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FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF GLIMEPIRIDE

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Abstract:

Floating tablets of Glimepiride were developed to prolong the gastric residence time and there by increased drug bioavailability. Diabetes condition influences the gastric emptying time which affect the absorption of the drug. Glimepiride was chosen as model drug because it has incomplete absorption due to less gastric residence time. The tablets were prepared by direct compression technique, using polymers such as HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 974P, and Xanthan Gum. Tablets were evaluated for various parameters such as hardness, % friability, in-vitro drug release profile, swelling characteristics, floating capacity, and drug content. Gas generating system plays an important role in floating lag time and drug release. It was found that the best formulation for F5 was having the floating lag time of 20 sec and showed 98.62% drug release at the end of 12hours.

Key Words: *Glimepiride, Floating tablet, Direct compression technique,Non fickian diffusion,HPMC,Carbapol 974P, Xanthan Gum.*

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INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. However, this route has several physiological problems, including an unpredictable gastric emptying rate that varies from person to person, a brief gastrointestinal transit time (8–12 h), and the existence of an absorption window in the upper small intestine for several drugs [1-3]. These difficulties have prompted researchers to design a drug delivery system which can stay in the stomach for prolonged and predictable period. Attempts are being made to develop a controlled drug delivery/system, which can provide therapeutically effective plasma drug concentration for a longer period, thereby reducing the dosing frequency and minimizing fluctuations in plasma drug concentration at steady-state by delivering the drug in a controlled and reproducible manner. Various approaches for gastro retentive dosage forms have been proposed including mucoadhesive systems, swellable and floating systems. Floating drug delivery systems were first described by Davis in1968. These systems were used to prolong thegastric residence time of drug delivery systems [4,5,6]. 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), are unstable in lower parts of GIT, or are poorly absorbed in the intestine. Floating dosage forms are floating due to an intrinsic density lower than that of the gastric content, which is reported as 1.004–1.010 g/cm^3, or due to the formation of a gaseous phase inside the system after contact with gastric fluid. This attribute allows them to remain afloat on the surface of the gastric content for a longer period of time without affecting the rate of emptying [7,8,9]. Glimepiride is a first third generation sulphonyl urea agent for the treatment type II diabetes mellitus [10-15]. Oral bioavailability is 50-60% due to narrow absorption window. Biological half-life of Glimepiride is 5 hrs. Glimepiride is given once daily in doses from 1-8 mg. In the present investigation, thepreparation and evaluation of gastroretentive floating tablets of Glimepiride was studied. The main objective of present work was to develop gastroretentive floating tablet by using natural polymer xanthan gum and synthetic polymers HPMC K4, HPMC K15, HPMC K100 and Carbopol 974. Floatingtablet of Glimepiride was prepared to increase bioavailability and for maximum absorption.Floating tablets of Glimepiride were developed to enhance its bioavailability by prolonging the gastric residence time in which Glimepiride was chosen as a model drug because of it has incomplete absorption due to its low gastric residence time.

MATERIALS AND METHODS:

Materials:

Glimepiride is obtained as a gift sample from Watson pharmaceutical,Goa, India. Hydroxyl Propyl Methyl Cellulose (K4M, K15M, K100M) obtained from Loba chemicals pvt ltd, India, Xanthan gum, Sodium bicarbonate, Citric acid, , Magnesium stearate, Talc obtained from Concept Pharma Aurangabad, Carbopol974P, PVP K30 obtained from FDC Ltd. Jogeshwari, West Mumbai. All other chemicals and solvents were of analytical grade.

Method:

The composition of different formulations of Glimepiride floating tablets,Glimepiride, Xanthan gum and sodium bicarbonate, Citric acid were weighed and sift through # 40 sieve. Mix the sifted ingredients with HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 974p, PVP K30 by geometric mixing.Blend was lubricated with magnesium Stearate and Talc.Amount of powder mixture (approximate 100 mg) were weighed and compressed using 6.5 mm shallow concave punch. Eight formulation were prepared and coded them F1 to F8.

Evaluation of Gastroretentive Floating Tablet:

Uniformity of Weight: The weights were determined to within ±1mg by using Shimadzu Corporation, Japan. Weight control is based on a sample of 20 tablets. Determination were made in triplicate.

Tablet Hardness: The crushing tolerance of tablet was measured using an Electrolab model EL500. Determination was made in triplicate.

Tablet Friability: The friability of the tablets was measured in Electrolab .Tablets of a known weight or a sample of 20 tablets arededusted in a drum for a fixed time. (100 revolution) and weight again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%. Determination was made in triplicate.

Friability = [(initial weight –final weight) / (initial weight)] x 100.

Drug Content:

Twenty tablets from each batch were weighed and powdered. Powder equivalent to 4 mg of Glimepiride was accurately weighed and transferred into a 100 ml volumetric flask and shake with 100 ml of methanol for 10 min. The 10 ml of methanolic solution was diluted up to 100 ml with 0.1N HCl with 0.5% w/v of sodium lauryl sulphate and sonicated for 5 min. to get a concentration in the range of 4µg/ml. A portion of the sample was filtered through 0.45µ membrane

filter and analyzed by Shimadzu UV/VIS double beam spectrometer at 228nm.

***In-vitro* Buoyancy Studies:**

*In-vitro*buoyancy studies were performed for all the formulations as per the method described by Rosa *et al*. The randomly selected tablets from each formulation were kept in a 100 ml beaker containing 0.1 N HCL (pH 1.2). The time taken for the tablet to rise to the surface and float was taken as floating lag time (FLT). The duration of time the dosage form constantly remained on the surface of medium was determined as the total floating time (TFT).

Water Uptake Study :(Determination of Swelling Index %):

One tablet was weighed and placed in a beaker containing 200 ml of distilled water. After each hour the tablet was removed from beaker and weighed again up to 12 hours. The % weight gain by the tablet was calculated by the formula,

Swelling Index (S.I.) = {(Wt-Wo)/Wo} ×100

Where,

S.I. = swelling index, Wt = weight of tablet at time t.

Wo = weight of tablet before immersion

***In-Vitro* Dissolution Study:**

The drug release profiles of Glimepiride floating tablets were determined using Type IDissolution Apparatus(BasketType). The dissolution medium was 900 ml, 0.1 N HCl with 0.5% w/v of sodium lauryl sulphate (pH 1.2) at 37±0.50C with agitation speed of 50 rpm. Samples were withdrawn at regular intervals over an 12 h period, filtered through 0.45µ membrane filter. Filtered samples analyzed by Shimadzu UV/VIS double beam spectrometerat 228nm. The cumulative percentage drug release was calculated.

Table 1: Composition of Formulation of Floating Tablet of Glimepiride

Ingredients (mg)	Formulation Codes							
	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride	2	2	2	2	2	2	2	2
HPMC K4M	25	35	-	15	-	-	-	-
HPMC K15M	25	-	35	-	-	-	-	-
HPMC K100M	-	-	-	35	50	50	-	15
Xanthum Gum	-	15	15	-	-	15	15	-
Carbopol 974 P	15	15	15	15	15	-	50	50
PVP K30	10	10	10	10	10	10	10	10
Sodium bicarbonate	15	15	15	15	15	15	15	15
Citric Acid	2	2	2	2	2	2	2	2
Magnesium stearate	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3
Total weight	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION:

In the present study an attempt has been made to design and evaluate gastroretentive floating tablets of Glimepiride by direct compression method.Drug–excipient compatibility studieswere carried outusing FTIR spectrophotometer&DSC.From the FTIR study, it has been observed that FTIR spectrum of drug and polymers shows that majorfrequencies of functional groups of pure drug remain intact in granules containing different polymers; hence there is no chemical interaction between Glimepiride and the excipients used in the study which shown in the figure 1 and 2 respectively. The DSC thermogram obtained from these studies shows the sharp endothermic peak at 206.60ºC for pure Glimepiride corresponding to its melting point. The endothermic peak of formulation F5 showed at 205.04ºC, which are shown in figure 3 and 4 respectively. A total of eight formulations of floating tablet were design. These tablets were evaluated for pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, Hausner's ratio and post-compression parameters such as hardness, thickness, friability, weight variation, *in-vitro* dissolution study, Buoyancy study, water uptake and drug content uniformity.As the blends were free flowing (angle of repose $<30^0$ and Carr's index <15% Table 2).The post compression parameters are shown in table 3. Tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per IP specification i.e., below ±10%. Drug content found to be in the range of 99.10 to 101.17 %. Which is within acceptable limits. Hardness of the tablets was found to be in the range of3.56 – 3.97 kg/cm^2. Friability below 1% was an indication of good mechanical resistance of the tablets. The floating time was determined and result obtained shows that batch F1 to F3 float for 10 hours and batch F4 to F8 float for 12 hours shown in Table 4. The buoyancy lag time was obtained in the range of 15 to 120 seconds shown in Table 4. The tablets were evaluated for water uptake study (Swelling index %) shown in Fig.5. The results show's that swelling index increases with increase in viscosity of polymer. *In-vitro* drug release profile of all the fabricated batches are shown in the Figure 6. Addition of surfactant in dissolution medium was used to provide sink condition, which simulated the physiological environment. All the batches showed sustained release pattern. As expected, the drug release profile was dependent on the viscosity grade and concentration of the release rate controlling polymers used. From the *In-vitro* results, it was observed from the drug release graph of formulation batch (F5) having better drug release rate retarding ability which is suitable to formulate once daily formulation. Drug release graph of the formulations F1, F2, F3, F4, F6, F7, F8 having less drug release rate retarding ability as compared to F5. It was observed that as the concentration of HPMC K100M increased, the release rate of Glimepiridefrom the formulations was decreased which indicates release rate retardant nature of HPMC K100M.The results of kinetic models for Glimepiride release from floating tablets are shown in Table V. The coefficient of regression (r^2) was used as indicator of the best fitting for each of the models considered. To explore the mechanism of drug release, the results of *in-vitro* data were fitted into the Zero order, First order, Higuchi, Hixson-Crowell and Korsemeyer Peppas models. The results revealed that all formulations of floating tablets fitted best the Korsemeyer&Peppas model. The release profile of the optimized batch F5 was fitted best to the Korsemeyer&Peppas model (r^2 = 0.995) and it was confirmed that F5 batch is the best batch. As coefficient of regression (r^2=0.995) is linear for Korsmeyer&Peppas model the best fit model is Korsmeyer&Peppas model and according to Korsmeyer&Peppas equation (n=0.625) confirms diffusion mechanism is Anomalous (non Fickian) diffusion.In near future, Glimepiride floating tablet may be the drug of choice for the treatment of Type2 diabetes mellitus to improve the clinical efficiency.

Table 2:Pre-Compression Evaluation Parameters

Batch code	Angle of Repose(θ) (°)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index (%)	Hausner's Ratio
F1	29.71	0.53	0.59	10.16	1.11
F2	27.03	0.51	0.54	5.55	1.09
F3	25.61	0.58	0.62	6.45	1.06
F4	33.21	0.54	0.58	6.89	1.07
F5	28.31	0.52	0.55	5.45	1.05
F6	25.62	0.53	0.56	8.08	1.11
F7	28.23	0.53	0.57	10.52	1.11
F8	27.01	0.52	0.55	5.45	1.05

Table 3: Post Compressional Evaluation Parameters

Batch code	Thickness (mm) ± S.D	Hardness (Kg/cm^2) ± S.D	Friability (%)	Drug Content (%)	Weight Variation (mg) ± S.D
F1	2.23±0.01	3.56±0.02	0.35	99.24±0.55	100.25 ± 0.25
F2	2.15±0.01	3.96±0.01	0.24	100.08±0.62	100.29±0.045
F3	2.17±0.01	3.97±0.01	0.25	100.58±0.46	99.88±0.015
F4	2.14±0.01	3.59±0.02	0.24	101.17±0.72	100.16±0.017
F5	2.17±0.01	3.71±0.01	0.22	100.01±0.29	100.2±0.02
F6	2.22±0.01	3.63±0.02	0.25	99.10 ±0.55	99.78±0.064
F7	2.17±0.02	3.70±0.01	0.24	99.82 ±0.37	100.20±0.035
F8	2.19±0.02	3.97±0.01	0.31	100.84±0.39	100.21±0.030

Table 4: Floating Properties

Batch Code	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
F1	15	8
F2	20	10
F3	45	10
F4	120	12
F5	20	12
F6	105	12
F7	50	12
F8	40	12

Table 5: Correlation Coefficient of Release Data of Gastroretentive Floating Tablet of Glimepiride

Formulation Code	r^2 Value				
	Zero order	First order	Higuchi model	Korsmeyer &peppas model	Hixson Crowell model
F1	0.980	0.880	0.899	0.991	0.950
F2	0.975	0.944	0.934	0.984	0.980
F3	0.977	0.927	0.934	0.985	0.976
F4	0.986	0.962	0.930	0.994	0.982
F5	0.991	0.887	0.921	0.995	0.959
F6	0.983	0.966	0.931	0.993	0.981
F7	0.982	0.970	0.933	0.993	0.983
F8	0.984	0.964	0.930	0.993	0.982

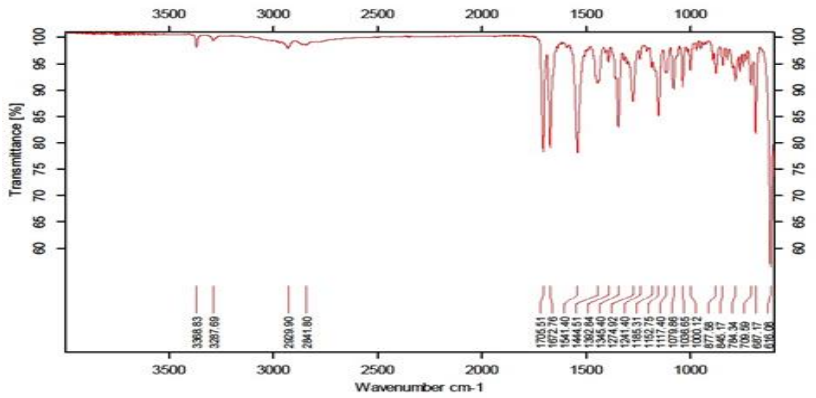

Fig. 1: FT-IR Spectra of Pure Drug (Glimepride)

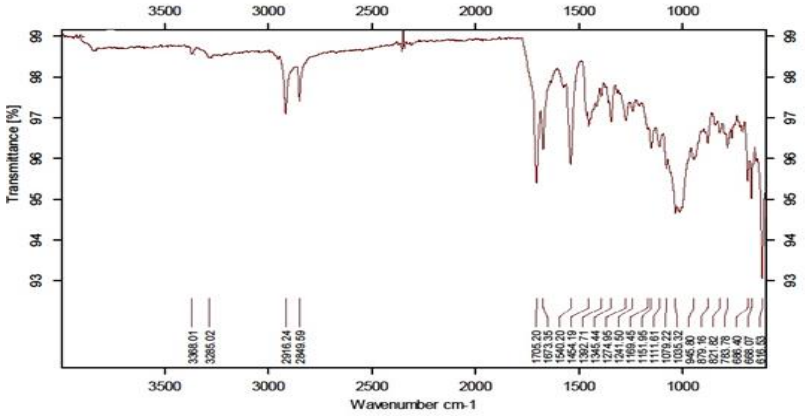

Fig. 2: FT-IR Spectra of Optimized Batch (F5)

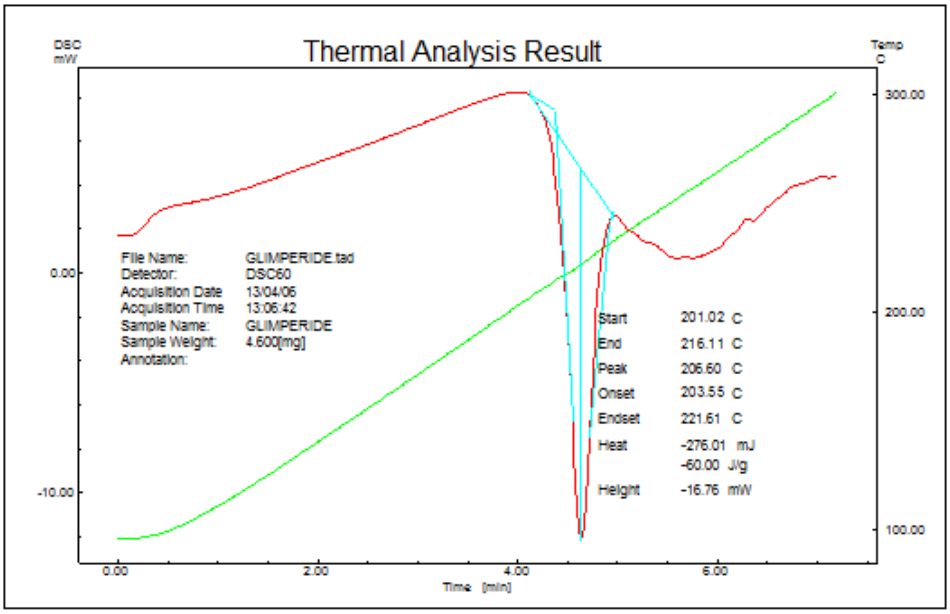

Fig 3: DSC Thermogram of Glimepiride

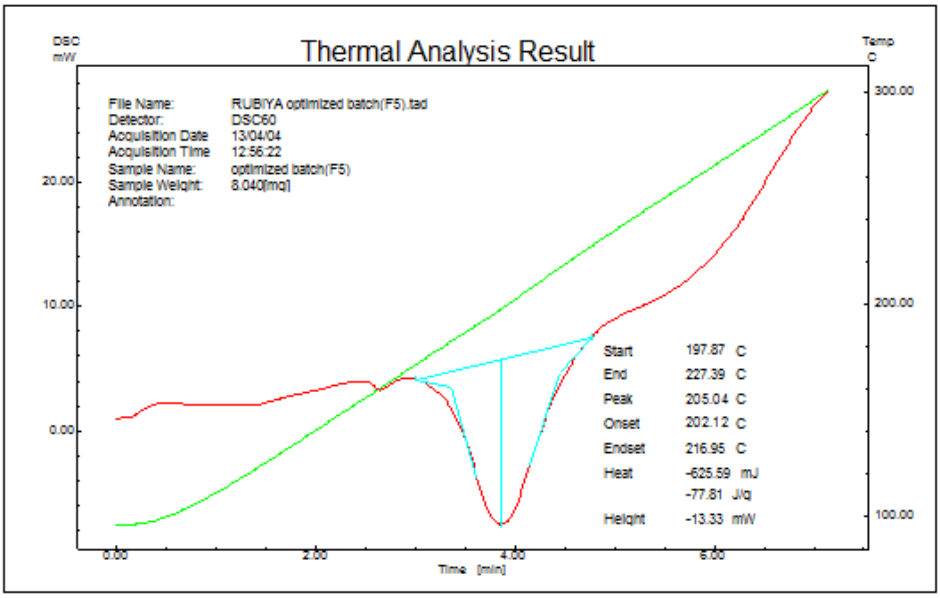

Fig 4: DSC Thermogram of Optimized Batch (F5)

The % Swelling Index Study of Batch F1 to Batch F8 Shown in Graph:-

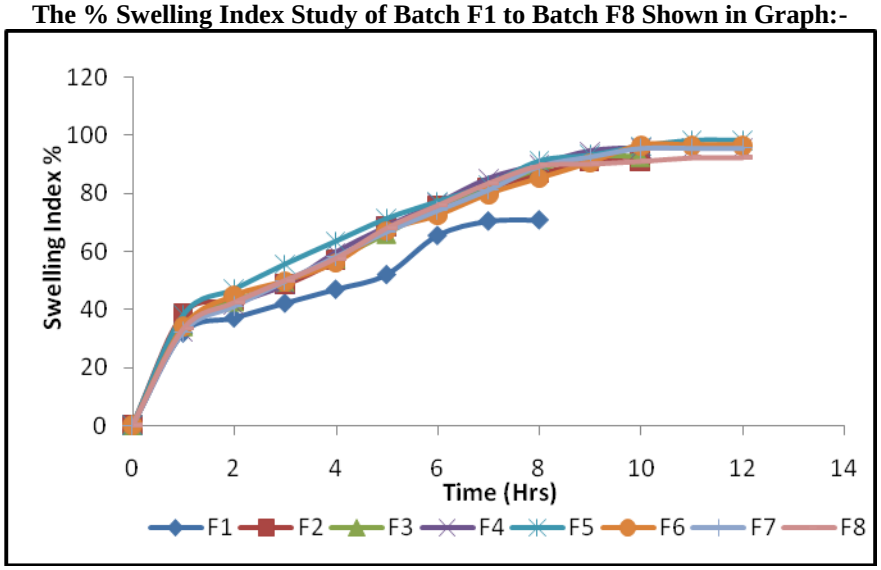

Fig 5: % Swelling Index for Batch F1 to Batch F8

The *In-Vitro* Drug Release Study of Batch F1 to Batch F8 Shown In Graph

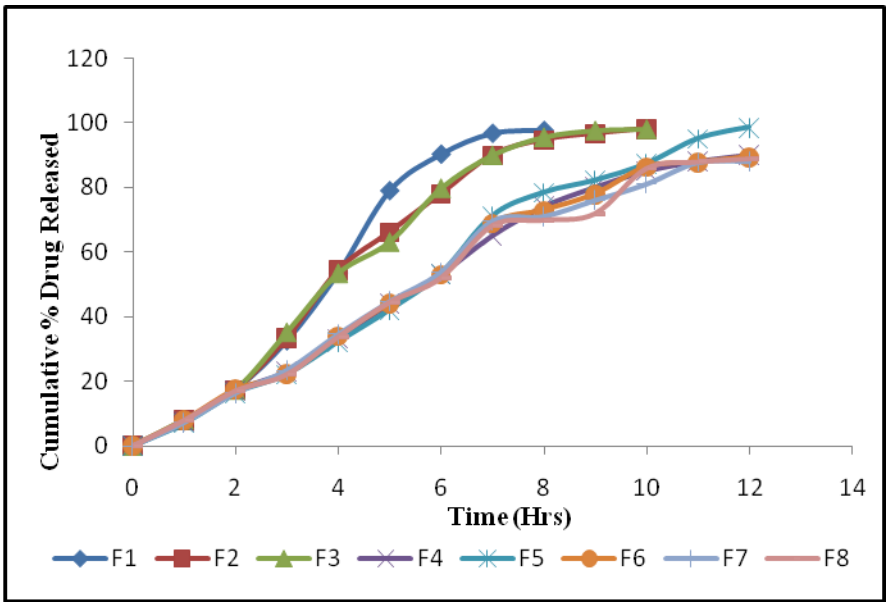

Fig 6: *In-Vitro* Drug Release for Batch F1 to Batch F8

CONCLUSION:

In the present research work gastroretentive floating tablets of Glimepiride were prepared successfully to enhance the oral bioavailability, increase the gastric residential time and increase the effectiveness of drug by localization at the site of action or providing the uniform drug delivery and patient compliance. The formulation F5 containing (HPMC K100M +Carbopol 974P) was found to be best among all the formulation batches. It's showed floating lag time (20sec) and prolonged floating duration up to (12 hrs) which was controlled release characteristic. The maximum release observed at 12 hrs was 98.62%. The results shows that drug release rate was decreased as viscosity of the polymer was increased. It was confirmed that effervescent floating tablet of Glimepiride containing HPMC K100M and Carbopol 974P provide better option for controlled release and improve bioavailability. From the kinetic data it was confirmed that the release of drug followed Anomalous diffusion mechanism. In the present study, *invitro* release profile could be best expressed by peppas plot as optimised formulation (F5) showed good linearity (r^2=0.995) while the drug release follows diffusion mechanism in **Anomalous** (non-Fickian) diffusion (n=0.625).

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