Preparation and Evaluation of Floating Drug Delivery System for Gastric Retention

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Abstract- The recent developments of Floating drug delivery system which includes the gastric physiology and different variables in formulation affects gastric retention in turn improves the bioavailability of drugs especially which have a narrow absorption window. The aim of the work was to develop and evaluate gastro retentive floating drug delivery of Metformin hydrochloride as a model drug to increase the gastric residence time. The tablets of Metformin hydrochloride were prepared with hydrophilic and hydrophobic polymers like HPMC K-15, Ethylcellulose with and without disintegrant carboxy methyl cellulose. Developed formulations were evaluated for the pre compression parameters, post compression parameters, FLT, and *in vitro* dissolution study. From the results it was concluded the formulation F6 showed comparatively good release which complies with the dissolution requirements.

Index Terms- Metformin Hydrochloride, Floating drug delivery, HPMC k-15, Ethylcellulose

INTRODUCTION

Drug release from a controlled release drug delivery systems is at a predetermined, predictable and controlled rate. Most drug delivery systems available in market are oral dosage forms[1] because of the low cost and ease of administration. Gastro retentive systems prolong the gastric residence time of drugs by remaining in the gastric region for several hours this reduces drug waste, improves solubility, bioavailability for drugs. Floating drug delivery systems modulate the gastro intestine transit time of a drug for the maximum gastro intestinal absorption of drugs and site specific delivery[2]

Modified release systems, on the other hand, have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects[3]. Oral extended release dosage forms offer the opportunity to provide constant or nearly constant drug plasma levels over an extended period of time following administration[4]. Extended release DDS include single-unit, such as tablets or capsules, and multiple-unit dosage forms, such as minitablets, pellets, beads or granules, either as coated (reservoir) or matrix devices[5].

Metformin is an anti hyperglycemic agent with type 2 diabetes, lowering postprandial plasma glucose. Metformin decreases intestinal absorption and increases insulin production. Metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects and does not cause hyperinsulinemia.

METHODOLOGY

Preparation of Metformin Hydrochloride floating tablets[6]

Metformin Hydrochloride floating tablets were developed by wet granulation techniques using different concentrations of various polymers.All the ingredients except talc and magnesium stearate were shifted through sieve no 40 then blend. After sufficient mixing, the blend was wetted by adding sufficient quantity of isopropyl alcohol as a granulating agent. Prepared wet mass was granulated by passing through sieve no 18. Prepared granules were dried at 50^{o}C – 60^{o}C for 20 min in hot air oven. After drying, dried granules were lubricated by adding sufficient quantity of magnesium stearate and talc for 5min. 10 mm punches were used to compress the tablets. The tablets weight was kept constant for tablets of all formulations, which was 800 mg.

Table 1: Formulation of Metformin hydrochloride floating tablets

Ingredient	F1	F2	F3	F4	F5	F6
Metformin HCl	500	500	500	500	500	500
HPMC	135	135	135	135	135	135
Ethyl cellulose	60	50	40	60	50	40
Sodium bicarbonate	30	30	30	30	30	30
Lactose	40	50	55	30	40	50
Talc	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5
PVP	20	20	25	25	25	25
Carboxy methyl cellulose	-	-	-	5	5	5
Total	**800**	**800**	**800**	**800**	**800**	**800**

PRE-FORMULATION STUDIES

Bulk density (BD)

Thebulk density was found by using the formula,

$$\textbf{Bulk density (BD)} = M/V_b$$

Tapped Density (TD)

The tapped density was found by using the formula,

$$\textbf{Tapped density (TD)} = M/V_t$$

Compressibility Index (CI)

Compressibility index is calculated from BD and TD using the formula,

$$\textbf{CI} = \textbf{TD-BD/TD x 100}$$

Hausner Ratio (HR)

Hausner Ratio is calculated from BD and TD using the formula,

$$\textbf{Hausner ratio} = \textbf{TD/BD}$$

Angle of Repose (AR)

The angle of repose for the granulesof each formulation was determined by the funnel method. The granule masswas allowed to flow out of the funnel orifice on a plane paper kept on thehorizontal surface. The radius (r) and height (h) determined from the pileformed on the paper. The results were sown in table no.2.

$$\textbf{Angle of repose } (\Theta) = \tan^{-1} (h/r)$$

EVALUATION OF TABLETS

Weight variation (WV)

Twenty tablets from each formulation were taken and individually weighed in milligrams. The average weight and standard deviation of 20tablets was calculated[5]. The results were sown in table no.3.

Hardness (H)

Twenty tablets from each formulation were taken and measured in kg/cm2 using Monsanto type hardness tester. The standarddeviation was calculated form average hardness[5].The results were sown in table no.3.

Friability (F)

Twenty tablets were weighed from each formulation and after weighing accurately placed in the friabilator. The rotation speed offriabilator was kept at 20 rpm for 5 minute. After 5 minutes, the tablets werededusted and weighed again. The percentage friability was calculated[5]. The results were sown in table no.3.

In vitro buoyancy Test[7]

Buoyancy test was performed by placing them in a beaker containing 500 ml of 0.1 N HCL (pH 1.2,temp.37±0.5°c). The time between its initial and its buoyancy in the medium was calculated for the determination of lag time and total buoyancy time by visual observation. The time taken for dosage form to move to the surface of medium called floating lag time (FLT) or buoyancy lag time (BLT).The results were sown in table no.3 and fig no. 1.

In vitro dissolution study[8]

The dissolution study was carried out using USPII (paddle method) apparatus in 900 ml of 0.1 N HCL (pH1.2) for 480 mins. The temperature of the dissolution medium was kept at 37±0.5°c and the paddle was set at 100 rpm. 10ml of sample solution was withdrawn at specified interval of time and filtered through what man filter paper and the same amount of fresh 0.1N HCL was replaced in dissolution medium. The sample was diluted to a suitable concentration with 0.1N HCL. The absorbance was measured at λmax 233 nm using a UV-spectrophotometer.The results were sown in fig. no.2.

Kinetic analysis of *In Vitro* drug release[8]

From the result of *In Vitro* release profile obtained the optimized formulations were plotted in models of data the results were shown in table 4

RESULTS

Table2: Pre-compression evaluation parameters

S. NO.	TESTS	F1	F2	F3	F4	F5	F6
1	Bulk density (g/ml)	0.36	0.34	0.33	0.35	0.34	0.32
2	Tapped density (g/ml)	0.44	0.43	0.42	0.46	0.44	0.45
3	Hausner Ratio	1.22	1.25	1.23	1.24	1.26	1.22
4	Angle of repose (°)	25.74	25.55	26.58	25.68	25.70	25.62
5	Compressibility Index (g)	18.29	19.25	19.07	19.03	18.90	19.01

Table3: Evaluation of tablets

S.NO.	TESTS	F1	F2	F3	F4	F5	F6
1	Appearance	Round and white	Round and white	Round and white	Round and white	Round and white	Round and white

2	Thickness (cm)	3.35±0.13	3.32±0.04	3.32±0.01	3.33±0.16	3.35±0.01	3.34±0.17
4	Hardness (Kg/cm)	3.0±0.44	3±0.57	3.5±0.32	3.5±0.28	3.9 ±0.52	4±0.69
5	Weight variation (%)	2.2	3.2	2.3	2.6	3.1	2.8
6	Friability (%)	0.61%	0.6%	0.65%	0.61%	0.59%	0.64%
7	Assay (%)	100	100	99.1	99.7	99.2	99.5
8	*In Vitro* Buoyancy Test(Buoyancy lag time in second)	4	5	4	5	6	6

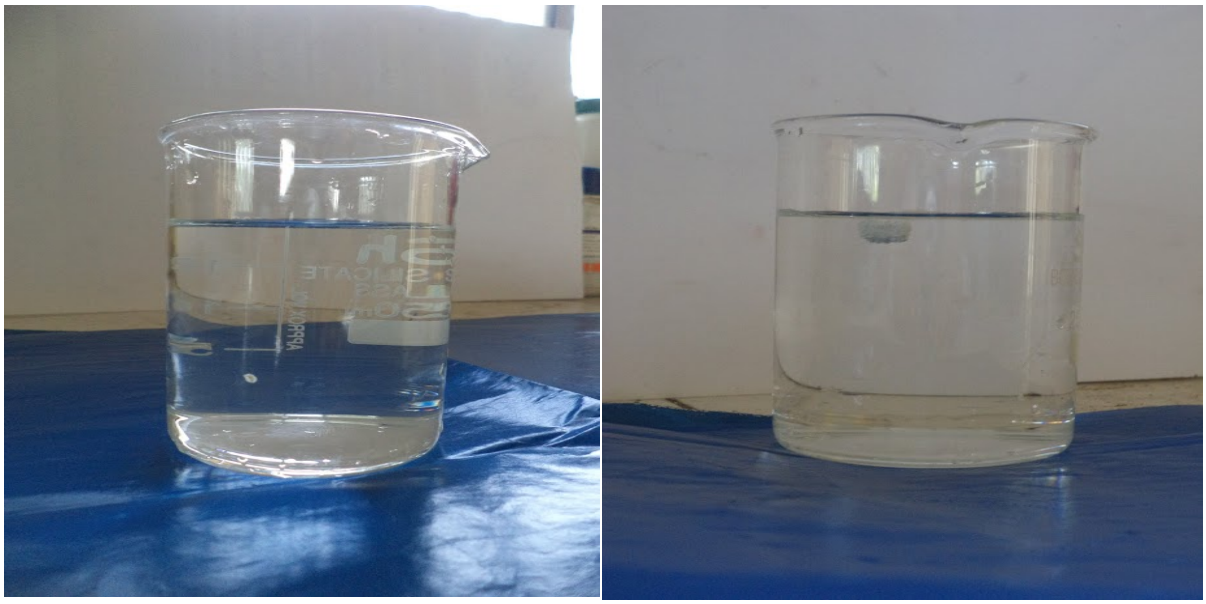

Figure 1: Photographs of prepared floating tablet

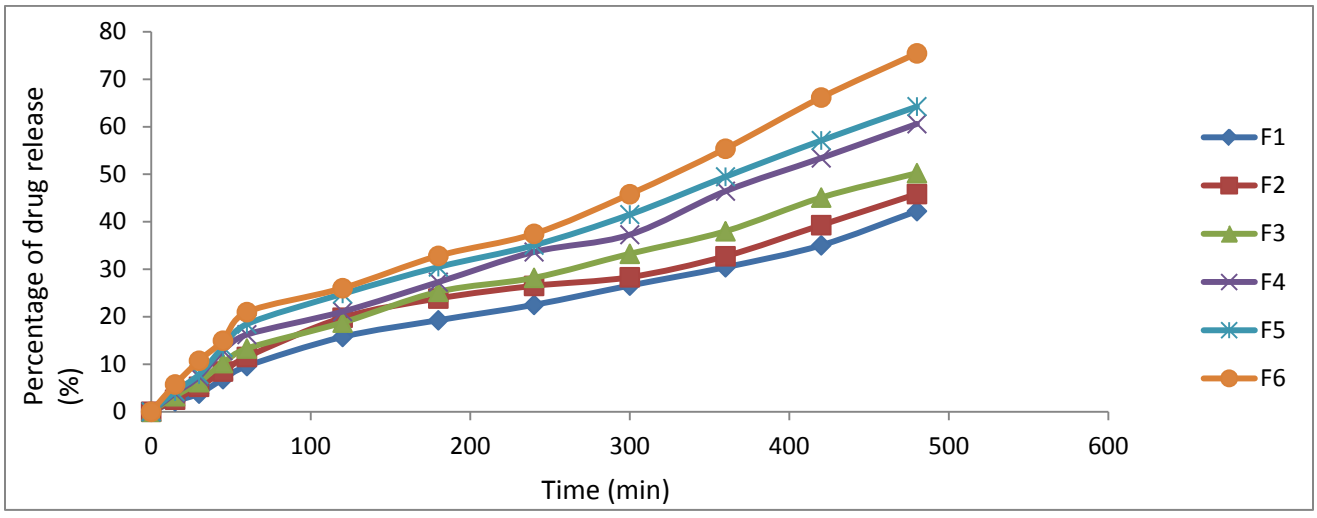

Fig 2*: In vitro* dissolution graph of prepared formulations

Table4: Kinetic analysis for optimized formulation (F6).

Zero Order	First Order	Higuchi Kinetics	Peppa's model	
R^2	R^2	R^2	n	R^2
0.981	0.938	0.955	0.714	0.981

DiscDiscussion

The angle of repose for the formulated blend wasfound to be in the range of 25.55^{o} to26.58^{o}. Hence the entire formulations blend was found to be good, passable flow property. Compressibility index was carried out and it was found between18.29%to19.25% indicating the powder blend has the required flow property for compression. Hausner's ratio was calculated for the blend, it found between 1.22-1.26 indicating powder blend has the required flow property for compression. The results were shown in table no.2.

The measured hardness of tablets of each batch ranged between 3.0 to4.0 kg/cm^2.This ensures good handling characteristics of all batches.The percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable. All the formulations (F1 to F6) passed weight variation test as the percentage weight variation was within the pharmacopoeial limits of 5% of the weight.The measured thickness of tablets of each batch ranged between 3.32to3.35 for uncoated tablets. The percentage of drug content for F1 to F6 was found to 99.1% to 100% of it complies with official specifications. The results were shown in table no. 3.
All the formulations were subjected to *in vitro* release studies. Dissolution profiles of all formulations were compared by cumulative percentage drug release versus time. The percentage release at the end of 480 min. for formulations F1, F2, F3, F4, F5 and F6 was found to be 42.24±0.26%, 45.84±0.44%, 50.24±0.62%, 60.62±0.24%, 64.26±0.42% and 75.46±0.26%. From dissolution result it was confirmed that formulation F6 was showing good dissolution profile in comparison to other batches. From the *in vitro* dissolution data, zero order, first order and Higuchi type release kinetics of drug release were calculated. Korsemeyer-Peppas semi-empirical models were also employed to find out mechanism of release. Zero order seemed to be the most appropriate model describing kinetics for the optimized formulations (correlation coefficient 0.981). On the other hand n values ($0.5 \leq n \geq 1.0$) for optimized formulations indicated the order of drug release by anomalous diffusion (non-Fickian) type. So, the drug release is the combined actions of both diffusion and erosion.

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