International Journal for Pharmaceutical Research Scholars (IJPRS)
ISSN No: 2277-7873
RESEARCH ARTICLE
V-1, I-2, 2012

Formulation and Evaluation of Gastroretentive Drug Delivery System for a Selective Ant diabetic Drug

Shah SV*[1], Lakhani KM[1], Patel KN[1], Patel BA[1], Patel PA[1]
[1]*Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gujarat-382421, India*
Manuscript No: IJPRS/V1/I2/00068, Received On: 11/05/2012, Accepted On: 16/05/2012

ABSTRACT

Convenience of administration and patient compliance are gaining significant importance in design of dosage form. Sustained release gastroretentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Gastroretentive floating drug delivery systems (GFDDS) of metformin hydrochloride, an antidiabetic drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed and evaluated. Xanthan gum and different grades of Hydroxy propyl methyl cellulose (HPMC) were used as strong gelling agent and sodium bicarbonate as gas generating agent to reduce floating lag time. Tablets were prepared by wet granulation method. Drug-excipients compatibility was studied by FTIR and Differential Scanning Calorimetry (DSC). Floating tablets were evaluated for pre-formulation parameters and for hardness, friability, weight variation, drug content, floating properties and *in vitro* release pattern. Formulation M3 showed minimum floating lag time and maximum floating time of 12 hours and gave slow and maximum drug release of Metformin HCl spread over 12 hours. The release of drug from the formulation followed zero order kinetics and was governed by non-Fickian diffusion mechanism. The optimized formulation was subjected to stability study.

KEYWORDS

Metformin hydrochloride, Floating drug delivery system, Xanthan gum, HPMC

INTRODUCTION

Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost-effective manufacturing process[1]. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8–12 h), and the existence of an absorption window in the upper small intestine for several drugs[2-3]. These difficulties have prompted researchers to design gastroretentive drug delivery systems (GRDDS)[3-4].

***Address for Correspondence:**
Shah Shweta V.
Department of Pharmaceutics, Shree Swaminarayan Sanskar Pharmacy College, Zundal, Gujarat, India.
E-mail Id: shweta.pharma07@gmail.com

GRDDS are primarily controlled release drug delivery systems, which gets retained in the stomach for longer period of time, thus helping in absorption of drug for the intended duration of time. This in turn improves bioavailability, reduces drug wastage and improves solubility of drugs that are less soluble at high pH environment (e.g. weakly basic drugs like papaverine, domperidone). It also helps in achieving local delivery of drug to the stomach and proximal small intestine. Gastric retentive drug delivery devices can be useful for the spatial and temporal delivery of many drugs.

Many drugs categorized as once a day delivery have demonstrated to have sub optimal absorption due to dependence on transit time of the dosage form. Therefore, a system designed

for longer gastric retention will extended the time within which drug absorption can occur in small intestine. Thus it has been suggested that compounding the drugs with narrow absorption window in a unique dosage form prolongs gastric residence time and would enable an extended absorption phase of these drugs[5]. Different methodologies have been reported in the literature to increase the gastric retention of drugs, like intra-gastric floating systems, hydrodynamically balanced systems, extendable or expandable and super porous biodegradable hydrogel systems[6]. The floating drug delivery systems result in long lasting intra-gastric buoyancy which may not only provide a sustained site of specific therapeutic action but also may lead to a reduction in side effects and better patient compliance[7]. Natural gums are among the most popular hydrophilic polymers because of their cost-effectiveness and regulatory acceptance.

Xanthan gum is a high-molecular-weight extracellular polysaccharide produced by fermentation process of gram negative bacterium *Xanthomonas campestris.* Xanthan gum is biodegradable and biocompatible and forms gel in water hence, appears to be gaining appreciation for the fabrication of matrices with controlled drug release characteristics[8-11].

Hydroxypropylmethylcellulose (HPMC) is hydrophilic cellulose ether widely used as a pH-independent gelling agent in controlled release preparation, due to their release behavior of the drug[12]. Due to non-toxicity, easy handling and no requirement of specified technology for production of sustained release tablets, HPMC is often used as release retarding materials[13]. The gel forming properties of HPMC and XG can be used to develop sustained release dosage forms. Hydrophilic matrix system release drug sequentially by swelling to form gel, diffusion of drug molecules and finally surface erosion of matrix[9].

Metformin HCl, the only available biguanide, remains the first line drug therapy for patients with Type 2 diabetes mellitus (T2DM), acts by decreasing hepatic glucose output and peripheral insulin resistance[14]. The advantages of metformin are a very low risk of hypoglycaemia, weight neutrality and reduced risk of cardiovascular morbidity and mortality[15]. It is an oral anti-hyperglycemic agent, shows incomplete absorption from the gastrointestinal tract and the absolute bioavailability is 50 – 60 % with relatively short plasma half-life of 1.5 - 4.5 h[16, 17].

An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea, that especially occur during the initial weeks of treatment[18]. Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. A sustained-release (SR) formulation that would maintain plasma levels of the drug for 10 to 16 hours might be sufficient for once-daily dosing of metformin. The overall objective of this study was to develop matrix sustained-release tablets of metformin using natural gums (xanthan gum) as suitable hydrophilic matrix systems compared with the extensively investigated hydrophilic matrices (hydroxypropyl methylcellulose) with respect to *in vitro* drug release rate.

MATERIALS AND METHODS

MATERIALS

Metformin Hydrochloride was received as a gift samples from Srinivas Chemical Limited., India. Avicel CL 611 was gifted by BCM Pharmaceuticals, India. Xanthan gun was obtained from W.S. Medicinal Company, India. HPMC K4M, HPMC K15M and HPMC K100M were gifted by colorcon Asia Pvt. Ltd., India. Sodium bicarbonate was obtained from Rankem Laboratories Limited, India. Povidone K30 was gifted by Haozuo Yuanhai Fine chemicals, China. Magnesium Stearate was received by Vishal Industries, India.

Drug – excipients interaction studies[19]

Differential scanning calorimetry of drug molecule and excipients was carried out on a differential scanning calorimeter Shimadzu

DSC-60. A 1:1 ratio of drug and excipient was weighed into aluminum crucible. And sample was analyzed by heating at a scanning rate of 200°C over a temperature range 200-300°C under nitrogen environment.

Preparation of floating tablets of Metformin HCl

Floating matrix tablets containing 510 mg of Metformin Hydrochloride were prepared using wet granulation method using xanthan gum, HPMC K4M, HPMC K15M and HPMC K100M as strong gelling agent. All ingredients and drug metformin HCl were accurately weighed and individually passed through sieve no. 60 and mixed thoroughly. The above blend was granulated with PVP K30 in isopropyl alcohol. The wet mass was passed through sieve no.16 and dried at 45°C for 2h. Dried granules were passed through sieve no. 24. Then prepared granules were mixed with weighed quantity of sodium bicarbonate and lubricated with magnesium stearate.

Composition of floating matrix tablets of Metformin HCl

Granules were compressed using 19*9 mm biconvex punch into tablets using rotary tablet compression machine. The prepared tablets were evaluated for various physicomechanical and release characteristics

Evaluation of tablet powder blend[20]

Angle of repose

Angle of repose was determined by using funnel method. Tablet blend were poured from funnel, that can be raised vertically until a maximum cone height h was obtained Diameter D was measured to calculate the angle of repose Φ by formula

$$\Phi = \tan^{-1} h/r$$

Where, h = height of the heap

R = radius of the heap

Bulk density

Apparent bulk density (D_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was calculated by using formula

$$D_b = M/V_b$$

Table 1: Formulation of batches containing Metformin HCl

Ingredients	M1 (mg)	M2 (mg)	M3 (mg)	M4 (mg)	M5 (mg)	M6 (mg)	M7 (mg)	M8 (mg)	M9 (mg)	M10 (mg)	M11 (mg)	M12 (mg)
Metformin HCl	510	510	510	510	510	510	510	510	510	510	510	510
AvicelCL 611	131	87	43	131	87	43	87	43	131	87	43	43
Xanthan gum	44	88	132	-	-	-	-	-	-	-	-	-
HPMC K 4M	-	-	-	44	88	132	-	-	-	-	-	-
HPMC K 15M	-	-	-	-	-	-	44	88	132	-	-	-
HPMC K 100M	-	-	-	-	-	-	-	-	-	44	88	132
Povidone K 30	17	17	17	17	17	17	17	17	17	17	17	17
IPA:water (1:1)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Sodium bicarbonate	176	176	176	176	176	176	176	176	176	176	176	176
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	880	880	880	880	880	880	880	880	880	880	880	880

Tapped density

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and weight of the blend (M) were measured. The tapped density (D_t) was calculated by using formula

$$D_t = M/V_t$$

Where,

M = Weight of powder taken

V_t = tapped volume

Compressibility Index

The simplest way for measuring free flow of a powder was compressibility, an indication of the ease with which a material can be induced to flow is given by Compressibility Index (I) was calculated by using formula

$$\text{Compressibility Index} = (V_o - V_t) / V_o \times 100$$

Where,

V_o = bulk volume

V_t = tapped volume

Hausner's ratio

Hausner's ratio was an indirect index of ease of powder flow. It was calculated by following formula

$$\text{Hausner's ratio} = D_t / D_b$$

Where,

D_t = tapped density

D_b = bulk density

Loss on Drying

Mix and accurately weigh the substance to be tested, and conduct the determination on 1 to 2 gm. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Dry the test specimen at the temperature and for the time specified in the monograph.

This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified.

Evaluation Parameters of Floating Tablet

Weight variation[21]

Twenty tablets were selected randomly and the average weight was determined. Then individual tablets were weighed and the individual weight was compared with the average weight.

Thickness[21]

The thickness of the tablet was measured by using digital vernier scale and in Erweka Hardness Tester. Thickness was expressed in mm.

Hardness (Tablet Breaking Force)[22]

For each formulation, the hardness of five tablets was checked using the Erweka hardness tester, average values are shown in Table 5.

Friability[21]

Friability of the tablets was checked using Lab hosp friabilator. Preweighed sample of tablets (n=10) was placed in the friabilator, operated for 100 revolutions. Tablets were then dusted and reweighed. The experiment was repeated three times.

Floating Lag Time[21]

This parameter determines how much time the tablet will take to start to float. This is performed *in-vitro* by placing the tablets in 900ml of 0.1 N HCl and the time taken by the tablet to come up to the surface of solution in beaker.

Floating Time[21]

This parameter determines for how much time the tablets will float in GIT conditions. This is performed *in-vitro* by placing the tablets in 900 ml of 0.1 N HCl and the time of floating is noted down.

Assay[21]

Instrument: Systronics UV visible spectrophotometer 118

Standard Preparation

Weigh and transfer accurately about 50 mg of metformin working/reference standard to 50ml

volumetric flask. Add 30ml of water and sonicate to dissolve. Cool the volumetric flask and make up the volume with water and mix. Dilute 10ml of above solution to 100ml with water and mix. Further dilute 10ml of above solution to 100ml with water and mix.

Sample preparation

Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of metformin, to a 100ml volumetric flask. Add about 70ml of water and sonicate for 15 minutes, dilute with water to volume and mix. Filter the solution through 0.45µ syringe filter, discarding the first 20ml of the filtrate. Dilute 10ml of the filtrate with water to 100ml and mix. Further dilute 10ml of the resulting solution with water to 100ml and mix.

Acceptance Criteria: Not less than 95.0% and not more than 105.0% of the labeled amount of metformin.

Dissolution[22]

Dissolution studies were performed for all the formulation combinations, in triplicate, determined using USP type II dissolution apparatus (Electro lab) where 900 ml of 0.1 N HCl was used as dissolution media maintained at 37^{o}C (±0.5^{o}C) at 100 rpm . The release rates from the tablets were conducted in the dissolution medium of 0.1 N HCl at 1, 2, 4, 6, 8, 10 and 12 hours with replacement of fresh media. Solution samples were analyzed after suitable dilution by above UV method. The actual content in samples was read by comparison with standard Metformin HCl. Drug release profiles were drawn using MS-Excel Software and the values were obtained by interpolation from Excel Graph.

Similarity Factor[23]

FDA recommends the use of f2 value to compare the dissolution data when the coefficient of variation is not more than 20% at the earlier time point and not more than 10% at other dissolution time points.

The similarity may be compared by model independent or model dependent method e.g. by linear regression of the percentage dissolved at specific time points, by statistical comparison of the parameters of the weibull function or by calculating similarity factor as f_2:

$$\mathbf{F_2 = LOG\ ((\{[(\sum (R-T)^2)/n] + 1\}^{-1/2}) * 1OO) * 50}$$

Where,

f_2 = similarity factor

n = number of observations

R = mean percent drug dissolved of reference product

T = mean percent drug dissolved of test product

Drug release kinetics[24]

In order to investigate the model of release from tablets, the drug release data of the formulation was analyzed with the following models, Qt = Qo – Ko t (Zero Order kinetics), Log C = Log C_0 - kt / 2.303 (first order kinetics) , $Q_0^{1/3}$ – $Qt^{1/3}$ = K_{HC} t (Hixon crowell model), Qt = k_H $(t)^{0.5}$ (Higuchi Model) and Koresmeyer-peppas equation(Log (Mt/ M&) = log K + nlog t. where Mt is the amount of the drug release at time t, M∞ is the amount of drug release after infinite time, K is a release rate constant and n is the diffusion exponent indications of the drug release mechanism.

Stability study of optimized batch[25, 26]

The promising formulation was tested for a period of 4 weeks at 40^{o}C with 75% RH, for for any physical changes, changes in drug content, floating lag time, total floating time and *in vitro* drug release study.

RESULTS AND DISCUSSION

Differential scanning calorimetry (DSC) analysis

The DSC analysis (Figure 1) of pure metformin HCl showed a characteristic, sharp endotherm peak at 226°C corresponding to its melting point and indicates the crystalline nature of the drug. The DSC analysis of physical mixture of drug and excipients (figure 1) showed the little change in melting point of drug from 226ºC to

225ºC, indicating no modification or interaction between the drug and excipients.

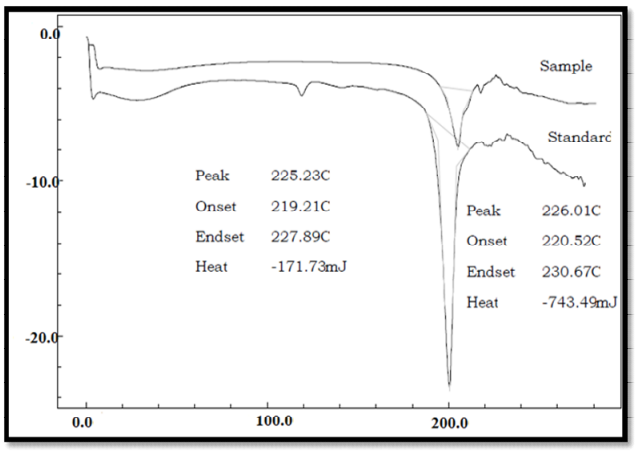

Figure 1: DSC Thermogram of physical mixture of drug and excipients

Evaluation of Powder Blends of Batch M1 to M12

The prepared formulations showed good flow property and compressibility index. Angle of repose ranged from 24.37 to 29.52, Hausner's ratio ranged from 1.08 to 1.19 and the compressibility index ranged from 10 to 16.27. The bulk density and tapped density of the prepared granules ranged from 0.449 to 0.568 and 0.532 to 0.721 respectively. The results of angle of repose indicates good flow property of the granules and the value of compressibility index further showed support for the excellent flow property.

Evaluation of floating matrix tablets:

All prepared batches were evaluated for various physical characteristic like Hardness, Thickness, Friability, Weight variation test and Drug content.

Table 2: Flow Properties of Powder Blend of Batch M1 to M12

Test Parameters	Results											
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Bulk density (gm/ml)	0.449	0.536	0.542	0.546	0.568	0.544	0.568	0.555	0.528	0.523	0.542	0.557
Tapped density(gm/ml)	0.532	0.625	0.644	0.620	0.648	0.621	0.646	0.645	0.587	0.583	0.639	0.648
Angle of repose	24.37	27.68	25.49	24.56	26.34	26.34	25.24	27.48	28.56	25.45	29.52	26.43
%Carr's index	15.55	14.28	16.27	13.55	12.35	12.11	11.11	11.12	10	10.29	15.18	14.04
Hausner's ratio	1.18	1.16	1.19	1.13	1.14	1.13	1.16	1.15	1.11	1.11	1.12	1.16

Table 3: Physical and Chemical Characteristic Evaluation of Tablets of Batch M1 to M12

Test Parameters	**Results**											
	M1	**M2**	**M3**	**M4**	**M5**	**M6**	**M7**	**M8**	**M9**	**M10**	**M11**	**M12**
Weight variation test[#]	882± 0.002	885± 0.002	881 ±0.001	878 ±0.003	881 ±0.001	883 ±0.002	882 ±0.001	878 ±0.001	876 ±0.001	877± 0.003	880± 0.001	882± 0.001
Thickness (mm)[*]	6.4± 0.03	6.2± 0.02	6.5± 0.05	6.7± 0.10	6.8± 0.06	7.8± 0.05	7.1± 0.10	7.6± 0.10	6.9± 0.07	7.2±0 .06	6.6±0 .05	6.8±0 .05
Diameter(mm)[*]	19.5 ±0.01	19.2 ±0.01	18.8 ±0.04	19.2 ±0.04	18.9 ±0.01	18.2 ±0.02	19.2 ±0.03	18.7 ±0.05	18.6 ±0.02	19.3± 0.04	19.1± 0.01	18.9± 0.01
Hardness (Kg/cm^2)[*]	6.1± 0.01	6.7± 0.03	7.1± 0.12	6.8± 0.05	7.2± 0.03	6.9± 0.01	6.4± 0.12	7.2± 0.05	7.2± 0.15	7.1±0 .15	6.7±0 .11	6.3±0 .12
Friability (%)[$]	0.12 ±0.06	0.08 ±0.06	0.15 ±0.04	0.15 ±0.07	0.14 ±0.06	0.19 ±0.07	0.11 ±0.07	0.17 ±0.05	0.15 ±0.05	0.12± 0.06	0.15± 0.05	0.14± 0.02
% Drug Content[*]	99.2 ±1.53	98.4 ±0.16	99.8 ±1.77	96.7 ±1.52	96.3 ±0.68	98.9 ±0.19	95.4 ±0.67	97.2 ±0.01	95.2 ± 0.57	98.2± 1.43	97.5± 0.62	99.8± 0.35
Floating lag time	58 sec	45 sec	32 sec	56 sec	42 sec	31 sec	3.2 min	2.5 min	1.2 min	6.2 min	4.5 min	3.7 min
Floating time(hr)	>12	>12	>12	>12	>12	>12	>8	>10	>10	>6	>8	>8

Where,

*n = 3, [$]n = 10, [#]n = 20

The batches M1 – M12 were prepared to explore the potential of xanthan gum. The thickness and diameter of tablets were measured by vernier calipers and ranged between 6.2 ± 0.02 to 7.8± 0.05 mm, 18.2 ± 0.02 to 19.5 ± 0.07 mm respectively. The hardness of the tablets was measured by Erweka tester and was in between 6.1±0.01 to 7.2±0.05 Kg/cm^2. The friability was measured by friabilator (Lab Hosp) and was found to be 0.08±0.06 to 0.19±0.07%, which is an indication of satisfactory mechanical resistance of the tablets. The drug content estimations showed values in the range of 95.2±0.57 to 99.8±1.77% which passes acceptance criteria i.e. not less than 95.0% and not more than 105.0% of the labeled amount of metformin. Therefore it reflects good uniformity in drug content among different formulations. All the tablets passed weight variation test as the % weight variation was within the Pharmacopoeial limits of ±5% of the weight. All the formulations showed values within the prescribed limits for tests like hardness, friability and weight variation which indicate that the prepared tablets are of standard quality. From the results, it is evident, that formulation M3 containing 15% xanthan gum showed least floating lag time (32 sec) and good

total floating time (>12hrs), while the formulation M6 containing 15% HPMC K4M showed least floating lag time (31 sec) and good total floating time >12hrs, the formulation M9 containing 15% HPMC K15M showed floating lag time (1.2 min) and total floating time >10hrs, while the formulation M12 containing 15% HPMC K100M showed floating lag time (3 min 7 sec) and total floating time of >8 hrs. This may be due to high viscosity grade of HPMC K15M as well as of HPMC K100M. Reduction in the level of HPMC, prolong floating lag time and decrease total floating time.

Therefore, the results revealed that higher concentration of gas generating agent was associated with least floating lag time and higher concentration of polymer was associated with prolonged duration of total floating time of the tablet.

In-vitro Drug Release Study

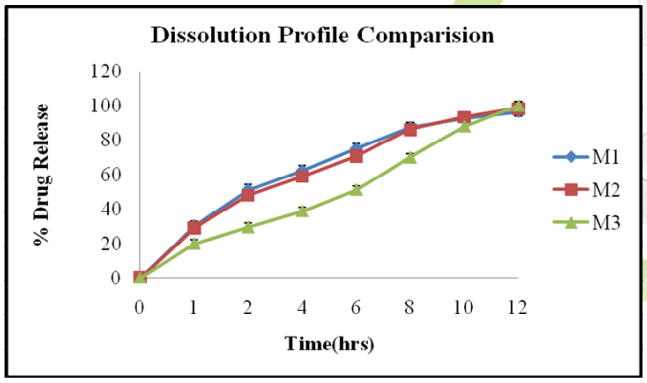

Figure 2: Comparison of *in vitro* dissolution profiles of M1 to M3

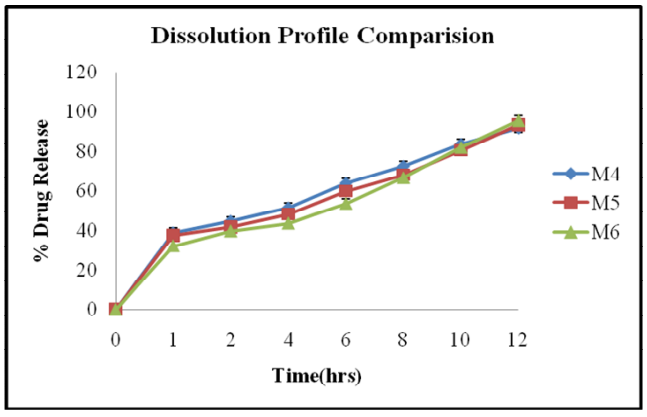

Figure 3: Comparison of *in vitro* dissolution profiles of M4 to M6

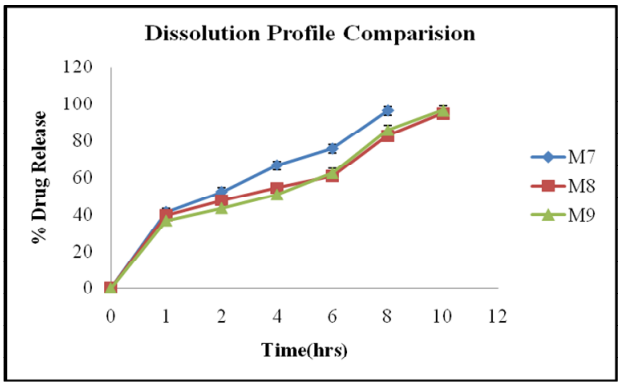

Figure 4: Comparison of *in vitro* dissolution profiles of M7 to M9

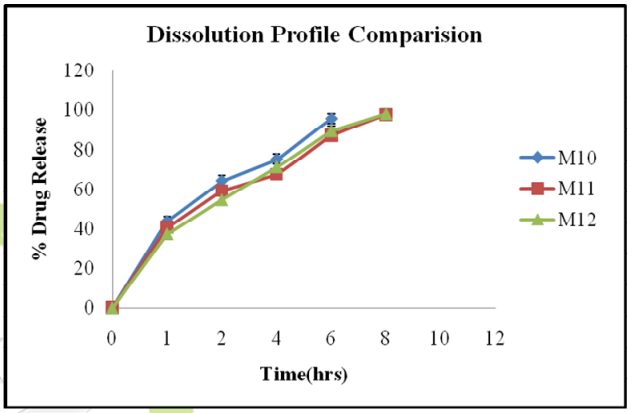

Figure 5: Comparison of *in vitro* dissolution profiles of M10 to M12

The batches M1 – M12 were prepared to explore the potential of xanthan gum and different grades of viscosity of HPMC. Metformin hydrochloride release from the floating tablets was studied in 0.1 N HCl. Formulation M3 released 19.92±2.14% of the drug in 1 hour and 99.96±2.19% of the drug in 12 hours. So higher concentration of xanthan gum gives better sustained and complete drug release over 12 hours. Formulation M6 released 32.14±2.46% of the drug in 1 hour and 95.46±2.29% of the drug in 12 hours. Formulation M9 released 36.64±2.34% of the drug in 1 hour and 96.43±2.38% of the drug in 10 hours. Formulation M12 released 37.29±2.46% of the drug in 1 hour and 98.03±2.37% of the drug in 8 hours. From the results, it is evident that drug release from HPMC K15M and HPMC K100M was lesser owing to its high viscosity and also due to less permeability of water. Therefore, could not bear

their matrix shape until 12 hours and released the drug before 12 hours. After 1 hour the drug dissolved from floating tablets composed of HPMC K4M (Batch M6 containing 15% HPMC K4M) was less than tablets containing different concentration of HPMC K15M and HPMC K100M. This showed that high viscosity grade of HPMC hydrated more rapidly than low viscosity grade of HPMC in the presence of 0.1 N HCl. So the formulation M6 containing 15% HPMC K4M gives better controlled release of the drug.

Comparison of formulated dosage form with market product

Formulated metformin hydrochloride floating matrix tablets were compared with marketed product Gluformin XL-500 mg, a commercial sustained release formulation of Metformin HCl. Metformin hydrochloride floating matrix tablets are not available in the market. Hence, for the purpose of comparison only, commercial sustained release formulation was selected. Since comparison is done with commercial sustained release formulation there's only one parameter which can be compared & that is *in vitro* drug release.

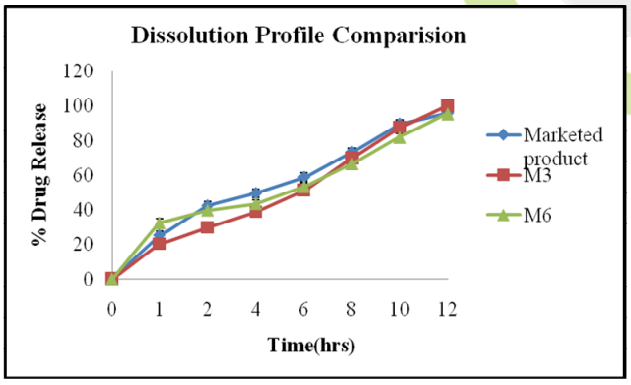

Figure 6: Comparison of *in vitro* dissolution profiles of marketed product with batch M3 and M6

Upon comparison, the results showed that formulation M3 containing 15% xanthan gum and 20% sodium bicarbonate evident better controlled release of the drug than M6 containing 15% HPMC K4M. So it was evident that xanthan gum worked as better gelling agent as well better release retarding agent compared to HPMC K4M. Therefore, on the basis of all evaluation parameters and comparison with marketed product, batch M3 containing 15% xanthan gum and 20% sodium bicarbonate was optimized.

Comparison of Dissolution Profiles by Similarity Factor f2:

Dissolution profile of marketed product and optimized batch M3 and M6 were compared for similarity factor (f2).

An f_2 value between 50 and 100 suggests that the two dissolution profiles are similar. Similarity factor for M3 and M6 was found to be 78.54 and 48.56 % respectively. It shows that f2 value of batch M6 was found to be less than 50. So it is dissimilar with marketed product while batch M3 has similarity value near to 100. So, the result of similarity factor indicates equivalence of the curve. It indicates that batch M3 is similar to marketed product.

Table 4: Evaluation parameters of optimized formulation

PRECOMPRESSION EVALUATION PARAMETERS	
Bulk Density(gm/ml)	0.542
Tapped Density(gm/ml)	0.644
Angle of Repose	25.49
Compressibilty Index (%)	16.27
Hausner's Ratio	1.19
EVALUATION PARAMETERS OF TABLETS	
Weight variation	881±0.001
Thickness (mm)	6.5±0.05
Diameter (mm)	18.8±0.04
Hardness (kg/cm^2)	7.1±0.12
Friability (%)	0.15±0.04
% Drug content	99.8±1.77
Floating Lag Time (sec)	32 sec
Total Floating Time (hrs)	>12
% Drug release in 12 hrs	99.96±2.19

Drug release kinetics

Table 8 enlists the regression parameters obtained after fitting dissolution release profile to various kinetics models. The *in vitro* release data were kinetically analyzed for establishing kinetics of drug release. Zero-order, first-order, Higuchi, Korsmeyer-Peppas and Hixson Crowell models were tested.

Table 5: Model Fitting for Optimized Batch (M3)

Model	R^2	Slop	Intercept	Equation
Zero Order Kinetic	0.983	7.796	7.647	Y = 7.796x + 7.647
First order Kinetic	0.767	-0.143	2.284	Y = -0.143x + 2.284
Higuchi	0.952	32.40	-18.90	Y = 32.40x - 18.90
Korsmeyer-Peppas	0.970	0.642	1.264	Y = 0.642x + 1.264
Hixon-Crowell	0.690	0.280	1.755	Y = 0.280x + 1.755

The best fit model was selected on the basis of R^2 value. It is evident from the data the Zero Order Kinetic and **Korsmeyer-Peppas** model were the best fit model for batch M9.The value of n is indicative of release mechanism. Here $0.5 < n < 1$ so, anamolous (non-fickian) diffusion was seen. The values of diffusional exponent (n) of all batches are between 0.5-1.0, so all batches showed diffusion and erosion controlled release mechanism.

Stability study of optimized batch

Stability study was done to see the effect of temperature and humidity on tablets.

Storage conditions:

(1) Accelerated temperature (40 °C)

(2) Accelerated temperature at 75 %RH.

Time period: 4 weeks (nearly one month).

At intervals of every one week, the tablets were visually examined for any physical changes, changes in drug content, floating lag time, total floating time and *in vitro* drug release study.

The results indicate no significant change in the tablet properties. Hence it can be concluded that the formulated floating matrix tablets are stable under appropriate storage conditions.

CONCLUSION

The present study underlines the importance of gastroretentive formulation. Floating matrix tablets containing Metformin hydrochloride were prepared by wet granulation method. By using optimum amount of strong gelling agent as well as gas generating agent, it is possible to prepare floating matrix tablets of Metformin HCl with acceptable mechanical strength and rapid disintegration, to provide desired drug release property. *In-vitro* drug release study was performed in 0.1N HCl, which shows that all formulations follow zero order drug release pattern and non-fickian as a drug release mechanism. The result revealed that increase in the proportion of polymer (xanthan gum and HPMC K4M) was associated with decreased in the overall cumulative drug release rate.

The optimized batch (M3) containing xanthan gum shows drug release in a controlled manner for 12 hours and good stability was observed after 1 month during stability studies. By applying different model for Batch M3, the Korsemeyer model was good fit with linearity value 0.970. The drug release followed Korsemeyer model and which indicates a coupling of diffusion and erosion mechanisms so called anomalous diffusion. The results of stability indicated that there was no change in the formulation after 1 month accelerated stability study. The prepared formulation of Metformin HCl sustained release floating matrix tablet was stable.

Table 6: Results of stability study

No. of weeks	Hardness (Kg/cm^2)	Friability (%)	% Drug Content	Floating lag time (sec)	Total Floating Time (hrs)	*In vitro* drug release study
0	7.2±0.15	0.15±0.07	99.8±0.67	32	12	99.96±2.19
1	7.4±0.12	0.16±0.06	99.8±0.78	34	12	99.96±2.62
2	7.5±0.06	0.16±0.07	99.8±1.42	34	12	99.83±2.76
3	7.6±0.12	0.18±0.07	99.8±1.58	35	12	99.78±2.34
4	7.8±0.15	0.19±0.06	99.8±1.38	36	12	99.75±2.52

REFERENCES

1. Debojit B, "Recent trends in sustained release matrix drug delivery system-an overview" www.pharmainfo.net
2. Agyilirah GA, Green M, Ducret R "Evaluation of the gastric retention properties of a crosslinked polymer coated tablet versus those of a non-disintegrating tablets", International Journal of Pharmaceutics, 1991, 75, 241-247.
3. Hoffman F, Pressman JH, Code CF "Controlled entry of orally administered drugs: physiological considerations", Drug Development and Industrial Pharmacy, 1983, 9, 1077-1085.
4. Deshpande AA, Shah NH, Rhodes CT "Controlled release drug delivery systems for prolonged gastric residence: an overview", Drug Development and Industrial Pharmacy, 1996, 22, 531-539.
5. Hwang SJ, Park H, Park K "Gastric retentive drug delivery systems", Critical Reviews in Therapeutic Drug Carrier System, 1998, 15, 243-248.
6. Gholap SB and Banarjee SK, "Hollow microspheres: a review" International Journal of Pharmaceutical sciences Review and Research, 2010, 1(1), 74-79.
7. Singh N, Kim KH "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention", Journal of Controlled Release, 2000, 63, 235-259.
8. Lu MF, Woodward L, Borodkin S, "Xanthan gum and alginate based controlled release theophylline formulations", Drug Development and Industrial Pharmacy, 1991, 17, 1987-2004.
9. Talukdar MM, Plaizier-Vercammen J, "Evaluation of xanthan gum as a hydrophillic matrix for controlled release dosage form preparations", Drug Development and Industrial Pharmacy, 1993, 19, 1037-1046.
10. Tobyn MJ, Staniforth JN, Baichwal AR, McCall TW, "Prediction of physical properties of a novel polysaccharide controlled release system", International Journal of Pharmaceutics, 1996, 128, 113-122.
11. Gohel MC, Parikh RK, Nagori SA, Jena DG, "Fabrication of modified release tablet formulation of metoprolol succinate using hydroxypropyl methylcellulose and xanthan gum", American Association of Pharmaceutical scientists and Technology, 2009, 10, 62-68.
12. Alderman DA, "A review of cellulose ethers in hydrophilic matrices of oral controlled

release dosage forms", International Journal of Pharmaceutics, 1984, 5, 1-9.
13. Yan G, Li H, Zhang R , Ding D , "Preparation and evaluation of a sustained release formulation of Nifedipine HPMC tablets", Drug Development and Industrial Pharmacy, 2000, 26, 681-686.
14. Nathan DM , Buse JB , Davidson MB, Ferrannini E, Holman RR, Sherwin R, "Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes", Diabetes Care, 2009, 32, 193−203.
15. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA, "10-year follow up of intensive glucose control in type 2 diabetes, The New England Journal of Medicine, 2008, 359, 1577−1589.
16. Dunn CJ, Peters DH, "Metformin: A review of its pharmacological properties and therapeutic use in non-insulin-dependent diabetes mellitus", Drugs, 1995, 49, 721-749.
17. Defang O, Shufang N, Wei L, "In vitro and in vivo evaluation of two extended Release preparations of combination metformin and glipizide", Drug Development and Industrial Pharmacy, 2005, 31, 677–685.
18. Stepensky D, Friedman M, Srour W, Raz I, Hoffman A, "Preclinical evaluation of pharmacokinetic–pharmacodynamicrationale for oral CR metformin formulation", Journal of Controlled Release, 2001, 71, 107–115.
19. Kumar R, Patil S, Patil MB, "Isolation and evaluation of disintegrant properties of fenugreek seed mucilage" International Journal of PharmTech Research, 2009, 1(4), 982-996.
20. Marshall K, Lachman L Liberman HA Kanig JL, Theory and Practice of Industrial Pharmacy, 3rd Edn, Varghese publishing house, Bombay, pp 66-99.
21. Howard Ansel, Introduction to Pharmaceutical Dosage Forms, 3rd Edn, K.M Varghese Company, Bombay, pp 221-245.
22. Metformin tablets dissolution, USP NF 2007, pp 196-210.
23. Note for the guidance on investigation of Bioavailability and Bioequivalence, EMEA, London, 2001.
24. Singhvi G and Singh M, "Review: In vitro drug release characterization model" International Journal of Pharmaceutical Studies and Research, 2011, 2(1), 77-84.
25. "Note for guidance on stability testing: Stability testing of new drug substances and products", 2003, http://www.ich.org/cache/compo/363-272-1.html.
26. Lachman L, Libermam HA, Kanig JL. The theory and practice of Industrial pharmacy; 3rd Edn; Mumbai varghose publishing house, 1990, pp 296-302.

