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FORMULATION AND EVALUATION OF FLOATING BILAYER TABLETS OF METFORMIN AND PIOGLITAZONE

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ABSTRACT

The objective of present investigation was to design the concept of hydro dynamically balanced bilayered tablet containing pioglitazone hydrochloride as immediate release layer and metformin hydrochloride as sustain release floating layer. Floating layer of metformin hydrochloride was prepared by employing different grades of gel forming agent and by various gas generating agent. The floating tablets were evaluated for uniformity of weight, hardness, friability, drug content, *in vitro* buoyancy, swelling index and dissolution studies. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good *in vitro* buoyancy. The tablet swelled radially and axially during *in vitro* buoyancy studies. It was observed that the tablet remained buoyant for 12 hours. The drug release from the tablets was sufficiently sustained.

KEYWORDS: Bilayer tablets, Polymers, swelling index, hydrodynamic.

1. INTRODUCTION

The idea objective of any drug delivery points two critical aspects of utmost importance i.e. spatial placement and temporal delivery. Drug delivery system is becoming increasingly sophisticated as pharmaceutical scientists better understand the physicochemical and biological parameters pertinent to their performances.[1] Among the various systems; gastric floating drug delivery systems (GFDDS) offer advantages. This system floats on the gastric contents; the drug is released slowly at a desired rate from the stomach.[2] Metformin hydrochloride is an orally administered biguanide derivative widely used in the treatment of non-insulin dependent diabetes mellitus. It improves glycaemic control by enhancing insulin sensitivity in liver and muscle. In humans, metformin hydrochloride is incompletely absorbed

and predominantly excreted in urine with a half life of 4-6 hours.[3] Metformin Hydrochloride has a property of a strong base (pKa = 11.5) and is protonated under physiological pH condition. The ionized metformin hydrochloride has a tendency to be absorbed to the negatively charged intestinal epithelium affecting the drug absorption pattern.[4] Thus, the absorption window is predominantly in small intestine and follows a saturable dose dependent mechanism,[5,6] A conventional oral sustained release formulation however, releases most of the drug content in a colon, which requires that the drug should have absorption window either in colon or throughout the GIT. Metformin hydrochloride has poor colonic absorption in healthy human subjects,[6,7] Release of metformin hydrochloride after the small intestine is thus, of no therapeutic value. The conventional strategies of prolonging the release of metformin hydrochloride from the dosage forms throughout the GIT would not be effective for metformin hydrochloride formulation as it is primarily absorbed from the small intestine.[8] Thus development of gastro retentive sustained release formulation for metformin hydrochloride would be a better alternative to the conventional sustained release formulations. Pioglitazone hydrochloride selectively stimulates the nuclear receptor PPAR-γ and to a lesser extent PPAR-α. It modulates the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism muscle, adipose tissue, and the liver. As a result, pioglitazone hydrochloride reduces insulin resistance peroxisome proliferator-activated receptor in the in the liver and a peripheral tissue increases the expense of insulin-dependent glucose, decreases withdrawal of glucose from the liver, reduces quantity of glucose, insulin and glycated heamoglobin in the blood stream. Thus, sustained release gastro retentive tablet would be ideally suited to formulate in which metformin hydrochloride as gastro retentive layer (FDDS) in the light of its PK/PD properties as already discussed. With these considerations, the aim of present study was to design the concept of bilayer gastro retentive tablet containing pioglitazone hydrochloride for immediate release using sodium starch glycollate as super disintegrant and floating sustained release layer of metformin hydrochloride using HPMC, Sodium carboxy methyl cellulose as viscosity inhancer, carbopol as gel forming agent and sodium bicarbonate, citric acid a gas-generating agent. Thus, an effervescent floating tablet was developed and evaluated for floating lag time and in vitro drug release and in vivo studies.

2. MATERIALS AND METHODS

2.1.MATERIALS

Metformin HCl and Pioglitazone HCl were obtaines as gift samples from Lupin Pvt Ltd, Hyderabad. HPMC K100LV, HPMC K15M, HPMC K4M, HPMC K100M, Betacyclodextrin and Carbopal 934, Sodium bicarbonate, citric acid, Microcrystalline cellulose PH 102, Cross povidone, Sodium starch glycolate, PVP K30, Sodium Carboxy methyl cellulose obtained as a gift sample Signet Chemical Corporation and Vijlak Pharma Limited.

2.2 Evaluation of Pre-compression parameters

The granules of all the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index, hausner ratio as per the procedure described in I.P.

2.3 Drug-Excipient Interaction Studies

Fourier transform Infrared spectroscopy(FT-IR)

The Infrared spectra of Pioglitazone and metformin pure drug, exipients, physical mixture of drug and excipients (Optimised formula) were recorded between 400 to 4000 cm^{-1}. The IR spectra were obtained using KBr disk method using an FTIR spectrophotometer.[9]

2.4. Formulation of floating bilayered tablets of pioglitazone hcl and metformin hcl

The composition of different formulations of pioglitazone and metformin floating bi layered tablets are shown in Table. For SR layer, metformin, HPMC K4M,HPMC K15M,HPMC K100M were passed through the sieve No 40.[10,11] All the ingredients were mixed in the proportions shown in Table. Granules are prepared by using wet granulation method. The granule blends were lubricated with Magnesium stearate (1% w/w) and Talc (1% w/w) and mixed for two to three minutes. For IR layer, pioglitazone, SSG, CCS were passed through the sieve No 40. . All the ingredients were mixed in the proportions shown in Table.[12,13] The powder blends were lubricated with Magnesium stearate (1% w/w) and Talc (1% w/w) and mixed for two to three minutes. For this layer direct compression method was used. First SR layer was placed and precompressed using low compression force. Then IR layer was placed on this precompressed layer and compressed using required final force. The compression force was adjusted to obtain tablets with hardness in the range of 4.5 to 6 kg/cm2.[14,15] Blends were compressed into bi layer tablet using 19 x 9 mm concave faced tooling on a multiple punch tablet machine (Rimek mini press II). Each bi layer tablet contained 15 mg of pioglitazone and 500 mg of metformin. For IR layer 8 formulations were prepared and coded as P_1 toP_8. For SR layer 12 formulations were prepared and coded as M_1 to M_{12}.[16,17]

Table 1: Preparation of immediate release layer of pioglitazone HCl

Ingredients	Formulations(weight in mg)							
	P1	P2	P3	P4	P5	P6	P7	P8
Pioglitazone HCl	15	15	15	15	15	15	15	15
Micro crystalline cellulose	128.7	127.2	125.7	124.2	128.7	127.2	125.7	124.2
Cross carmellose sodium	3	4.5	6	7.5	-	-	-	-
Sodium starch glycolate	-	-	-	-	3	4.5	6	7.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Iron oxide	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Total tablet weight	150	150	150	150	150	150	150	150

Table 2: Preparation of sustained release layer of Metformin HCl

Ingredients	Formulations(weight in mg)											
	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
Metformin HCl	500	500	500	500	500	500	500	500	500	500	500	500
HPMC K4M	100	130	160	-	-	-	-	-	50	60	-	60
HPMC K15M	-	-	-	-	-	-	100	130	-	-	40	40
HPMC K100M	-	-	-	100	130	160	-	-	80	100	60	-
Micro crystalline cellulose	131	101	71	131	101	71	131	101	101	71	131	131
PVP K-30	30	30	30	30	30	30	30	30	30	30	30	30
Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Sodium bi carbonate	32	32	32	32	32	32	32	32	32	32	32	32
Citric acid	32	32	32	32	32	32	32	32	32	32	32	32
Magnesium stearate	15	15	15	15	15	15	15	15	15	15	15	15
Talc	10	10	10	10	10	10	10	10	10	10	10	10
Total tablet weight	850	850	850	850	850	850	850	850	850	850	850	850

2.5 In vitro buoyancy determination

The floating characteristics of the GFDDS are essential, since they influence the in vivo behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication

2.6 Floating Lag Time

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5˚C paddle rotation at 50 rpm it is measured using stopwatch.[18]

2.7. Total Floating Time

The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37 ± 0.5˚C, paddle rotation at 50 rpm,.it is measured using stopwatch.[19]

2.8. Determination of swelling index

The swelling behavior of a dosage unit was measured by studying its weight gain. The swelling index of tablet was determined by placing the tablets in 200 ml beaker using 0.1 N HCL. After every one hour up to 12 hours, each tablet was removed and blotted with tissue paper to remove the excess water and weighed on the balance.[20,21] The experiment was performed in triplicate for each time point. The swelling index is expressed as a percentage and was calculated from the equation

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

Where, Wt = weight of tablet at time t

Wo = weight of tablet before immersion.

2.9. In vitro dissolution studies

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Labindia) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium (900ml). It was maintained at 37 ± 5˚C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the pioglitazone and metformin at 270 nm and 217 nm respectively by using a double beam UV spectrophotometer (Labindia-3000).[22,23] Each dissolution study was performed for three times and the mean values were taken. % drug release was calculated using simultaneous equation method. To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order equation rate describes the systems where the drug release rate is independent of its concentration, The first order Equation describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Equation.[24] The Hixson-Crowell cube root law Equation describes the release from systems where there is a change in surface area and diameter of particles or tablets

3. RESULTS AND DISCUSSION

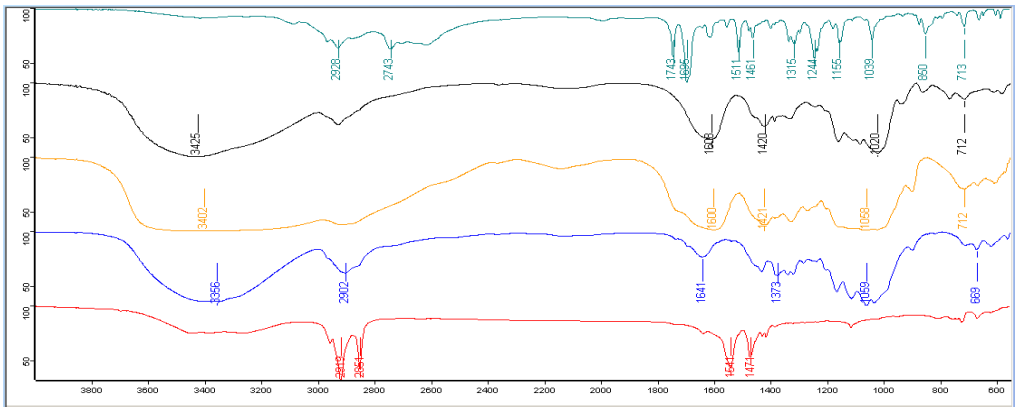
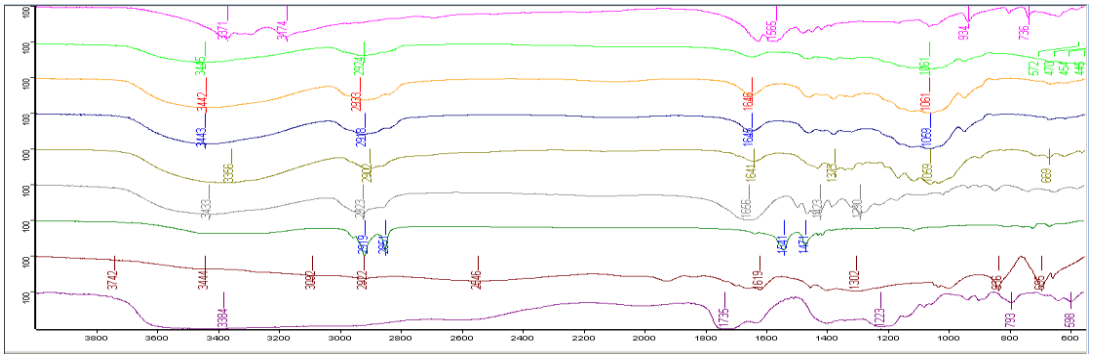


Figure 1: comparative FTIR spectra of pioglitazone formulation

Figure 2: comparative FTIR spectra of metformin formulation



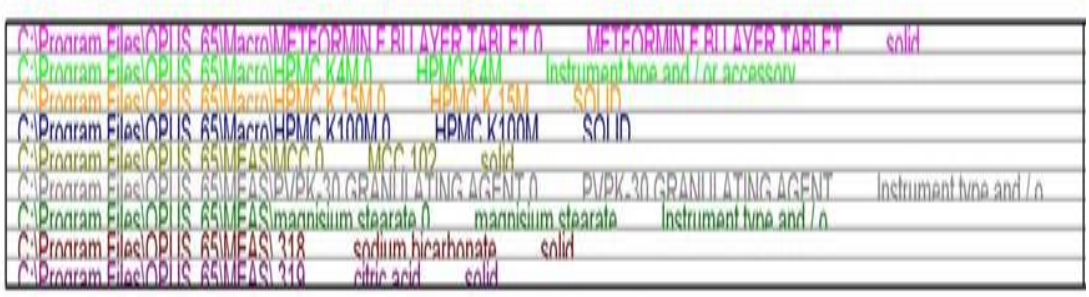


Table 3: Physical properties of Pioglitazone powder blend

Formulation code	Angle of repose (Ɵ)	Bulk density(gm/cm3) gm/cm3) (gm/cm3)	Tapped density(gm/cm3)	Carr's index	Hausner ratio (HR)
P1	27.14	0.461	0.552	11.95	1.06
P2	25.89	0.342	0.455	10.25	1.10
P3	24.22	0.51	0.598	12.71	1.07
P4	26.43	0.481	0.550	10.10	1.01
P5	27.6	0.376	0.451	10.52	1.03
P6	26.56	0.529	0.597	11.39	1.02
P7	25.27	0.512	0.598	14.38	1.06
P8	27.69	0.320	0.491	10.01	1.04

Table 4: Physical properties of Metformin granules

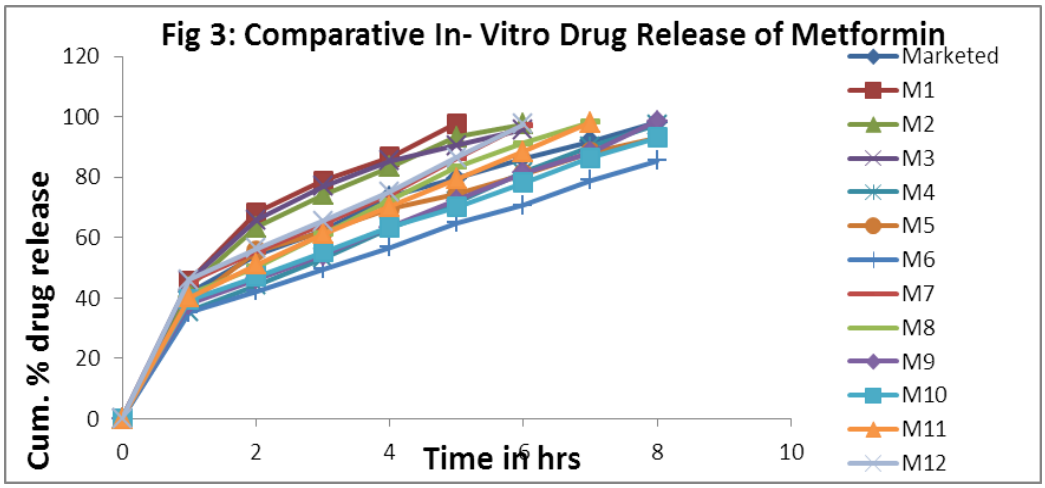
Formulation code	Angle of repose (Ɵ)	Bulk density(gm/cm3) gm/cm3) (gm/cm3)	Tapped density(gm/cm3	Carr's index (%)	Hausner ratio (HR)
M1	28.14	0.561	0.652	13.95	1.16
M2	26.89	0.542	0.655	27.25	1.20
M3	24.22	0.51	0.598	14.71	1.17
M4	27.43	0.581	0.650	11.10	1.11
M5	27.6	0.576	0.651	11.52	1.13
M6	26.56	0.529	0.597	11.39	1.12
M7	25.27	0.512	0.598	14.38	1.16
M8	27.69	0.520	0.591	12.01	1.13
M9	26.91	0.512	0.611	16.2	1.19
M10	24.34	0.553	0.637	13.18	1.15
M11	25.97	0.530	0.631	16.0	1.19
M12	21.8	0.525	0.620	15.32	1.18

Table 5: Post compression parameters of floating bilayered tablets

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
P1M1	1006 ± 9.06	5.8 ± 0.2	3.5 ± 0.05	0.27
P2M2	1000 ± 8.43	5.8 ± 0.3	3.5 ± 0.03	0.35
P3M3	999 ± 9.78	5.5 ± 0.3	3.6 ± 0.04	0.24
P4M4	1002 ± 11	5.8 ± 0.5	3.5 ± 0.06	0.30
P5M5	1000.5± 6.25	4.8 ± 0.3	3.7 ± 0.05	0.32
P6M6	995± 8.75	5.7 ± 0.2	3.5 ± 0.03	0.27
P7M7	998 ± 7.83	6.0 ± 0.2	3.4 ± 0.04	0.18
P8M8	1004.5 ± 7.24	5.5 ± 0.4	3.6 ± 0.04	0.19
P8M9	1000± 8.56	5.8 ± 0.3	3.5 ± 0.03	0.18
P8M10	1006± 10.28	5.5 ± 0.2	3.6 ± 0.04	0.20
P8M11	997 ± 10.91	5.8 ± 0.3	3.5 ± 0.04	0.17
P8M12	1000 ± 8.64	4.8 ± 0.2	3.7 ± 0.04	0.18

Table 6: In vitro buoyancy study of floating bilayered tablets

Formulation code	Buoyancy Lag Time (sec)	Total Floating Time (hrs)
P1M1	40	>12
P2M2	55	>12
P3M3	45	>12
P4M4	50	>12
P5M5	77	>12
P6M6	84	>12
P7M7	90	>12
P8M8	87	>12
P8M9	40	>12
P8M10	53	>12
P8M11	48	>12
P8M12	58	>12



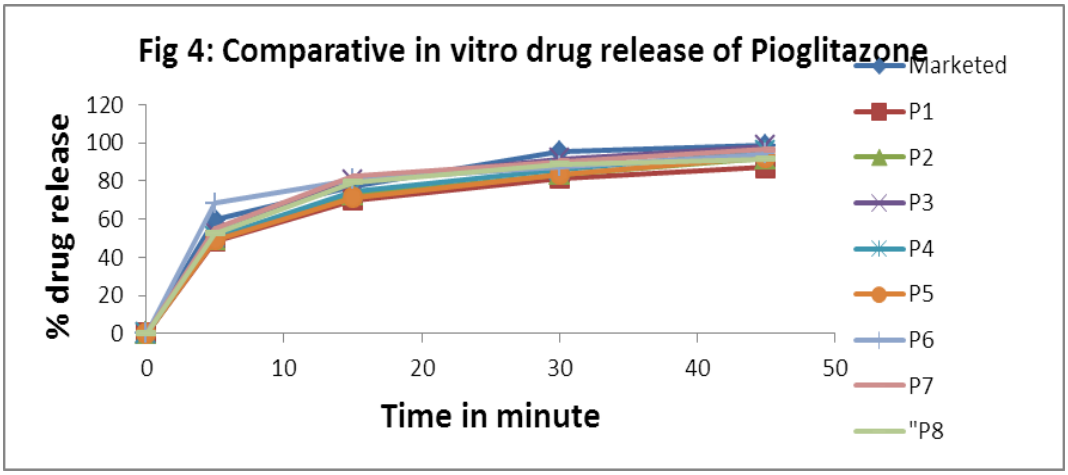


Table 7: Regression coefficient (R^2) values of floating bilayered tablets for different kinetic models

Formulation code	Zero order	First order	Higuchi	Korsemayer		Hixon
	R^2	R^2	R^2	R^2	n	R^2
F1	0.995	0.881	0.974	0.986	0.665	0.92
F2	0.992	0.913	0.984	0.995	0.713	0.968
F3	0.943	0.973	0.975	0.986	0.813	0.839
F4	0.997	0.693	0.971	0.984	0.745	0.872
F5	0.953	0.683	0.985	0.97	0.701	0.946
F6	0.991	0.867	0.98	0.969	0.508	0.954
F7	0.988	0.785	0.969	0.947	0.355	0.924
F8	0.985	0.815	0.965	0.964	0.402	0.746
F9	0.994	0.867	0.999	0.996	0.457	0.974
F10	0.989	0.799	0.947	0.948	0.503	0.895
F11	0.992	0.990	0.981	0.976	0.65	0.994
F12	0.993	0.988	0.989	0.993	0.653	0.996
Marketed	0.981	0.877	0.996	0.987	0.456	0.954

The present work involves the formulation and in-vitro evaluation of floating bilayer tablet containing Pioglitazone HCl in the immediate release layer and Metformin HCl in sustained release layer. Using croscarmellose sodium and sodium starch glycolate as superdisintegrant for the immediate release layer and the hydrophilic polymers such as HPMC K4M, HPMC K15M and HPMC K100M for the sustained release layer.

Metformin has absorption window in the upper part of the GI tract. Due to this reason this formulation was designed to floating bilayer tablet. Floating may enhance the absorption of metformin. Bilayer tablet showed as initial burst effect to provide dose of immediate release layer, Pioglitazone HCl followed by sustained release of Metformin HCl for 8 hours indicating a promising potential for the floating bilayer tablet of Metformin HCl sustained release and immediate release of Pioglitazone HCl as an alternative to the conventional dosage form for the treatment of type 2 diabetes mellitus. From the pre-formulation studies for drug excipient compatibility it was observed that there was no physical incompatibility between the drug and other excipients.All formulations were evaluated for Compressibility Index, Angle of repose, Hausner ratio, bulk density and tap density. The results indicated that the final blend of both drugs had good flow. All formulations were tested for physicochemical parameters like hardness, thickness, weight

variation, friability and drug content. All estimated parameters were found to be within the limits. This indicated that all the prepared formulations were good.All formulations were tested for buoyancy properties like floating lag time & total floating time. Almost all the formulations showed satisfactory results. All formulations were tested for *in vitro* drug release.The optimized formulation in immediate release layer was P3 and the optimized formulation in sustained release layer was M9. These formulations showed better release when compared with marketed product. Formulations were subjected to curve fitting analysis. M9 optimised formulation followed higuchi model.

CONCLUSION

In the floating bilayer tablet, gel forming polymers such as HPMC K100M, HPMC K15M, HPMC K4M and croscarmellose sodium, sodium starch glycolate as superdisintegrant were used. Sodium bi carbonate was used as gas generating agent which was responsible for floating. From the literature Metformin HCl and pioglitazone HCl, individual dosage form was used in the management of diabetes mellitus. Combination of pioglitazone HCl as immediate release layer and Metformin HCl as sustained release layer improves the patient compliance.From the above results, P3 and M9 were considered as optimized formulations. These formulations showed better release when compared to marketed product. The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that optimized formulation followed higuchi model.

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