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Floating drug delivery system using Methocel K100M and E50: Formulation and characterization

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Abstract

The aim of the present study was to formulate and characterize a floating drug delivery system, using Methocel K100M and E50. Metformin hydrochloride (Biopharmaceutics Classification System class III) was used as the model drug for the investigation. Effervescent floating tablets of metformin hydrochloride were prepared, employing two different grades of Methocel K100M and E50, by wet granulation method. The two grades were evaluated for their gel forming properties. The floating tablets were evaluated for pre-compression properties as well as *in vitro* drug release. The prepared tablets exhibited satisfactory pre-compression characteristics. The data obtained from the study was fitted in different models viz. zero order, first order, Korsmeyer-Peppas model, Higuchi model and Hixon Crowell model. The drug was found to be released by a combination of diffusion and erosion. The slope from Korsmeyer-Peppas model revealed that the drug release followed non-Fickian-type transport mechanism. It was concluded that the formulation F5 (containing 160 mg of Methocel K100M and 40 mg of Methocel E50) was the optimum formulation amongst all the test batches. It may also be concluded from the investigation that a combination of Methocel K100M and Methocel E50 in the ratio of 4:1 may be satisfactorily employed in the formulation of a floating drug delivery system.

Keywords: gastroretentive, *in vitro* buoyancy, HPMC, hydrodynamically balanced system

Introduction

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for sustained release system, oral route of administration has received more attention and success because gastrointestinal (GI) physiology offers more flexibility in dosage form design than other routes. Development of a successful oral sustained release dosage form requires an understanding of three aspects: (1) gastrointestinal physiology (2) physiochemical properties of the drug and (3) dosage form characteristics (Robinson and Lee 1987, Chien 1992) Oral sustained drug delivery system is complicated by limited gastric residence time. Rapid gastrointestinal transit can prevent complete drug release in the absorption zone and reduce the efficacy of administered dose, since the majority of drugs are absorbed in stomach or the upper part of small intestine (Choi et al. 2008). Dosage forms that can be retained in the stomach are called gastroretentive drug delivery systems (GRDDS). Floating drug

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delivery systems, also known as hydrodynamically balanced systems, are a type of GRDDS. These have bulk density less than one, which enables them to float in the stomach for a prolonged period of time without affecting the gastric emptying rate.

Hydrophilic matrix tablet is the simplest and the most cost-effective method of fabricating a sustained release (SR) solid oral dosage form. Typical HPMC (Hydroxypropylmethylcellulose) grades utilized for SR formulations range in viscosity from 50 to 100000 cps at 20°C, and include Methocel E50 Premium LV, K100 Premium LV CR, K4M Premium CR, K15M Premium CR, K100M Premium CR, E4M Premium CR and E10M Premium CR. The mechanism of drug release from hydrophilic matrix tablets following ingestion is complex, but is known to be based on dissolution of the drug (if soluble), diffusion of the drug through the hydrated portion of the matrix and erosion of the outer hydrated polymer on the surface of the matrix (Hogan 1989).

Typically, when the matrix tablet is exposed to an aqueous solution or gastrointestinal fluids, the surface of the tablet is wetted and the polymer hydrates to form a jelly-like structure around the matrix, which is commonly referred to as the "gel layer". This process is also termed as a glassy-to-rubbery state transition of the polymer (surface layer). The core of the tablet remains essentially dry at this stage. The gel layer (rubbery state) grows with time as more water permeates into the core of the matrix, increasing the thickness of the gel layer and providing a diffusion barrier to drug release. Simultaneously, as the outer layer becomes fully hydrated, the polymer chains become completely relaxed and can no longer maintain the integrity of the gel layer, leading to disentanglement and erosion from the surface of the matrix. Water continues to penetrate towards the core of the tablet, through the gel layer, until it has been completely eroded. Whereas soluble drugs are released by this combination of diffusion and erosion mechanisms, erosion is the predominant mechanism for insoluble drugs, regardless of dose (Mitchell et al. 1993, Gao et al. 1996, Huang et al. 2003, Hardy et al. 2006, Rane et al. 2010).

In view of this phenomenon of drug release, various high viscosity grades of HPMC have found use in the formulation of sustained release dosage forms of many drugs, which release the drug through diffusion. However, a combination of a high viscosity and low viscosity grade of the polymer would release the drug by diffusion as well as erosion mechanism (The Dow Chemical Company Product Guide 1996).

The aim of the present study was to formulate an optimized floating drug delivery system using Methocel K100M (high viscosity grade) and Methocel E50 (low viscosity grade) for a highly soluble drug, where the former provides the necessary gel strength and the latter allows for consistent erosion of the drug. The use of this combination of polymers is not reported in the literature. Metformin hydrochloride (BCS class III) has been taken as the model drug for carrying out the present study.

The drug chosen for the present investigation, metformin hydrochloride, a biguanide, is an orally active antidiabetic agent. It is effectively used in the treatment of non-insulin dependent diabetes mellitus (NIDDM). Unlike sulfonylurea, metformin usually does not produce hypoglycemia in diabetic and non-diabetic individuals. So, it is more appropriately referred to as anti-hyperglycemic agent and found to be well-tolerated and safe on chronic use. On oral

administration, it is absorbed through upper part of GI tract and absolute bioavailability of metformin is approximately 50- 60%. Metformin negligibly binds to plasma proteins (Tripathi 2003). It is excreted unchanged in the urine and does not undergo hepatic metabolism. It has a plasma elimination half-life of 3 hours. Its daily oral dose is 0.5 to 3 g/day in divided doses (Glucophage Product Guide 2004).

The absorption of the metformin HCl is limited to upper part of the GI tract and therefore, its bioavailability from both, immediate and sustained release, marketed dosage forms is 50-60%. It has a biological half-life of 3 h. Hence, it requires three-times a day dosing. As the dose of metformin is 500 mg (marketed controlled release formulations of metformin are available in strengths of 500 mg and 1000 mg). Adverse events associated with metformin use are often gastrointestinal in nature (e.g. anorexia, nausea, vomiting, and occasionally diarrhea, etc.). These adverse events may be partially avoided using sustained release dosage form. All these factors make this drug a suitable candidate for the formulation of GRDDS.

Materials and Methods

Metformin HCl was purchased from K Pharma Pvt. Ltd., India. Methocel E50 was purchased from K Pharma Pvt. Ltd., India. Methocel K100M was received as a gift sample from Lincoln Pharmaceuticals Ltd., India. Sodium bicarbonate and citric acid was received as a gift sample from Omega Remedies, India. Magnesium stearate and talc was procured from Qualikems Pvt. Ltd., India.

Preparation of Metformin HCl effervescent floating tablets

Formulations of effervescent floating tablets have been given in Table 1. All the ingredients were weighed carefully and passed through sieve no.40. Metformin HCl, Methocel, sodium bicarbonate, citric acid was mixed with isopropyl alcohol (IPA). Granules were made by passing the wet mass through sieve no.18. At the end, magnesium stearate and talc were added as a lubricant and glidant, respectively. The granules were compressed in rotary punch (16 stations) tablet machine.

Table 1. Formulation of effervescent floating tablets of Metformin HCl

Ingredients (mg per tablet)	F1	F2	F3	F4	F5	F6
Metformin HCl	500	500	500	500	500	500
Methocel E-50	200	160	120	80	40	-----
Methocel k100M	------	40	80	120	160	200
Sodium bicarbonate	70	70	70	70	70	70
Citric acid	5	5	5	5	5	5
Magnesium stearate	3	3	3	3	3	3
Talc	2	2	2	2	2	2

Flow properties of granules

The flow properties of granules (before compression) were characterized in terms of, bulk density, Carr's index, Hausner ratio and angle of repose. For determination of angle of repose, the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0 cm above the hard surface. The granules were poured till the time when upper tip of pile surface touched the lower tip of the funnel. The $\tan^{-1}$ (height of the pile/radius of its base) gave the angle of repose.

Evaluation of floating tablets

The prepared floating tablets were evaluated for diameter, thickness, hardness, uniformity of weight variation, friability (Roche type friabilator), drug content, *in vitro* buoyancy, and *in vitro* dissolution studies. The results are expressed as mean ± S.D. The thickness and diameter of tablets were determined by Vernier caliper. The hardness of the floating tablets was determined by using Monsanto hardness tester.

Drug content estimation

The drug content in each formulation was determined by triturating 20 tablets. A quantity of powder containing 0.1g of metformin hydrochloride was accurately weighed, shaken with 70 mL of water for 15 min, and diluted to 100 mL with water, and then filtered.10 mL of the filtrate was then, diluted to 100 mL with water. Further, 10 mL of resulting solution was diluted to 100 mL with water. Absorbance of the resulting solution was measured at λ_{max} 232 nm. The content of metformin hydrochloride was then estimated taking 798 as specific absorbance at λ_{max} 232 nm.

In vitro buoyancy study

In vitro buoyancy studies were performed to determine the floating lag time, as per the method described by Rosa et al. The tablets were placed in 100 mL beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as the floating lag time. The time duration for which the dosage form constantly remained on the surface of the medium was determined as the total floating time.

In vitro release study

The release rate of metformin floating tablets was determined using United States Pharmacopoeia (USP) dissolution testing apparatus 2 (paddle type) (Electrolab, TDT 08L, India). The dissolution test was performed using 900 mL of 0.1N hydrochloric acid, at 37±0.5°C and at 50 rpm. A sample of solution was withdrawn from the dissolution apparatus hourly and the samples were filtered and diluted to a suitable concentration with 0.1N hydrochloric acid. Also the dissolution medium was replaced with the same volume of fresh medium. Absorbance of these solutions was measured at λ_{max} 233nm using UV/Vis double-beam spectrophotometer (Shimadzu UV-1800, Japan). Cumulative percentage drug release was calculated using the equation obtained from the standard curve.

Comparison of dissolution profiles

In vitro drug release of the formulations was compared with a marketed formulation, by determining the similarity factor *f2*, as per the SUPAC guidelines for the modified release dosage forms. The following equation was used:

$$f_2 = 50 \times \log \{[1+(1/n) S_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\}$$

Where, R_t and T_t represent the average percent dissolved at time t for reference and test, respectively, and n is the number of time points tested. The dissolution profiles are considered to be similar when f_2 is between 50 to100.

Results and Discussion

Flow properties of granules

The granules prepared for compression of floating tablets were evaluated for their flow properties. Angle of repose was in the range of 25-30°.Tapped density was found to be in the range 0.49-0.53 g/ml. Carr's index was in the range of 11-15% and, Hausner ratio was in the

range of 1.12-1.18 for the granules of different formulations. These values indicate that the prepared granules exhibited good flow properties.

Table 2. Pre-compression flow properties of granules of metformin hydrochloride

Batch	Tapped density (g/mL)	Carr's index (%)	Hausner ratio	Angle of repose (θ ± S.D) n=3
F1	0.51	13.2	1.15	27.76 ± 0.25
F2	0.52	13.7	1.16	27.76 ± 0.31
F3	0.50	13.3	1.15	28.26 ± 0.59
F4	0.49	12.6	1.14	27.76 ± 0.25
F5	0.51	14.6	1.17	28.43 ± 0.50
F6	0.53	12.4	1.14	27.13 ± 0.89

Evaluation of floating tablets

The prepared tablets were evaluated for parameters such as weight variation, hardness, friability, thickness, diameter, floating lag time, drug content and *in vitro* dissolution profile.

The weight of the tablet varied b/w 778-782 mg. The variation in weight was within the range of ±5%, complying with pharmacopoeial specifications. The hardness of different formulations was found to be between 6.15-6.83 kg/cm², indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The drug content varied b/w 98.12 -102.24 mg in different formulations, with low standard deviation indicating drug content uniformity in the prepared batches.

Table 3. Post-compression properties of metformin hydrochloride floating tablets

Batch	F1	F2	F3	F4	F5	F6
Mean Hardness (kg/cm²±SD)*	6.15±0.10	6.26±0.18	6.23±0.10	6.33±0.14	6.26±0.10	6.38±0.12
Mean Thickness (mm±SD)*	6.00±0.05	5.95±0.09	6±0.082	6±0.075	6±0.082	6±0.075
Mean Diameter (mm±S.D)*	13.50±0.05	13.5±0.06	13.50±0.05	13.50±0.04	13.50±0.05	13.5±0.041
Friability (% w/w)**	0.49	0.51	0.54	0.48	0.52	0.61
Weight variation (mg±S.D)***	779.85±1.23	779.55±2.00	779.2±0.9	779.30±0.80	779.60±0.99	779.4±1.05
Mean drug content (%±S.D)****	101.21±0.85	99.99±1.10	101.11±2.10	98.12±1.00	102.24±1.90	99.33±1.97

*n= 6; **n=10; ***n= 20; ****n= 3

All the batches of tablets were found to exhibit short floating lag times due to the presence of sodium bicarbonate and citric acid. The tablets with low-viscosity grade Methocel E50 exhibited shorter floating lag time, as compared with the formulations containing high viscosity grade Methocel K100M. This indicated that the molecular weight distribution or viscosity of the gel-forming polymer Methocel influenced the *in vitro* buoyancy. Optimum formulation (F5) showed a good floating lag time of 3 min. (Table 4, Fig. 1)

Table 4. *In vitro* buoyancy study

S. No.	Formulation code	Floating lag time (sec)	Floating time (h)
1	F1	20	>12
2	F2	45	>12
3	F3	55	>12
4	F4	110	>12
5	F5	180	>12
6	F6	250	>12

All the tablets were prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induces carbon dioxide generation in presence of dissolution medium (0.1N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided desired floating ability and therefore, this combination was selected for the formulation of the floating tablets. It was observed that the gas generated is entrapped and protected within the gel, formed by hydration of the polymer (methocel), thus, decreasing the density of the tablet below 1 g/cm^3, and, the tablet became buoyant.

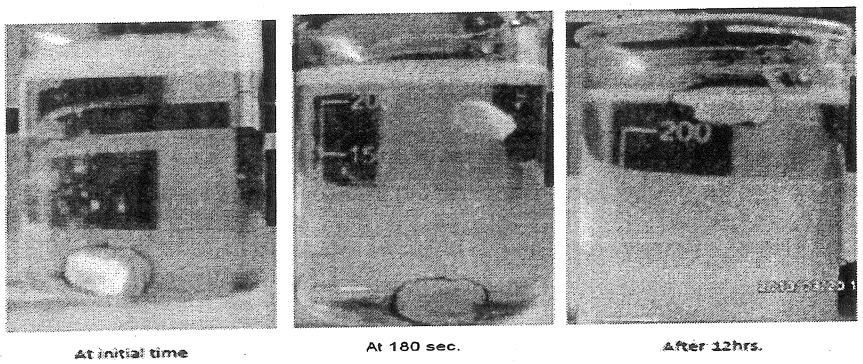

Figure 1. *In vitro* buoyancy study (optimized formulation F5)

The pH of the stomach is elevated under fed condition (~3.5), therefore, citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate; moreover citric acid has a stabilizing effect on metformin formulation.

In vitro drug release study

All the tablets showed good floating property during their dissolution, and *in vitro* dissolution data showed that, with the increase in the concentration of the high viscosity polymer (Methocel K100M), the drug release rate decreases, as shown in Fig. 2.

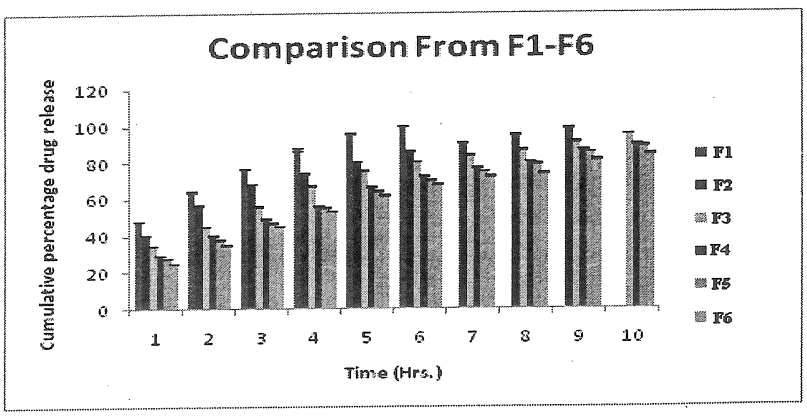

Figure 2. Comparison of drug release from formulations F1-F6

The data obtained from the *in vitro* dissolution studies was fitted in different models *viz.* zero order, first order, Korsmeyer-Peppas model, Higuchi model and Hixon Crowell model, as shown in Fig. 3.

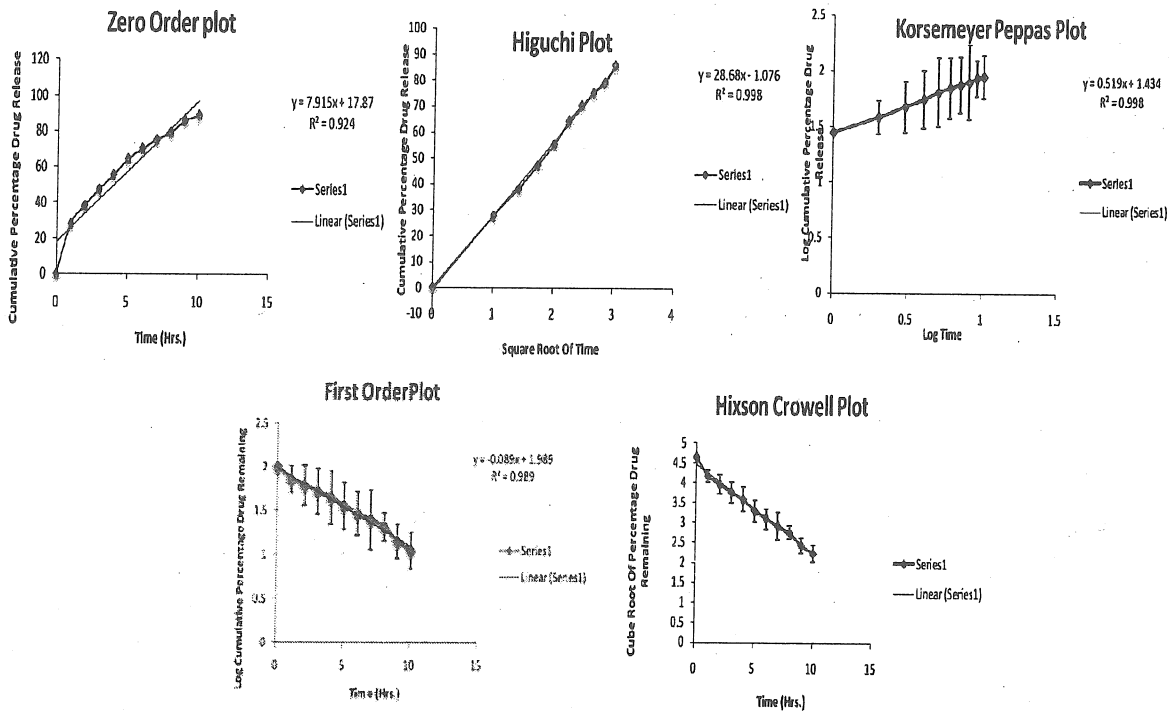

Figure 3. Kinetic evaluation of optimized formulation (F5)

The Higuchi plot was found to be very linear in case of F5 formulation, as indicated by regression value (r^2=0.998), hence, the mechanism of drug release was diffusion and, also to some extent, erosion (as indicated by Hixon Crowell plot). To confirm the exact mechanism of drug release from the tablets, the data was fitted according to Korsmeyer-Peppas equation and the slope value, n, was found to be b/w 0.45-0.89. This suggests that the release of metformin from floating tablets followed non-Fickian transport mechanism, as shown in Table 4.

Table 4. Kinetic evaluation of floating tablet formulations (F1-F6)

Batch	Zero Order	First Order	Higuchi	Korsmeyer-Peppas		Hixon Crowell	Release mechanism
	R^2	R^2	R^2	R^2	n	R^2	
F1	0.857	0.967	0.992	0.998	0.415	0.976	Fickian
F2	0.831	0.975	0.982	0.986	0.385	0.965	Fickian
F3	0.870	0.978	0.989	0.991	0.445	0.970	Fickian
F4	0.911	0.989	0.992	0.996	0.499	0.985	Non- Fickian
F5	0.924	0.989	0.998	0.998	0.519	0.985	Non- Fickian
F6	0.919	0.988	0.991	0.995	0.542	0.983	Non-Fickian

Dissolution profiles of batches F2-F6 were also compared with the dissolution profile of a marketed formulation, and the value of similarity factors was found to be 13.0, 25.0, 51.5, 67.78, and 60.89, respectively. Hence, the best value was obtained with the formulation F5. It is evident from the data that, as the concentration of Methcel K100M increases, the value of similarity factor (f_2) also increases, but further increase in the concentration of the high viscosity polymer, causes a decrease in the similarity factor, as obtained in case of formulation F6.

Further, various test batches were also compared with the marketed formulation for the time taken by the formulation to release the loading dose, as well as, the time taken for the drug concentration in the formulation to reduce to its half. The two time points were designated as t_{25} and t_{50} respectively (Table 5). The time taken by the formulation to release the loading dose has been taken as the time required for the drug concentration to reduce by 25%. The results have been reported in the table given below. It is clear from the data obtained, that the results of formulation F5 are closest to that of the marketed formulation (Figure 5).

Table 5. Comparison of t_{25} and t_{50} for various formulations with the marketed product

Formulation	t_{25} (min)	t_{50} (min)
F1	25.00	72.12
F2	38.34	90.00
F3	47.56	138.10
F4	55.12	180.00
F5	60.50	198.10
F6	70.15	220.45
Marketed	62.10	203.30

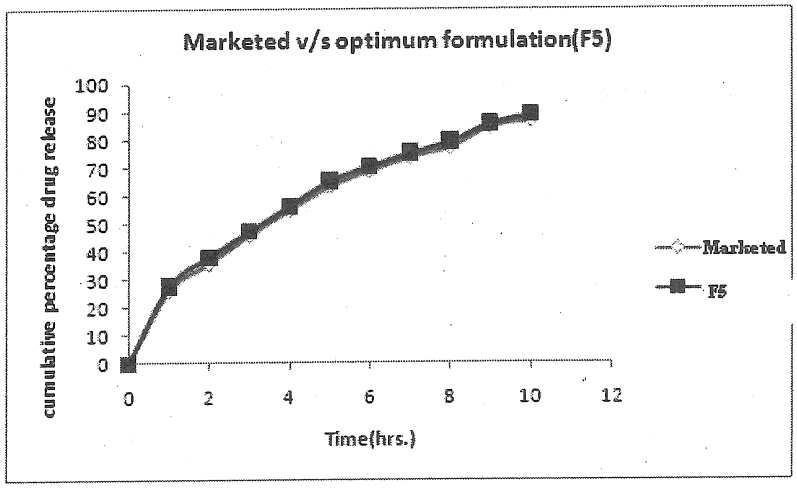

Figure 5. Comparison of *in vitro* release b/w optimum formulation (F5) and marketed formulation

Conclusion

From the present study, it was concluded that the formulation F5 (containing 160 mg of Methocel K100M and 40 mg of Methocel E50) was the optimum formulation amongst all the test batches. It exhibited satisfactory pre-compression properties, as well as, showed satisfactory dissolution profile as a sustained release formulation. Not only this, the formulation was also

found to possess appropriate floating characteristics, as revealed in the *in vitro* buoyancy studies. Moreover, the dissolution profile of the optimized formulation showed similarity to the marketed formulation. Therefore, it may be concluded from the investigation that a combination of Methocel K100M and Methocel E50 in the ratio of 4:1 may be satisfactorily used in the formulation of floating drug delivery system for a freely soluble drug such as metformin.

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