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Formulation and Evaluation Studies of Floating Matrix Tablets of Metformin Hydrochloride

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ABSTRACT

Sustained release dosage forms enable for prolonged and continuous release. In the present study. Floating drug delivery system of Metformin HCl was developed using a HPMCK 4 M used as rate controlling polymer in different ratios and sodium bicarbonate was acting as gas generating agent to reduce floating time. Tablets were prepared by direct compression method. Floating tablets were evaluated for hardness, friability, weight variation, drug content, buoyancy lag time, duration of buoyancy and invitro release studies. From the Precompression and post compression parameters it was observed that Formulation F4 was found to be best one when compared with the marketed sample and the results were presented.

Key words: Metformin Hcl, HPMC K 4 M, PVP K-30, Floating tablets

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INTRODUCTION

For many decades treatment of an acute disease or chronic illness has been mostly accomplished by delivery of drug to patients using various pharmaceutical dosage forms. Recently several technical advancements resulted in the development of new technique for drug delivery. These techniques are capable of controlling the rate of drug delivery, extending the duration of therapeutic activity and targeting the delivery of drug tissue [1].

Floating drug delivery system is one of the currently utilized methods in the prolongation of gastric retention time (GRT). All floating dosage forms have the common property of possessing density lower than that of gastric fluids. So they can float in the stomach for a long period of time. Emptying rate is not completed until the level of the gastric fluid approaches the base of the stomach [2].

Depending on the mechanism of the buoyancy two distinctly different methods viz: effervescent systems have been used in the development of floating drug delivery system [3].

These are matrix types of systems prepared with the help of swellable polymers such as methylcellulose and effervescent compounds like sodium bicarbonate. They formulated in such a way that when in contact with the acid gastric contents, Carbon dioxide is liberated and gets entrapped in swollen hydrocollids which provides buoyancy to the dosage forms [4].

Metformin hydrochloride is a biguanide antihyperglycemic agent that improves glucose tolerance in patients with Type II Diabetes. A plethora of antidiabetic drugs are used in clinic of which Metformin hydrochloride is a biguanide classification worldwide accepted drug. Unlike other antidiabetics Metformin hydrochloride does not induce hypoglycemia at any reasonable doses and hence it is usually called an Antihyperglycemic or Euglycemic. In spite of its favourable clinical response and lack of significant drawbacks chronic therapy with Metformin suffers with certain problems of which the most prominent of high dose (1.5-2.0g/day) low bioavailability and high incidence of GI side effects. However the bioavailability of drug has been reduced further with SR dosage form probably due to fact that passage of SR single unit dosage form the absorption region of the drug is faster than its release and most of drug release at colon where Metformin hydrochloride is poorly absorbed. SR formulation suitable for Metformin hydrochloride therefore should be gastrorentive dosage form (floating drug delivery) which releases the drug slowly in the stomach for gradual absorption in the intestine. The slow and complicated drug release in the stomach is expected to increase the bioavailability of drug as well as its complete utilization which may results to lower dose and GI side effects. A traditional oral multiple release formulation releases the drug with undesirable peak and troughs. These drawbacks can be overcome by designing a suitable sustained release Metformin hydrochloride formulation [5].

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MATERIALS AND METHODS

Materials

Metformin HCl and HPMCK4M were received as gift sample from Micro Labs Ltd Hosur. All other chemicals are used in this experiment were obtained commercially as analytical grade.

Formulation of Floating Tablets

Metformin HCL, HPMCK4M, sodium bicarbonate was sifted through #40 mesh. The diluent lactose and binder PVP K-30 was sifted through #30 mesh, it was added to the previous blend allowed and the blend was thoroughly mixed using mortar and pestle . The mixed blend was lubricated with magnesium stearate and talc (Table-1).

TABLE: 1 Formulation of Metformin HCl Floating Tablets

S.NO	Ingredients(mg)	F1	F2	F3	F4
1	Metformin HCl	250	250	250	250
2	HPMCK4M	30	30	60	90
3	Sodium bicarbonate	12.5	25	50	75
4	Lactose	191.5	179	124	69
5	PVP K-30	10	10	10	10
6	Talc	2	2	2	2
7	Magnesium Stearate	4	4	4	4

Evaluation of Powder Blend

Angle of Repose [6]

The angle of was determined by using funnel method. The diameter of the powder cone was measured and the angle of repose was calculated using the following equation.

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

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

Bulk Density [7]

An accurately weighed quantity of the blend was transferred in to 250 ml measuring cylinder. The initial and final volume was measured before and after tapping. The tapping was continued until no further change in volume (until a constant volume) was adjusted. The bulk was calculated suing the following formula.

Bulk Density is the ratio between the mass of the powder and its bulk volume

Bulk Density = Mass of the Powder**/** Bulk volume

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Tapped Density [7]

Tapped density is the ratio between a given mass of powder and the constant (or) fixed volume of powder or granules after tapping.

Tapped Density = Mass of the Powder/Tapped volume

Compressibility Index and Hausner Ratio [8]

The two most commonly used measures of the relative importance of the interparticulate interaction are the Compressibility Index and the Hausner Ratio.
The compressibility index and Hausner ratio may be calculated (using measured values of bulk density and tapped density) as follows

$$\text{Compressibility index} = \frac{\text{Bulk density} - \text{Tapped density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner ratio} = \text{Bulk Density} / \text{Tapped density}$$

Evaluation of Metformin Hydrochloride floating Tablets

Hardness test or crushing strength

Hardness which is now more appropriately called crushing strength determinations are made during tablet production. The hardness of tablets (kg\cm^2) was carried out by using Monsanto type hardness tester.

The tablet was placed horizontally in contact with the lower plunger of the Monsanto hardness tester and zero reading was adjusted. Then the tablet was compressed by forcing the upper plunger until the tablets breaks and this force was noted.

Weight variation test [9]

Twenty tablets of each formulation were selected at random and weighed individually. The weight of individual tablet was noted. Average weight was calculated from the total weight of the tablets. The weight of not more than two tablets must not deviate from the average weight by more than the percentage given in the standard table and no tablet should deviate by more than double the percentage. The percentage deviation was calculated by using the formula:

$$\text{Percentage deviation} = \frac{\text{individual weight} - \text{average weight}}{\text{average weight}} \times 100$$

Friability Test [10]

Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed.

The percentage friability was determined using the formula,

Percentage friability = Initial weight - Final weight/Initial Weight × 100

This test is applicable to compressed tablets and is intended to determine physical strength of tablets.

Estimation of Drug Content

The amount of active drug present in each formulation were calculated using the UV spctrophotmetric method. 20 tablets were taken and crushed to powder with mortar and pestle. The powder equivalent to 100mg of Metformin hydrochloride was taken to a 1000ml volumetric flask and dissolved in 300ml of methanol and sonicated for 10minutes. Then 500ml of boiling water was added shaken well and sonicated for 20minutes. The flask was kept aside for some time until it reached to room temperature. Finally the volume was make up with distilled water and allowed to settle for 20minutes. From this 2ml of supernatant liquid was taken and make upto 100 ml with distilled water. The amount of Metformin hydrochloride was calculated by measuring the absorbance at 233nm using distilled water as a blank UV spectrophotometer was used for the analysis.

IR Spectral Analysis

It is used to determine the interaction between the drug polymer and excipients. The drug and polymer must be compatible with one another to produce a product stable, efficacious and safe.

The KBR disc method was used for preparation of sample and spectra were recorded over the wave number 4000 to 500cm^{-1} in a SHIMADZU FTIR Spectrophotometer. The IR spectral analysis for drug and polymer was carried out. If there is no change in peaks of mixture when compared to pure drug, it indicates the absence of interactions.

In Vitro Release Studies

In vitro release studies were carried out by using USP paddle II dissolution test apparatus. 900ml of 0.1N HCl was taken in the dissolution apparatus as dissolution medium and maintained temperature of 37ºC±1ºC. The paddle was set for 50rpm. Six tablets selected at random from F1 were studied. 10ml of sample was withdrawn at every 1hour interval upto

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8hours. The same volume of fresh dissolution medium was replaced after every withdrawal. The samples were analysed by UV-Visible spectrophotometer at 233nm.

The experiment was repeated in the same manner for all other formulations such as F2, F3 and F4.

RESULTS AND DISCUSSION

Hydrodynamically balanced tablets of Metformin Hcl (intra gastric buoyant tablets) were prepared and evaluated to increase its local action. In the present study four 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 at 37±0.5^{o}C tablets floats immediately and remain buoyant upto 8-18 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).

Evaluation of Powder Blend

The angle of repose for all the formulations was within 35º indicates all the formulations has good flow property. If the compressibility index of the granules was between 11-15% it shows good flow character. If the Hausner's ratio was within 1.12-1.18, it showed good flow property of the granules. It indicates all the formulations have god flow property (table-2).

Table:2 Evaluation of Powder Blend

S.NO	Parameters	F1	F2	F3	F4
1	Angle of Repose	34.01±0.61	32.45±0.20	33.46±0.75	32.98±0.34
2	Bulk Density	0.45±0.01	0.39±0.002	0.47±0.007	0.51±0.003
3	Tapped Density	0.51±0.003	0.45±0.02	0.55± 0.002	0.58±0.003
4	Compressibility Index	11.76±0.11	13.33±0.02	14.54±0.11	12.76±0.07
5	Hausner Ratio	1.13±0.004	1.15±0.02	1.17±0.01	1.13±0.02

All values are expressed as mean ± SD (n=3)

Evaluation of compressed tablets

Hardness of the tablets was in the range of 4 to 6 kg/cm2.This ensures good handling characteristics of all the batches. Weight loss in the friability test was not less than 1% in all the cases, ensuring that the tablets were mechanically stable. All the floating tablets prepared contained the drug within 99.93±5% of the label claim. All the formulated tablets (F1 to F4) passed the weight variation test as the % weight variation was within the pharmacopeial limits of ± 5% of the average weight.

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The result were presented in Table -3

Table :3 Evaluation of the entire formulated Tablet

S.NO	Parameters	F1	F2	F3	F4
1	Hardness (kg/cm^2)	5.21±0.28	4.97±0.16	5.01±0.03	5.13±0.12
2	Uniformity of Weight	499±0.02	502±0.45	501±1.3	500±1.2
3	Friability (%)	0.12±0.05	0.21±0.01	0.17±0.03	0.14±0.04
4	Drug content (%)	98.31±0.55	99.93±1.11	97.11±1.03	98.71±0.01
5	Buoyancy lag time	1min04sec	31sec	20sec	12sec
6	Total floating time in hours	4hours	>10hours	>18hours	>18hours

All values are expressed as mean ± SD (n=3)

Buoyancy Determinations

The buoyancy lag time and duration of buoyancy for all the formulations (F1-F4) shown in Table-2. The result showed that there was change in buoyancy lag time and duration of buoyancy with the change in the proportions of HPMC K4M:Sodium bicarbonate. Buoyancy lag time for F1, F2, F3 and F4 were 1min04sec, 31sec, 20sec and 12sec respectively.

The formulation F1 showed duration of buoyancy only 4hrs, F2 showed not less than 10 hours and F3,F4 showed duration of buoyancy not less than 18hours. The F2,F3 and F4 floated for more than 8hrs. The buoyancy lag time and duration of buoyancy depends upon the proportion of HPMC K4M and Sodium bicarbonate. In formulation F1 duration of buoyancy was only 4hrs and buoyancy lag time was high 1min04sec because lower proportion of HPMCK4M and Sodium Bicarbonate. In formulation F2 sodium bicarbonate proportion was increased the duration of buoyancy and buoyancy lag time was increased to 31sec and NLT 10hrs. In F3 and F4 as the HPMCK4M and Sodium bicarbonate concentration was increased duration of buoyancy was NLT 18hrs but in F4 formulation buoyancy lag time was 12sec because f higher proportion of HPMCK4M and Sodium bicarbonate. When these formulations contact with dissolution medium sodium bicarbonate generates carbon dioxide which accumulates between the polymer matrix of the tablets. This entrapment of carbon dioxide in the matrix system helps in a flotation and increased duration of buoyancy.

In Vitro release study

The F1 formulation produced 53.71% of drug released after 1hours and nearly 96.73% released within 7hrs. The formulation F2 produced 41.4% of drug release in 1hour and 93.4% released within 8hrs. The formulation F1 and F2 shows quicker drug release since these formulations contain lesser proportion f polymer.

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The formulation F3 produced higher drug release initially comparing with F4 formulation and there after sustained release upto 8hrs. This sustained release due to proportion of polymer and sodium bicarbonate.

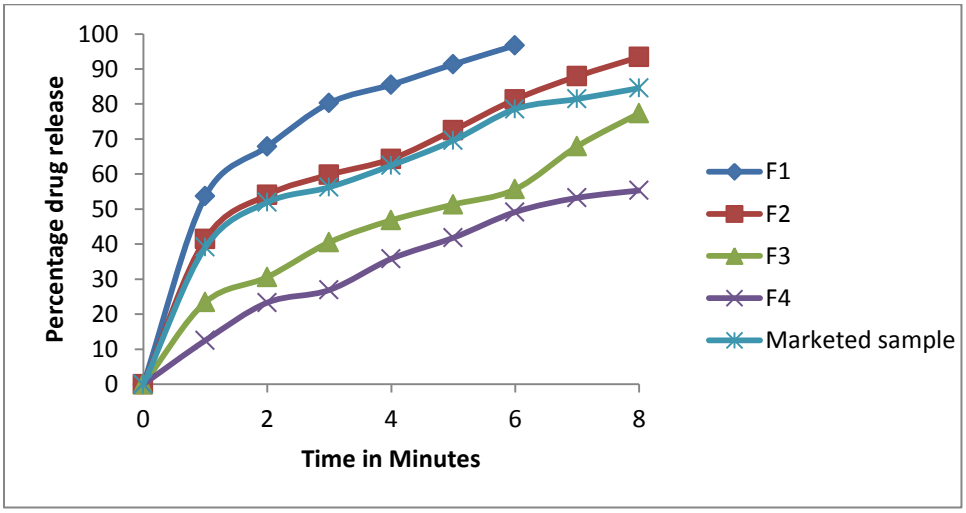
The formulations F4 showed slower drug release due to presence of higher proportion of the polymer. The result showed that the drug polymer and sodium bicarbonate ratio is the predominant controlling factor for the release Metformin HCl from the floating matrix tablets. This is in conformity with the reports of Manoj N. Gambhire et al. When compared with marketed sample of Obimet SR 500 the release was more with best formulation (F3). The results are presented in table -4 and Figure-1.

Table:4 Dissolution release profile

Formulations	1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	7th hour	8th hour
F1	53.71±0.85	67.84±0.73	80.25±0.15	85.51±0.35	91.32±1.15	96.73±0.41	-	-
F2	41.4±0.15	54.0±0.37	59.8±0.25	64.3±0.18	72.5±0.19	81.3±0.32	87.9±0.41	93.4±0.25
F3	23.4±0.31	30.6±0.27	40.5±0.21	46.8±0.35	51.3±0.61	55.65±1.21	67.92±0.62	77.31±.21
F4	12.5±0.14	23.3±0.95	26.9±0.13	35.8±2.14	41.8±0.97	49.15±1.13	53.21±0.27	55.31±0.25
Marketed Product	39.13±0.25	51.92±0.53	56.25±0.35	62.47±0.12	69.58±0.16	78.56±0.13	81.43±0.23	84.52±0.71

All values are expressed as mean ± SD (n=3)

Figure 1 Percentage drug release of Metformin HCl floating tablets



CONCLUSION

The release of Metformin HCl formulated with HPMC K4M was slow and release upto 8 hours nearly 77.31% in formulation F3 showed that formulation is best formulation.

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REFERENCES

[1] Yie W Chein. Novel Drug Delivery System, 2nd edition. Marcel Dekker,New York, 1992; 1-3.

[2] Baskar SC, Nageswara Rao K, Manavalan R and Rama Rao. Ind J Pharm Sci 2004; 66: 313-316.

[3] Hilton AK and Desay PB. Int J Pharm 1992; 86: 79-88.

[4] Michales AS, Bashwa J.D and Zaffaroni. A floating drug delivery system-A Review U S Patent No:3901232,1975.

[5] Thomas WYL, Joseph RR. Controlled Release Drug Delivery Systems. In Gennaro AR Remington. The Science and Practice of Pharmacy. Lippincott Williams and Wilkins. Philadelphia.2000; 903-906.

[6] Subramaniyan CVS. Text Book of Physical Pharmaceutics, Vallabh Prakasan, New Delhi, 1st edition, 1998; 215 – 223.

[7] Manavalan R and Ramasamy C. Physical pharmaceutics, Vignesh Publisher, Chennai. 2004; 328.

[8] Shah D, Shab Y and Rampradhan M. Drug Dev Ind Pharm 1977; 23: 567-574.

[9] Rippe E. Compression of solids and compressed dosage forms. In: Encyclopedia of Pharamaceutical Technology , Swarbrick. J, (Eds) Marcel Dekker Inc. New York; 1990; 3: 149-166.

[10] Lachman Leon, Liberman HA and Kanig JL. The Theory and Practice of Industrial Pharmacy. Varghese publishing house, Bombay.3rd edition.430-456; 171-195.

[11] Manoj N Gambhir. AAPS 2009; 8: E1-E9.