Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Spl Issue [5] 2022 :286-298

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

ORIGINAL ARTICLE **OPEN ACCESS**

Formulation and Evaluation of Floating Tablet of Metformin Hydrochloride by Using Natural Polymer

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ABSTRACT
Diabetes mellitus especially type II is a complex metabolic disorder. This is associated with high glucose level in blood due to insulin resistance, unbalanced and β cell dysfunction. There are many diabetes induced complications such as nephropathy, cardiovascular problems, retinopathy and neuropathy. So for the treatment of diabetes and its complications. Metformin HCL is widely used for its glycaemia, body weight and insulin control potential. The aim of this study was to design, develop and evaluate a floating drug delivery system for Metformin hydrochloride by using guar gum and pectin polymer for the diabetes disorder. The wet granulation method was followed to prepare the Metformin HCI tablet. Preformulation study like melting point and solubility and compressibility (Carr's Index) was performed to know the polymers and drug compatibility. The evaluation parameters including Bulk density, Tapped density, Hausner's ratio, Carr's index and angle of repose were performed. In vitro release rate and dissolution study of the metformin HCl formulations was determined by using different kinetics models. The melting point and solubility index checked medication compatibility with other excipients. For various physicochemical assessments of tablets such as tablet size, hardness, time and in vitro drug release, formulated tablets were within acceptable limits. In comparison with other formulations prepared, formulation F4 has shown good floating behavior along with better controlled drug release. The best fits to the Hixon Crowell model and zero-order kinetics were formulated floating tablets.
Keywords: *Diabetes Mellitus, Floating drug delivery system, Metformin HCI, Pectin, Guar gum.*

Received 14.10.2022 Revised 23.11.2022 Accepted 20.12.2022

INTRODUCATION

Hyperglycemia is a symptom of diabetes mellitus, which can be caused by an imbalance between insulin secretion and insulin resistance. Diabetes affected 9.3 percent of the global population in2019; this figure is expected to rise to 10.2 percent by 2030 and 10.9 percent by 2045 [1]. Diabetes affects a large proportion of the Indian population; India with 69.2 million diabetic (type-II) people, is the country with the second highest number of people living with diabetes mellitus in the world, behind only China [2]. Diabetes is more prevalent in poor countries than in developed nations. Diabetes affects around 61.2 million people in India, with the number expected to rise to 101.2 million by 2030 [3].

Metformin(3-(diaminomethylidene)-1,1-dimethylguanidine) (Fig. 1**:** Chemical structure of Metformin Hydrochloride) is a biguanide derivative derived from the fusion of two guanidines found in Galega officinalis, and it was initially used in mediaeval Europe to treat diabetes-related polyuria [4].It has become a well-known first-line anti-diabetic medication for people with type- II diabetes mellitus due to its potential efficacy in decreasing blood glucose levels, as well as a favorable influence on plasma lipids, body weight, and the risk of microvascular and macrovascular problems [5]. It can be used as mono therapy as well as combination therapy with others antidiabetic dose regimen [6]. There are various pharmacological diabetes therapies where Metformin hydrochloride (HCL) is the first line drug of choice for diabetic type II patients. It is popular over 40 years because of its strong ability to ameliorate the glucose level and weight gain problem [7]. However, due to low water solubility, poor stability and rapid evacuation, metabolism, certain medicaments have poor oral bioavailability [8] Metformin HCl can't use for oral purpose. The oral route is still advanced due to convenience, low price, painless and most acceptable to patients, despite rapid advances on parenteral drug delivery technology.

The floating medication method for the Metformin HCL was designed to enhance its dosage frequency by slowing yet safe release of the medicine into the GI tract. The drug's residence at the optimal absorption site is one of the most critical factors affecting bioavailability [9].The GDDS is indeed a way of maintaining medication release when the medicinal material is still in the gastrointestinal tract (GIT) [10].The GDDS are categorized as floating, muco-adhesive and high-density systems, swelling systems and magnet system according to their mechanisms [11].

The most attention has been paid to floating systems with a density of 1.0 g/cm3 [12].Floating systems are classified into two types: effervescent and non-effervescent [13].The effervescent system, as the name indicates, contains a foaming ingredient such as sodium bicarbonate (NaHCO3) [14].

Various research have been published on the construction of the floating system and floating metformin loaded system [15-16].The bulk of the research mentioned above, however, requires the use of sodium bicarbonate or floating polymers in the deployment of gastric retention mechanisms. Furthermore, the development of gastric retention system comprises a complex and fuel production process, including the extrusion of hot melt.In order to overcome the aforesaid limitations, a single floating mechanism is necessary.

We have presented a unique and creative floating tablet design that does not require the use of 3D printers in this study.The tablet's major feature is its hollow core, which allows it to float in the stomach, extending gastro-retentive time and increasing oral bioavailability.As a model medication, floating tablet loading metformin hydrochloride was produced and tested in vitro.The pharmacokinetic research was conducted to further assess the resilience of this delivery method.

MATERIAL AND METHODS

Metformin HCL was procured as a gift sample from Panacea Biotech Pvt.Ltd. Baddi (HP, India), Talc was purchased from (Lobachemie Pvt. Ltd. Mumbai, India) and all other chemicals (isopropyl alcohol, lactose, sodium bicarbonate, citric acid, guar gum, pectin, magnesium stearate) were purchased from CDH chemical company, New Delhi, India.

Preformulation studies

Preformulation studies are performed before formulation development to know the drug compatibility with other excipients.

Melting Point

The melting point was determined using melting point apparatus (Manti Lab solutions, Haryana –India). For this procedure a capillary was closed from the one end using burner flame and drug is filled from the other end. To settle down the drug powder the capillary is tapped carefully. Then the tube is placed into melting point apparatus hole. The temperature is noted with the help of thermometer when drug started to melt. Finally, the obtained value is compared with reference value.

Solubility studies

The solubility study was determined by dissolving Metformin (1g) into 0.1 NHCI (pH 2-3). The glass bottle was kept aside for 24 hour at 37^{o} C. Then the solution was filter and diluted for determination of absorption spectrum at maximum wavelength.

Compression and flow properties

Tapped density, Hausner's ratio, angle of repose, Carr's index and bulk density of the experimental powder was used to determine flow measurement and compress ability of the experimental powder.

Flow Measurement

Angle of Repose

The angle of repose was examined by fixed funnel method [17]. The weighed amount of powder was added into the funnel from a fixed height or in such a way to avoid aggregation into the funnel. The height of funnel adjusted like tip of the funnel just touches the apex of powder heap. The powder mass height (h) was measured in triplicate and angle of repose was calculated by the following equation:

$$\text{Tan } \theta = h/r$$

Where θ = angle of repose, h = powder cone height, r = radius of the powder cone.

Hausner's Ratio

It is an indicator of ease of powder flow. It is given by following equation [18]:

$$\text{Hausner's Ratio} = {}^{Dt}/_{Da}$$

Where D_t = Tapped density and D_b = bulk density

Compressibility Index

Bulk density (D_b) and Tapped Density (D_j)

The pre weight powder was sieved (no. 18) and added into a measuring cylinder (100mL), and volume is recorded. This procedure was repeated three times and average reading was considered. In case of

tapped density, the cylinder is situated on a mechanical tapper apparatus. The apparatus is tapped at a height of 10 cm. at 2 sec. interval. The tapping was continued until the volume has reached a minimum volume.

Hence, the bulk density and tapped density [19] was calculated by using underneath formula. The bulk density (Eq. 1) and tapped density(Eq. 2) was recorded using following equation.

$$D_b = M/V_b \quad (1)$$

$D_t = M/V$ (2)

Where M= mass of powder (g); V_b = bulk volume of the powder (ml) and V= tapped volume (ml)

2.3.2.2 Carr's index

It indicates powder flow properties and expressed in (%) percentage (Carr, 1965).

$$CI = {}^{Dt - Db}/_{Dt} \times 100 \quad (3)$$

Where D_t = Tapped density and D_b = bulk density of the powder

Evaluation of tablets

The physiological parameter such as general appearance, thickness, weight variation, hardness, friability and buoyancy lag–time study of tablets were followed to characterize the prepared tablet.

Weight Variation

This test is necessary to represents that in single batches all tablets are of same potency and are within acceptable limit. The twenty tablets (20) weighed separately and average weight is calculated from the total weight. Further, weight variation was calculated by comparing tablet individual weight with average weight [20].

Hardness

Tablets hardness: It is defined as force applied across the tablets diameters in order to break the tablets. The test is performed due to safety of tablets during packaging, loading and shipping. The hardness of the tablets was determined using Monsanto hardness tester [21].

Tablets thickness

This is an important parameter associated with tablet hardness. Ten (10) tablets from each batch are selected randomly then thickness and diameter of tablets is measured using vernier caliper in millimeters.

Friability (F)

It is a measured of mechanical strength of the tablets and measured using Roche friabilator[22]. The 10 tablets of initially weighted and then placed into friabilator. It was revolved at 25 rpm for four minutes. Then again tablets were weighted. Here, loss of tablets due to abrasion was the measure of tablets friability. The percentage of friability was calculated using following equation:

$$\% F = \frac{(W0 - W)}{W0} \times 100$$

Where W_0 = initial weight, W= final weight of the tablets.

Fabrication of Metformin tablets

The tablets were fabricated by wet granulation method using chemicals and excipients given in table 1. The metformin (500mg) was mixed with adequate amount of polymers and other ingredients. The entire ingredients were passed through the sieve (no. 40). Further, intra granular excipients were mixed and moistened with PVP-K30 (2%) solution in isopropyl alcohol until to attain required consistency. Then, the wet granules rapped into aluminum foil and dried in hot air oven at 45^o C for 120 minutes. Further, granules were passed through sieve (no. 20) and lubricated with talc and magnesium stearate. Finally, compression machine was used to compress granules into tablets with standard concave tooling of 8.6 mm diameter [23].

In vitro buoyancy study

It is the measure of floating duration of the prepared tablets. The buoyancy of metformin tablet was tested in vitro using the USP equipment II (Paddle method).The dissolving device was filled with 100ml of dissolution medium comprising gastric solution (pH1.2) and kept at 37°C with a rotating speed of 50 rpm. The floating lag time (FLT) is the measure of time taken by the tablet to come out on the surface and the duration of floating (FDT) in the gastric solution. This test was performed three times and average was computed. The technique of preparation was somewhat altered from the literature [24]).The FLT and FDT were performed in triplicate to determine in vitro buoyancy tendency according to the viscosity of polymers (i.e. pectin and guar gum).

In-vitroRelease study

The in vitro release study of Metformin tablet was studied by dissolution testing apparatus USP II, (paddle) using dissolution tester (Electro lab dissolution tester, Electro lab, India). The temperature of the assembly was adjusted (37 ± 0.5 °C) at 50 rpm. For dissolution media 900 ml of simulated gastric fluid 0.1 NHCI at (pH-1.2) was used. At regular interval of time aliquot (5 ml) of sample was taken out and

replaced with fresh media in the same amount. Then, the media was filtered through 0.45μmfiltration medium and further released metformin was assayed by UV- spectrophotometer at 234 nm (UV-1700 Shimadzu Corporation, Japan.). The cumulative % drug release was calculated for the formulations [8]. The different formulations were prepared using different polymers (guar gum and pectin) and lactose as diluents.

In vitro drug release data was analysed by using various kinetic models such as: (Zero order, First order, Higuchi and Korsmeyer-Peppas). Rate of drug release doesn't depend on the concentration in case of zero order kinetics [25]represented by equation 4while first order kinetics, rate of drug release depends on the concentration [26] explained in equation 5. Fickian diffusion process based (Eq. 6), drug release rate from insoluble matrix as a square root of time was explained by Higuchi and mentioned in equation 5. The (F2) square value was considered to decide which model best for the study. A simple mathematical relationship which described the drug release from a polymeric system (Eq. 7) was derived by Korsmeyer et al., 1983 [27].

$$C = \kappa ot \qquad (4)$$

Where, C is the concentration of drug at time t, t is the time and k_0 is zero-order rate constant (Conc./time)

$$\text{Log Co} - \text{Log C} = \frac{kt}{2.303} \qquad (5)$$

Where, C_0 is the initial concentration of drug and k is the first order rate constant.

$$C = KH\sqrt{t} \qquad (6)$$

Where, K_H is the constant reflecting the design variables of the system.

$$\frac{Mt}{M\infty} = K_{KPt}n \qquad (7)$$

Where Mt/M∞ is the fraction of drug released at time t, KKP is the rate constant and n is the release exponent.

Drug Content

This assay for metformin tablet is explained in IP 1996.For this procedure, twenty tablets selected randomly, weighed and powdered using mortar pestle. Then, 100 mg drug powder added into volumetric flask of (100mL) containing 0.1 NHCL solution. Then, 10 mL of filtrate was diluted with 0.1N HCL up to 100 ml. Further, 10 ml of this was also diluted with the 0.1 N HCI up to 100 ml. Then, the solution was filtered and finally drug content was determined using UV- spectrometer at 234nm.

RESULT AND DISCUSSION

Preformulation studies

The melting point was measured using a melting point apparatus. The recorded value was compared with the literature value as shown in the following table 2. The observed melting point of formulated metformin was 204° C which is nearly equal to IP standard 206 ° C. This result shows that practical and theoretical values are nearly the same, which means that Metformin is in a pure state. The Metformin solubility in media (0.1N HCL) is given in table 3. Based on the used media for the solubility, the drug was found freely soluble in aqueous solvent like as water or alcohol while insoluble in organic solvent like as acetone, methylene chloride and so on.

Compression and flow properties

The flow properties of all the formulation were examined by angle of repose (AOP) and Hausner's while compress ability was estimated by Bulk density, tapped density, and Carr's index. Table 4.reveled the flow properties of the powder that can be used for tablet formulation. The angle of repose of all the formulation was between ranges 24.042 – 38.602 showed that good flow properties. The value of bulk density and tapped density were noticed in the range of 0.492 to 0.690 g/cm^3 and 0.626 – 0.785 respectively g/cm^3. In the similar way the observed value of Carr's index and Hausner's ratio were 10.9 to 19.0 and 1.1 to 1.2 respectively for the all formulation showed that powder had good flow properties.

Evaluation tests for tablets

After compression of granules, the tablet was evaluated for organoleptic characteristics like color, odor, diameter and physical characteristics like hardness, friability, and dispersion time and dissolution studies. The result showed that thickness, weight and hardness were within pharmacopoeias limits and hence they passed the above tests. Friability was performed for all the batches (F1 to F3) and the data are presented in table 5. Thus all these result like friability, hardness, weight variation, thickness were found to provide satisfactory results for all batches. The hardness was found to be 4.5 to 5.6 kg/cm^2. The examined value of friability for all the formulations were found between in the range of 0.265 to 0.410 % that is less than one signaling tablet were mechanically stable. All the tablets passed the weighed

variation tests i.e. noticed with in pharmaceutical limit ± 5% of the weight. The weight was found to be uniform with low standard deviation. The thickness and drug content percentage of all tablets were measured 4.64 – 6.16% and 90.4 to 97.0% respectively for all the formulations.

In vitro buoyancy study

For all of the formulations, an in vitro buoyancy study was conducted in terms of FLT and FDT. Because metformin is absorbed primarily in the stomach and upper GI tract, floatability would be advantageous. The immediate rise and maintained flotation achieving local drug absorption can prevent tablet excretion into the small intestine. Table 6 shows the FLT and FDT values for various formulations. All of the formulations floated immediately upon contact with the medium (FLT=0), regardless of the viscosity of the polymer. In the case of the FDT, the formulations F1 and F2 disintegrated rapidly in the medium due to the use of polymer in the tablet development. Strusi et al., demonstrated some in vivo studies for confirmation that the in vitro floating ability of void configuration was maintained also in the human stomach [28]. The floating time of tablets after immersion in 0.1 N HCI at 37 ^{o} C was more than 12 hours.

In-vitro release study

Metformin is an extremely hydrophilic drug. Under physiological conditions, the existing form is mostly positively charged. The formulations were prepared using guar gum and pectin polymers (table 7, 8)and dissolution rate and release profile of F4 formulation (table 9) is mentioned in fig 2. Effect of polymer concentration over drug release, 3. Dissolution profile of formulation with different polymers). In order to determine the release mechanism of prepared Metformin tablets from all batches the dissolution study was evaluated in accordance to the kinetic model. The release mechanism was examined by following zero order kinetics (table 10), first order kinetics (table 11), Hixon – Crowell's kinetics (table 12),Higuchi kinetics (table 13), and Korsmeyer- Peppas (table 14) kinetics models [29]. To find the regression coefficient (R^2) value released data was fitted in these different models. The R^2 near to one indicates the model fitting of the release mechanism. As listed in table 15, the best fit model was Hixon Crowell's model for the drug release profile. The data found from the drug release kinetics study resulted that F4 batch (Fig. 4. Metformin release kinetic of F4 according to Zero order kinetics 5. Metformin release kinetic of F4 according to First order kinetics, 6. Metformin release kinetic of F4 according to Hixon Crowell's kinetics, 7. Metformin release kinetic of F4 according to Higuchi kinetics model 8. Metformin release kinetic of F4 according to Korsmeyer Peppas kinetics) showed the highest F2 value of 0.993 in Hixon Crowell's model with a total release of 89.13% drug at the end of 12 hours. So, it was concluded that F4 was the one of the best batch among total eight batches.

Drug Content

Uniformity of all the formulations was carried out by UV spectrophotometer. The drug content of all the formulation was found to be in the range of 90.4% to 97% which showed that there was uniform distribution of all drug throughout the batch.The formulation and evaluation of gastro retentive floating tablets of metformin was carried out successfully using various concentrations of guar gum and pectin.

CONCLUSION

In this study, we have developed floating metformin-loaded formulation for diabetes type II management by wet granulation method based on effervescent approach.Guar Gum and pectin were used as the polymers and sodium bicarbonate was used as gas generating approach.Active molecular preformulation studies were carried out to identify physical-chemical properties of the drug that are relevant for the design and manufacture of dosage forms.The melting point and solubility index checked medication compatibility with other excipients, while the compression and flow properties were determined by bulk density, tapped density, angle of repose, Hausner's ratio, Carr's index. For various physicochemical assessments of tablets such as tablet size, hardness, time and in vitro drug release, formulated tablets were within acceptable limits. In comparison with other formulations prepared, formulation F4 has shown good floating behavior along with better controlled drug release. The best fits to the Hixon Crowell model and zero-order kinetics were formulated floating tablets.

ACKNOWLEDGEMENTS

I would like to appreciate Baba Masthnath University, Haryana for his valuable support and guidance.

Compliance with ethical standards

The authors have taken all the necessary permissions as per ethical guidelines wherever applicable. The authors will be responsible for all the technical content mentioned in the manuscript. Journal and Publisher will not be responsible for any copyright infringement and plagiarism issue.

Conflict of interest

"The authors report no declarations of interest".

Availability of data and material

"Samples can be acquired from the first author upon request".

Table 1. Composition of floating metformin tablet formulations

Ingredients (mg)	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Metformin HCL	500	500	500	500	500	500	500	500
Lactose	190	190	140	140	90	90	190	290
Sodium bicarbonate	70	70	70	70	70	70	70	70
Citric acid	30	30	30	30	30	30	30	30
Guar gum	100	100	150	150	200	200	200	-
Pectin	100	100	100	100	100	100	-	100
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5

Table 2. Theoretical and observed melting point value of Metformin

Melting Point of Metformin (experimental value)	Reference value
204° C	206° C

Table 3. Solubility of Metformin in 0.1 N HCL

Media	Solubility Drug (mg)/media (mL)	Category
Water	4.61	Freely soluble
Alcohol	4.37	Slightly soluble
Acetone	4.7	Insoluble
Methylene chloride	4.1	Insoluble

Table 4.Micromeritic properties of formulations

Batch	Bulk density (g/mL)	Tapped density (g/mL)	Carr's Index (%)	Hausner's ratio	Angle of repose (°)
F1	0.690	0.785	12.1 (Good)	1.1 (Good)	32.6 (Fair)
F2	0.538	0.647	16.9 (Fair)	1.2 (Fair)	26.3 (Good)
F3	0.567	0.637	10.9 (Good)	1.12 (Good)	38.6 (Passable)
F4	0.522	0.626	16.61 (Fair)	1.2 (Fair)	33.4 (Fair)
F5	0.539	0.635	15.11 (Fair)	1.2 (Fair)	24.0 (Excellent)
F6	0.580	0.694	17.3 (Fair)	1.2 (Fair)	25.0(Excellent)
F7	0.543	0.656	17.2 (Fair)	1.20 (Fair)	27.6 (Excellent)
F8	0.492	0.650	19.0 (Fair)	1.20 (Fair)	26.6 (Excellent)

Table 5. Evaluation of Metformin tablet

Batch	Hardness (Kg/cm^3)	Friability (%)	Weight variation in mg (Indian Ph.)	Drug Content (%)	Thickness (mm)
F1	-	-	870.5	-	4.64
F2	4.8	0.290	963.4	90.4	6.08
F3	4.4	0.295	960.2	92.2	6.06
F4	4.5	0.296	961.2	93.5	6.10
F5	5.2	0.310	963.3	94.6	6.12
F6	5.2	0.311	964.2	95.5	6.16

Table 6. The FLT and FDT of various formulation of metformin HCL (n = 3)

Formulations	Floating lag time (FLT; s)	Floating duration time (FDT; h)
F1	-	<12
F2	2.10	<12
F3	2.08	<12
F4	2.09	<12
F5	1.57	<12

Table 7. Release profile of formulation using different polymers

Time (h.)	Cumulative drug release (%)							
	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0	0	0	0	0	0	0
2	14.90	15.65	12.62	13.63	15.40	16.41	22.12	23.13
3	17.50	18.51	15.20	16.21	18.50	19.51	25.50	26.51
4	37.40	38.41	35.42	36.43	30.60	31.61	38.10	50.11
5	47.12	47.14	45.54	46.52	47.62	48.60	49.14	55.15
6	56.48	57.49	53.62	54.64	57.65	58.67	60.15	65.16
7	65.12	66.13	62.54	63.50	67.12	68.13	72.18	75.19
8	75.65	76.67	68.40	69.41	70.50	71.12	75.19	80.13
9	78.12	79.68	75.12	76.15	77.12	78.10	79.13	84.14
10	80.15	81.16	84.10	85.17	83.40	84.41	81.12	90.13
11	85.20	86.22	86.42	87.50	88.12	87.17	82.13	92.14
12	87.12	88.19	88.12	89.13	89.20	90.12	83.11	93.12

Table 8. Dissolution profile of formulation with different polymers

Time (h.)	Cumulative drug release (%)	
	Guar gum	Pectin
1	0	0
2	22.12	23.13
3	25.5	26.51
4	38.1	50.11
5	49.14	55.15
6	60.15	65.16
7	72.18	75.19
8	75.19	80.13
9	79.13	84.14
10	81.12	90.13
11	82.13	92.14
12	83.11	93.12

Table 9 In - Vitro drug release studies of F4

Time (h.)	% CDR	Log % CDR	Cube root of % drug remaining	Log % cumulative drug remaining	Square root time	Log Time
0	0	0	4.6415	2.000	0	0
1	13.63	1.1344	4.4203	1.9363	1	0
2	16.21	1.2097	4.3758	1.9231	1.33	0.3031
3	36.43	1.5614	3.9910	1.8032	1.73	0.4771
4	46.52	1.6676	3.7675	1.7281	2.00	0.6021
5	54.64	1.7375	3.5663	1.6566	2.23	0.6990
6	63.50	1.8027	3.3171	1.5652	2.44	0.7782
7	69.41	1.8414	3.1274	1.4855	2.64	0.8451
8	76.15	1.8816	2.8784	1.3774	2.83	0.9031
9	85.17	1.9302	2.4568	1.1711	3.00	0.9542
10	87.50	1.9420	2.3207	1.9691	3.16	1.000
11	89.13	1.9500	2.2151	1.0362	3.31	1.0414
12	93.21	1.9694	1.8936	0.8318	3.46	1.0792

Table 10. Metformin release kinetic of F4 according to Zero order kinetics

Time (h.)	% CDR	Log % CDR Remaining
0	0	0
1	13.63	1.1344
2	16.21	1.2097
3	36.43	1.5614
4	46.52	1.6676
5	54.64	1.7375
6	63.5	1.8027
7	69.41	1.8414
8	76.15	1.8816
9	85.17	1.9302
10	87.5	1.942
11	89.13	1.95
12	93.21	1.9694

Table 11. Metformin release kinetic of batch F4 according to First Order kinetics

Time (h.)	Log % CDR Remaining
0	0
1	1.1344
2	1.2097
3	1.5614
4	1.6676
5	1.7375
6	1.8027
7	1.8414
8	1.8816
9	1.9302
10	1.942
11	1.95
12	1.9694

Table 12. Metformin release kinetic of batch F4 according to Hixon Crowell's kinetics

Time (h.)	Cube root of % drug remaining
0	4.6415
1	4.4203
2	4.3758
3	3.991
4	3.7675
5	3.5663
6	3.3171
7	3.1274
8	2.8784
9	2.4568
10	2.3207
11	2.2151
12	1.8936

Table 13. Metformin release kinetic of F4 according to Higuchi kinetics model

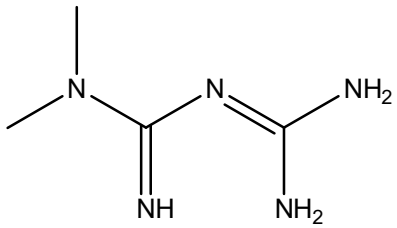
Square root time	% CDR
0	0
1	13.63
1.33	16.21
1.73	36.43
2.0	46.52
2.23	54.64
2.44	63.5
2.64	69.41
2.83	76.15
3.0	85.17
3.16	87.5
3.31	89.13
3.46	93.21

Table 14. Metformin release kinetic of F4 according to Korsmeyer Peppas kinetics

Log Time	Log % CDR
0	0
0	1.1344
0.3031	1.2097
0.4771	1.5614
0.6021	1.6676
0.699	1.7375
0.7782	1.8027
0.8451	1.8414
0.9031	1.8816
0.9542	1.9302
1	1.942
1.0414	1.95

Table 15. The Statistical Kinetic values for F4

Kinetics model	R^2
Zero order kinetics	0.955
First order kinetics	0.636
Hixon Crowell's model	0.993
Higuchi model	0.967
Korsmeyer Peppas model	0.768



3-(diaminomethylidene)-1, 1-dimethylguanidine

Fig 1. Chemical structure of Metformin Hydrochloride

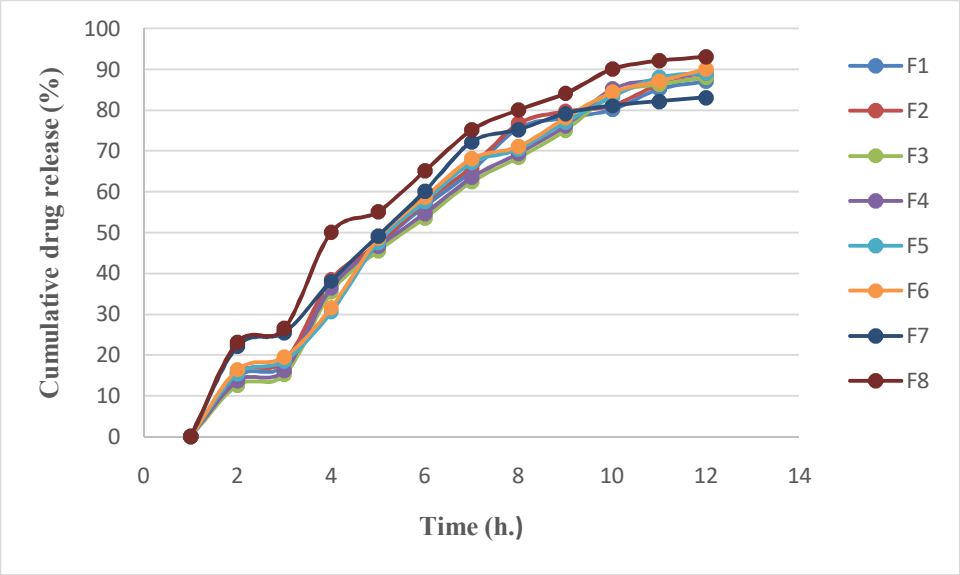


Fig 2. Effect of polymer concentration over drug release

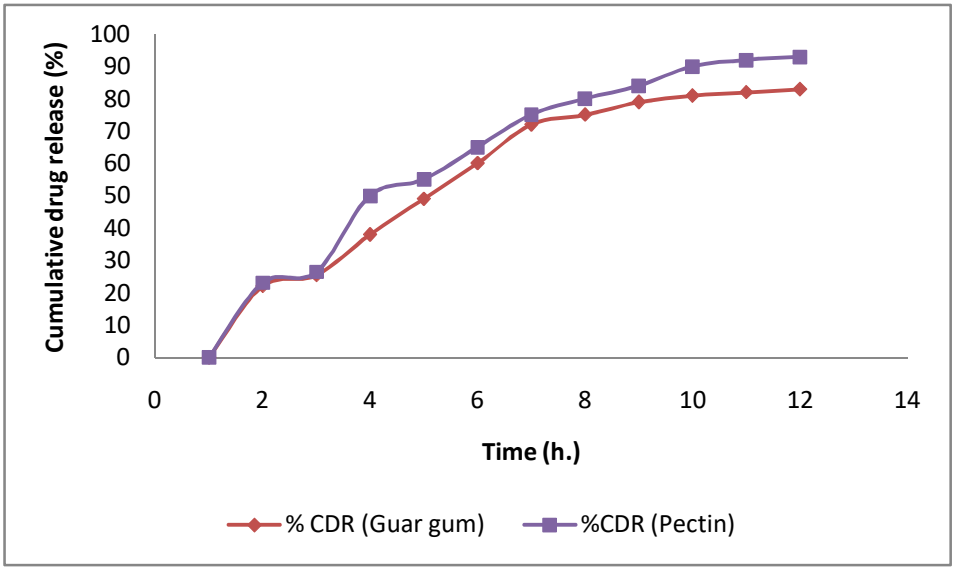


Fig 3. Dissolution profile of formulation with different polymer

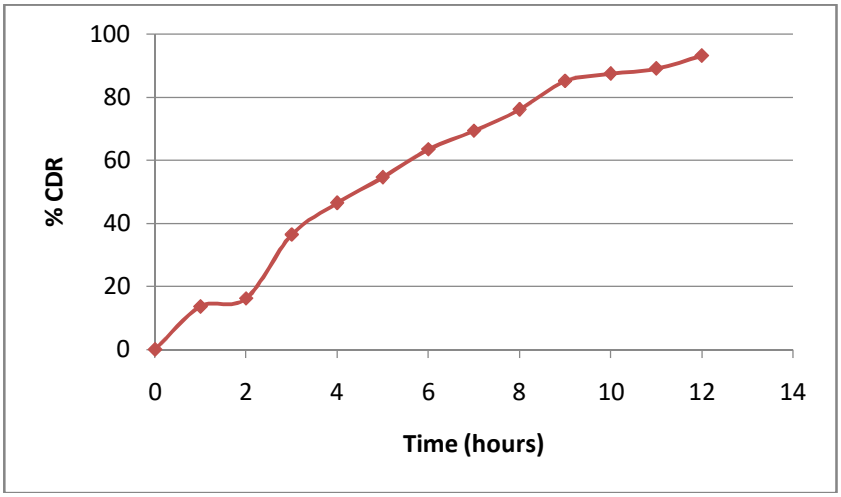


Fig 4 Metformin release kinetic of F4 according to Zero order kinetics

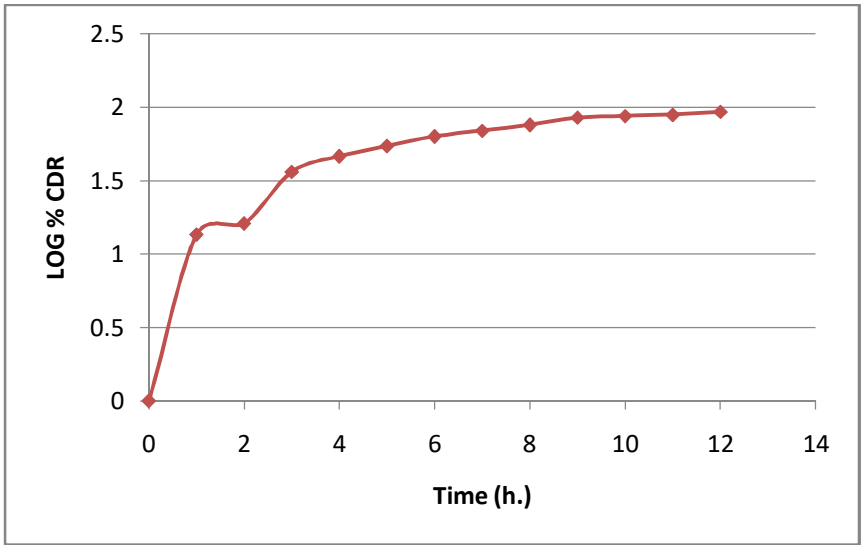


Fig 5. Metformin release kinetic of F4 according to First order kinetics

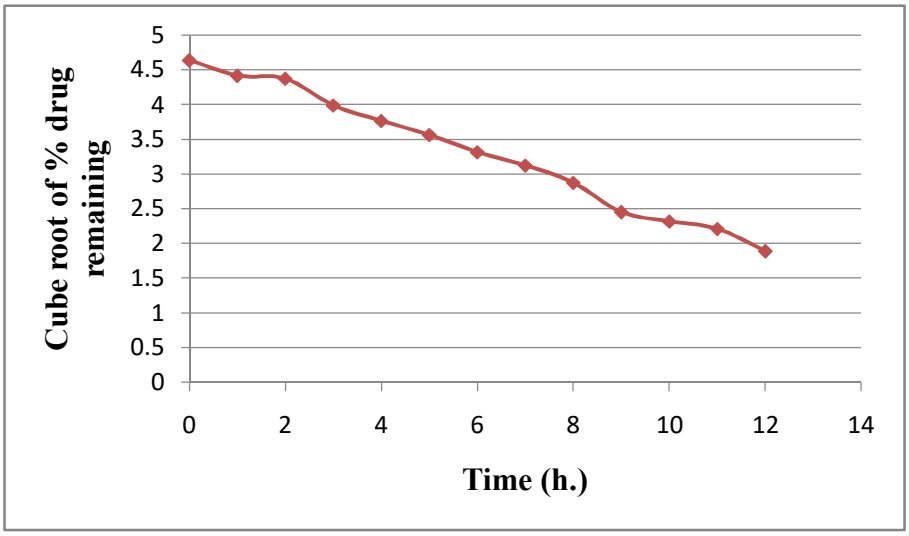


Fig 6. Metformin release kinetic of F4 according to Hixon Crowell's kinetics

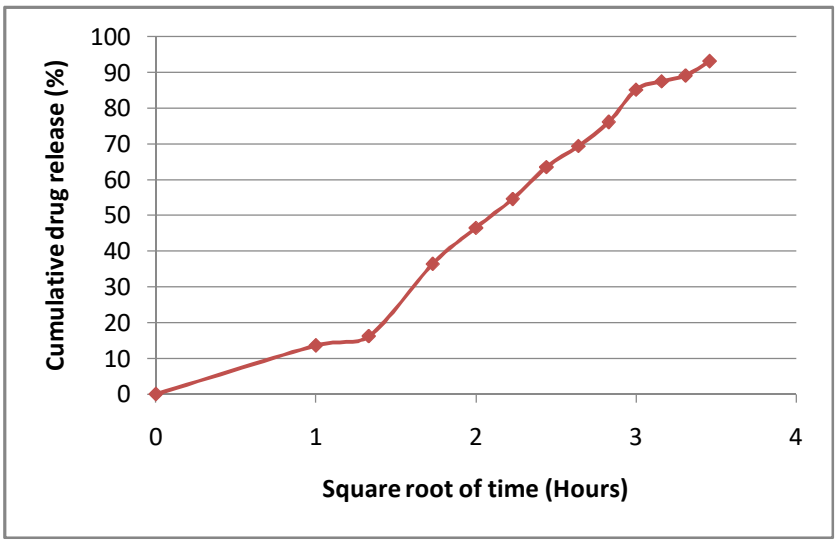


Fig 7. Metformin release kinetic of F4 according to Higuchi kinetics model

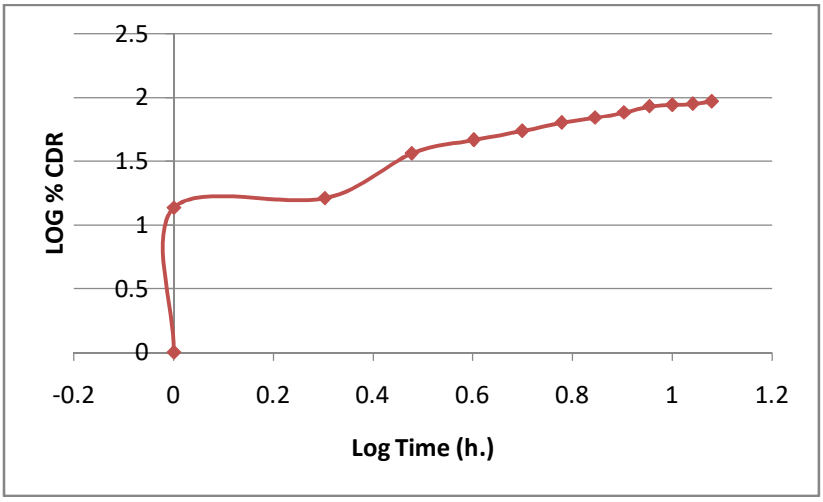


Fig 8. Metformin release kinetic of F4 according to Korsmeyer -Peppas kinetics

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CITATION OF THIS ARTICLE

Reena Budhwar, Pawan Jalwal, Tinku: Formulation And Evaluation Of Floating Tablet Of Metformin Hydrochloride By Using Natural Polymer. Bull. Env.Pharmacol. Life Sci., Spl Issue [5]: 2022: 286-298.