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Design and *in vitro* testing of a floatable gastroretentive tablet of metformin hydrochloride

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Metformin hydrochloride, which is better absorbed in the upper intestine, was formulated as a floating (buoyant) matrix tablet using a gas generating agent (sodium bicarbonate) and a gel forming hydrophilic polymer (hydroxypropyl methylcellulose). The formulation was optimized on the basis of floating ability and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity and low tablet friability. All tablets but one exhibited satisfactory (gradual and near complete) drug release and buoyancy. *In vitro* drug release tests of these tablets indicated controlled sustained release of metformin hydrochloride and 96–99% released at the end of 8 h. Two formulations of fabricated tablets containing metformin hydrochloride (500 mg), sodium bicarbonate (75 mg), hydroxypropyl methylcellulose-K 4M (170–180 mg), citric acid (between 15 and 20 mg) and polyvinyl pyrrolidone K90 (32–40 mg) with hardness between 6.8 to 7.5 kg/cm^2 showed a floating time of more than 8 h and promising drug release results. The release followed the Higuchi kinetic model, indicating diffusion dominated drug release.

1. Introduction

Metformin hydrochloride is slowly and incompletely absorbed from the gastrointestinal tract, with its absolute bioavailability reported to be about 50 to 60% (Sweetman 2002). It is freely soluble in water. Oral absorption of metformin is confined to the proximal part of the small intestine (Gusler et al. 2001; Stepensky et al. 2002). Absorption becomes less as the drug passes beyond this.

A traditional oral controlled release formulation releases the drug throughout the gastrointestinal tract, and therefore the drug should have an absorption window throughout the gastrointestinal tract. Hence a controlled release dosage form of metformin hydrochloride prepared with conventional technology may not be successful. Therefore, a gastroretentive dosage form (GRDF) can assist in improving the oral controlled delivery of a variety of important drugs, including metformin hydrochloride, which are characterized by a narrow absorption window in the upper part of the gastrointestinal tract i.e. the stomach and small intestine. The underlying principle of the gastroretentive system is very simple, i.e. to prolong release and restrict the region of delivery to the upper small intestine. It is suggested that formulating metformin hydrochloride in a unique pharmaceutical dosage form (DF) with gastroretentive properties would allow an extended absorption phase of the drug. After oral administration, such a dosage form would be retained in the stomach and release the drug there in a controlled and prolonged manner, so that the drug could be supplied continuously to its absorption site in the upper gastrointestinal tract.

Several approaches are currently utilized to prolong gastric retention time (Hwang et al. 1998). These include low density of the dosage form causing buoyancy above the gastric fluid (floating system) (Singh and Kim 2000); a high density DF that is retained in the bottom of the stomach (Moes 1993); polymeric bioadhesion to the stomach mucosa (Moes 1993); expansion with swelling to large size which limits emptying of the DF through the pyloric sphincter (Klausner et al. 2003); and other delayed gastric emptying mechanisms. The current investigation employs a floating system approach that has recently become the leading methodology in this field, to develop a gastroretentive metformin hydrochloride dosage form. The principle of a buoyant preparation offers a simple and practical approach to achieve increased gastric residence/retention (GRT) time. Gas generation using sodium bicarbonate in a hydrophilic matrix formulation was successfully used to achieve a low density DF in previously reported work (Icikawa et al. 1991). There are a few research reports on the formulation of oral controlled release products of metformin hydrochloride with a reduced dosing frequency (Yuen et al. 1999; Di Colo et al. 2002; Di Colo et al. 2005). Recently several studies have been carried out to investigate the pharmacokinetic and pharmacodynamic advantages of controlled release dosage forms for metformin hydrochloride (Balan et al. 2001; Fujioka et al. 2003; Cullen et al. 2004; Bhansali and Masoodi 2005).

The objective of the present investigation was to formulate floating matrix tablets of metformin hydrochloride using gas generating components in a hydrophilic matrix with

set limits (to be mentioned later) of dissolution profile and optimum *in vitro* buoyancy (floating ability). We attempted a systematic approach to developing floatable gastroretentive matrix tablets of metformin hydrochloride that is retained in the stomach and subsequently provides delivery of the drug over the period of time of GRT. Further, the release kinetics of metformin hydrochloride from HPMC based matrix tablets were analyzed utilizing three important mathematical models.

2. Investigations and results

The results for angle of repose and compressibility index ranged from 26.97 ± 0.11 to 29.80 ± 0.07 and 13.54 ± 0.06 to 17.82 ± 0.03 respectively (Table 1). An angle of repose of less than 30 degrees indicates good flow properties (Aultron 1998). This was further supported by the lower compressibility index. Granules with Carr's index values around 18% and below are considered to have fair to excellent flow properties (Aultron 1998). Table 2 gives the physical parameters (hardness and thickness) and *in vitro* buoyancy (floating lag time and floating time) of all the fabricated tablets. Table 2 also shows the drug content of these tablets. The tablet formulations in all the batches prepared contained metformin hydrochloride within $100 \pm 5\%$ of labeled content. All the tablet formulations showed acceptable pharmacotechnical properties and complied with pharmacopoeial specifications for weight variation and friability (less than 0.3%).

In the trial study to determine the optimum concentration of gas generating agent and hydrophilic matrix to entrap gas, 75 mg sodium bicarbonate and a range of 170 to 200 mg HPMC K4M per tablet showed good consistency, with the desired floating ability and sustained release. The attempt to increase the hardness of the tablets with the objective of reducing tablet thickness (to improve patient acceptance) from more than 5.0 mm to 5.0 or less, in F-V and F-VI, resulted in better floating duration. This is probably due to the gas generated (sodium bicarbonate induced CO_2 generation) beeing trapped and well protected within the polymer gel, formed by hydration in the presence of water, with sufficient strength resulting from the higher compression force. Thus hardness of tablets ($\sim$7 kg/cm^2) was essential to achieve optimum *in vitro* buoyancy. Reliable GRT is best produced in the fed condition preferably with fatty meals. And since the pH of the stomach in under fed conditions is elevated (3.5 to 4.0), citric acid was incorporated in the formulation to provide an acidic environment for the sodium bicarbonate for CO_2 generation.

The results of dissolution studies of formulations F-I, F-II and F-III are shown in Fig. 1. Tablets F-I, F-II and F-III, released $46.53 \pm 0.31\%$, $50.87 \pm 2.53\%$ and $54.82 \pm 1.47\%$ respectively, of their metformin hydrochloride content at the end of 2 h. Each data point in the dissolution profile represents the mean of three determinations. All the three values of percentage release at 2 h for the different formulations differed significantly (single factor ANOVA) at $P > 0.001$

Table 1: Properties of granules

Formulation	Angle of repose	Tapped bulk density (g/ml)	Loose bulk density (g/ml)	Compressibility index
F-I	29.80 (0.07)	0.526 (0.02)	0.432 (0.05)	17.82 (0.03)
F-II	27.06 (0.09)	0.580 (0.03)	0.482 (0.04)	16.97 (0.10)
F-III	28.33 (0.05)	0.456 (0.05)	0.383 (0.05)	15.96 (0.11)
F-IV	26.97 (0.11)	0.430 (0.04)	0.372 (0.04)	13.54 (0.06)
F-V	27.06 (0.13)	0.505 (0.01)	0.425 (0.03)	15.86 (0.09)
F-VI	29.10 (0.04)	0.514 (0.04)	0.441 (0.01)	14.12 (0.07)

Figures in parentheses represent $\pm$ SD, n = 3

Table 2: Properties of compressed metformin matrix tablets

Formulation	Hardness kg/cm^2 $\pm$ SD (n = 3)	Thickness mm $\pm$ SD (n = 5)	Floating lag time, sec $\pm$ SD (n = 3)	Floating time h $\pm$ SD (n = 3)	Drug content %
F-I	3.5 (0.32)	5.24 (0.04)	29 (3.5)	5.8 (0.03)	99.60 (0.13)
F-II	5.0 (0.40)	5.21 (0.02)	15 (0.5)	7.8 (0.04)	98.60 (0.13)
F-III	5.8 (0.23)	5.15 (0.07)	18 (0.8)	8.0 (0.03)	97.37 (0.12)
F-IV	5.1 (0.40)	5.47 (0.02)	42 (3.2)	7.9 (0.08)	97.92 (0.22)
F-V	6.8 (0.27)	4.96 (0.02)	32 (1.2)	8.3 (0.07)	97.50 (0.15)
F-VI	7.5 (0.35)	4.85 (0.04)	36 (0.9)	8.4 (0.09)	98.12 (0.10)

All figures in parentheses represent $\pm$ SD, n = 3, except thickness where n = 5

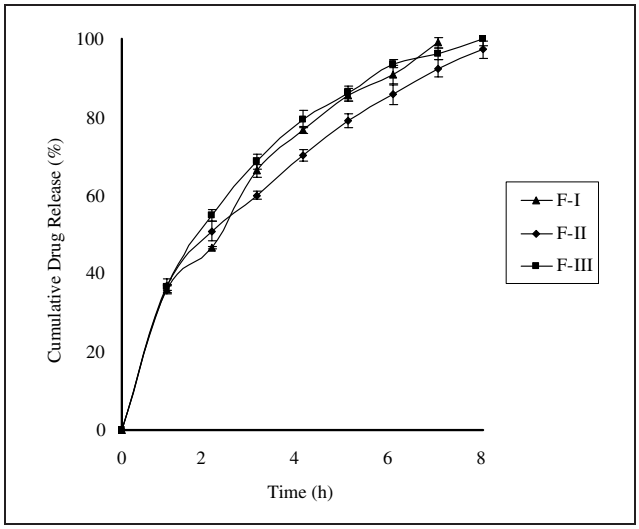

Fig. 1: *In vitro* release profiles of metformin from formulations F-I, F-II and F-III tablets
In vitro cumulative release of metformin from formulation F-I (—▲—), F-II (—◆—) and F-III (—■—) Each point represents mean $\pm$ SD, n = 3

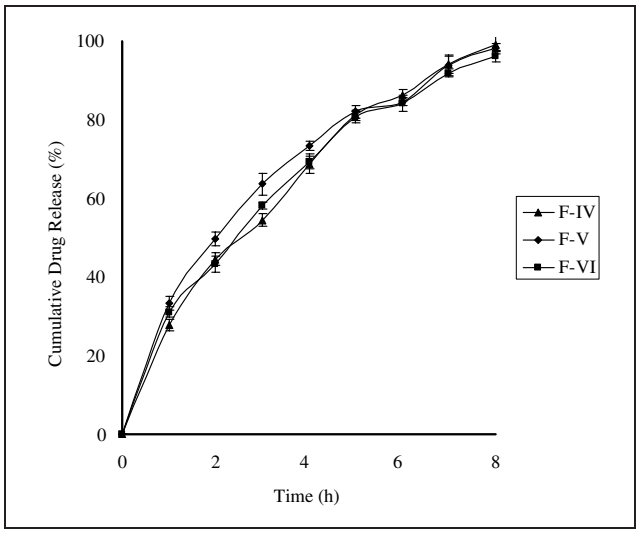

Fig. 2: *In vitro* release profiles of metformin from formulations F-IV, F-V and F-VI tablets
In vitro cumulative release of metformin from formulation F-IV (—▲—), F-V (—◆—) and F-VI (—■—) Each point represents mean $\pm$ SD, n = 3

Table 3: *In vitro* release kinetic values of metformin from selected formulations*

Formulation	First order[1] R^2	Higuchi[2] R^2	Korsmeyer-Peppas[3] R^2	Slope
F-V	0.9050	0.9906	0.9880	0.5196
F-VI	0.9120	0.9914	0.9910	0.5665

* Formulations F-V and F-VI. [1] First order equation, $\log c = \log c_0 - kt/2.303$, [2] Higuchi equation, $Q = kt^{1/2}$, [3] Korsmeyer-Peppas equation, $M_t/M_\infty = kt^n$

($DF = 2$, $F = 40.5$). Formulation F-I, containing a higher amount of PVP without citric acid, failed to sustain release beyond 7 h. This formulation remained buoyant only for 5.64 h, probably due to less gas generation in the absence of citric acid. Hence we conclude that there is a direct relationship of buoyancy and extended duration of release (sustained release) of drug. Figure 2 indicates that F-IV, F-V and F-VI released $44.56 \pm 1.62\%$, $49.69 \pm 1.64\%$, and $43.25 \pm 1.96\%$ of metformin hydrochloride at the end of 2 h and $99.25 \pm 1.95\%$, $98.12 \pm 1.4\%$, and $96.2 \pm 1.4\%$ at the end of 8 h, respectively. The differences between 2 h release values for F-IV, F-V and F-VI were significant at $P > 0.001$ ($DF = 2$, $F = 19$). However, no significant differences were observed between the 8 h release values ($P = 0.1$, $DF = 2$ and $F = 3.46$). Incorporation of higher amounts of HPMC K4M in F-V and F-VI was found to be more suitable to give good floating ability, with better drug release characteristics and consistency.

3. Discussion

The dissolution data for batches F-V and F-VI were fitted to first-order, Higuchi and Korsmeyer-Peppas models. As clearly indicated by Fig. 2, the formulations did not follow zero-order release kinetics. The model that best fitted the release data was evaluated by correlation coefficient (R^2). R^2 values for F-V and F-VI in various models are given in Table 3. When the data were plotted according to a first-order equation, the formulations showed a fair linearity, with regression values 0.9050 and 0.9120. Release of a drug from a hydrophilic matrix tablet generally involves diffusion. The release profiles of F-V and F-VI could be best explained by the Higuchi model, as the plots showed high linearity, with correlation coefficient (R^2) values of 0.9906 and 0.9914 respectively. The diffusion mechanism of drug release was further confirmed by Korsmeyer-Peppas plots that showed good linearity (R^2 values 0.9880 and 0.9910), with slope values 0.5196 and 0.5665 respectively, indicating that drug release from the selected tablets was diffusion controlled. The results of the study demonstrate that it is possible to prepare gastroretentive matrix tablets of metformin hydrochloride. The gas generating floating dosage form is a promising approach to achieve *in vitro* buoyancy and sustained release. It may be concluded from the present study that floating matrix metformin hydrochloride tablets can be prepared by incorporating sodium bicarbonate as a gas generating agent in association with citric acid in a gel forming polymer HPMC K4M.

4. Experimental

4.1. Materials

Metformin hydrochloride was obtained from New Drug and Chemical Company, Mumbai, India. HPMC K4M, a grade of hydroxypropyl methylcellulose, was procured from Colorcon Asia Pvt. Ltd., Mumbai, India, PVP K90 (Polyvinyl pyrrolidone K-90), microcrystalline cellulose (MCC, Avicel pH 101) and lactose were purchased from Coveral and Company, Chennai, India. Materials and excipients used in preparing tablets were Indian Pharmacopoeia grades. All other ingredients used throughout the study were of analytical grades and were used as received.

Table 4: Formulations of metformin hydrochloride floating tablets

Ingredients mg/tab.	Formulations F-I	F-II	F-III	F-IV	F-V	F-VI
Metformin HCl	500	500	500	500	500	500
Sodium bicarbonate	75	75	75	75	75	75
HPMC K4M	150	150	170	150	180	170
Citric acid	–	20	20	15	15	20
MCC	20	10	08	33	03	00
PVP K90	60	50	32	32	32	40
Magnesium stearate	15	15	15	15	15	15
Talc	10	10	10	10	10	10
Total	830	830	830	830	830	830

4.2. Methods

4.2.1. Estimation of metformin hydrochloride

An ultraviolet (UV) spectrophotometric (Shimadzu 1601 UV/VIS spectrophotometer, Kyoto, Japan) method based on measurement of absorption at 232 nm in water was used for the estimation of metformin hydrochloride (Indian Pharmacopoeia 1996a). The method showed very good linearity (R^2 value 0.9998) in the concentration range of 0–20 μg/ml. When a standard drug solution was assayed a number of times ($n = 6$) the relative error (accuracy) and the relative standard deviation were found to be 0.8% and 0.47% respectively.

4.2.2. Preparation of floating matrix tablets

Floating matrix tablets each containing 500 mg metformin hydrochloride were prepared by a conventional wet granulation method employing sodium bicarbonate as gas generating agent and HPMC K4M as hydrophilic matrix. The composition with respect to polymer (grade) was selected on the basis of trial preparation of tablets. The optimal concentration of gas generating agent (sodium bicarbonate) was developed concentration under experimental formulae and conditions of preparation. The formulation in each formula code, specified in Table 4, was developed to adjust drug release according to predetermined limits (to be mentioned later) and a minimum 8 h floating ability. MCC was incorporated as a filler excipient to maintain tablet weight constant. This water insoluble filler was incorporated also to counterbalance the faster solubility of the drug in the presence of the hydrophilic polymer and to provide a stable monolithic matrix. A batch of 3000 tablets was prepared with each formula. The ingredients were passed through a 60 mesh sieve. A blend of all ingredients except glidant and lubricant was thoroughly mixed for 8–10 min in a polythene bag.

Granulation was done manually with a solution of the calculated quantity of PVP K90 in sufficient isopropyl alcohol. The wet masses were passed through a 12 mesh sieve and the wet granules produced were first air dried for 10 min and finally at 45–55 °C in a tray drier for 2 h. The dried granules were sized on a 20 mesh sieve and mixed with 8% (200g/batch) of fines (granules passed through 20 mesh). Magnesium stearate and talc were added as glidant and lubricant and blended for 10 min in a twin-shell blender. Granules thus obtained were compressed into tablets on a 16-station rotary Cadmach machine (Cadmach, Ahmedabad, India) using 19.5 mm oval punches. Prior to compression, granules were evaluated for their flow and compressibility characteristics.

4.2.3. Evaluation of granules

Angle of repose (θ) of granules was determined by the funnel method. The diameter of the powder cone was measured and angle of repose was calculated using the following equation (Carter 1986):

$$\text{Tan}\,\theta = h/r \quad (1)$$

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

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. LBD and TBD were calculated using the following equations (Shah et al 1997):

$$\text{LBD} = \text{weight of the powder/volume of the packing} \quad (2)$$

$$\text{TBD} = \text{weight of the powder/tapped volume} \quad (3)$$

The compressibility index of the granules was determined by Carr's index (Carr 1965) using the following equation:

$$\text{Carr's index} = [(\text{TBD-LBD}) \times 100)]/\text{TBD} \quad (4)$$

4.2.4. Evaluation of tablets

The prepared floating matrix tablets were evaluated for hardness, weight variation, thickness, friability and drug content. Hardness of the tablets was tested using a Strong-Cobb hardness tester (Tab-machine, Mumbai, India). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai, India). The thickness of the tablets was measured by vernier caliper. Weight variation test was performed according to the official method (Indian Pharmacopoeia 1996b).

4.2.5. Buoyancy determination

The *in vitro* buoyancy was determined using the method described by Rosa et al. (1994). The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float is the floating lag time. The duration of floating (floating time) is the time the tablets float in the medium (including floating lag time).

4.2.6. In vitro drug release studies

Drug release from tablets was studied using a USP 24 dissolution apparatus type 2 (USP 2000) (Tab-Machine, Mumbai, India), in 900 ml 0.1N HCl at 37 ± 0.5 °C and at 100 rpm. Sink condition was maintained for the whole experiment. Ten millilitres of the sample was withdrawn at regular intervals and the same volume of pre-warmed (37 ± 0.5 °C) fresh dissolution medium was replaced. The samples withdrawn were filtered through a 0.45 µm membrane filter (Nunc, New Delhi, India) and the drug content in each sample was analyzed after suitable dilution with a Shimadzu 1601 UV/VIS spectrophotometer (Kyoto, Japan) at 232 nm. The content of metformin hydrochloride was calculated taking 798 as value A (1%, 1 cm) at 232 nm. The predetermined drug release requirement, based on a method described earlier (Basak et al. 2004) and in order to provide theoretical release of metformin hydrochloride (calculated using available pharmacokinetic data) (AHFS Drug Information 2003, Scheen 1996) was set at between 30–50% at 1 h, between 45–65% at 3 h, between 60–85% at 6 h and not less than 80% at 8 h.

4.2.7. Analysis of release data

The release data obtained, for two selected batches, were treated according to first-order (log cumulative percentage of drug remaining versus time), Higuchi (Higuichi 1963) (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (Korsmeyer et al. 1983; Peppas 1985) (log cumulative percentage of drug released versus log time) equation models.

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