EFFECT OF DIFFERENT VISCOCITY GRADE HPMC POLYMERS ON GASTRORETANTIVE DRUG DELIVERY OF METFORMIN HCL

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ABSTRACT

The objective of the present study was to develop a hydro dynamically balanced system of metformin as a single unit floating tablet. Various grades of low-density polymers were used for the formulation of this system. They were prepared by physical blending of metformin and the polymers in varying ratios. The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated gastric fluid pH 1.2. Effect of Carbopol as a release modifier was studied to ensure the delivery of drug from the floating tables over a prolonged time period. Tablets prepared with HPMC K15M and Carbopol gave the best in vitro percentage release and were taken as the optimized formulation. By fitting the data into zero order, first order, Korsmeyer and peppas, and Higuchi model it was concluded that the release followed Korsmeyer and peppas release, as the correlation coefficient (R^2 value) was higher for Korsmeyer and Peppas release.

All the six formulations produced robust tablets with optimum hardness, consistent weight uniformity and low tablet friability. In vitro drug release tests of these tablets indicated controlled sustained release of Metformin HCl and 96-99% released at the end of 8hr in formulation containing high viscosity polymers.

Keywordds: Metformin hydrochloride, gastroretentive, floating drug delivery, sustained release. HPMC, in vitro Buoyancy

INTRODUCTION

Drug absorption from gastrointestinal tract is a complex procedure and is subject to many variables. It has been reported that the extent of GIT drug absorption is related to contact time with the small intestinal mucosa. Gastro retentive systems can remain in the gastric region for several hours and therefore significantly prolong the gastric residence time of drugs[1].

Many approaches have been reported in the literature for the formulation of HBS systems viz. muco-adhesion, Floatation, sedimentation, expansion, modified shape systems or by the simultaneous administration of pharmacological agents which delay gastric emptying. Both single unit systems (tablets or capsules) and multiple unit systems (multi particulate systems) have been reported in the literature[2]. Floating drug delivery offers a number of applications for drugs having poor bioavailability because of narrow absorption window in the upper part of gastrointestinal tract. It retains the dosage form at the site of absorption and thus enhances the bioavailability. Metformin is an anti-hyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of metformin when given orally is 50–60%. Biological half-life of metformin is 1.5–1.6 h and the main site of its absorption is proximal small intestines[3,4]. A HBS system was planned for metformin as such a system when administered would remain buoyant on the gastric fluids for a prolonged period of time and the drug would be available in the dissolved form at the main site of its absorption i.e., proximal small intestines. This would lead to improvement in the bioavailability of

the drug. In this way it stands an advantage over conventional dosage form, which needs to be administered twice or thrice a day[5-7].

MATERIALS AND METHODS

Materials

Metformin was obtained as a gift sample from USV limited Mumbai. HPMCK100LV, HPMC K15M and Carbopal 934 was obtained from , sodiumbicarbonate, citric acid, MCC ,Mg.sterate, PVP K90 etc were purchased from commercial sources (Burgoyne chemicals new Delhi).Rest of all the chemicals are of laboratory grade.

Method (By usig effervacent technology) [9-12]

Composition of six different formulations of Metformin floating tablets is shown in table 1. All ingredients were passed through sieve no 120,then weighed accurately and mixed thoroughly (except magnecium state) .Tablets were prepared by wet granulation method using pvpk90 as a binder.solution of pvpk90 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 45°c for 1 hr .Dried granules were sized through sieve no 40 placed over sieve no 60 , lubricated with mg.sterate .Tablets were made by multi tooling lab scale punching machine (Karnavati) at slow speed and high compression pressure to avoid capping.

Table 1: Composition of floating Tablets of Metformin HCL With Corresponding Formulations

Ingredients per tablet (mg)					
Formulation Code	Metformin	Citric acid	Sodium bicarbonate	HpmcK15M/ K100LV	Carbopol
F1	500	50	50	0 (0 /170)	0
F2	500	50	50	0 (0 /170)	42.5
F3	500	50	50	0.5 (85/ 85)	0
F4	500	50	50	0.5 (85/85)	42.5
F5	500	50	50	1 (170/0)	0
F6	500	50	50	1 (170 /0)	42.5

Characterization / Evaluation of floating tablets

Various parameters that need to be evaluated in gastroretentive formulations include floating lag time and total floating time, dissolution profiles, determination of swelling index , kinetic modeling, as well as general evaluation tests like content uniformity, hardness, thickness, wt. variation , friability etc.

Prior to this evaluation prformulation study was carried out these includes, IR studty, differential scanning calorimetry (DSC), for drug and polymer compatibility, solubility analysis, melting point determination, particle size analysis, flow properties, and mechanical properties are also performed .

In vitro buoyancy studies[19, 21]:

The in vitro buoyancy was determined by floating lag time as per the method described by Rosa et al The tablets wereplaced in a 100-mL beaker

containing 0.1N HCl. The time required for the tablet to rise to the surface and float wasdetermined as floating lag time, and the total time duration till the tablet float on that 100ml 0.1N HCL was recorded as total floating time. Total floating time more than 8 hr should be desired for achieving sustained release action. Generally polymer with low viscosity shows better floating profile as compare to high viscosity polymers. Results for in vitro buoyancy study is shown in table no 3

Water uptake study: (determination of swelling index) [18-21]

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of % weight gain by the tablet.

Method

One tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again upto 5 hours. The % weight gain by the tablet was calculated by the formula,

Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100

Where, S.I. = swelling index.,Wt = weight of tablet at time t.

Wo = weight of tablet before immersion.

Result of water uptake study is shown in table no 4

In vitro drug release studies [49]

The release rate of Metformin HCl from floating tablets was determined using *United States Pharmacopeia (USP)* 24.Dissolution Testing Apparatus basket method. The dissolution test was performed using 900 mL o buffer solution having Ph 1.2 at 37 ± 0.5°C and 100 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 through a 0.45-µmembrane filter and diluted to a suitable concentration with same buffer

Absorbance of these solutions was measured at 233nm using a Shimadzu UV-1601 UV/ Vis double-beam spectrophotometer (Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a standard curve. Results for invitro drug release study is shown in table no 5.

Analysis of in vitro drug release [22]

To analyze the mechanism of drug release from the tablets the in vitro dissolution data were fitted in to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer and Peppas mode. The equations for the said models are given in Table 2.

Table 2 Kinetics of optimized formulation of metformin hydrochloride

S no	Model	Equation	R²	K
1	Zero order	$F = k \cdot t$ (where F is the fraction of drug release, k is the release constant and t is the time)	0.9688	8.9049
2	First order	$\ln F = k \cdot t$ (where F is the fraction of drug release, k is the Const &. t is the time)	0.8847	-2.197
3	Higuchi	$F = k\sqrt{p}t$	0.9773	25.7616
4	Hixson and Crow.	$F = 100(1 \_ (1 \_ kt)^3$	0.9660	17.2918
5	Korsmeyer & Peppas	$F = kt^n$	0.9900	-0.0503

The software pcp dissov3 developed by Anant Ketkar et al was adopted for deciding the most appropriate model.

RESULT AND DISCUSSION

In vitro bouyancy study

Floating time was observed in all six formulations, all the six formulations shows the floating time more than eight hours which is sufficient to achieve sustained release action. Formulation F1 and F2 shows the highest floating time because they contain low viscosity polymer ie HPMCK100LV as compare to high viscosity polymer containing formulation F5 and F6.Hence it can be concluded that formulation with low viscosity polymer shows better floating ability.

Water uptake study /determination of swelling index

From the results of swelling study it was concluded that swelling increase as the time passes because the polymer gradually absorbed water due to hydrophilic in nature and swell. In F5 and F6, the higher swelling index was found for tablets of batch F6 which contain HPMC K 15M having nominal viscosity of 15,000 cps and carbopol while former contain same amount of HPMC K15M without addition of carbopol. On the other hand formulation no F1 & F2 containing low viscosity polymer ie HPMCK100 LV shows lower swelling index as compare to Formulation F5 & F6Thus, the viscosity of polymer had major influence on swelling process, matrix integrity as well as floating capability, hence from above result it can be concluded that the linear relationship may be there in between swelling process and viscosity of polymer. The finding also supported by Parakh[121] et al, who studied water absorption rate of swellable matrices. They reported that water absorption rate increases as the viscosity of the polymer increases and at the end of experiment, polymer of the higher viscosity showed the maximum absorption.

Formulations which contain carbopol shows better swelling index hence it can be concluded that carbopol is having synergistic effect on swelling when combined with HPMC

Table 3: Determination of floating lag time & total floating time.

Formulation code	Floating lag time(min) (n=3)	Total floating time (hr)
F1	2.18±0.4	14.25
F2	2.45±0.3	11.15
F3	0.43±1.5	12:50
F4	1.34±1	10:22
F5	1.56±0.1	11:07
F6	2.49±0.3	9:22

In vitro drug release

Since the pH of stomach is elevated under fed condition (~3.5), citric acid was incorporated in the formulation to provide an acidic medium for sodium bicarbonate. When we observe the in vitro release profile for each formulation then it is clear that though formulation F1 and F2 shows max floating time as compare to other formulations due to low viscosity (100cp) but their drug release profile was not satisfactory as compare formulation containing high viscosity (15000) ie formulation F5 and F6.

From the results it can be concluded that, as the viscosity of polymer increases in the formulation the release decreases which may be due to increased strength of the gel matrix of the HPMC. Similarly, presence of carbopol in the formulation also decreases the drug release, which may be attributed due to increased imbibition of water into polymer. Similarly, increases the swelling of carbopol which holds the water inside the matrix and thus decreases the release of drug from the dosage form.

When we compare the optimized formulation F6 with the formulation F5 then one thing is clear that though both these formulation contain the same polymer ie HPMC of same viscosity and in same concentration but due to addition of carbopol in formulation F6, it shows better invitro drug release profile as compare to formulation F5 .This shows that carbopol shows synnergestic effect with HPMC as it increases release retardant effect of HPMC.

Table 4: Determination of water uptake of polymer in respective formulations

Time (hr)	Formulation Code					
	F1	F2	F3	F4	F5	F6
1	30.55	56.55	50.83	64.56	65.50	91.21
2	31.65	68.74	52.44	67.83	86.75	98.50
3	33.80	91.85	61.12	103.88	97.82	118.40
4	47-33	105.25	79.03	119.66	128.55	155.90
5	48.29	107.42	95.23	125.12	141.47	168.43

Table 5: % CUMULATIVE DRUG RELEASE PROFILE OF ALL FORMULATIONS (F1-F6)

Time (hr)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	24.482	21.15	17.551	18.902	9.18	9.091
60	29.976	28.71	23.944	22.324	15.12	12.782
120	45.191	41.85	35.288	33.758	30.6	27.995
180	56.267	50.85	44.293	43.573	39.78	35.289
240	70.225	66.15	61.940	60.859	44.64	42.044
300	80.944	77.76	71.848	67.707	49.68	46.099
360	94.544	90.9	88.058	85.896	53.1	51.504
420	98.155	93.6	91.848	88.966	58.68	55.651
480	99.966	96.3	95.458	91.857	78.3	76.719
540		99.9	97.269	94.567	89.28	83.748
600			99.080	98.178	98.1	94.559
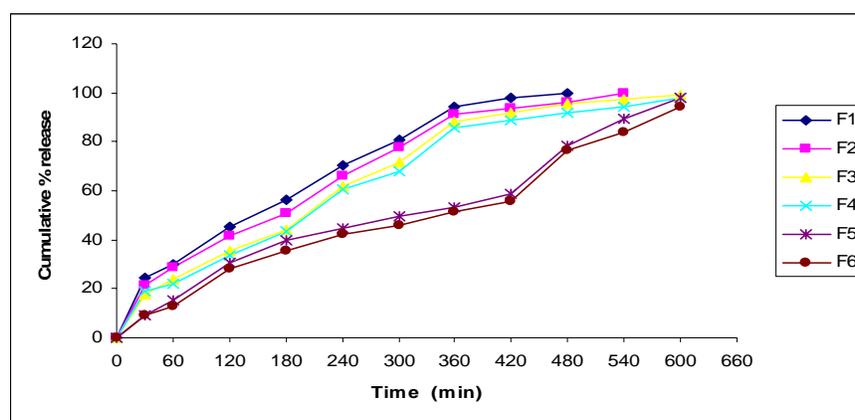
Fig. 2: *In-vitro* **cumulative % drug released V/s time for formulations F1-F6**

However when we see the comparative floting time profile of all formulations then it is observed that formulations which contain carbopol shows lower floating time duration as compare to formulations which are devoid of carbopol. This shows that carbopol represents negative trends towards floating time duration which is not desirable in floating drug delivery system.there fore excees concentration of carbopol (with HPMC) should be avoided.

From the above absorvations it can be concluded that formulation no F6 shows better release profile due to presence of high viscosity polymer and release modifier Carbopol 934.Hence high viscosity polymers are beneficial for formulatig SR drug delivery.

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