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PREPARATION AND EVALUATION OF FLOATING TABLET OF METFORMIN HCL

Rehana Parveen[1]* and Ranjeet Kumar Bhargav[2]

*1, 2Spectrum Institute of Pharmaceutical Sciences & Reasearch, Greater Noida (U.P.), India.

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***Corresponding Author**
Rehana Parveen
Spectrum Institute of Pharmaceutical Sciences & Reasearch, Greater Noida (U.P.), India

ABSTRACT

The objective of the research work was to provide a gastroretentive system for sustained release of metformin HCl in proximal part gastrointestinal tract (GIT) in the form of oral floating tablet. Metformin HCl is an anti-diabetic biguanid with poor bioavailability and absorption window at the upper part of GIT. Floating tablets were prepared by wet granulation method incorporating natural polymers guar gum and k-Carrageen and a synthetic polymer HPMC K100 (HPMC) either alone or in combination. Sodium bicarbonate and citric acid was used as gas generating agent. Floating tablets were evaluated for weight variation, hardness, and friability, drug content, swelling index, in vitro buoyancy and in vitro drug release study. The formulation optimized based on floating ability, matrix integrity, and in vitro drug release in simulated gastric fluid pH 1.2. Formulation prepared with combination of 6% w/w k-carrageen and 11%w/w guar gum showed good gel strength, stable and persistent buoyancy for 12h, least floating lag time of 58 sec with good matrix integrity throughout dissolution period. The mechanism of drug release was appears to be diffusion mechanism. Stability studies indicated absence of any drug degradation on storage for 3 months at 40oC.

KEYWORDS: Floating, Buoyancy, Gastro retentative, Sustained Release.

INTRODUCTION

The oral route considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of drug 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. As once the drug passes down the absorption site, the remaining quantity goes unabsorbed. The gastric emptying of dosage form in human is affected by several factors because of which wide inter and intra-subject variations are observed.[1] Hence, a 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 controlled gastric retention of solid dosage forms may be achieved by the mechanism of mucoadhesion[2, 3] floatation[4], sedimentation[5, 6], expansion[7, 8], modified shape systems[9,10] or by the administration of pharmacological agents[11, 12] that delaying gastric emptying. Based upon these approaches, floating drug delivery systems seems to be the promising delivery systems for control release of drugs. Floating drug delivery system (FDDS) possesses a bulk density lower than gastric fluids and thus remain buoyant in the gastric fluids for a prolonged period without affecting the gastric emptying rate. While the system is floating on the gastric content, the drug released slowly at desired rate from the system.[13] Based on the mechanism of buoyancy, two distinctly different technologies, non-effervescent and effervescent systems have been utilized in the development of FDDS. Thus produces an upward motion of the system maintaining buoyancy.[14] Metformin hydrochloride, a BCS class III drug, has taken as the model drug for the present study. It is an antihyperglycemic 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 to 1.6h and the main site of its absorption is proximal small intestines.[15, 16] 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.[17]

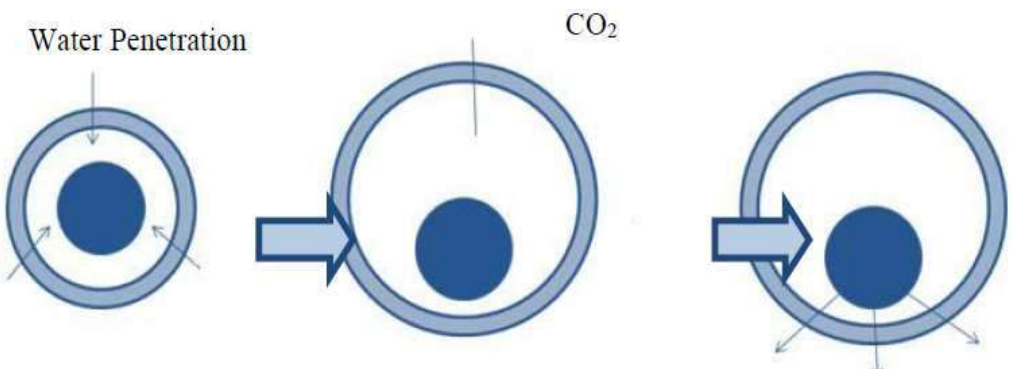


Figure:1 Working Principle of Effervescent Floating Drug Delivery System

MATERIALS AND METHODS

Materials: Metformin HCl was supplied by Ranbaxy Pharmaceuticals Ltd, Gurgaon. -Carrageenan was procured from Aquagri Processing Pvt. Ltd.Tamil Nadu. Gaur gum was purchased from SD Fine Chemicals, Mumbai. HPMC obtained as a gift sample from Colorcon Asia Pvt. Ltd. Goa. All other chemicals were of analytical grades as required.

Methods: Floating tablets were prepared by effervescent technology.[18] Each floating tablet containing metformin HCl500mg was prepared by conventional wet granulation method employing sodium bicarbonate and citric acid as gas generating agents. Preliminary studies for optimizing the floating timewere carried out. Once floating was optimized\ the same concentration of sodium bicarbonate and citric acid was used in all other formulations. The compositions of the formulations are given in the Table 1. Weighed quantities of all the ingredients were sifted through stainless steel sieve (#40). Sifted materials were dry mixed in geometric dilution by spatulation without addition of magnesium stearate and talc. Distilled waterwas added to dry-mixed blend of drug and excipients, slowly and the wet mass was mixed to get desired doughy consistency. The doughy mass passed through stainless steel sieve (#16) to form granules. Granules were dried in hot air oven at 50°C for 30 min and mixed with lubricant magnesium stearate and glidant talc. The lubricated granules were compressed on a ten station tablet mini press (Rimek, India) using a 13 mm flat punch. Compression force adjusted to obtain hardness in the range of 3-5 kg/cm2.

Table 1: Composition Of Floating Tablets Of Metformin Hcl

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCL	500	500	500	500	500	500	500	500
HPMC	166	-	106	60	-	-	-	34
K-Carrageenam	-	-	60	106	60	132	34	132
Guar GUM	-	166	-	-	106	34	132	-
Sodium Bicarbonate	230	30	230	230	230	230	230	230
Citric ACID	10	10	10	10	10	10	10	10
Magnesium Stearate	7	7	7	7	7	7	7	7
Talc	7	7	7	7	7	7	7	7
Total Weight of Tablets	920	920	920	920	920	920	920	920

Infrared Spectra Analysis: FTIR studies were carried out in order to determine any possible interaction between drug and excipients used. IR absorption spectrum of metformin HCl was determined using FTIR spectrophotometer (Jasco-V-530).Briefly, about 2 mg of sample of was ground thoroughly with previously dried KBr at 120ºC for 30 min; uniformly mixed with drug and kept in sample holder and the spectra was recorded over the wave number 400-

4000cm-1. IR spectrums of pure drug, physical mixture of ingredients of the formulation and optimized tablet wererecorded. Pure, completely dried KBr used as blank and before running the sample.

Evaluation of Granules: The angle of repose of the granules was determined by using funnel method. Bulk density (BD) and tapped density (TD) were calculated by formulae:BD = Bulk mass / Bulk Volume; TD=Bulk density = Bulk mass / Bulk Volume. Compressibility index and Hausner's ratio of the granules was determined by using the formula: CI(%) = [(TDBD/ BD)] ×100 and HR=TD/BD, respectively. The experiments were performed in triplicate and average value with SD werenoted. 3, 10

Evaluation of Tablets: Uniformity of weight was determined according to method reported in I. PWeight variation was determined by weighing 20 tablets using an analytical balance and the deviation of individual tablet from the average weight of the tablets was determined. Hardness of the tablets tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Thickness and diameter measured by vernier caliper.[19, 20]

Drug content: Twenty tablets weighed and powdered. The stock solution was prepared by dissolving powder equivalent to 10 mg of drug in 10 mL water. Stock solution was sonicated for 20 min. The resulting solution was further diluted with water to achieve concentration 10µg/mL and the absorbance measured at the 233 nm by UV spectrophotometer.

In -vitro buoyancy study: In vitro buoyancy was characterized from floating lag time and total floating timedescribed by Rosa et al.[21, 22] The test was performed using a USP dissolution test type II apparatus (Electro lab) using 900 mL of 0.1 N HCl at rotation of 50 rpm at 37±0.5oC. The time required for the tablet to rise to the surface of the dissolution medium and the duration of time the tablet constantly floated on the dissolution medium wasrecorded as floating lag time and total floating time, respectively.

Water uptake study: The swelling properties of floating tablets were determined by placing the tablet in the dissolution test apparatus, in 900 mL of 0.1 N HCl at 37 ± 0.5^{0}C. After a specified time intervals, the tablet was withdrawn, blotted to remove excess water and weighed. Swelling characteristics were expressed as percentage water uptake (%WU).[23]

$$WU\% = \frac{\text{Weight of swollen tablet} - \text{Initial weight of the tablet}}{\text{Initial weight of the tablet}}$$

In vitro dissolution studies: In vitro dissolution studies were performed using USP type- II dissolution test apparatus (TDT 08L, Electro lab Pvt. Ltd., Mumbai, India). The test was performed using 900Ml of 0.1N HCl at 37±0.5°C at 50 rpm. Accurately 5 mL sample of dissolution medium was withdrawn from the vessel hourly for total 12h and the withdrawn sample was replaced with equal amount of fresh dissolution medium. The sample was filtered through 0.45µ membrane filter and diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions were measured at _max 233nm using UV spectrophotometer (JASCO UV530). Analysis of data done was performed using PCP Disso V-3 software.[24]

Stability Studies: The optimized metformin hydrochloride floating tablets (batch F5) were packed and subjected to accelerated stability studies as per ICH guidelines (40°C ± 2 °C /75 % ± 5 % RH).[25] The sample were withdrawn periodically at the end of 30, 60, 90 days, respectively and evaluated for the different parameters.

Comparative study: Dissolution profile of optimized formulation (F5)compared with that of marketed formulation (Glycomet® SR-500mg)

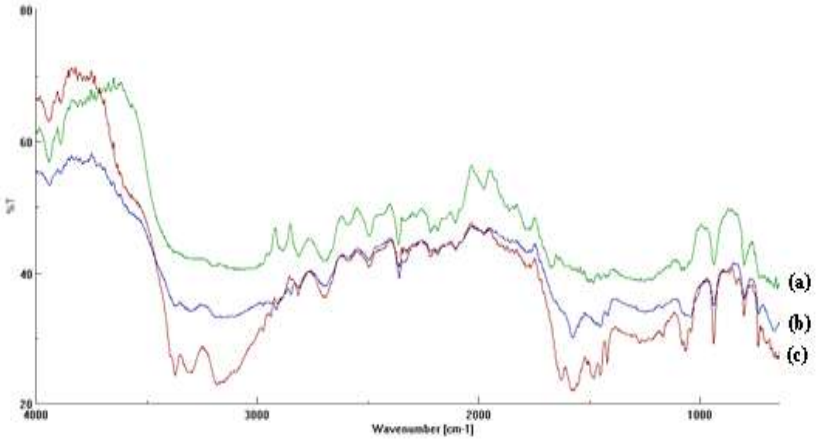
ADVANTAGES OF EFFERVESCENT FLOATING DRUG DELIVERY SYSTEM

- Increases the oral bioavailability of drug.
- Enhanced first pass biotransformation.
- Sustained drug delivery/ reduced frequency of dosing.
- Reduced fluctuations of drug concentration.
- Improved receptor activation selectivity.
- Reduced counter-activity of body.
- Extended time over critical (Effective) concentration.
- Minimized adverse activity at the colon.

RESULTS AND DISCUSSION

Infrared Spectra Analysis

FTIR studies revealed that fundamental peaks of the metformin HCl retained in the optimized tablet and physical mixture. The results, Fig. 1, indicated absence of any significant interactions between the drug and polymers used in the formulation and hence, these can be used in the formulation of floating tablet of metformin HCl.



Fifure: 2 Overlain FTIR spectrums

Table 2: Granule Properties of all the batches

Batch	Bulk density(g/cm3)	Tapped density (g/cm3)	Carr's index	Hausner's ratio	Angle of repose (°)
F1	0.0471±0.003	0.4591±0.001	11.32±0.36	1.09±0.04	27.37±0.43
F2	0.3758±0.001	0.4269±0.002	11.96±0.24	1.13±0.03	22.63±0.41
F3	0.3998±0.002	0.4698±0.003	14.87±1.88	1.17±0.02	26.42±0.12
F4	0.4033±0.003	0.4505±0.009	11.10±1.55	1.36±0.04	24.80±0.17
F5	0.4031±0.006	0.4598±0.003	12.32±1.13	1.14±0.06	20.83±0.13
F6	0.4202±0.007	0.4798±0.004	12.69±1.77	1.75±0.02	27.43±0.12
F7	0.4133±0.009	0.4681±0.001	11.36±0.55	1.14±0.01	24.51±0.14
F8	0.3333±0.007	0.4166±0.006	19.99±0.45	1.25±0.07	25.31±0.21

Evaluation of Granules: The bulk density of granules was in the range 0.3333±0.007 to 0.4202±0.007 g/cm3 and tap density in the range 0.4166±0.006-0.4798±0.004 g/cm3 as shown in Table 2. The observation indicates good packing capacity of granules.Carr's index was in the range of 11.10±1.55 to 19.99± 0.45% whereas Hausnerratio was in the range of 1.09±0.04to 1.75±0.02indicating good flowability. The angle of repose was within the range of 25º to 30°. The observations suggest good flow ability of the granules.

Evaluation of Tablets: The weights of the tablet were varied between 917±0.79to 921±0.84 mg. The variation in weight was within the range of ±5%, complying with pharmacopoeial specifications. Thickness was in range of 4.30± 0.07 to 4.95±0.07mm. The hardness of found in the range 4.39 ± 0.17 to 4.73±0.39Kg/cm2 indicating satisfactory mechanical strength. All formulations, Table 3, exhibited a weight loss of <1% and the loss were in the range of 0.49 ± 0.05 to 0.89±0.02. It ensures that the tablets can withstand mechanical impacts during packing, transportation and other processing operations.The drug content was in the range of 97.53±0.29 to101.18±0.12 mg, complying drug content uniformity test.

In Vitro Buoyancy Studies: All the tablets prepared by effervescent approach. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced CO2 generation in the presence of dissolution medium (0.1 M HCl). Generated gas was trapped and protected within the gelformed by hydration of polymer, decreasing the density of the tablet. As density of the tablet falls below one the tablet became buoyant. Floating lag times were in the range of 58 to 540 sec. Formulations F3, F4, F8 prepared as combination of HPMC and _-Carrageen showed floating lag time of 135, 105, 370 sec, respectively, and remain buoyant for 10, 8, 5h, respectively, Table 4, till completely eroded. On the other hand, formulation F5, F6, F7 prepared with combination of _-Carrageenan and guar gum showed decrease in floating lag time and increased floating duration time. This might be due to viscous nature of guar gum, which maintains the integrity of the tablets for longer duration by reducing the effect of erosion thus resulting in increase in floating time. The selected formulation F5 showed floating lag time 58 sec, Fig. 2, with floating duration time >12 h. Hence, Batch F5 with floating lag time <1 was optimized batch.

Table 3: Floating Properties of metformin HCl tablets

Batch code	Floating lag time (sec)	Matrix integrity	Floating duration (h)
F1	75	-	>12
F2	540	-	>12
F3	135	-	Disintegrated after 10 hrs
F4	105	-	Disintegrated after 8 hrs
F5	58	-	>12
F6	210	-	>12
F7	430	-	>12
F8	370	-	Disintegrated after 5 hrs

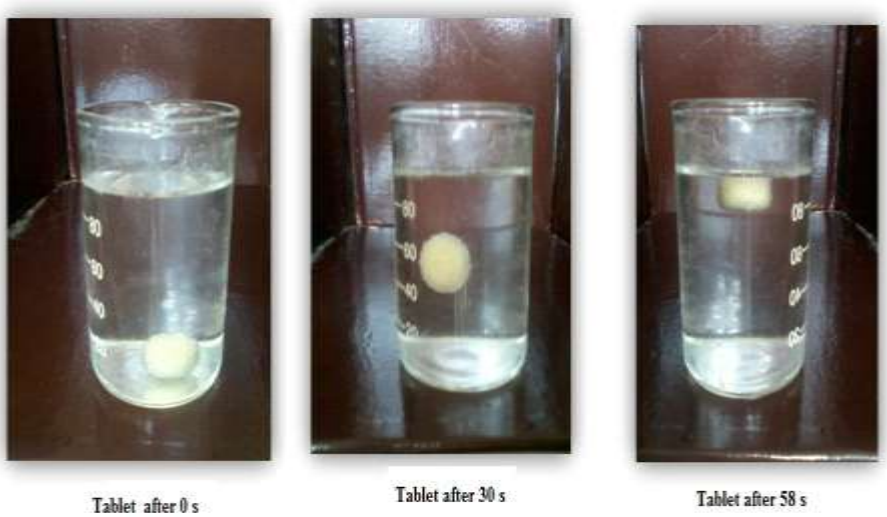


Figure 3: Photographs of in-vitro buoyancy study of F5 batchbcontaining _-Carrageenan and guar gum

Swelling Characteristics: The swelling indices were calculated with respect to times. As time increases, the swelling index was increased, because weight gain by tablet increased proportionally with rate of hydration. Later on, it was decreased gradually due to dissolution of outermost-gelled layer of tablet into dissolution medium. Formulation F1 showed maximum swelling in 12h with sharp increase up to 5h, this might due to higher concentration of HPMC, which has higher water absorption capacity and form thick swollen mass. From observed swelling indices of batches F5, F6 and F7, Fig. 3, it was revealed that swelling indices were increased as the concentration of _-Carrageenan increased. _-Carrageenan binds with water extensively and get hydrated because of the high mobility of water molecules between polymer chains and sulphategroups24. The optimized formulations F5 show maximum swelling up to 5h followed by decrease in swelling index, Fig. 3. Reason behind this may be erosion process initiation at the end of 5h attributing gradual decrease in percent swelling after 5h.

Dissolution Studies: In vitro drug release studies performed as per procedure described in methodology section. The percentage drug release plotted against time to obtain drug release profile, Based on the dissolution profiles the formulations can be arranged in the following order of their controlling efficiency as F4>F5>F8>F1>F7>F2>F3>F6. The mean diffusion exponent values (n) for batches F1, F3, F4, F6, F8 were in the range of 0.3509 to 0.4265, Table 5, indicating the drug release govern by Fickian diffusion mechanism. On the other hand, batch F2 and F5 showed n values in the range of 0.6127 and 0.9480; indicating the drug release governed by Anomalous transport mechanism. By comparing the r-values of different models, Korsmeyer- Peppas model found to be the best fit with higher values of correlation coefficient. In-vitro dissolution data gave us information about the effect of change in polymer type and concentration on drug release and swelling capability of formulation. Formulation F1 and F2 released 95.80% and 85.14% of drug, respectively, in 12h.This difference may be due to lack of enough gelling strength of HPMC to control the drug release and less water permeability of guar gumcompared to HPMC. Dissolution data of formulation F3, F4, F5, F6, F7 and F8 revealed increase in drug release with concentration of _-Carrageenan and further decreases at its highest concentration employed._-Carrageenan-guar gum combination imparts good matrix integrity compared to _- Carrageenan-HPMC. Formulation F5 showed better drug release than other formulations with least floating lag time, persistent buoyancy, and good matrix integrity throughout dissolution period. Hence, formulation F5 was considered as the best formulation.

Table 4: Dissolution data and release kinetics of Korsmeyer-Peppas model

Batch	% Drug release after 12h	n	k	r	Best fit model
F1	95.80	0.4265	34.1116	0.9811	Matrix
F2	85.14	0.6127	20.7729	0.9815	Matrix
F3	81.76	0.3713	34.1381	0.9782	Peppas
F4	s99.35	0.3897	37.1290	0.9783	Matrix
F5	98.76	0.9480	10.0109	0.9906	Peppas
F6	79.94	0.3626	35.0946	0.9546	Peppas
F7	85.64	0.3509	38.1292	0.9091	Matrix
F8	96.69	0.8736	8.6181	0.9810	Zero order

DSC Studies: DSC thermogram of pure metformin HCl, Fig. 5, showed sharp endothermic peak starting at 209ºC with melting peak at 225.1ºC and in the thermogram of optimized batch the endothermic peak appeared at 208.1ºC. Shifting of endothermic peaks to left side with decrease in its intensity indicates amorphization of drug. Another peak observed in formulation at 160.3ºC may be due to polymer.

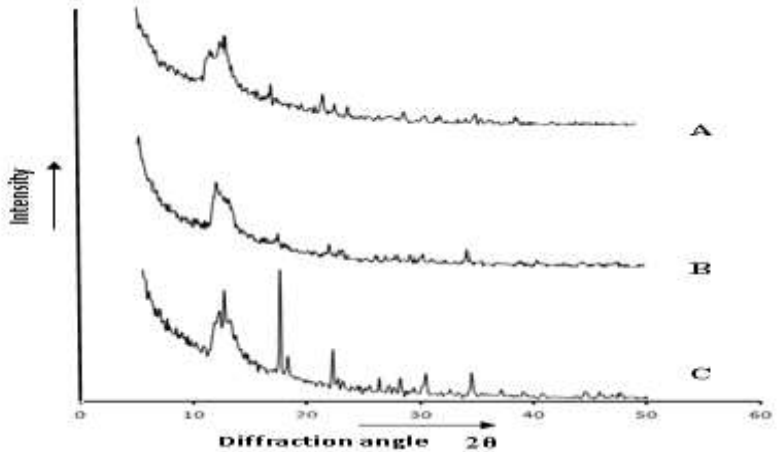
Figure 4: DSC thermograms.

PXRD Studies

The overlay of PX-RD pattern of Metformin HCl, physical mixture and optimized formulation F5 showed in Fig.6. 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 the metformin HCl.

Stability Study of Batch F5

The results of stability studies, shown in Table 6, indicate no evident change in the physical properties of formulations after subjecting them to 30, 60 and 90 days accelerated stability studies. Thus, itconcludes that the drug does not undergo degradation on storage.



Overlain Powder X-ray diffractograms. Key: (A)
Physical mixture (B) Optimized batch F5 and (C) Metformin HCl

Comparison of Optimized Formulation with Marketed Product

The marketed product had showed 94.8% drug release in 12h, where as the optimized formulation F5 showed 98.7% drug release in 12h. Comparison study with marketed product of Glutamet® SR 500mg,has showed that the optimized formulation F5 has better drug release in comparison to the marketed product as showed in Fig. 8. The optimized formulation F5 remained floatable in the stomach for 12h. Hence, it has one of the advantages over marketed formulation that it increases absorption of metformin HCl drug. It is, thus concluded that effervescent floating tablet containing metformin HCl (F5) gives better and but complete drug release over 12h.

CONCLUSION

Metformin HCl floating tablets were prepared by combination of HPMC and _- Carrageenan and guar gum in different concentration. Formulation F5 made by combination of natural polymers, _-Carrageenan (6%) and guar gum (11%) exhibited the best results in terms of the required in vitro buoyancy study, good matrix integrity and drug release in sustained release manner. There was absence of any significant change in nature of drug or any interaction between drug and polymers. Scanning electron microscopy revealed drug release from matrix was by diffusion mechanism. Stability studies indicated absence of degradation on storage. Comparative study with marketed tablet formulation showed better and complete release characteristics. Natural polymers areadventitious over synthetic ones. Finally, it can be concluded that the prepared drug delivery system containing natural polymers can be

considered as one of the promising formulation technique for preparing floating drug delivery systems of metformin HCl in the management of diabetes mellitus.

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