zero order r^2	First order r^2	Higuchi Kinetics r^2	Peppas equation	
				n	r^2
F1	0.9819	0.8845	0.9033	0.5201	0.8980
F2	0.976	0.843	0.921	0.409	0.874
F3	0.923	0.842	0.965	0.513	0.798
F4	0.897	0.740	0.899	0.486	0.756
F5	0.962	0.782	0.974	0.471	0.854
F6	0.872	0.910	0.958	0.584	0.792
F7	0.931	0.922	0.923	0.572	0.893
F8	0.942	0.794	0.898	0.493	0.941
F9	0.952	0.765	0.977	0.562	0.725
F10	0.899	0.821	0.963	0.498	0.744
F11	0.954	0.964	0.951	0.518	0.856
F12	0.939	0.723	0.964	0.514	0.827

DISCUSSION

The precompression evaluation like bulk density, true density, compressibility, angle of repose were found as per standard range all the data indicating suitable formulation of the floating tablet. The post compression

evaluation for the all formulation is complies with the standard monograph. The post compression parameters like hardness, friability, thickness. The obtained data was best fitted for the floating tablet. The drug release data were explored for the type of release mechanism followed. The best fit with the highest determination r coefficients was shown by both the zero order and Higuchi models. Zero order release describes the release rate independent of drug concentration.

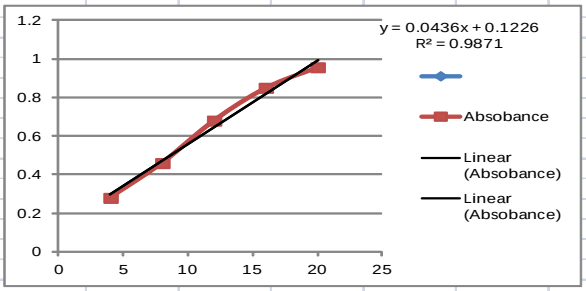
Higuchi square root kinetic model describes, release drug from the insoluble matrix as square root of time dependent process. It describes release of drug by simple diffusion mechanism. The values of n with regression coefficient for all the formulations were showed in the table 4.

The values of n were in the range (n is more than 0.5) indicating Nonfickian release governed by the drug diffusion. However as indicated by the values of R^2 both of the models (Higuchi and Peppas) were found to be efficient in describe the release of Metformin from the floating tablets. All the parameters were run 3 times (n=3).

CONCLUSION

This study discusses the preparation of gastroretentive tablets of Metformin hydrochoride. The effervescent-based floating drug delivery was a promising approach to achieve in vitro buoyancy. The addition of gel-forming polymer HMC K 100M, HPMC K4M, natural polymers such as gellan gum, xantha gum and gas-generating agent sodium bicarbonate was essential to achieve in vitro buoyancy. The release kinetics of the formulation F2 shows better sustained release i.e 96.52% with in 12hours as compared to remaining other formuation.

	Concentration	Absobance
	4	0.28
	8	0.46
	12	0.68
	16	0.85
	20	0.956



Dissolution data

Time in hours

Time in hours	% CUMULATIVE DRUG RELEASE		
	F1	F2	F3
0.5	25.98	5.27	3.98
1	45.76	15.76	5.26
2	53.47	23.69	10.57
3	66.54	31.92	13.44
4	76.23	38.9	15.13
5	89.27	44.72	20.27
6	96.72	49.99	24.52
7	-	55.9	28.48
8	-	60.96	30.76
9	-	75.95	32.88
10	-	83.92	43.46
11	-	89.34	53.67
12	-	96.52	66.84

REFERENCES

1. Formulation and in vitro evaluation, AAPS PharmSciTech. 2003; 4(4):1-9.
2. Histamine H2 antagonists. In: Drug Facts and Comparisons. Fifty Sixth editions. St Louis, MO: Wolters Kluwer Co; 2002;1192-1197.
3. Whitehead L .Floating dosage forms: an in vivo study demonstrating prolonged gastric retention" Journal of Controlled Release. 1998;55:3–12.
4. Basak SC. Design and in vitro testing of a floatable gastroretentive tablet of metformin Hcl. Pharmazie. 2007;62(2):145-148
5. Shashank R. Joshi.Metformin: Old Wine in New Bottle - Evolving Technology and Therapy in Diabetes. JAPI . 2005;53:963-971.
6. Alexander Streubee. Drug delivery to the upper small intestine window using gastro retentive technologies.
7. Current Opinion in Pharmacology. 2006; 6:501–508.
8. Hardman JG and Limbird PB. Goodman & Gilman's - The Pharmacological basis of Therapeutics". 11th edition. New york : Mc Graw Hill Medical Publishing Division 2001;1701-1710
9. Cooper J and Gun C. Powder Flow and Compaction. Inc Carter SJ, Eds. Tutorial Pharmacy. New Delhi, hidix CBS Publishers and Distributors. 1986;211233.
10. Shah D, Shah Y and Ramprashad M. Development and Evaluation of Controlled release Diltiazem hydrochloride microparticles using cross-linked poly (vinyl-alcohol). Drug Dev Ind Pharm. 1997;23(6):567-574.
11. Aulton ME and Wells TI. Pharmaceutics: The Science of Dosage Form Design. London, England, Churchill Livingston; 1998;247.
12. Martin A., Micromeretics, In: Martin A., ed. Physical Pharmacy. Baltimores, MD: Lippincott Williams and Wilkins. 2001;423-454.
13. Reddy KR, Mutalik S and Reddy S. Once-daily sustained release matrix tablets of Nicorandil.