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Formulation and *In Vitro* Evaluation of Metformin Hydrochloride Floating Tablets by Using Natural Polymer

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ABSTRACT

The purpose of the present study is to develop an optimized gastric floating drug delivery system containing Metformin Hydrochloride using Gum Kondagogu and investigate the effect of formulation and processing parameters. The effervescent granules were prepared by wet granulation technique using Gum Kondagogu as a controlled release Natural polymer. Sodium bicarbonate was incorporated as a gas-generating agent. The granules were lubricated with magnesium stearate and talc and compressed. Tablets were characterized for physical properties, floating characteristics (floating lag-time, floating time), swelling index, wetting time, drug content and evaluated for in vitro release characteristics for 10 hrs in 0.1N HCl at 37⁰C. The similarity factor, t_{50} and t_{90} were used as parameters for selection of the best formulation compared with commercial product. The tablet erosion, drug diffusion, polymer swelling and the resulting release patterns varied significantly with the type of matrix forming Natural polymer used. Hence Gum Kondagogu can be ascertained as a low dense compound which has gas evolving as well as binding properties and thus, excellent in vitro floating behavior of the tablet was found out. Comparable release profiles between the commercial product and the designed system (F4) were obtained. Altering the concentration of Natural polymer, binding agent and gas-evolving agent are found to have a significant influence on the release rate with accurate control and prolongation of the drug release patterns. The drug release from all the formulations followed zero order kinetics and Korsmeyer-Peppas mechanism.

Key words: Metformin Hydrochloride, Gum Kondagogu, gastric floating tablets, controlled release

INTRODUCTION

The traditional oral delivery system has certain disadvantages that need to be overcome, such as the short retention time in the gastrointestinal (GI) tract, protection of GI-labile drugs from the hostile intestine environment, etc. Many attempts have been made in recent years to provide a dosage form with a longer transit time and therefore a more efficient absorption. These approaches include utilization of passage-delaying agents, use of large single-unit dosage forms, development of bioadhesive drug delivery system, and design of “heavy” pellets, magnetic and extendable or expandable hydro gel systems and floating dosage forms [1, 2]. Compared to these approaches, the gastric floating drug delivery system (GFDDS) developed has provided several advantages, as shown by the encouraging results reported earlier.

Floating drug delivery systems (FDDS) or hydrodynamically balanced systems were first described by Davis *et al* [3]. It is possible to prolong the gastric residence time (GRT) of drugs using this system [4]. FDDS float due to their lower bulk density than the gastric contents or due to gaseous phase formed inside the system in the gastric environment [5]. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastrointestinal tract (GIT), unstable in lower parts of GIT, or are poorly absorbed in the intestine [6]. An important issue in the development of such a dosage form is to ensure its presence in the upper GIT until the entire drug is released for the desired period of time [7].

Metformin Hydrochloride is an anti-hyperglycemic agent, which improves the glucose tolerance in Type 2 diabetes. The indicated oral dosage is 500 mg 3times daily or 850 mg twice daily, usually at a dose of 2g (maximum of 3g) per day [8]. The absolute bioavailability is 50-60%, biological half-life is 1.5-3 hrs and the main site of absorption is proximal small intestine [9, 10]. For these reasons the GFDDS was planned for Metformin Hydrochloride, as such system when administered would remain buoyant on the gastric fluids for a prolonged period of time and the drug would be available in the dissolved form at the main site of its absorption.

Drug release from hydrophilic matrices is known to be a complex interaction involving swelling, diffusion and erosion mechanisms [11-14]. This work was an attempt to determine the relative contribution of the different drug release mechanisms exhibited by Metformin Hydrochloride matrix tablets produced with Gum Kondagogu [15].

EXPERIMENTAL SECTION

Materials:

Metformin Hydrochloride a gift sample from Fegasus Farmaco Ltd., Roorkee, India. Gum Kondagogu was purchased from Girijan Co-operative Society, Tirupathi, India. Polyvinylpyrrolidone K-30 (PVPK-30) was also a gift sample from M/S Seeko Biotech, Vijayawada, India. Sodium bicarbonate was purchased from Merk Ltd., Mumbai, India. Magnesium stearate and Talc were purchased from S.D. Fine Chem. Ltd., Mumbai, India. All other ingredients were of laboratory grade.

Compatibility study:

The physicochemical compatibility studies between Metformin Hydrochloride & Gum Kondagogu used in the research were carried out by subjecting to IR Spectral studies using Perkin Elmer FTIR Spectrophotometer, Shelton, USA. The samples were scanned under diffuse reflectance mold and the graph was plotted by KBr pellet method and spectra were recorded in the wavelength region between 4000cm^{-1} to 400cm^{-1} . The spectra obtained for Metformin Hydrochloride, Gum Kondagogu and physical mixtures of Metformin Hydrochloride with Gum Kondagogu were compared.

Preparation of Metformin Hydrochloride Floating Matrix Tablets:

Effervescent type floating tablets were prepared by wet granulation technique using a low density Natural polymer i.e., Gum Kondagogu. The composition of the prepared tablets was shown in **table no: 1**. The components were blended for 15 min, moistened with water to form a damp mass and wet granules were produced by passing through sieve no.12. The obtained wet granules were dried at 50°C in hot air oven. Then the granules were passed through sieve no.16, lubricated with magnesium stearate & talc, there by compressed on 16 station tablet punching machine (Cadmach, Ahmedabad, India) with flat-faced punches and dies (12mm diameter).

Table No: 1 Composition of Metformin Hydrochloride floating tablets

Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Metformin Hydrochloride	500	500	500	500	500	500	500	500	500	500
Gum Kondagogu	300	250	200	175	175	175	175	175	175	175
Sodium bicarbonate	120	100	80	80	100	70	80	80	80	80
PVP(K30)	140	120	120	120	120	120	80	100	140	160
Magnesium Stearate	10	10	10	10	10	10	10	10	10	10
Talc	8	8	8	8	8	8	8	8	8	8

Floating behavior of the tablets:

The *in vitro* buoyancy was determined by floating lag time, per method described by Rosa *et al* [16]. The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to surface and float was determined as floating lag time.

Floating time: The total duration of time that the tablet floats on dissolution medium.

Wetting Time:

A piece of tissue paper was folded twice and placed in a petridish containing 10 ml of 0.1 N HCl, tablet was placed on the paper and wetting time was noted by observing the complete wetting of tablet.

Swelling Index:

The tablet was weighed and placed in dissolution medium containing 0.1 N HCl maintained at 37 °C. At predetermined time intervals the tablet was withdrawn and blotted to remove excess water and weighed [17]. The percentage of swelling index calculated.

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

Where W_t = final weight of the tablet

W_o = initial weight of the tablet.

Drug Content:

Twenty tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of Metformin Hydrochloride was dissolved in 0.1 N HCl diluted to 100ml with 0.1N HCl then the solution was filtered and suitably diluted. The drug content was estimated spectrophotometrically at 233 nm [18].

In Vitro Dissolution Studies:

Dissolution rate was studied using USP II paddle dissolution apparatus, in 900 ml of 0.1 N HCl at 37±0.5°C at 100 rpm [19]. Aliquot of dissolution medium was withdrawn at regular time intervals and the same volume of fresh dissolution medium was replaced. The samples were filtered and diluted to a suitable concentration with 0.1N HCl. The absorbance of these solutions was measured at 233 nm using Shimadzu UV-1700 spectrophotometer. Cumulative percentage drug release was calculated using PCP Disso Version 2.08 software (Poona College of Pharmacy, Pune, India) [20]; the time required for 50% and 90% drug release was calculated based on the Korsmeyer and Peppas model [21].

Comparison of Optimized Formulation with Glycomet SR 500 mg commercial Tablet:

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles of products were compared using f_2 which is calculated from the following formula,

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{j=1}^n (R_j - T_j)^2 \right]^{-0.5} \times 100 \right\}$$

Where, n is the dissolution time, R_j and T_j are the reference (here this is the theoretical dissolution profile of Metformin Hydrochloride for 8 hrs using a sustained release formulation) and test dissolution values at time t . the similarity factor fit the result between 0 and 100. It approached '0' as the dissimilarity of the test and the reference profile increased, whereas, it attained 100 when the test and the reference profile were identical [22, 23, 24].

RESULTS AND DISCUSSION**Compatibility study:**

Compatibility study of drug and polymer were conducted by employing I.R. Spectral studies. The IR spectrum of Metformin Hydrochloride, Gum Kondagogu & its physical mixture is shown in **figure: 1-3**. The following characteristic peaks were observed with Metformin Hydrochloride as well as the formulations containing Metformin Hydrochloride. C=N - (stretching) 1629.55, 1655.59, 1669 cm^{-1} , C-N - (stretching) 1061.62, 1029.48, 1030.77 cm^{-1} , N-H - (stretching) 3397.96, 3378.67, 3394.1 cm^{-1} . As the identical principle peaks were observed in all the cases, hence it shall be confirmed that interactions do not exist between the drug and polymer.

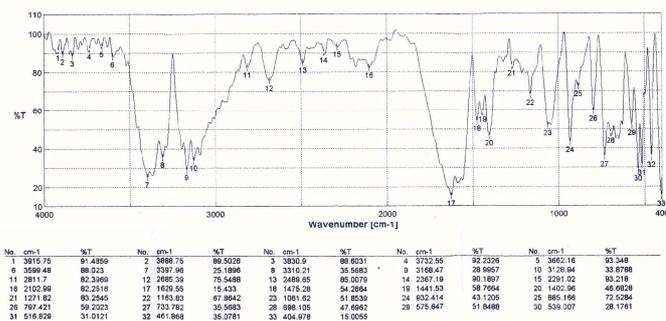


Figure 1. I.R Spectra of Metformin Hydrochloride

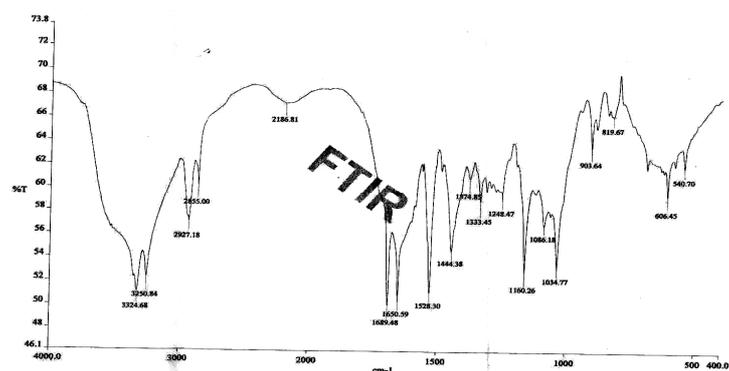


Figure 2. I.R Spectra of Gum Kondagogu

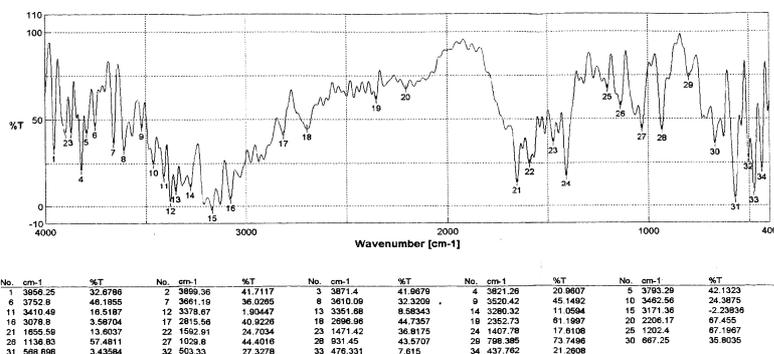


Figure 3. I.R Spectra of Metformin Hydrochloride with Gum Kondagogu

Studies on Metformin Hydrochloride floating tablets formulated with Gum Kondagogu:

The quality control tests adopted for the tablets were depicted in **table: 2**. Weight variation of the tablets ranged from 2.36% -3.36%. The hardness of floating tablets ranged between 8.0 Kg/Cm² to 8.8 Kg/Cm² and thickness of the tablets range between 4.1 mm to 5.0 mm. The percent friability of the prepared tablets was well within acceptable limit. There was no significant weight variation observed between average weight and individual weight.

The floating characteristics results were given in **table: 2**. All the formulations have desired floating lag time (<5min) and total floating time between 8-10 hrs regardless of concentration of Natural polymer and type of binder incorporated. This is mainly due to the evolution of CO₂

entrapped inside the hydrated polymeric gum resulting from interaction between the gas generating agent (sodium bicarbonate) and dissolution medium (0.1N HCl with pH 1.2) that led to lowered density enabling the tablet to float.

The wetting time results (**table: 2**) were found in between 14 to 27 min. The wetting time of tablet increased with increase in thickness of the tablet. These results suggest that the wetting process of the tablets, which is closely related to the inner structure of the tablets, especially pore size, which affects water penetration into the tablets.

The swelling index results are depicted (**table: 2**). It was observed that increase in percent swelling was found with increasing concentration of Natural polymer. Further results suggested that the Metformin Hydrochloride release from the Natural polymer was more by diffusion and less by erosion mechanism that correlates with the results of release kinetics.

The drug content in all the formulations is within the range of 499.3 mg to 499.8 mg, ensuring uniformity of drug content in the formulations.

Table: 2 Physical Properties of Metformin Hydrochloride Floating Tablets

Formulation	Weight variation (%)	Hardness (Kg/Cm ²)	Thickness (mm)	Friability (%)	Floating Lag time (min)	Floating Time (hr)	Swelling index (%)	Wetting Time (min)	Drug content (mg)
F1	2.44	8.8	5.0	0.72	3.5	>10	79.54	27	499.6
F2	2.36	8.7	4.9	0.70	4.2	>10	74.63	24	499.4
F3	2.88	8.5	4.7	0.63	4.5	>10	69.75	22	499.7
F4	3.06	8.3	4.4	0.73	4.7	>10	63.50	19	499.6
F5	3.12	8.4	4.5	0.82	4.1	>10	65.90	20	499.5
F6	2.52	8.2	4.3	0.65	4.9	>10	59.94	18	499.6
F7	2.45	8.0	4.2	0.84	4.6	8	53.61	14	499.3
F8	3.36	8.1	4.1	0.81	4.8	9	57.07	16	499.8
F9	2.49	8.4	4.5	0.54	4.3	>10	65.87	20	499.5
F10	2.86	8.6	4.8	0.56	4	>10	72.76	23	499.6

Influence of concentration of Gum Kondagogu on release rate of Metformin Hydrochloride:

To study the effect of Gum Kondagogu on release rate of Metformin Hydrochloride from the tablets, different concentrations of gum (300 mg to 175 mg) were employed by kneading the other process variables versus concentration of other excipients; method of preparation and hardness were kept constant. The dissolution profiles are shown in **figure: 4**, the drug release followed zero order kinetics, the graph plotted between the amount of drug release and time was found to be linear. To ascertain the mechanism of drug release the data was subjected to Higuchi & Korsmeyer-Peppas equation. Application of Korsmeyer-Peppas equation to the data revealed the mechanism of drug release of Metformin Hydrochloride from Gum Kondagogu matrix which is governed by predominant non fickian diffusion (slope $n > 0.5$). The release rate was found to have the influence of Natural polymer employed in the preparation of tablets (**table: 3**). Good correlation has been observed between the concentration of polymer and release rate constant. It

could arise because of increased viscosity of dissolution media with the increased concentration of Natural polymer.

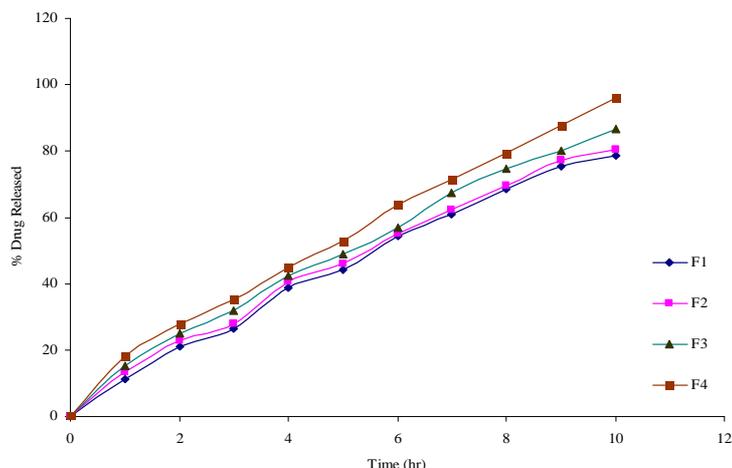


Figure: 4. Dissolution Profiles of Metformin Hydrochloride Floating Tablets with Various Concentrations of Gum Kondagogu

Influence of concentration of Sodium bicarbonate on release rate of Metformin Hydrochloride formulated with Gum Kondagogu:

To study the effect of sodium bicarbonate on release rate of Metformin Hydrochloride from the tablets, different concentrations of sodium bicarbonate (70mg to 100 mg) were employed by kneading the other process variables versus concentration of other excipients; method of preparation and hardness were kept constant. The dissolution profiles are showed in **figure: 5**, the drug release followed zero order kinetics and the graph plotted between the amount of drug release and time was found to be linear. To ascertain the mechanism of drug release the data was subjected to Higuchi & Korsmeyer-Peppas equation. Application of Korsmeyer-Peppas equation to the data showed that the mechanism of drug release of Metformin Hydrochloride from Gum Kondagogu matrix is governed by predominant non fickian diffusion (slope $n > 0.5$). It was also observed that the release rate was found to have impact on sodium bicarbonate employed in the preparation of tablets (**table: 3**). Good correlation was observed between the concentration of sodium bicarbonate and release rate constant. This may be attributed to the increase in concentration of sodium bicarbonate and decrease in viscosity of dissolution media at alkaline pH.

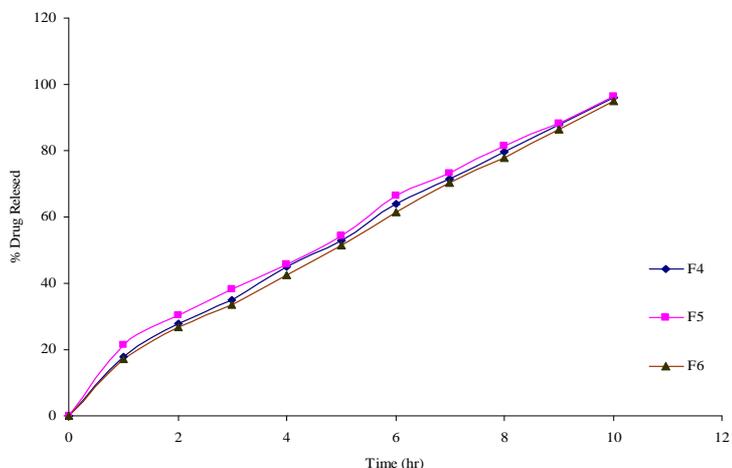


Figure: 5. Dissolution Profiles of Metformin Hydrochloride Floating Tablets with Various Concentrations of Sodium Bicarbonate

Influence of concentration of binding agent on release rate of Metformin Hydrochloride floating tablets formulated with Gum Kondagogu:

To study the effect of binding agent on release rate of Metformin Hydrochloride from the tablets, different concentrations of binding agent (80 mg to 160 mg) were employed by kneading the other process variables versus concentration of other excipients, method of preparation and hardness were kept constant. The dissolution profiles are shown in **figure: 6**, the drug release followed zero order kinetics, the graph plotted between the amount of drug release and time was found to be linear. To ascertain the mechanism of drug release the data was subjected to Higuchi & Korsmeyer-Peppas equation. Application of Korsmeyer-Peppas equation to the data showed that the mechanism of drug release of Metformin Hydrochloride from Gum Kondagogu matrix is governed by predominant non fickian diffusion (slope $n > 0.5$). The release rate was found to have influence of binding agent employed in the preparation of tablets as shown in **table: 3**. Good correlation was observed between the concentration of binding agent and release rate constant. This may be attributed to the increase in concentration of the binding agent and decrease in the release rate of the drug due to uniformity in hardness of the tablet.

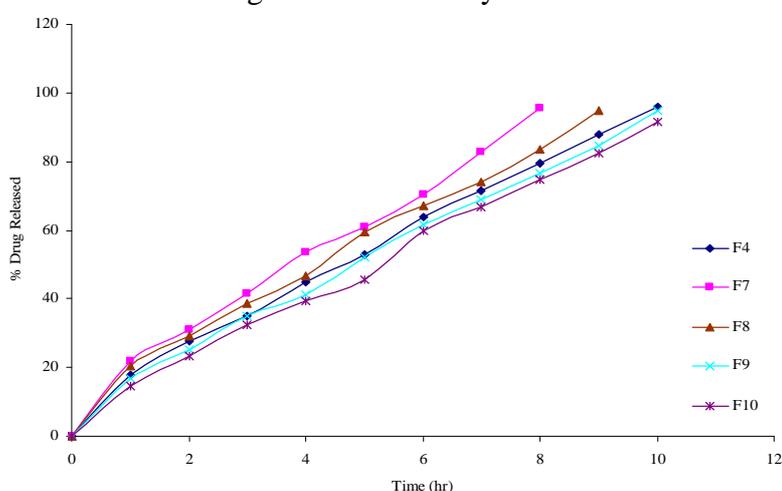


Figure: 6. Dissolution profiles of Metformin Hydrochloride floating tablets with various concentrations of binding agent

Table: 3 Dissolution kinetics of Metformin Hydrochloride floating tablet with various concentrations of Gum Kondagogu

Formulation	Correlation Coefficient (R^2)				K (mg/hr)	'n' Value	T_{50} (h)	T_{90} (h)
	Zero Order	First Order	Higuchi	Peppas				
F1	0.99004	0.9862	0.9680	0.9997	42.54	0.7866	5.6	12.1
F2	0.9899	0.9846	0.9641	0.9996	43.10	0.7941	5.4	11.2
F3	0.9893	0.9741	0.9636	0.9980	46.29	0.7707	5.2	10.4
F4	0.9884	0.9271	0.9645	0.9959	48.36	0.7394	4.7	9.5
F5	0.9884	0.9271	0.9645	0.9959	48.36	0.7394	4.7	9.5
F6	0.9849	0.9280	0.9692	0.9973	48.27	0.7187	4.5	9.3
F7	0.9890	0.9612	0.9623	0.9947	46.91	0.7536	4.9	9.7

F8	0.9833	0.9170	0.9704	0.9949	54.34	0.7001	4.5	8.4
F9	0.9916	0.9141	0.9602	0.9977	47.39	0.7759	4.8	9.6
F10	0.9946	0.9408	0.9518	0.9963	46.62	0.8061	5.4	9.8
Commercial	0.9930	0.8595	0.9577	0.9991	62.05	0.8801	3.6	7.2

Comparison of Optimized Formulation with Glycomet SR 500 mg commercial Tablet:

The comparison of the drug release from the tablets formulated with Gum Kondagogu (F4) with commercial S.R tablet (Glycomet) were assessed by using the similarity factor f_2 test and the floating lag-time of each formulation.

The dissolutions profile showed in (figure: 7). Similarity factor (f_2) of the two formulations was found to be 77.90% indicating the significant differences in between the selected and commercial formulation. Other criteria for the selection of the best batch from the formulation is the release drug in a predictable and controlled manner and have a Floating Lag Time less than <5min. To further evaluate the similarity, two check points (t_{50} and t_{90}) were considered in the dissolution profiles of F4 and the theoretical profile

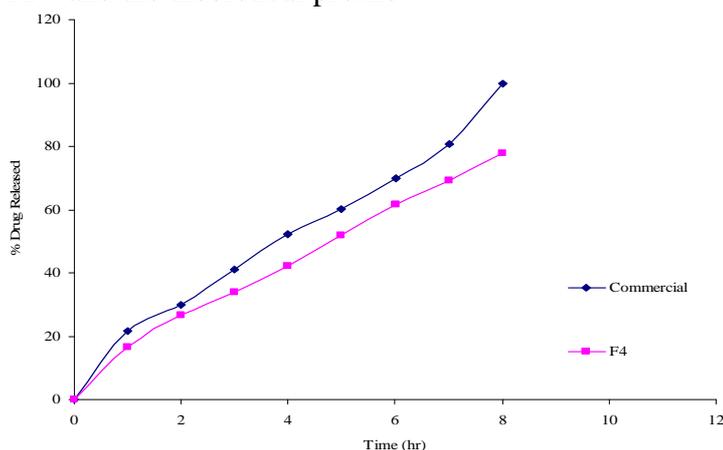


Figure: 7. Similarity factor profile of Metformin Hydrochloride formulated and commercial

CONCLUSION

From the data obtained above, it can be concluded that:

- Development of sustained release formulation of Metformin hydrochloride can be advantageous to provide prolonged gastric retention and increase the efficacy of the dosage form, there by improve bioavailability of the drug.
- The Natural polymer (Gum Kondagogu) selected as the polymer is more reliable as it released the drug slowly, extending the release over a longer period of time.
- Formulated tablets gave satisfactory results for various physical properties for tablets like tablet thickness, hardness, weight variation, friability, floating time, floating lag time, swelling index, wetting time, content uniformity and *in vitro* drug release.
- Moreover the high swelling capacity of this polymer helped in maintaining the buoyancy with the minimal utilization of gas-evolving excipients such as Sodium bicarbonate which if increased would make a marked impact on the G.I.T. fluids by their alkaline nature. Altering

concentrations of Natural polymer, binding agent and gas-evolving agent has a significant influence on the release rate of the drug.

- Formulated floating tablets best fitted to Korsmeyer-Peppas model and zero order kinetics.
- Further it is concluded that formulation (F4) has the desired release profile by adjusting the different parameters that ultimately affect the release behavior of the matrices. The optimized formulation can be obtained with minimum expenditure of time and money.
- Thus the objective of formulating a floating dosage form of Metformin hydrochloride by using optimization technique has been achieved by sustained release gastro retentive floating drug delivery system using low density Natural polymer.

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