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Research Article

Design and evaluation of floating drug delivery systems of Metformin with natural gums as release retarding polymers

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Abstract

Metformin hydrochloride floating tablets were prepared by wet granulation method by using optimized concentrations of gas generating agents, binding agents and natural gums as polymers like gum kondagogu and gum karaya. The formulations F_1-F_4 with concentrations 2-3.5% were prepared to optimize binding agent and formulations F_5-F_7 with concentrations 15-20% to optimize gas generating agent where optimum percentage of binding agent was found around 2.3% and gas generating agent was found around 17.25% to get quick floating lag time. The prepared granules evaluated for various parameters showed good results in which the Carr's index, hausner ratio and angle of repose, the values were found in between 9.05-16.78, 1.02-1.46 and 23.17-32.64 respectively. All compressed formulations were evaluated for various parameters and results of hardness, friability, drug content, were found around 7.1-8.8kg/cm^2, 0.56-1.48% and 499.3-499.8mg respectively. The tablets prepared by these granules of two natural gums as polymers showed desired floating properties. F_6 formulation containing gum kondagogu and F_{11} formulation containing gum karaya showed good release retardation with release 99.42% and 99.75% respectively after 12 hours in *in vitro* drug release studies. Formulations F_6 and F_{11} after stability studies showed good results proving stable. *In vivo* studies also showed good correlation with the results of *in vitro* and X-ray pictograms proved the formulations is stable *in vivo*. Formulations F_6 and F_{11} contains natural gums Kondagogu and karaya with 17.25% concentration were considered as best formulation as they showed good release retardation and, in release kinetic studies the n-value found appropriate for controlled release formulations.

1. Introduction

Gastric emptying of dosage forms is an extremely variable process and ability to prolong and control the emptying time is a valuable asset for dosage forms, which reside in the stomach for a longer period of time than conventional dosage forms. Several difficulties are faced in designing controlled release systems for better absorption and enhanced bioavailability. One of such difficulties is the inability to confine the dosage form in the desired area of the gastrointestinal tract. Drug absorption from the gastrointestinal tract is a complex procedure and is subject to many variables. It is widely acknowledged that the extent of gastrointestinal tract drug absorption is related to contact time with the small intestinal mucosa[1]. Thus, small intestinal transit time is an important parameter for drugs that are incompletely absorbed. Retention of drug delivery systems in the stomach prolongs overall gastrointestinal transit time, thereby resulting in improved

bioavailability.

The controlled gastric retention of solid dosage forms may be achieved by the mechanisms of mucoadhesion, floatation[2], sedimentation, expansion, modified shape systems[3], or by the simultaneous administration of pharmacological agents that delay gastric emptying.

Metformin Hydrochloride[4-5] is an oral anti-hyperglycemic drug used in the management of type 2 diabetes. Metformin Hydrochloride (N, N-dimethylimidodicarbonimidic diamide mono hydrochloride) is not chemically or pharmacologically related to sulfonylureas, thiazolidinediones, or α-glucosidase inhibitors. It is a white to off-white crystalline compound with a molecular formula of $C_4H_{12}ClN_5$ (monohydrochloride) and a molecular weight of 165.63. Metformin Hydrochloride is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of Metformin Hydrochloride is 12.4. The pH of a 1% aqueous solution of Metformin Hydrochloride is 6.68.

Gum Karaya, often known as Sterculia gum, is the dried exudation of the "*Sterculia Urens*" tree and other species of Sterculia and belong to Sterculiaceae family[6]. The tree is native to India. The highest grade of Gum Karaya is white, translucent and almost free from bark. Powdered Gum Karaya is white to grayish white. Powdered gum karaya swells in cold water to an extent that a 3 to 4% solution will produce a heavy gel of uniform smoothness and texture. Gum Kondagogu is a natural gum exudates[7] obtained from stems and branches of "*Cochlospermum gossypium"* and belongs to Bixaceae family. It occurs as pale brown to brown in color. The specific rotation is 53.5 (±7.37). The water binding capacity for gum kondagogu is 35.1 mL g^{-1}. It is swellable in water.

Here an attempt was made to prepare and evaluate controlled release floating drug delivery systems of metformin with gum karaya and gum kondagogu.

2. Materials and Method

Metformin Hydrochloride was obtained as gift samples from Aurobindo Pharma Ltd, Hyderabad. Gum Kondagogu and Gum Karaya were obtained from Girijan Co-operative Corporation Ltd., Visakhapatnam. Methanol, Potassium Di Hydrogen Phosphate, Sodium Hydroxide, Hydrochloric Acid, Barium Sulfate and Sodium Bicarbonate were obtained from M/s. Qualigens Fine Chemicals, Mumbai. Magnesium Stearate and Chloroform were obtained from M/s. S. D. Fine-Chem Ltd., Mumbai. Poly Vinyl Pyrrolidone was obtained from M/s. Himedia Laboratories Pvt. Ltd., Mumbai. Glycomet – 500 mg SR tablets (M/s USV Limited, Mumbai; Batch No. 28001178; Mfg. date: 4-2008; Exp. Date: 3-2010) were procured from local market.

2.1 Estimation of Metformin Hydrochloride: A spectrophotometric method based on the measurement of absorption at extinction 233 nm[5] in a 0.1N hydrochloric acid solution was used in the present study for the estimation of metformin hydrochloride.

2.2 Preformulation Studies: Compatibility studies between metformin hydrochloride and natural gums were studied by subjecting the formulation samples to DSC & IR spectral studies.

2.3 Differential Scanning Calorimetry: Differential Scanning Calorimetry (DSC) curves were obtained by a differential scanning calorimeter (DSC 220C, Seiko, Tokyo, Japan) at a heating rate of 10^{O}C/min from 30 to 300^{O}C in a nitrogen atmosphere 20 mL/min with a sample weight of 3 mg.

2.4 Infrared Spectroscopic Studies: Fourier–Transform Infrared (FT–IR) spectra were obtained on a Perkin Elmer 2000 FT–IR system (Perkin Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 400 to 4000 cm^{-1} and the resolution was 1cm^{-1}.

2.5 Formulation of Metformin Hydrochloride Tablets: Effervescent type metformin hydrochloride floating drug delivery systems were formulated separately with the gum kondagogu and gum karaya. The influence of formulation variables like concentration of binding agent, gas-generating agent and concentration of gums on performance of tablet were studied. These process variables were optimized and the optimized concentrations of these key excipients were incorporated in the final tablet formulations.

In order to study the influence of binder concentration on physical appearance and performance of tablet, different concentrations of binding agent poly vinyl pyrrolidone (2 to 3.5 %w/w) were incorporated. The compositions of these tablets are shown in (Table 1) and were formulated by wet granulation technique. The components were blended for 15 min, moistened with water to form a damp mass and passed through Sieve No #12 to get granules. The obtained wet granules

were dried at 60 ^{O}C in hot air oven. Then the granules were passed through Sieve No. #16, lubricated with magnesium stearate & talc and compressed as tablet weighing 870mg by using Cadmach 16 station tablet compression machine with flat-faced punches (12 mm diameter). Similarly the tablets were formulated with different concentrations of gas generating agent (15 to 20 %w/w) sodium bicarbonate, various concentrations (15 to 20 %w/w) of gum kondagogu and gum karaya to study the influence of these agents on release rate.

Table 1: Composition of Metformin Hydrochloride Tablets

Ingredients	Quantity (mg) per Tablet													
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Gum Kondagogu	150	150	150	150	150	150	150	175	125	100	-	-	-	-
Gum Karaya	-	-	-	-	-	-	-	-	-	-	150	175	125	100
Sodium Bicarbonate	100	100	100	100	120	150	180	150	150	150	150	150	150	150
PVP K30	10	15	20	25	20	20	20	20	20	20	20	20	20	20
Magnesium Stearate	05	05	05	05	05	05	05	05	05	05	05	05	05	05
Dicalcium Phosphate	105	100	95	90	75	45	15	20	70	95	45	20	70	95
Total Weight	870	870	870	870	870	870	870	870	870	870	870	870	870	870

2.6 Evaluation of Granules: Metformin hydrochloride granules formulated with various concentrations of binder, gas-generating agent and gums were subjected to micromeritic studies and other parameters like:

2.6.1 Angle of Repose: The flow properties of granules were studied by measuring the angle of repose employing fixed funnel method. The angle of repose was calculated by using the following formula[8].

$$\text{Tan } \alpha = \frac{h}{r} \text{ or } \alpha = \text{Tan}^{-1} \frac{h}{r}$$

Where h = height of the pile, cm

r = radius of the base of the pile, cm

2.6.2 Hausner Ratio and Carr's Index: Hausner ratio and Carr's index were determined from the poured and tapped bulk densities of a known weight of sample using a measuring cylinder. The following formulas were used for calculating Hausner ratio[9] and Carr's Index[10]

$$\text{Hausner ratio} = \frac{D_p}{D_t}$$

$$\text{Carr's index} = \frac{(D_p - D_t)}{D_p} \times 100$$

where D_p (poured density) = weight/V_p (poured volume), D_t (tapped density) = weight/V_t (tapped volume).

2.6.3 Moisture Content: Granules (1.0 g) were kept in an oven which was maintained at 105 ^{O}C and dried up to constant weight. Moisture content was calculated using the following formulae.

$$\text{Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

2.6.4 Loss on Drying: Granules (1.0 g) were kept in an oven at 105 ^{O}C and dried up to constant weight. Loss on drying was calculated using the following formulae[11].

$$\text{Loss on drying} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

2.7 Evaluation of Metformin Hydrochloride Tablets: The formulated tablets were subjected to following quality control tests.

2.7.1 Weight Variation: The formulated tablets were tested for weight uniformity. 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is with in permissible limits or not. The following formula was used to calculate weight variation.

$$\%\ \text{Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

2.7.2 Drug Content: Twenty tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of Metformin Hydrochloride was dissolved in 0.1N HCl, diluted to 100 mL with 0.1N HCl then the solution was filtered and the filtrate was suitably diluted with 0.1N HCl. The drug content was estimated spectrometrically at 233 nm[12].

2.7.3 Hardness: The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester[13].

2.7.4 Friability: The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability was calculated using the formula[14].

$$\%\ \text{Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

2.7.5 Floating Lag Time: The tablet was placed in dissolution apparatus and the time taken to float on the dissolution medium was noted[15].

2.7.6 Total Floating Time: The total duration of the time that the tablets float on dissolution medium was noted[15].

2.7.7 Swelling Index: The tablet was weighed (Wo) and placed in dissolution medium containing 0.1N HCl maintained at 37 ^{O}C. At 3rd hour, the tablet was withdrawn and blotted to remove excess water and weighed (W_t). The percentage of swelling index calculated with the following formulae[16].

$$\text{Swelling index} = \frac{W_t - W_0}{W_0} \times 100$$

where W_t = weight of the tablet

at 3rd hour; W_0 = weight of the tablet at initial time

2.7.8 Erosion Study: The pre weighed tablets (W_o) were placed in dissolution medium containing 0.1N HCl maintained at 37 ^{O}C. At 4th hour, the tablets were withdrawn and dried in an oven at 105 ^{O}C and cooled to room temperature and weighed (W_e). The percentage of erosion (E%) was calculated with the following formula[17].

$$E\% = \frac{W_o - W_e}{W_o} \times 100$$

Where W_o = initial weight of the tablet;

W_e = final weight of the tablet

2.7.9 *In Vitro* Drug Release Studies: Dissolution rate was studied using USP II paddle dissolution apparatus, in 900 ml of

0.1N HCl at 37 ± 0.5 ^{O}C at 100 rpm. Aliquot of dissolution medium was withdrawn at regular time intervals and the same volume of pre-warmed (37 ± 0.5 ^{O}C) fresh dissolution medium was replaced. The samples were filtered and drug content of metformin hydrochloride in each sample were analyzed after suitable dilution by Shimadzu UV-1700 double beam spectrophotometer (Shimadzu Corporation, Japan) at 233 nm. Further the *in vitro* drug release studies were also carried out with metformin hydrochloride tablets containing 70 mg of metformin hydrochloride, gum kondagogu/gum karaya (18.23 %w/w), sodium bicarbonate (18.23 %w/w) and PVP (2.31 %w/w).

2.7.10 Determination Of Gastric Retention Period: Evaluation of gastric retention of metformin hydrochloride floating tablet was preformed on rabbit by the use of radio opaque marker barium sulfate. *X-Ray* scintigraphic identification provides a non-invasive method of monitoring total G I residence time without affecting normal G I motility. Healthy rabbit of 2.3 ± 0.5 kg was fasted over night and on the next day morning, selected tablet (F_6) which was adjusted to rabbit dose and containing barium sulfate in place of metformin hydrochloride was administrated followed by giving 25 mL of water. At different time intervals of 0, 1, 2, 4, 6 and 8 hours, rabbit G.I.T. was *X-Ray* photographed and observed for the nature and position of the metformin hydrochloride floating tablet[18].

2.7.11 Stability Studies: An ideal controlled release dosage form apart from other requirements should provide consistency in drug release through out its shelf life. The stability and drug release from the floating tablets developed in this investigation (F_6) was also evaluated according to ICH guide lines[19]. The selected floating tablets were packed separately in the screw capped bottles and stored at 30 ^{O}C ± 2 ^{O}C/65 %RH±5 %RH. All the products were stored for 6 months. After 6 months the release of metformin hydrochloride from the stored products were studied separately.

2.7.12 Pharmacodynamic Studies: Pharmacodynamic studies were carried out in rabbits separately for metformin hydrochloride formulations. The blood sugar levels were measured after administration and compared with the standard drug to determine the efficiency of the selected formulations. The experimental procedures were discussed below.

3.7.13 *In Vivo* Evaluation Of Metformin Hydrochloride Floating Tablets: *In vivo* evaluation studies were conducted on metformin hydrochloride tablets and metformin hydrochloride pure drug separately in normal, healthy rabbits (n = 5) by measuring serum glucose levels following their oral administration at a dose equivalent to 35 mg/kg. The tablets were reformulated to contain 70 mg of metformin hydrochloride and 2.31, 18.23 and 18.23 %w/w of Poly vinyl pyrrolidone, sodium bicarbonate and gum kondagogu/gum karaya respectively for suitable administration to rabbits. The study protocol was approved by IAEC (Institutional Animal Ethics Committee) before the commencement of the study. In this investigation Latin Square design was employed to minimize subject-subject variation by keeping one week wash out period in between administration of two different formulations and the design was depicted in (Table 2). The standard and the selected formulations were administered orally following overnight fasting. The animals were deprived of food during the experimental period. The blood samples were collected from the marginal ear vein at 0, 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24 hrs and analyzed for blood glucose levels with glucose oxidase method[20].

Table 2: Experimental Design for Pharmacodynamic Studies of Metformin Hydrochloride Formulations

Subject	Formulation Administered		
	First Week	Second Week	Third Week
A	P	F6	F11
B	P	F6	F11
C	P	F6	F11
D	P	F6	F11
E	P	F6	F11

P= Pure drug Metformin Hydrochloride

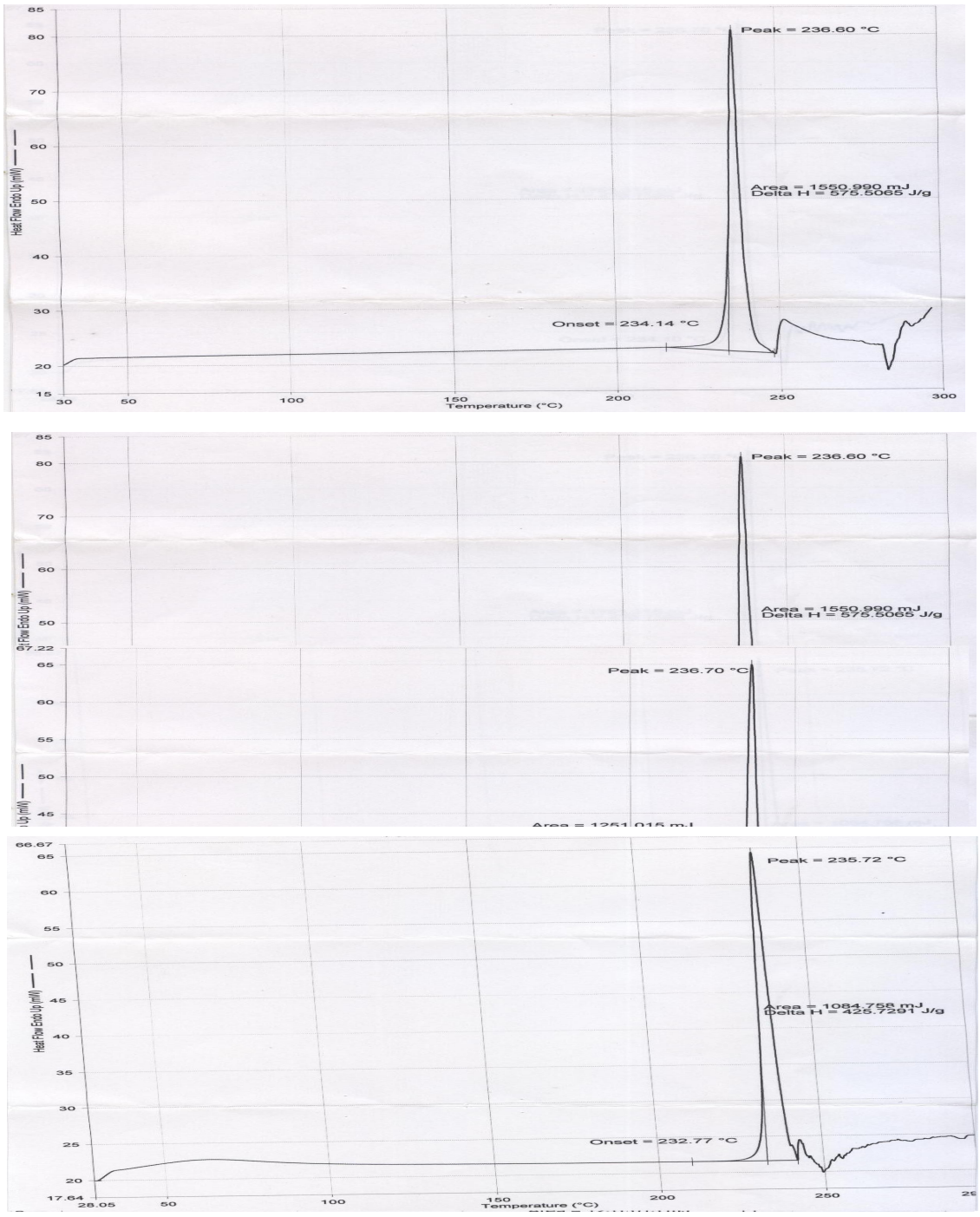
F_6 = Metformin Hydrochloride tablets containing 18.23 %w/w gum kondagogu, 18.23 % w/w sodium bicarbonate and 2.31 %w/w Poly vinyl pyrrolidone

F_{11} = Metformin Hydrochloride tablets containing 18.23 %w/w gum karaya, 18.23 % w/w sodium bicarbonate and 2.31 %w/w Poly vinyl pyrrolidone.

3. Results

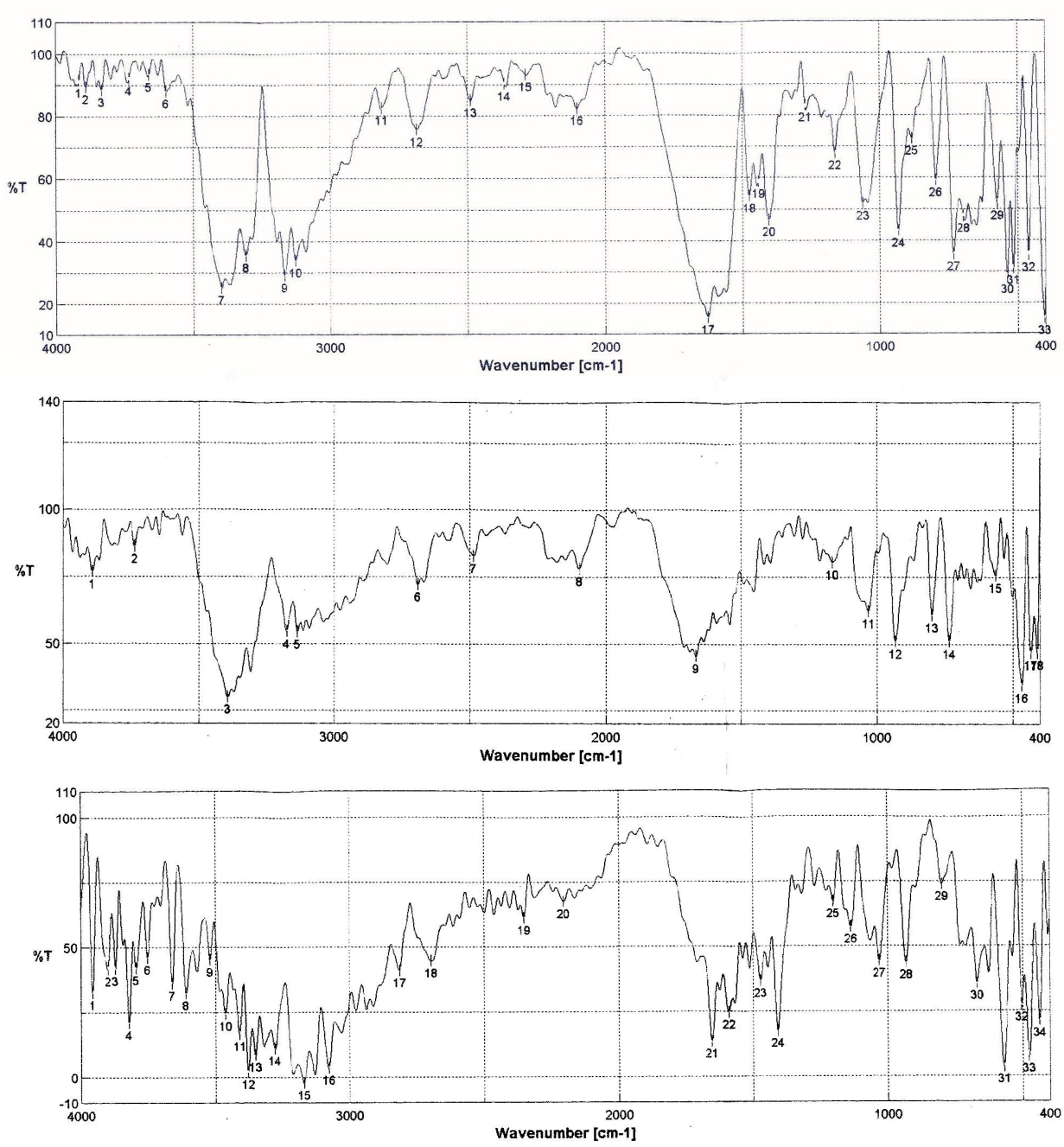
3.1 Preformulation Studies: DSC scans of metformin hydrochloride and drug–excepient mixtures were showed in (Fig. 1a to 1c). The DSC scan of metformin hydrochloride showed a short endothermic peak at 236.60^{O}C. The thermo gram of tablets formulated with gum kondagogu & gum karaya showed an endothermic peak of drug at 236.70^{O}C and 235.72^{O}C respectively indicating no interactions.

Figure 1a, 1b, 1c: DSC Thermograms of Metformin Hydrochloride and pure drug with Gum Kondagogu and Gum Karaya



The IR spectrum of metformin hydrochloride and the formulations containing metformin hydrochloride were showed in (Fig 2a to 2c). The following characteristic bands were observed C=N-(stretching) 1629.55 cm^{-1}, 1655.59 cm^{-1}, 1669 cm^{-1}, C-N-(stretching)1061.62 cm^{-1}, 1029.48 cm^{-1}, 1030.77 cm^{-1}, N-H–(stretching) 3397.96 cm^{-1}, 3378.67 cm^{-1}, 3394.1 cm^{-1} in each case. Hence it was concluded that there is no chemical incompatibility between metformin hydrochloride and the polymers gum kondagogu and gum karaya.

Figure 2a, 2b, 2c: IR Spectra of Metformin Hydrochloride pure drug, with Gum Kondagogu and Gum Karaya



3.2 Studies On Metformin Hydrochloride Floating Tablets

3.2.1 Studies on Binding Agent (PVP): To study the influence of binder on granules and tablet properties the binder PVP was incorporated at a concentration ranging from 1 to 3.5 %w/w. The flow properties of these granules were determined and

showed in (Table 3) and the physical properties of the tablets were showed in the (Table 4). The granules of formulations F_1 and F_2 exhibited poor flow properties. The tablets formulated with these granules showed high friability values (>1%) and hence these formulations were not subjected to *in vitro* drug release studies. The drug release data from these formulations were showed in (Table 6). The release rate followed zero order kinetics and mechanism of drug release was governed by peppas model and the exponential coefficient values were above 0.5 (Table 5) indicating non-Fickian drug release. Metformin hydrochloride tablets formulated with the binder PVP (2.33 %w/w) was selected for further studies.

Table 3: Physical Properties of Metformin Hydrochloride Granules Formulated with Various Concentrations of Binding Agent

Formulation	Average Particle Size(μ)	Bulk Density (g/cm3)	Carr's Index	Hausner's Ratio	Angle of Repose	Moisture Content (%)	Loss on Drying (%)
F1	812.34 ± 0.03	0.25 ± 0.05	16.78 ± 0.08	1.46 ± 0.06	32.64 ± 0.01	5.4 ± 0.08	5.1 ± 0.07
F2	937.12 ± 0.03	0.26 ± 0.04	14.28 ± 0.02	1.35 ± 0.06	28.37 ± 0.03	6.5 ± 0.07	6.3 ± 0.05
F3	1036.90 ± 0.05	0.31 ± 0.03	10.10 ± 0.04	1.17 ± 0.03	23.17 ± 0.01	7.6 ± 0.03	7.2 ± 0.02
F4	1149.74 ± 0.06	0.32 ± 0.04	9.94 ± 0.01	1.06 ± 0.03	24.59 ± 0.06	7.7 ± 0.05	7.4 ± 0.07
F5	1047.89 ± 0.04	0.29 ± 0.05	10.55 ± 0.07	1.10 ± 0.02	23.97 ± 0.06	7.8 ± 0.05	7.4 ± 0.02
F6	1062.47 ± 0.08	0.28 ± 0.02	10.86 ± 0.05	1.12 ± 0.02	24.52 ± 0.04	7.9 ± 0.07	7.5 ± 0.02
F7	1068.12 ± 0.06	0.28 ± 0.06	10.78 ± 0.03	1.11 ± 0.04	24.28 ± 0.05	8.2 ± 0.06	7.5 ± 0.03
F8	1089.12 ± 0.05	0.30 ± 0.04	10.12 ± 0.07	1.09 ± 0.05	24.16 ± 0.06	8.6 ± 0.08	8.3 ± 0.06
F9	1029.74 ± 0.06	0.27 ± 0.01	12.05 ± 0.04	1.12 ± 0.02	25.02 ± 0.04	5.8 ± 0.03	5.2 ± 0.04
F10	948.14 ± 0.04	0.26 ± 0.02	13.81 ± 0.03	1.13 ± 0.05	25.19 ± 0.07	5.2 ± 0.07	4.8 ± 0.03
F11	1018.64 ± 0.03	0.22 ± 0.05	9.54 ± 0.01	1.05 ± 0.02	24.28 ± 0.06	6.8 ± 0.04	6.9 ± 0.06
F12	1045.14 ± 0.05	0.26 ± 0.04	9.05 ± 0.02	1.02 ± 0.02	23.35 ± 0.01	7.5 ± 0.02	7.6 ± 0.02
F13	986.84 ± 0.04	0.21 ± 0.02	9.97 ± 0.04	1.09 ± 0.03	24.94 ± 0.04	5.5 ± 0.04	4.9 ± 0.03
F14	945.78 ± 0.04	0.20 ± 0.02	10.51 ± 0.06	1.11 ± 0.05	25.10 ± 0.03	5.0 ± 0.05	4.4 ± 0.04

Table 4: Physical Properties of Metformin Hydrochloride Tablets Formulated with Various Concentrations of Binding Agent

Formulation	Weight Variation (%)	Drug Content (mg)	Hardness (kg/cm2)	Friability (%)	Floating Lag Time (min)	Floating Time (h)	Swelling Index (%)	Erosion (%)
F1	3.36 ± 0.02	499.8 ± 0.01	7.1 ± 0.05	0.95 ± 0.02	20 ± 0.02	> 12	94.07 ± 0.02	8.1 ± 0.05
F2	2.52 ± 0.02	499.6 ± 0.02	7.6 ± 0.01	0.61 ± 0.03	24 ± 0.03	> 12	95.94 ± 0.04	6.9 ± 0.04
F3	2.49 ± 0.06	499.5 ± 0.03	8.4 ± 0.04	0.64 ± 0.03	26 ± 0.02	> 12	96.87 ± 0.02	6.4 ± 0.03
F4	2.86 ± 0.04	499.6 ± 0.04	8.6 ± 0.03	0.56 ± 0.04	27 ± 0.01	> 12	96.92 ± 0.05	6.3 ± 0.04
F5	2.36 ± 0.04	499.4 ± 0.01	8.7 ± 0.02	0.70 ± 0.04	8 ± 0.01	> 12	98.63 ± 0.04	6.7 ± 0.04
F6	2.44 ± 0.03	499.6 ± 0.01	8.8 ± 0.02	0.72 ± 0.05	6 ± 0.01	> 12	102.21 ± 0.05	7.0 ± 0.02
F7	2.56 ± 0.08	496.5 ± 0.05	8.6 ± 0.05	0.91 ± 0.04	4 ± 0.03	> 12	100.86 ± 0.08	6.8 ± 0.05
F8	2.71 ± 0.06	499.3 ± 0.05	8.6 ± 0.07	0.68 ± 0.03	10 ± 0.05	> 12	118.78 ± 0.09	6.6 ± 0.08
F9	2.88 ± 0.04	499.7 ± 0.02	8.5 ± 0.03	0.63 ± 0.05	5 ± 0.02	> 12	94.46 ± 0.03	7.5 ± 0.05
F10	3.06 ± 0.03	499.6 ± 0.02	8.3 ± 0.03	0.73 ± 0.06	5 ± 0.02	> 12	73.49 ± 0.06	8.1 ± 0.01
F11	2.46 ± 0.02	499.5 ± 0.02	8.9 ± 0.01	0.86 ± 0.06	5 ± 0.03	> 12	95.12 ± 0.06	6.9 ± 0.02
F12	2.95 ± 0.01	499.4 ± 0.01	8.4 ± 0.02	0.75 ± 0.05	8 ± 0.01	> 12	109.36 ± 0.05	6.4 ± 0.03
F13	3.12 ± 0.04	499.6 ± 0.02	8.7 ± 0.02	0.82 ± 0.06	3 ± 0.01	> 12	85.49 ± 0.04	7.3 ± 0.04
F14	3.26 ± 0.05	499.6 ± 0.01	8.5 ± 0.03	0.85 ± 0.04	2 ± 0.01	> 12	60.78 ± 0.04	7.8 ± 0.03

 # ±S.D

3.2.2 Studies on Gas Generating Agent: The effect of gas generating agent sodium bicarbonate was studied with the incorporation of sodium bicarbonate in the formulation ranging from 15 to 20 %w/w. The micromeritic properties of granules were studied and reported in (Table 3). All the formulated granules exhibited good flow and compressibility properties. The tablets formulated with these granules were subjected to various quality control parameters and depicted in (Table 3, 4). These tablets passed all the quality control tests however difference in the floating lag time was observed from these formulations. Floating lag time was found to be decreased with the increased concentrations of gas generating agent. The drug release data was showed in (Table 6). The release rate followed zero order kinetics and controlled by non-Fickian diffusion. The release kinetics was showed in (Table 5) and release rate constant was treated statistically and significant difference in release rate constant between the formulations was observed. The formulation containing sodium bicarbonate at 17.25 %w/w offered the required release rate of metformin hydrochloride, Hence it was selected for further studies.

Table 5: Release Kinetics of Metformin Hydrochloride Tablets Prepared with Various Concentrations of Binding Agent

Formulation	Correlation Coefficient Values				Exponential Coefficient (n)	Release Rate Constant (mg/hr) K0
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Model		
F3	0.9972	0.7725	0.9167	0.9922	1.2740	42.22
F4	0.9966	0.7625	0.9097	0.9923	1.3151	41.46
F5	0.9972	0.7618	0.9236	0.9932	1.2012	43.15
F6	0.9976	0.8166	0.9396	0.9989	0.9890	43.93
F7	0.9987	0.7570	0.9402	0.9995	0.9399	46.47
F8	0.9974	0.9604	0.9168	0.9983	1.0529	28.88
F9	0.9931	0.8284	0.9501	0.9986	0.9258	49.57
F10	0.9962	0.8191	0.9414	0.9986	0.9685	66.78
F11	0.9931	0.8137	0.9496	0.9970	0.9404	45.68
F12	0.9983	0.9379	0.9129	0.9986	1.0223	34.59
F13	0.9883	0.8493	0.9550	0.9981	0.8884	51.00
F14	0.9946	0.8585	0.9469	0.9980	0.9614	76.70

3.2.3 Studies on Gum Kondagogu: To select the required concentration of gum kondagogu, different concentrations of gum (15 – 20 %w/w) were incorporated and formulated with wet granulation technique. Prior to compression the granules were evaluated for flow properties and showed in (Table 3). All the granules exhibited the required flow and hence they were compressed to form tablets. All the tablets were evaluated according pharmacopeias procedures and the data was showed in the (Table 4).

3.2.4 Studies on Gum Karaya: To select the required concentration of gum karaya, different concentrations of gum (15–20% w/w) were incorporated and formulated with wet granulation technique. Prior to compression the granules were evaluated for flow properties and the results were showed in (Table 3). All the granules exhibited the required flow and hence they were compressed to form tablets. All the tablets were evaluated according to official procedures and the data was showed in the (Table 4).

The above tablets satisfied all official requirements. The swelling index was found to be increased with the concentration of gum employed in its preparation. All the formulations were subjected to *in vitro* drug release studies and the data was showed in (Table 6). These formulations followed zero order release and controlled by non-Fickian diffusion. The release rate constant values were treated with ANOVA and significant difference in release rate was observed in between the formulations. Formulation F_6 and F_{11} were selected as best formulation (Table 7), as they offered the required release rate of metformin hydrochloride. Good correlation was observed in between release rate constant and swelling index (Fig. 3 and 4), as the swelling index is increased the release rate constant was found to be decreased.

Figure 3: Correlation between Swelling Index and Release Rate Constant of Metformin Hydrochloride Tablets Formulated with Gum Kondagogu

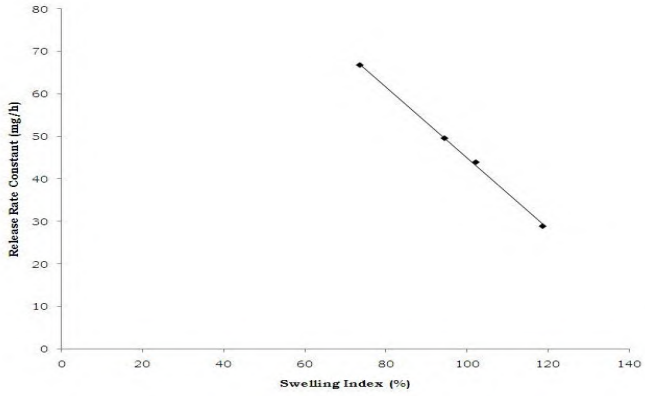


Figure 4: Correlation between Swelling Index and Release Rate Constant of Metformin Hydrochloride Tablets Formulated with Gum Karaya

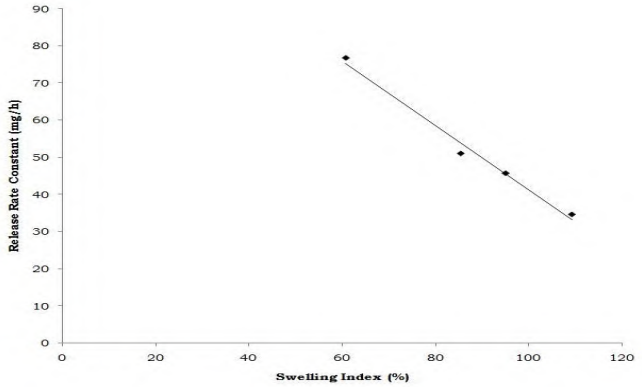


Table 7: Statistical Treatment of Release Rate Constant of Metformin Hydrochloride Tablets Prepared with Different Concentrations of Gas Generating Agent

Null Hypothesis (H0): The release rate constant from the tablets formulated with different concentrations of gas generating agents is similar.

S No	Release Rate Constant (mg/hr) K0			
	F3	F5	F6	F7
1	42.07	42.97	43.78	46.26
2	42.18	43.15	43.90	46.41
3	42.42	43.32	44.12	46.75

Result: Null hypothesis is rejected, as the calculated value (257.2) at df = 3, 8 and P = 0.01 exceeds the Table value (4.07). Alternative hypothesis is accepted, hence indicating the release rate constant obtained with different concentrations of gas generating agents is statistically significant.

Different concentrations of gum kondagogu

Null Hypothesis (H0): The release rate constant from the tablets formulated with various concentrations of gum kondagogu is similar.

S No	Release Rate Constant (mg/hr) K0			
	F6	F8	F9	F10
1	43.78	28.61	49.33	66.63
2	43.90	28.86	49.57	66.73
3	44.12	29.17	49.82	66.97

Result: Null hypothesis is rejected, as the calculated value (147.80) at df = 3, 8 and P = 0.01 exceeds the Table value (4.07). Alternative hypothesis is accepted, hence indicating the release rate constant obtained various concentrations of gum kondagogu is statistically significant.

Different concentrations of gum karaya

Null Hypothesis (H0): The release rate constant from the tablets formulated with various concentrations of gum karaya is similar.

S No	Release Rate Constant (mg/hr) K0			
	F11	F12	F13	F14
1	45.51	34.35	50.79	76.52
2	45.65	34.55	50.95	76.70
3	45.88	34.88	51.25	76.87

Result: Null hypothesis is rejected, as the calculated value (199.00) at df = 3, 8 and P = 0.01 exceeds the Table value (4.07). Alternative hypothesis is accepted, hence indicating the release rate constant obtained with various concentrations of gum karaya is statistically significant.

Table 6: Release Data of Metformin Hydrochloride Tablets Prepared with Various Concentrations of Gas Generating Agent

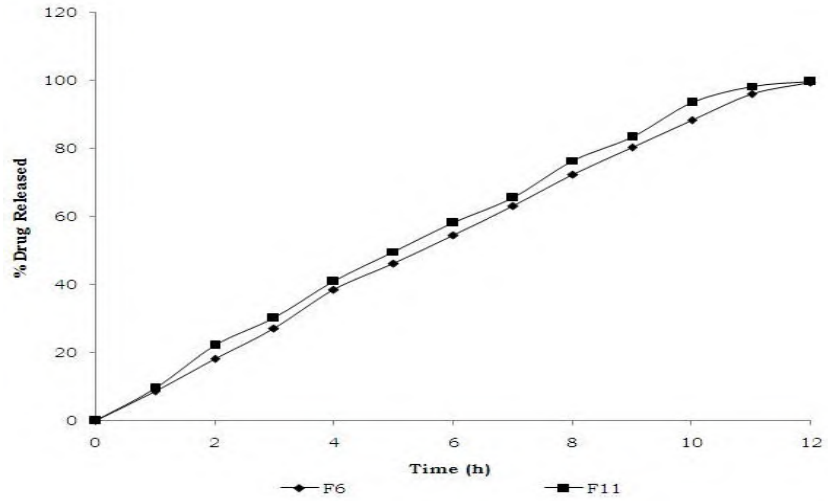
Time (h)	Percent Metformin Hydrochloride Released ($\bar{x}$ ± s.d.)											
	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
0	0	0	0	0	0	0	0	0	0	0	0	0
1	4.15 ± 0.33	3.86 ± 0.44	5.17 ± 0.22	8.67 ± 0.44	10.20 ± 0.22	4.81 ± 0.33	11.52 ± 0.22	14.36 ± 0.44	9.47 ± 0.33	6.56 ± 0.33	13.05 ± 0.44	16.26 ± 0.33
2	10.43 ± 0.58	9.11 ± 0.22	11.60 ± 0.33	18.16 ± 0.33	21.01 ± 0.33	11.60 ± 0.12	21.38 ± 0.44	26.85 ± 0.44	22.10 ± 0.55	14.37 ± 0.44	22.98 ± 0.33	32.25 ± 0.55
3	22.69 ± 0.44	21.16 ± 0.27	24.01 ± 0.44	26.94 ± 0.34	30.08 ± 0.46	16.86 ± 0.33	32.85 ± 0.55	40.74 ± 0.77	30.15 ± 0.44	19.64 ± 0.66	34.10 ± 0.44	46.44 ± 0.55
4	34.97 ± 0.66	33.00 ± 0.19	36.51 ± 0.44	38.42 ± 0.34	40.18 ± 0.34	22.50 ± 0.44	43.76 ± 0.34	54.35 ± 0.34	40.91 ± 0.34	25.20 ± 0.34	45.51 ± 0.44	65.16 ± 0.46
5	42.02 ± 0.44	40.99 ± 0.36	45.08 ± 0.44	46.20 ± 0.44	47.74 ± 0.44	27.55 ± 0.22	54.17 ± 0.12	70.02 ± 0.55	49.64 ± 0.21	32.01 ± 0.34	55.78 ± 0.67	79.97 ± 0.22
6	52.13 ± 0.31	50.30 ± 0.11	53.30 ± 1.08	54.34 ± 0.12	55.52 ± 0.34	34.81 ± 0.34	62.03 ± 0.34	83.01 ± 0.33	58.08 ± 0.13	39.42 ± 0.44	66.49 ± 0.55	95.16 ± 0.44
7	60.50 ± 0.28	58.16 ± 0.30	62.04 ± 0.44	63.01 ± 0.30	64.92 ± 0.44	40.17 ± 0.55	72.38 ± 0.22	95.87 ± 0.22	65.44 ± 0.33	46.97 ± 0.55	75.61 ± 0.55	99.42 ± 0.22
8	68.45 ± 0.17	67.12 ± 0.22	70.94 ± 0.31	72.20 ± 0.24	73.82 ± 0.58	45.90 ± 0.20	81.51 ± 0.22	99.70 ± 0.22	76.45 ± 0.22	54.25 ± 0.34	85.17 ± 0.44	---
9	76.62 ± 0.34	74.86 ± 0.34	78.39 ± 0.22	80.38 ± 0.34	84.33 ± 0.46	51.21 ± 0.34	91.74 ± 0.15	---	83.47 ± 0.34	62.11 ± 0.44	94.17 ± 0.22	---
10	85.17 ± 0.22	84.20 ± 0.44	86.57 ± 0.13	88.34 ± 0.13	92.67 ± 0.13	54.11 ± 0.34	96.51 ± 0.29	---	93.48 ± 0.44	70.64 ± 0.67	98.50 ± 0.19	---
11	93.21 ± 0.44	91.88 ± 0.22	95.13 ± 0.27	96.03 ± 0.28	99.77 ± 0.19	64.82 ± 0.66	99.68 ± 0.30	---	98.32 ± 0.22	77.65 ± 0.34	99.71 ± 0.13	---
12	99.66 ± 0.09	99.64 ± 0.30	99.83 ± 0.17	99.42 ± 0.10	---	72.99 ± 0.88	---	---	99.75 ± 0.10	85.25 ± 0.46	---	---

3.3 Comparative studies on Metformin Hydrochloride Tablets Prepared with Gum Kondagogu and Gum Karaya: To compare the effect of the gums on the release rate of metformin hydrochloride from the tablets, the formulations containing equal concentration of the polymers, gas generating agents and binder were subjected to *in vitro* release studies (F_6 & F_{11}). The drug release data of these two formulations was showed in the (Table 6). These two formulations followed zero order release and followed non-Fickian model. The release rate constant values were treated (Table 5) with unpaired t-test and significant difference in release rate was observed in between the formulations. Gum kondagogu offered much slower release rate of Metformin hydrochloride. Hence it is more suitable for design and development of oral sustained release formulations of Metformin hydrochloride. The difference in the release rate constant values from these two gums may be attributed due to the difference in viscosities and swelling index contributed by these two gums.

The swelling index values observed in 0.1N HCl at 3rd hour from the floating tablets containing same composition of excipients with variation only in nature of gum (either gum kondagogu and gum karaya) was 102.21 ± 0.05 and 95.12 ± 0.06 from gum kondagogu and gum karaya formulations respectively.

The viscosities of 1 %w/v aqueous dispersions of gum kondagogu and gum karaya were determined with Brookfield viscometer (DV – III *Ultra*). The viscometer was operated with spindle no. SC4-18 at a shear rate of 79.20 to 132.00 by employing small sample adapter (8 mL capacity). The viscosity values were analyzed with Rheocalc software. The data was fitted in bingham's plot. To compare the viscosities the gums were analyzed at a same shear rate and at room temperature. The viscosity values observed with gum kondagogu are relatively higher than gum karaya (Table 9).

Figure 5: Comparative Release Profiles of Metformin Hydrochloride Tablets Prepared with Gum Kondagogu and Gum Karaya



4.4 Comparison of the Metformin Hydrochloride Tablets Prepared with Gum Kondagogu and Marketed formulation: The drug release rate from the selected formulation (F_6) was compared with the marketed formulation (Glycomet SR, 500 mg). The corresponding release data was showed in (Table 6) and (Fig. 6). Both formulations followed zero order kinetics and controlled by non-Fickkin diffusion. The release kinetics were showed in (Table 8) and treated statistically with unpaired t test. They were found to be different in release characteristics. The formulation developed in this investigation offered a much slower release rate of Metformin hydrochloride.

Fig 6: Comparative Release Profiles of Selected Metformin Hydrochloride Tablets (F_6) and Marketed Formulation

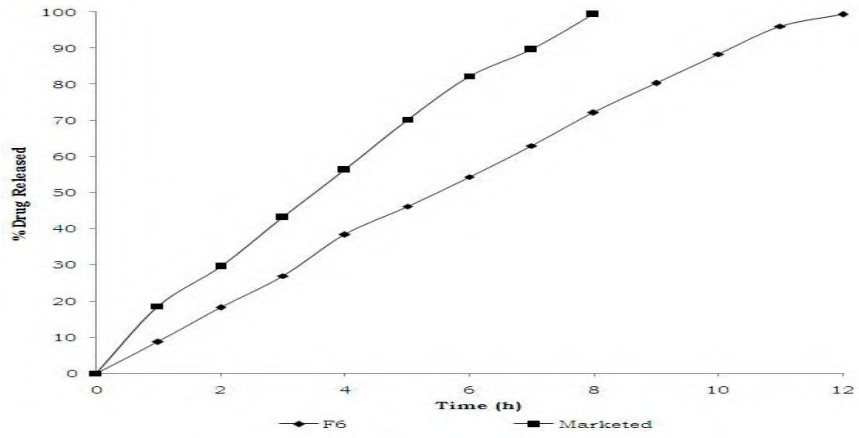


Table 8: Comparative Release Kinetics of Selected Metformin Hydrochloride Tablets (F_6) and Marketed Formulation

Formulation	Correlation Coefficient Values				Exponential Coefficient (n)	Release Rate Constant (mg/hr) K0
	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Model		
F6	0.9976	0.8166	0.9396	0.9989	0.9890	43.93
Marketed	0.9925	0.8355	0.9595	0.9979	0.8370	66.15

3.5 Influence of pH on Viscosity and Swelling Index: To study the influence of pH on swelling index about 1 g of gum was dispersed in 15 ml of pH 7.4 phosphate buffer or 0.1N Hydrochloric acid separately. The gums were collected at 3rd hour and reweighed. The swelling index values were calculated from the initial and final weight. The % swelling index observed with gum kondagogu in pH 7.4 phosphate buffer and 0.1N Hydrochloric acid were found to be 92.18 and 74.23% respectively. The swelling index was found to be more in alkaline conditions than acidic conditions. Similar results were also noticed with gum karaya (in pH 7.4 phosphate buffer 86.67 and 68.47% swelling index in 0.1N Hydrochloric acid).

The influence of pH on viscosity was carried out by subjecting 1 %w/v of gum dispersions for rheological studies. The viscosities noticed with gum kondagogu dispersions formulated with pH 7.4 phosphate buffer and 0.1N Hydrochloric acid at room temperature were 36.4 cP and 5.43 cP respectively. Gum karaya dispersions (1 %w/v) formulated with pH 7.4 phosphate buffer and 0.1N HCl showed 10.7 cP and 3.99 cP respectively at same temperature (Table 9). Thus these rheological studies clearly reveals that the viscosity of these dispersions were relatively much higher in alkaline conditions. It may be attributed due to the activation acetyl groups possessed by these gums. These gums consist of high molecular weight acetylated poly saccharides (20), which are likely to be suppressed in acidic conditions and they may be activated in alkaline conditions. It was concluded that more sustained release of active ingredients from these gum matrices can be achieved in alkaline conditions.

Table 9: Rheological Properties of Gum Kondagogu and Gum Karaya in 0.1N HCl

Speed (RPM)	Torque (%)	Shear Rate (1/sec)	Shear Stress (D/cm2)	Viscosity (cP)
Gum Kondagogu				
60.00	49.51	79.20	19.60	24.74
70.00	51.74	92.40	20.47	22.15
80.00	53.62	105.60	21.22	20.10
90.00	54.97	118.80	21.78	18.33
100.00	56.90	132.00	22.53	17.07
Yield Stress (D/cm2): 15.4		**Confidence of Fit: 99.7**		**Plastic Viscosity (cP): 5.43**
Gum Karaya				
60.00	21.04	79.20	8.31	10.50
70.00	22.83	92.40	9.03	9.77
80.00	24.52	105.60	9.70	9.19
90.00	25.94	118.80	10.25	8.63
100.00	26.13	132.00	10.33	7.83
Yield Stress (D/cm2): 5.31		Confidence of Fit: 98.3		Plastic Viscosity (cP): 3.99

3.6 Comparative Studies of Metformin Hydrochloride Tablets Formulated for Human Use and Usage in Rabbits: The formulated tablets containing 500 mg of metformin hydrochloride were weighing around 823 mg which found difficult to administer in rabbits. So, the tablets were reformulated to contain 70 mg of metformin hydrochloride (calculated dose for rabbits) with the same proportion of other excipients to obtain a tablet weight of 115.22 mg for convenient administration in rabbits by compressing with 5 mm diameter of die.

The drug release rate is likely to be influenced by the geometry of the tablet dosage form. The reformulated tablets were subjected to drug release studies and the data was compared with the formulations containing 500 mg of metformin hydrochloride (Fig. 7). The observed similarity factor was 76.58 thus indicating that these two formulations possess an identical release profiles. Similar results were also observed with gum karaya as a similarity factor of 76.16 was observed (Fig. 8). Hence these two newly formulated tablets were subjected to *X-ray* studies to identify the position of tablet in GIT and for pharmacodynamic studies to determine the efficacy of dosage form in reduction of blood sugar levels.

Figure 7: *In Vitro* Release Profiles of Metformin Hydrochloride Tablets Containing 70 mg of Metformin Hydrochloride and having Composition Similar to F_6

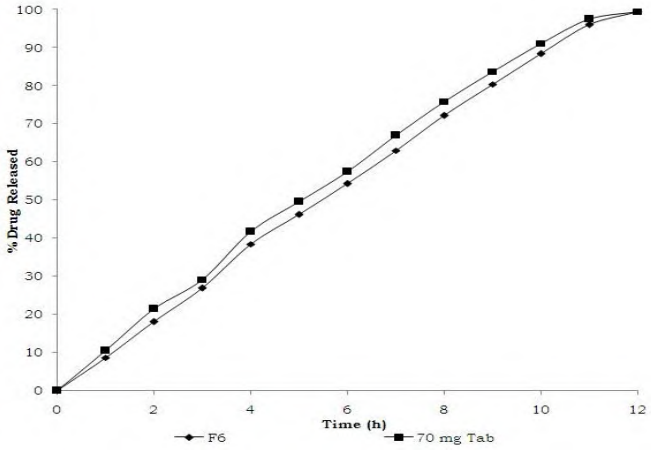
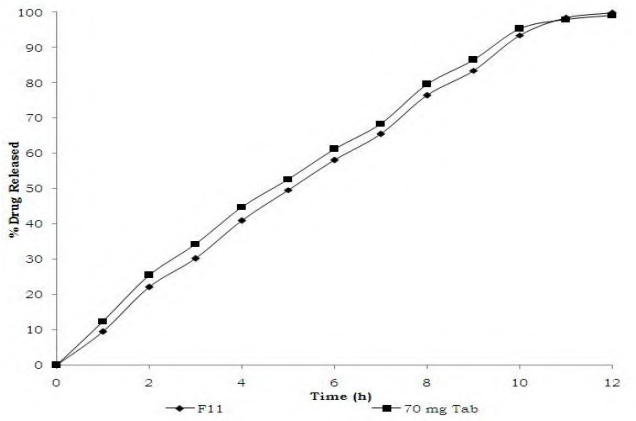
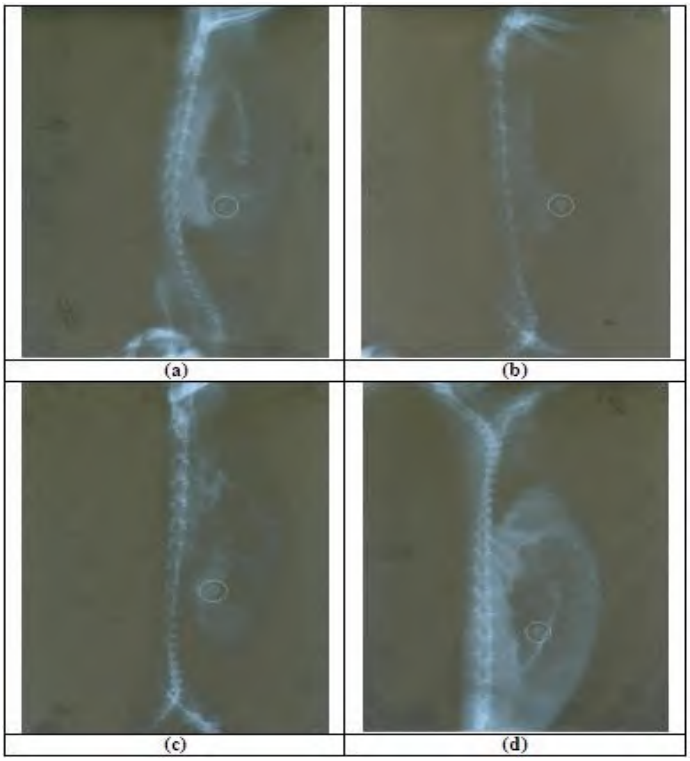


Figure 8: *In Vitro* Release Profiles of Metformin Hydrochloride Tablets Containing 70 mg of Metformin Hydrochloride and having Composition Similar to F11



3.6.1 Estimation of Gastric Resident Time of Metformin Hydrochloride Floating Tablets: GI Residence Time associated with the administration of kondagogu floating tablet containing barium sulphate (free from drug) was determined by *X-ray* photographs (Fig. 9). The *X-ray* studies showed that the floating tablets formulated with metformin hydrochloride and gum kondagogu remained in the gastric region even after 10 hours of administration indicating good retention of the tablets in the stomach region.

Figure 9: *X-Ray* Photographs of Following Administration of Floating Tablets Containing Gum Kondagogu and Barium Sulfate



3.7 Stability Studies: The stability in drug release profiles was conducted according to ICH guidelines. Metformin Hydrochloride floating tablets formulated with either 18.23 %w/w of gum kondagogu or gum karaya along with 2.31 %w/w binder poly vinyl pyrrolidone and 18.23 %w/w gas generating agent sodium bicarbonate were packed separately in a screw capped bottle and subjected to stability studies according to ICH guidelines. The drug release profiles were presented in (Table 10, 11). These profiles showed good stability of release from the floating tablets and it was supported by similarity factor value 74.23 & 71.06.

Table 10: Release Data of Metformin Hydrochloride Floating Tablets (F_6) Formulated with Gum Kondagogu Kept at 30^{O}C ± 2^{O}C/65 %RH ± 2 %RH

Time (h)	Avg. % Released ($\bar{x}$ = s.d.)		MDT (T)/ MDT (R)	AUC (T)/ AUC (R)
	Initial	6th Month		
0	0	0	0	0
1	8.67 ± 0.44	5.98 ± 0.33	1.000	0.689
2	18.16 ± 0.33	14.59 ± 0.22	1.066	0.747
3	26.94 ± 0.34	23.65 ± 0.33	1.084	0.804
4	38.42 ± 0.34	34.99 ± 0.44	1.065	0.845
5	46.20 ± 0.44	42.39 ± 0.33	1.051	0.871
6	54.34 ± 0.12	50.61 ± 0.22	1.049	0.887
7	63.01 ± 0.34	59.05 ± 0.34	1.041	0.900
8	72.20 ± 0.44	68.24 ± 0.22	1.039	0.909
9	80.38 ± 0.23	77.58 ± 0.34	1.050	0.919
10	88.34 ± 0.13	85.54 ± 0.46	1.044	0.928
11	96.03 ± 0.34	93.81 ± 0.34	1.045	0.935
12	99.42 ± 0.13	97.63 ± 0.33	1.047	0.942

Table 11: Release Data of Metformin Hydrochloride Floating Tablets (F_{11}) Formulated with Gum Karaya Kept at 30 ^{O}C ± 2 ^{O}C/65 %RH ± 2 %RH

Time (h)	Avg. % Released ($\bar{x}$ = s.d.)		MDT (T)/ MDT (R)	AUC (T)/ AUC (R)
	Initial	6th Month		
0	0	0	0	0
1	9.47 ± 0.33	6.27 ± 0.22	1.000	0.661
2	22.10 ± 0.55	18.75 ± 0.22	1.088	0.762
3	30.15 ± 0.44	27.52 ± 0.44	1.095	0.831
4	40.91 ± 0.34	36.38 ± 0.34	1.033	0.860
5	49.64 ± 0.21	44.30 ± 0.33	1.025	0.871
6	58.08 ± 0.13	53.03 ± 0.44	1.038	0.881
7	65.44 ± 0.33	60.38 ± 0.33	1.040	0.890
8	76.45 ± 0.22	72.92 ± 0.34	1.058	0.901
9	83.47 ± 0.34	80.59 ± 0.22	1.060	0.913
10	93.48 ± 0.44	89.51 ± 0.33	1.039	0.922
11	98.32 ± 0.22	95.66 ± 0.44	1.052	0.929
12	99.75 ± 0.10	98.54 ± 0.13	1.067	0.937

Pharmacodynamic Studies

3.8 Studies on floating tablets of Metformin hydrochloride: *In vivo* evaluation of the Metformin hydrochloride floating tablets containing 70 mg metformin hydrochloride and having a percent composition of other excipients similar to F_6 and F_{11} was carried out separately in healthy, normal rabbits by measuring the hypoglycemic effect produced after their oral administration. The blood sugar levels observed with the administration of the standard and test product were showed in (Fig. 10). When pure Metformin hydrochloride was administered as a standard (aqueous suspension containing 1 mg/mL), a rapid reduction in serum glucose levels was observed; a maximum reduction of 56.8% was observed at 1.0 hours after administration, and the glucose levels recovered rapidly to the normal level after a period of 4 hours. In the case of formulation containing gum kondagogu, the maximum reduction (52.49%) in blood glucose levels was observed at 2nd hour and the effect was found to be sustained up to 14th hour which is shown in (Fig. 11). In the case of formulation containing gum karaya, the maximum blood glucose levels was observed at 1.5th hour and sustained effect was observed till 12th hour. The sustained hypoglycemic effect observed over longer periods of time in the case of floating tablets prepared with gum kondagogu which may be due to the slow release and absorption of metformin hydrochloride. As the hypoglycemic effect of metformin hydrochloride is sustained over a period of 14 hours with the formulation prepared with gum kondagogu, hence it is more suitable than the formulation prepared with gum karaya.

Figure 10: Blood Glucose Levels Following the Administration of Metformin Hydrochloride and its Floating Tablets

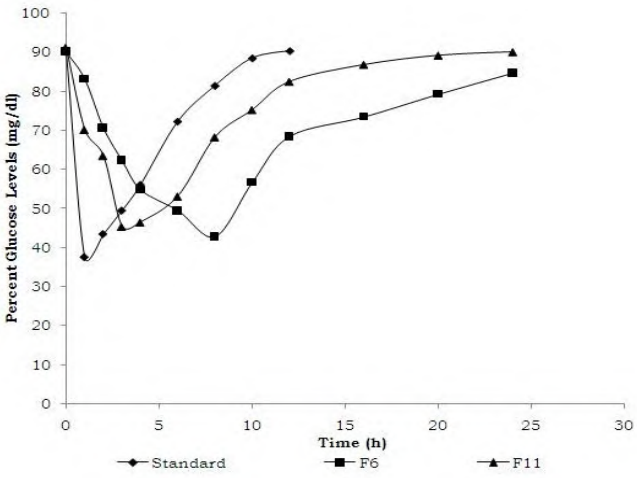
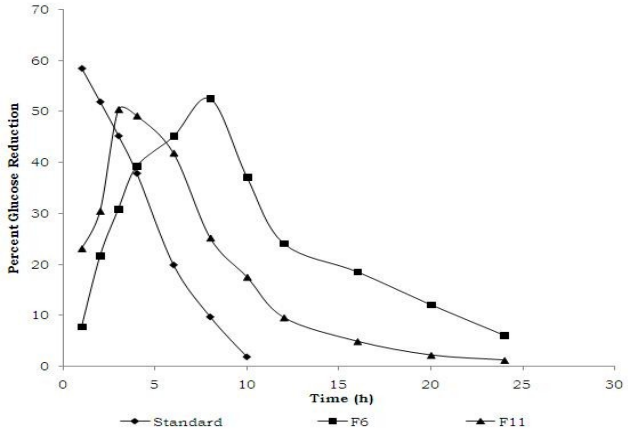


Figure 11: % Reduction of Blood Glucose Levels Following the Administration of Metformin Hydrochloride and its Tablets



Thus these pharmacodynamic studies indicated that the formulations containing gum kondagogu are more suitable maintenance of blood glucose levels for an extended period of time than formulations prepared with gum karaya as both microcapsules and floating tablets containing gum kondagogu showed more sustained hypoglycemic affect than the formulations containing gum karaya.

4. Discussion

Studies were carried out on floating tablets of metformin hydrochloride formulated with gum kondagogu and gum karaya. The influence of binding agent, gas generating agent on flow properties of granules, floating nature of tablet and on drug release were studied. Drug and polymer interaction studies were carried out with DSC and IR spectra. The stability of the drug release from gum kondagogu and gum karaya floating tablets and microcapsules developed in the investigation was studied as per ICH guidelines.

The selected floating tablets and the microcapsules were subjected to pharmacodynamic studies. The study was carried in 4 diurnally active normal, healthy rabbits and performed with Latin Square design, allowing a wash out period of one week between each treatment. Blood glucose levels and percent reduction in blood glucose levels were determined.

The results related to the floating tablets indicated that the concentration of binding agent employed in the

formulation influences the flow properties of the granules and mechanical strength of the tablet. The floating time was found to be highly influenced by the gas generating agent concentration. The drug release rate was found to be affected with concentration of gum employed in the preparation of floating tablets. Gum kondagogu was found to be a good matrix forming material for controlled release. The resulting tablet provided slow and controlled release of metformin hydrochloride over 12 hrs. Drug release from the floating tablets can be controlled by changing the amount of gum, gas generating agent and swelling index. The floating tablets exhibited good sustained release characteristics both *in vitro* and *in vivo*. Hence these floating tablets are recommended for oral controlled delivery of metformin hydrochloride. Thus the present investigation resulted in the development of floating tablets for oral controlled delivery of metformin hydrochloride fulfilling the other objective of the investigation.

5. Conclusion

Metformin hydrochloride found compatible with gum kondagogu and gum karaya with this work. The size and flow properties of granules are influenced by the binding agent concentration. Gas generating agent concentration controls the floating properties of the tablets. The rate of drug release decreases with the increase in concentration of the gum employed in the preparation of the tablet. The required release rate from the floating tablets can be readily obtained by changing the concentration of gas generating agent and the polymer. Gum karaya offers rapid release rate when compared with gum kondagogu in the concentration of 17.25% w/w. The floating tablets formulated with these two gums are quite stable.

The floating tablets formulated with gum kondagogu are more suitable to control blood sugar levels for an extended period of time. Thus all the major objectives of this investigation were fulfilled and appropriately placed in this article.

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