Formulation and Characterization of Metformin Hydrochloride Floating Capsules

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ABSTRACT

The present study was to develop a Hydro dynamically Balanced System (HBS) for metformin hydrochloride (MH) as a single unit floating capsule. Floating study of different polymers was studied. The formulation blends were prepared by physical blending of drug and polymer in varying concentration. Drug compatibility with polymer was confirmed by FTIR, DSC and XRD studies. The bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were determined to study the micromeritic properties of physical mixtures of different blends. Prepared HBS capsules were also evaluated for drug content and weight uniformity, in vitro drug release in HCl pH 1.2. The drug release pattern varied significantly with increased polymer concentration in the formulations. The release rate can be effectively modified by using hydrophobic and hydrophilic polymers. All the HBS capsules of MH extended drug release compared to capsule contains only pure MH. The release data was best fit to first, zero order kinetics as well as diffusion model. All formulations depicted n value confined between 0.5 and 1. This indicated anomalous transport through the hydrated matrix.

Keywords: Carr's index, Chitosan, Floating Capsule, HPMC, Hydro dynamically Balanced System, Metformin hydrochloride.

INTRODUCTION

The oral route considered as the most important route of drug delivery. Many factors affect this route of administration. These factors include gastric emptying time, drug release and its absorption. Most of the oral dosage forms possess several physiological limitations such as inability to restrain and locate the controlled drug delivery system within the desired region of the GIT due to variable gastric emptying and motility; shorter residence time of the dosage form in the stomach and incomplete absorption of drugs having absorption window especially in the upper part of the small intestine. Gastro intestinal drug delivery system (GDDS) is classified into two types based on mechanism of floatation:1) Effervescent floating drug delivery system and 2) Non-effervescent drug delivery system (HBS).[1] The hydro dynamically balanced system is designed to prolong the gastric residence time of the dosage forms. It can be formulate by one or more low density gel-forming hydrophilic polymers. The HBS capsule is comply with to form a cohesive gel barrier structure and attain a density less than that of gastric fluids after administration. It should dissolve slowly enough to serve as a "reservoir" for the delivery system.[2,3] Metformin hydrochloride is mainly used to control blood glucose in type 2 diabetes mellitus patients. Metformin has an oral bioavailability of 50–60% under fasting conditions, and is absorbed slowly. Short biological half life of 1.5-4.5 hours.[4] The mechanism of action of the anti-diabetic agents used for the treatment of type 2 diabetes, include increasing insulin release, increasing insulin sensitivity, controlling hepatic glucose release or inhibiting intestinal glucose

absorption.[5] Often, therapy with insulin and OHAs become less effective in controlling hyperglycemia, particularly as a result of weight gain, worsening insulin resistance and progressive failure of insulin secretion due to glucose toxicity. Insulin therapy alone or with hypoglycemic agents can produce weight gain due to reducing glucose excretion.[6-8] Among commonly used OHAs, thiazolidine diones and sulphonylurea contribute to weight gain, whereas metformin causes weight loss and dipeptidyl peptidase-4 inhibitors are weight neutral.[9,10] The insufficiency from insulin utilization can be corrected by administration of one or more of the currently available oral hypoglycemic agents.[11] Floating drug delivery systems were first described by Davis in 1968.[12,13] It is possible to prolong the gastric residence time of drugs using these systems. Floating drug delivery systems have a bulk density is lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on gastric contents, drug is released slowly at a desired rate from the system. After the release of drug, the residual system is emptied from the stomach. This result is increase in GRT and a better control of fluctuations in plasma drug concentrations .The beneficial delivery system would be one, which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site.

The objective of the present study was to develop HBS for Metformin hydrochloride as single-unit floating capsules with the help of low density polymer, tried to study the

different release modifier effect and $T_{90\%}$. We had tried to prolong the drug release and increase gastric residence time, to increase therapeutic efficacy of the drug compared to multiple conventional oral dosage forms.

MATERIALS AND METHODS

Materials

Metformin HCL (MH), Hydroxy propyl methyl cellulose (HPMC 4M), Chitosan, Ethyl cellulose, Polyethylene glycol 6000, Hard gelatin capsule shells(#00), Buffer solutions were purchased from Sigma Chemical Co., St. Louis. All water used was distilled and de-ionized. All other chemicals were of reagent grade and used as received.

Methods

Selection of polymers

Accurately weighed 200 mg of different low density hydrophilic polymers were added in appropriate size of empty hard gelatin capsule shell (size# 00), which upon administration would attain a density less than that of

gastric fluids and therefore would float. The polymer that shows maximum floating time was selected for further studies .

Floating capacity

Floating characteristics of the prepared formulations were determined by using USP 2 paddle apparatus at a paddle speed of 50 rpm in 900 ml of a 0.1 N HCl solution (pH=1.2) at 37±0.5°C for 12 h. The time between the introduction of capsule and its buoyancy on the simulated gastric fluid (floating lag time) and the time during which the dosage form remain buoyant (floating duration) were measured.

Formulation of HBS capsules

Metformin hydrochloride was weighed and physically blended with polymer using mortar and pestle until the whole blend has the same color(homogenous mixing) then, filled into hard gelatin capsule (size #00) manually. The qualitative amounts of drug and polymer are shown in table 1.

Table 1: Composition of HBS capsule formulations

Formula	MH(part)	Chitosan (part)	HPMC 4M (part)	Ethyl cellulose (part)	PEG6000 (part)
F1	1	0.25	-	-	-
F2	1	0.50	-	-	-
F3	1	0.75	-	-	-
F4	1	0.50		0.05	-
F5	1	0.50		-	0.05
F6	1	-	0.25		-
F7	1	-	0.50		-
F8	1	-	0.75		
F9	1		0.50	0.05	
F10	1		0.50		0.05

Table 2: Micromeritic properties of different formulations of MH

Formula	BD (g/cm³)	TD(g/cm³)	HR	Carr's Index (%)	Angle of Repose
Drug	0.500	1.000	2.000	50.000	47.730°
F1	0.289	0.295	1.021	2.034	17.200°
F2	0.236	0.260	1.102	9.231	18.340°
F3	0.200	0.230	1.150	13.043	20.130°
F4	0.220	0.245	1.113	10.204	19.990°
F5	0.144	0.289	2.006	16.500	45.850°
F6	0.167	0.200	1.198	16.500	43.200°

Micromeritic properties[14]

Bulk density and tapped density

Both bulk density (BD) and tapped density (TD) were determined. A known quantity of powder from each formula was transferred into a 10 ml of measuring cylinder. The initial volume was observed and tapped volume was measured till standard tapping using tapping

Equipment (Campbell Electronics model PD-100 Prabhadevin. Mumbai-25, INDIA). BD and TD were calculated using the following formula:

BD =mass of the powder / volume of the untapped powder

TD = mass of the powder / volume of the tapped powder

Compressibility index (CI)

The compressibility index of the powder formulation was determined by Carr's compressibility index: Carr's index (%) = [(TD-BD)x100]/TD

Hausner's ratio (HR)

Hausner's ratio was determined using BD and TD of the powder blend formulations:

$$H = TD/BD$$

Angle of repose

The angle of repose is the angle formed by the horizontal base of the bench surface and the edge of a cone-like pile of granules. Funnel used was a stainless steel funnel and the size of the orifice was 10 mm and the height from the beginning of funnel to end of orifice was 111 mm. The funnel was fixed in place, 4 cm above the bench surface. After the cone from 5 g of sample was built, height of the granules forming the cone (h) and the radius (r) of the base were measured. The angle of repose (θ) .The angle of repose (θ) was calculated as follows:

Tan θ= h/r; Angle of repose (θ) = Tan^{-1} θ

A value of <30° indicates 'excellent' flow whereas >56° indicates 'very poor' flow. The intermediate scale indicates 'good' (θ between 31–35°), 'fair' (ϑ between 36–40°), 'passable which may hang up' (θ between 41–45°), and 'poor which must be agitated or vibrated' (θ between 46–55°).

Evaluation of HBS capsules formulations

Weight uniformity

10 capsules were weighed individually and the average weight was determined. Test was performed according to the official method.

Drug content

The HBS capsules contain was dissolved in ethanol and make up volume up to 100 ml with HCl pH 1.2 solution (SGF) and filter. The absorbance was measured at 232 nm after suitable dilution by UV-Visible spectrophotometer (Shimadzu UV-1601, Japan).

Infrared analysis (FTIR)

The x-ray diffraction patterns of MH and F2 were performed in infrared spectrophotometer (Gensis II, Mattson, (England).Radiation was provided by a copper target(Cu anode 2000W:1.5418 high intensity x-ray tube operated at 40 KV and 35MA). The monochromator was a curved single crystal (one PW1752/00). Divergence slit and receiving slit were 1 and 0.1 respectively. The scanning speed of geniometry (PW/050/81) USED WAS 0.02.20/5 and the instrument were combined with a Philips PM8210 printing recorder with both analogue.

X-ray powder diffraction analysis (XRPD)

X-ray diffraction experiments were performed in a Scintag x-ray diffractometer (USA) using Cu K α radiation with a nickel filter, a voltage of 45 kV, and a current of 40 mA. Diffraction patterns for MH and F2 were obtained.

Differential scanning calorimetry (DSC)

Samples were placed in Al pan and heated at rate of 50°C/min with indium in the reference pan, in an atmosphere of nitrogen up to a temperature of 400°C. The DSC studies were performed for MH and F2.

In vitro drug release studies

The dissolution of different formulations of HBS compared to the plain drug, were determined using dissolution tester (VK 7000 Dissolution Testing Station, Vankel Industries, Inc., NJ) following the USP paddle method. All tests were conducted in 900 mL of 0.1N HCl (SGF) maintained at 37 ±0.5°C with a paddle rotation speed at 50 rpm. The amount of drug used was equivalent to 500 mg. After specified time intervals, samples of dissolution medium were withdrawn, filtered, and assayed for drug content Spectro photometrically at 232 nm after appropriate dilution with 0.1N HCl. The experiment was carried out in triplicate.

Effect of release modifiers

The ethyl cellulose (EC) and polyethylene glycol 6000 (PEG 6000) were used at 5% concentration in the formulation to study their effect on the in vitro drug release study (Table 1). The release modifiers were added to the powder blend, physically blended in mortar and pestle for 15 min and filled into hard gelatin capsule (size #00) manually.

Kinetic analysis of release data[15,16]

To analyze the mechanism of drug release from the HBS capsules the in vitro dissolution data were fitted to different model dependent kinetics and model independent approaches like zero order, first order, Higuchi release model and Korsmeyer-Peppas model.

RESULTS AND DISCUSSION

Floating capacity

The polymers selected were of inherent low specific gravity to formulate excellent HBS to achieve the required prolonged release drug delivery system for the highly soluble MH.

Floating capacity

The floating capacity of different HBS was not less than 7 hours, F2, F3 and F4 depicted floating capacity 11, 11.5 and 12 hours respectively.

Micromeritic properties

Table 2 illustrates the different micromeritic properties of different formulations.

F1, F2, F3 and F4 depicted excellent flow properties (HR<1.25, CI 5-15,angle of repose<30). This an indication to the prominant effect of both polymers used (HPMC and chitosan) on the poor flow properties of the drug

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which in turn improved the good mixing of drug with these concentrations of polymers used.

Evaluation of Hbs Capsules Formulations

Weight uniformity

The average weight of capsules within each formulation was found to be uniform. This indicates uniform filling of powder blend during capsule filling. Not more than two of the individual weights deviated from the average weight by more than 7.5% and none deviated by more than twice that percentage, which provided good weight uniformity.[17,18]

Drug content

In all the ten formulations, the values for drug content were found to be uniform among different batches of the floating drug delivery system (FDDS) and ranged between 96.6 and 102.0% of the theoretical value as per USP.[19] The value ensures good uniformity of the drug content in the capsules

Infrared spectra analysis

FTIR studies revealed that fundamental peaks of the MH. The results in Figure 1 indicated absence of chemical interaction between the drug and HPMC (no change in positions functional groups region). The fingerprint region in both drug and F2 (drug/polymer) were superimposed. This reflected the physical properties of MH.
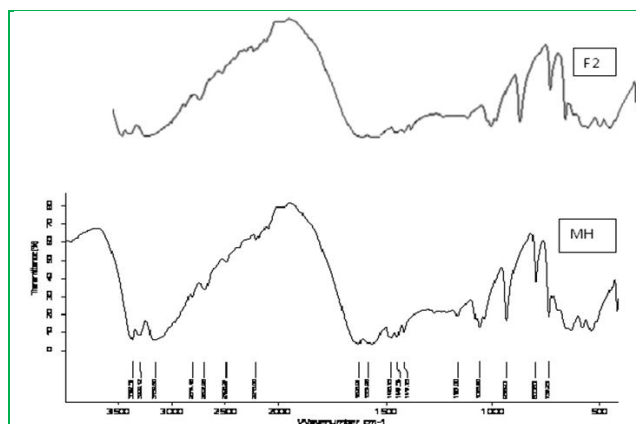

Figure 1: FTIR spectrum of plain MH and F2

DSC Studies

DSC thermogram of pure MH Figure 2A, showed sharp endothermic peak starting at 251°C with melting peak at 266.2C and in the F2 the endothermic peak appeared at 237°C. Shifting of endothermic peaks to left side with increase in its intensity indicates solid-solid transition in drug from higher melting point to the lower Figure 2B. This transition increased the homogenous distribution of drug throughout the polymer matrix.

XRPD Studies

The overlay of XRPD pattern of MH and formulation F2 showed in Figure 3. It reveals that the intensity of the peaks for the pure drug was sharp, but when it was

incorporated into the polymer matrix, the intensities of the peaks decreases due to decreased crystallinity of MH.
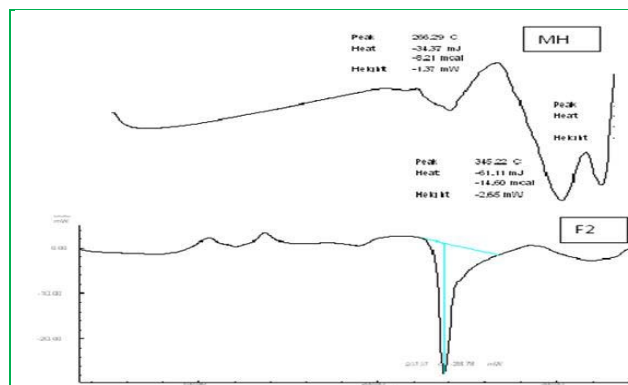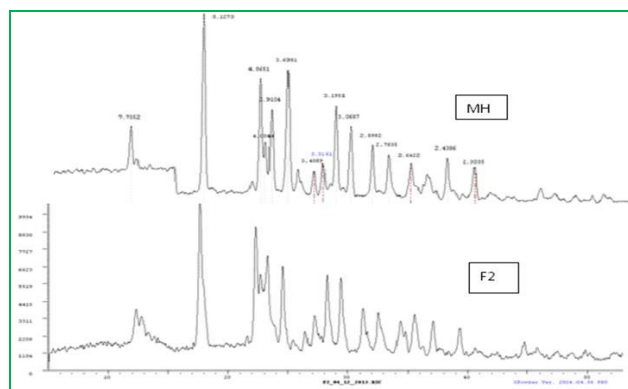

Figure 2: Thermograms of MH and F2

Figure 3: XRPD of MH and F2

In vitro Drug Release Study

Figure 4 depicted the release pattern of MH from HPMC matrix in absence (F1-F3) and presence of release modifiers (F4 and F5).The ranking of drug release after 10 hours was about 100, 100, 93, 86 and 79% for F5, F1, F2, F3 and F4 respectively. Incorporation of ethyl cellulose in formulation (F4) delayed the drug release from the polymeric matrix .This due to the hydrophobic nature of ethyl cellulose. The improved drug release from F5 was related to the channeling effect of the hydrophilic nature of PEG 6000. The release of MH from F6-F10 was very slow when compared to F1-F5. The presence of chitosan as a drug carrier retard the MH release to a great extent because chitosan is a cationic polymer insoluble in acid medium but swells forming stiff matrix retarding MH release. Presence of viscosity modifiers also affecter the release patterns from these formulations. PEG600 improved MH release to some extent. The release of MH from this formula after 10 hours was 58.2, 53, 44, 33.3 and 29.9% for F10, F6, F7, F8 and F9 respectively. The plain MH depicted the highest dissolution (100%) after 3 hours. The formulations F2,F3 and F4 showed good release profiles to control the drug release up to 12 h as compared to capsules contains only pure drug. Their $T_{90\%}$ (time required for 90% drug release) was 8.7, 11.7, 15.2 hours respectively.
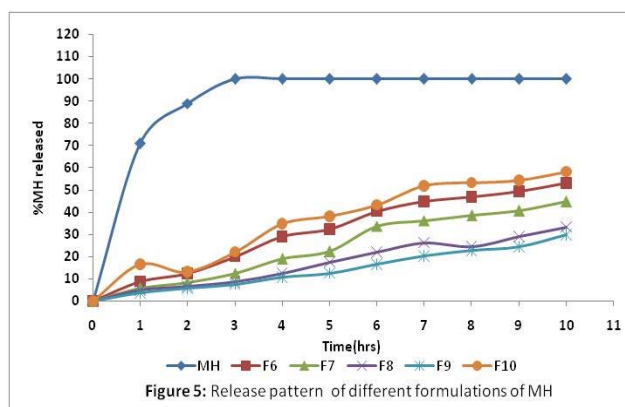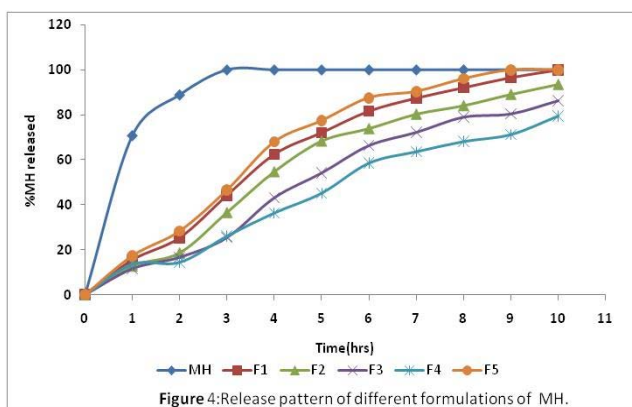
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Figure 4:Release pattern of different formulations of MH.

Figure 5: Release pattern of different formulations of MH

Table 3: Kinetic analysis of the release data of different MH formulations

Formula	Model	R^2	Slope	Y-Intercept	n	$T_{90\%}$ (hrs)	Mechanism of Release
F1	Zero	0.928	9.595	15.000	0.86	8.0	Diffusion
	First	0.601	-0.325	2.794			
	Diffusion	0.986	39.97	-21.000			
F2	Zero	0.929	9.345	9.89	0.85	8.7	Diffusion
	First	0.984	-0.125	2.141			
	Diffusion	0.985	38.890	-25.090			
F3	Zero	0.959	9.015	4.006	0.93	11.7	First
	First	0.986	-0.094	2.106			
	Diffusion	0.976	36.78	28.090			
F4	Zero	0.974	7.866	4.449	0.96	15.2	First
	First	0.980	-0.070	2.061			
	Diffusion	0.978	31.870	23.070			
F5	Zero	0.981	11.522	4.320	0.87	7.5	Zero
	First	0.954	-0.225	2.350			
	Diffusion	0.970	20.99	-17.64			
F6	Zero	0.888	5.137	5.413	0.85	27.5	Diffusion
	First	0.968	-0.033	1.990			
	Diffusion	0.982	20.99	-19.96			
F7	Zero	0.970	4.661	0.528	0.97	40.7	First
	First	0.972	-0.027	2.101			
	Diffusion	0.959	18.740	-15.450			
F8	Zero	0.974	3.255	0.624	0.94	55.9	First
	First	0.982	-0.018	2.006			
	Diffusion	0.945	12.960	-10.270			
F9	Zero	0.988	2.881	0.495	0.85	27.5	Zero
	First	0.982	-0.014	2.003			
	Diffusion	0.932	11.310	-9.771			
F10	Zero	0.942	5.297	9.385	0.68	21.1	Diffusion
	First	o.963	-0.037	1.981			
	Diffusion	0.967	21.700	-9.695			

Kinetic analysis of release data

According to Korsmeyer-Peppas equation, the values of n were confined between 0.5 and 1. This indicates that the diffusion through the hydrated matrix and the polymer relaxation was an anomalous transport.

CONCLUSION

It was concluded that, on the basis of in vitro drug release patterns and $T_{90\%}$ that the formulations F2, F3 and F4 showed good release profiles and suitable $T_{90\%}$ to control the drug release up to 12 h as compared to capsules contains only pure MH. The increased polymer concentration in the formulations decreased the rate of MH released. The incorporation of hydrophobic and hydrophilic release modifiers in the

formulations greatly affected the pattern of MH release from the polymer matrix.

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