

Sustained release micropellets of paracetamol followed zero-order release kinetic in comparison to conventional tablet dosage form: In vitro study

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Introduction

The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal milieu^{1,2}. Theoretically and desirably a sustained release delivery device, should release the drug by a zero order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion.³ Plasma drug concentration- profiles for a conventional tablet or capsule formulation, a sustained release formulation and a zero order sustain release formulation is always desired.

The major target of pharmaceutical sciences is to design a successful and suitable dosage forms for effective therapy, considering patients needs and compliance. Development of new dosage form using the existing technology is growing in importance and attracting increased interest, as they are specifically effective at a comparably low dose. Pellets falling in the size range of 1-1000 μm are of great interest in pharmaceutical industry for a variety of reasons which not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficacy of bioactive agents.⁴⁻⁸ The most important factor responsible for proliferation of pelletized products is the popularity of controlled release technology in the delivery of drugs. Moreover, controlled release pellets are less susceptible to dose dumping than the reservoir-type single unit formulations.

Sustained release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. Sustained release tablets and capsules are commonly taken once or twice daily, compared with counterpart conventional forms that may have to be taken 3 or 4 times daily to achieve the same therapeutic effect. The advantage of administering a single dose of a drug that is released over an extended pd. of time to maintain a near-constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use.⁹⁻¹⁰ Therefore, in present investigation, sustained release micropellets of paracetamol were prepared and characterized using various analytical and spectral techniques.

Materials and methods

Preparation of standard curve of paracetamol

Standard plot of model drug was constructed in phosphate buffer (pH 6.8) taking phosphate buffer (pH6.8) as blank to perform in-vitro dissolution studies. 100 mg of pure drug paracetamol was weighed and dissolved in 10 ml of methanol and diluted up to 100 ml with phosphate buffer in 100 volumetric flask. This was first stock solution and contains 1000 mcg/ml of drug. From first stock solution 1 ml was taken to another 100 ml volumetric flask and diluted upto the mark with phosphate buffer and contains 10 /ml of drug concentration. From this second stock various other concentrations were prepared 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml. Absorbance of each prepared solution was measured at 243 nm using Shimadzu UV-1700 double beam (10mm cuvette) spectrophotometer against phosphate buffer (pH 6.8) as blank. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.¹¹

Preparation and optimization of paracetamol micropellets

Micropellets of paracetamol for sustained release were prepared by Wet Extrusion/Spheronization technique. To produce pellets by Wet Extrusion/ Spheronization

the formulation must contain a pelletization aid and must meet specific rheological requirements for the process.¹²

Table 1: Optimization of paracetamol micropellets

FORMULA USED TO PREPARE MICROPELLETS BY WET EXTRUSION /SPHERONIZATION PROCESS			
S.NO	INGREDIENTS	F1	F2
1	PARACETAMOL	1000	1000
2	STARCH	75	75
3	STARCH DRIED	6	6
4	STARCH FOR PASTE	25	25
5	METHYL PARABEN	.08	.08
6	PROPYLPARABEN	.4	.4
7	HYDROXYPROPYLMETHYL CELLULOSEE50	-----	20
8	GUAR GUM	8	8
9	AEROSIL	6	6
10	MAGNESIUM STEARATE	6	6
11	TALC	6	6

Characterization of micropellets

Characterization based on flow properties of micropellets

The flow properties of micropellets were determined for:

Bulk density: Bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume indicating the contribution of the inter-particulate void volume. The bulk density is expressed in grams per ml (g/ml). Bulk density is determined by weighing powder into a dry graduated 250 ml cylinder. The powder was carefully levelled without compacting, volume (V_o) was recorded & bulk density g/ml was calculated using the following formula:

Bulk density = Mass / Volume (V_o)

Tapped density: Tapped density is obtained by mechanically tapping a graduated measuring cylinder or vessel containing a powder sample. After observing the initial powder volume to weight, the measuring cylinder or vessel is mechanically tapped, and volume readings are taken until little (less than 1%) further volume change is observed. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop under its own weight at specified distance. Secure the cylinder in the holder of the apparatus with weighed powder sample. Measure 100-200 taps and observe the corresponding volumes to the nearest graduated unit

Tapped density = Mass/ Tapped volume.

Carr’s Index: The Carr’s Index and Hausner’s ratio are measures of the porosity of a powder to be compressed. They measure the relative importance of interparticulate interactions. For poor flow materials, there are frequently greater interparticulate interactions and a greater difference between the bulk and tapped densities. These differences are reflected in the Compressibility Index and Hausner’s Ratio.

Carr’s Index was calculated using the following formula:

Carr’s Index= 100*(TD-BD)/TD.

Hausner’s Ratio :The Hausner’s Ratio is a number that is correlated to the flow ability of a powder or granular material. Hausner’s ratio is calculated using following formula:

Hausner’s ratio = TD/BD

Table 2: Characterization of micropellets

Carr’s index (%)	Flow character	Hausner’s Ratio
< 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45

32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Angle of Repose (θ): Angle of repose was measured according to the fixed funnel and free standing cone method of Banker and Anderson. A funnel with the end of stem cut perpendicular to the axis of symmetry is secured with its top at a given height, above paper placed on a flat horizontal surface. The granules were carefully poured through the funnel until the apex of the conical pile so formed just reached the tip of the funnel. Thus with r , being the radius of the base of granules conical pile and angle of repose (θ) was calculated by using the following equation:

$$\tan(\theta) = h/r$$

Where (θ)= angle of repose

h = height of heap of granules

r = radius of heap.

Characterization based on particle size and surface morphology

Measurement of the particle size distributed of micropellets was carried out with an optical microscope. Stage micrometer was used to calculate calibration factor. The particle size was calculated by multiplying the number of division of the ocular disc by the particle with calibration factor. 100 randomly chosen micropellets were taken to measure their individual size. Drug loaded Micro pellets were subjected to surface morphology analysis by using Scanning Electron Microscopy (SEM) Fei Quanta 200 F. SEM (Universal V5.45 TA Instruments). Micro pellets were mounted directly onto sample stub under reduced pressure (0.133 Pa). For examination of the internal structure of the drug loaded micro pellets, they were cut in half with a steel blade. Micropellets before dissolution were only subjected to SEM study since, after dissolution the pellets become swollen palpable mass.

Characterization based on crystallinity of drug by X-Ray Diffraction (XRD)

In order to determine the physical state of the drug whether amorphous or crystalline, X-ray diffraction (XRD) studies were carried out. The change in the form of drug from crystalline

to amorphous is indicated by characteristics peakless patterns. Study of crystallinity of the pure drug and drug loaded micropellets were carried out by X-Ray Diffraction (XRD) technique using X'Pert PRO, PANalytical diffractometer. XRD patterns were recorded at room temperature using X'Pert PRO, PANalytical diffractometer with Ni-filtered $\text{CuK}\alpha$ radiation operated at a voltage of 45 Kv, current 40 Ma, 1°min^{-1} scanning speed and 0° to 50° angle (2θ) range. The X-ray diffraction (XRD) pattern of formulations were recorded on a scanning X-RAY diffractometer using an X'Pert PRO instrument. The prepared formulations were triturated to get fine powder for obtaining the result.

Characterization based on fourier transforms infrared spectroscopy (FTIR)

Drug-polymer interactions were studied by using Fourier Transform Infrared Spectroscopy (FTIR). Pure drug sample and prepared formulations were subjected to Fourier Transform Infrared Spectroscopy analysis using Bruker FTIR Spectrophotometer. The spectrum was recorded for pure drug, physical mixture of combination of all the excipients and drug with Physical mixture of combination of all the excipients using Bruker FTIR Spectrophotometer. Pellets of sample were prepared in KBr disks (2 mg sample in 200 mg KBr) with a hydrostatic pressure at a force of 40 psi for 4 min. The scanning range was $4000 - 500 \text{ cm}^{-1}$.

In vitro dissolution study of paracetamol micropellets

In-vitro release of drug from tablets were carried out for 6 hrs using Paddle type Dissolution rate test apparatus USP STD containing 900 ml of dissolution medium maintained at $37 \pm 0.5^\circ \text{C}$ and speed of agitation at 50 RPM. An accurately weighed tablets were placed in dissolution media consisting of 900 ml of phosphate buffer solution (pH 6.8). Dissolution studies were studied for 6 hrs. At prefixed time; 5 ml of solution were withdrawn. Samples were analyzed (assayed) spectrophotometrically for the drug content at 243 nm using Shimadzu 1700 UV/Visible Spectrophotometer. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with the same dissolution medium. The analysis of drug release mechanism from pharmaceutical dosage form is important as it provides important information about the biopharmaceutical quality of a dosage form to determine the release profiles.

Drug release kinetics

In the present study, raw data obtained from in –vitro release studies were analysed where in data was fitted to different equations and kinetic models to calculate the percent drug release and release kinetics of sustained release micro pellets from the optimized formulation. The kinetic models used were a zero order, First order , Higuchi’s model and Koresmeyer – peppaskinetic models. The results of in -vitro release profiles obtained were fitted into four models of data treatment as follows:

- 1) Cumulative percent drug released Vs. time (zero order kinetic models).
- 2) Log cumulative percent drug remaining unreleased Vs. time (first order kinetic model).
- 3) Cumulative percent drug released Vs square root of time (Higuchi’s model).
- 4) Log cumulative percent drug released Vs log time (Koresmeyer –Peppas equation).

Results and Discussion

The main aim of the present research work is to develop and characterize micro pellets of paracetamol for sustained release, which after oral administration could prolong the therapeutic action and increase the bioavailability of the drug. In order to provide the sustained release and to minimize the dose dependent side effects as well as to improve patient compliance micro pellets were formulated.¹³⁻¹⁵

Characterization based on flow properties of micropellets

The formed micropellets are characterized for Bulk density, Tapped density, Hausner’s ratio, Carr’s Index and Angle of repose.

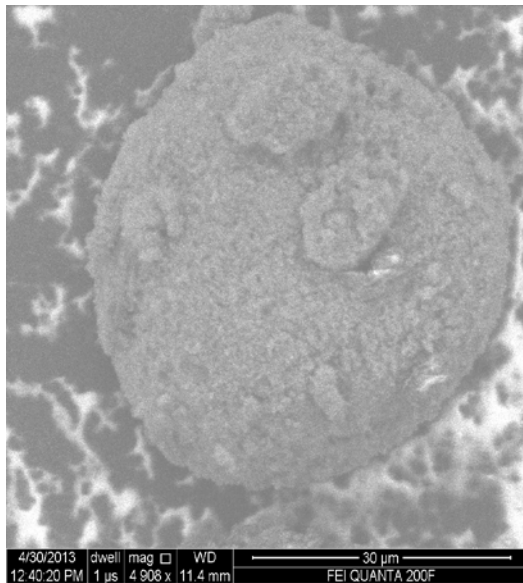
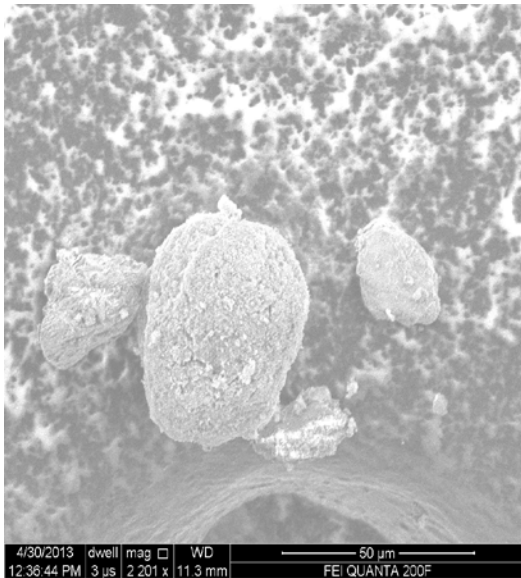
FORMULATION CODE	BULK DENSITY (g/cc)	TAPPED DENSITY (g/cc)	HAUSNER’S RATIO	CARR’S INDEX(%)	ANGLE OF REPOSE(θ)
F1	0.460	0.590	1.28	22.05	22.78
F2	0.390	0.470	1.25	19.72	19.54

Angle of repose, Hausner’s ratio, Carr’s Index, Bulk density, Tapped density were determined to predict flowability. A higher value indicates greater cohesion between particles with higher Carr’s Index is indication of the tendency to form bridges. As reported in literature $\tan(\theta)$ less than 20 shows excellent flow properties while $\tan(\theta)$ value exceeds in case of F1 that still determines reasonable flow characteristics for the formulation. For both the formulations the tapped , bulk density were comparable . Hausner’s ratio and Carr’s Index was little more for formulation F1 as compared to F2. Results showed that formulation code F2 were found to possess good flow characteristic based on these parameters.

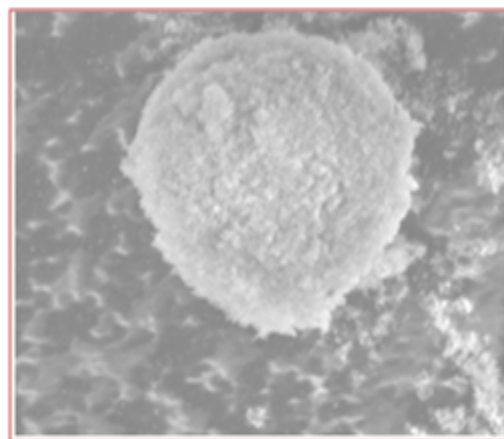
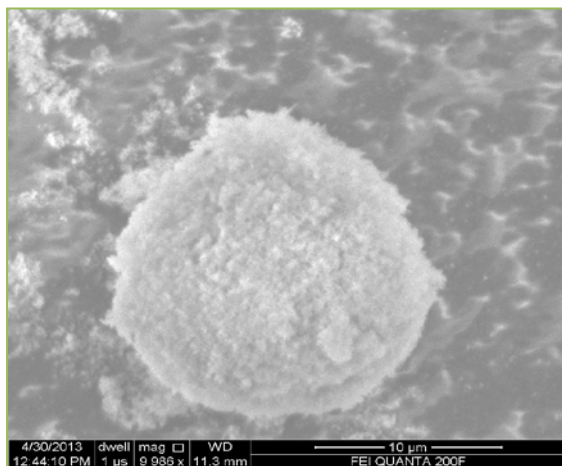
Characterization based on Particle size and surface morphology

MEAN PARTICLE SIZE OF BATCH F1	
Formulation code	Particle size (µm)
F1	215±12
MEAN PARTICLE SIZE OF BATCH F2	
Formulation code	Particle size (µm)
F2	355±02

The mean particle size of sustained release micropellets of optimized formulations was found to be F1 215± 12, F2 355±02. The maximum particle size was found to be in the case of F2 which was formulated using Starch, Guar gum, HPMC E50 hydrophilic polymers. It was observed that larger the particle size of micropellets, the drug release rate will decrease. Drug release mechanism was affected by the size of micropellets. From (Table 5.4 and 5.5) Batch F2 showed maximum particle size hence help in achieving sustained release of drug .For surface Morphology including shape, size of formed Micropellets Scanning Electron Microscopy (SEM) was done :



SEM pictures of formulation codeF1



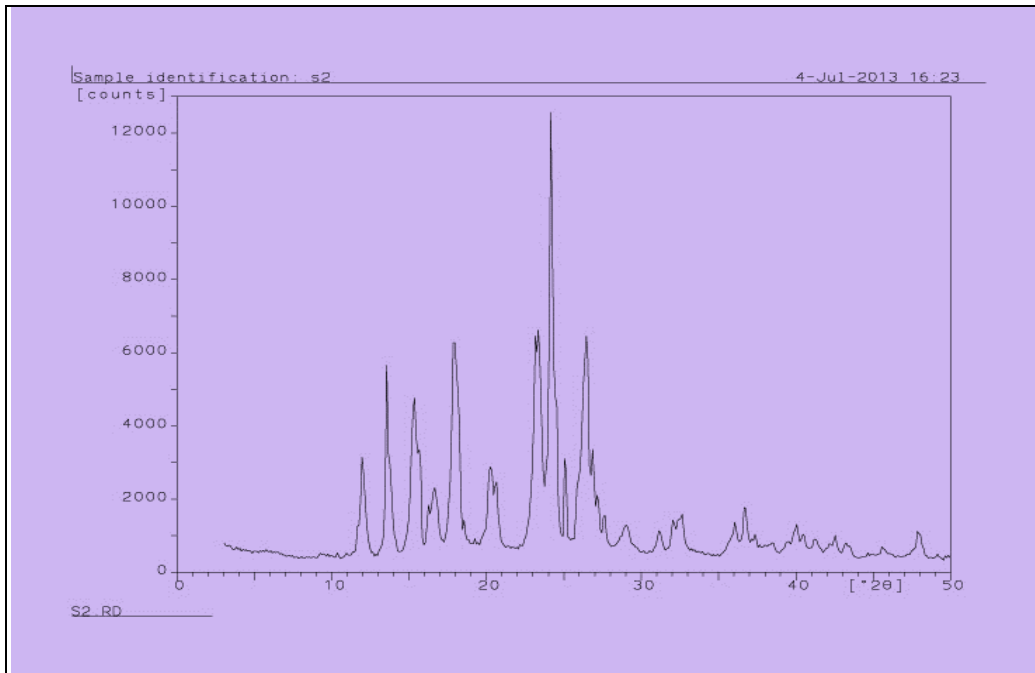
SEM pictures of Formulation code F2

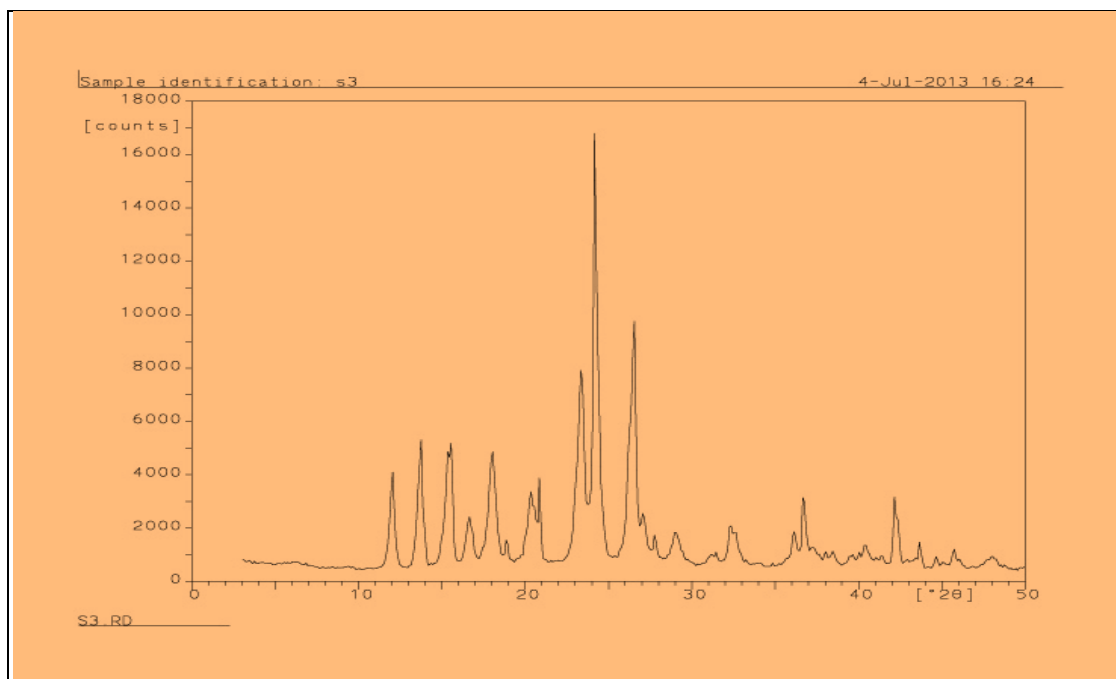
Scanning electron microscopy (SEM) was used to assess the microscopic aspects of the drug loaded micropellets. Results showed that micropellets of both formulations were predominantly spherical in shape with smooth surface. The characteristics internal structure of the micropellets, enclosed with the rigid shell constructed with drug and polymer was clearly evident. Micropellets (F1) containing starch, guar gum as polymers were found somewhat with elongation along with spherical nature with rough surface whereas micropellets prepared by using HPMC E50, guar gum, starch as polymer(F2) were found to be spherical with smooth surface it may be due to the addition of HPMC E50 polymer which quickly hydrate upon contact with water to form a gelatinous layer. Micropellets containing HPMC E50 hydrophilic polymer along with other polymers of F1 was found to spherical with smooth surface. The release rate retarding (swelling property) of hydrophilic nature of

polymers used in micropellets could indicate the delayed release behaviour and may be responsible for the drug release. The pictures further prove our stance of taking F2 as most optimized formulation.

Characterization based on crystallinity of drug

XRD spectra of model drug, drug loaded micropellets F1,F2.





XRD spectra of formulation code F2.

In vitro dissolution study of paracetamol micropellets

Drug release from tablets was sustained upto 6 hours. Both formulations showed different degree of release. The drug release was recorded for both formulations containing different hydrophilic polymers F1, F2. The drug release was found to be release in sustained manner in case of Batch F2 which was formulated using Starch and Guar gum , HPMC E50 hydrophilic polymers combination. The cumulative % Drug release for optimized formulation for batch code F1 showed 97.488 % drug release in 4 hrs whereas batch code F2 showed 93.871% drug release upto 6 hours in sustained release manner it may be due to the presence of HPMC E50 which on exposure to aqueous fluids, hydrates to form a viscous gelling layer which retards water or fluid penetration and acts as a barrier to drug release .The drug is released by diffusion or erosion of the matrix (barrier). Among both formulations formulation code F2 showed best drug release as shown in Table 6.1 as in this formulation release of Paracetamol was there in a sustained manner with constant fashion over extended period of time.

In- vitro release dissolution data for F1 , F2.

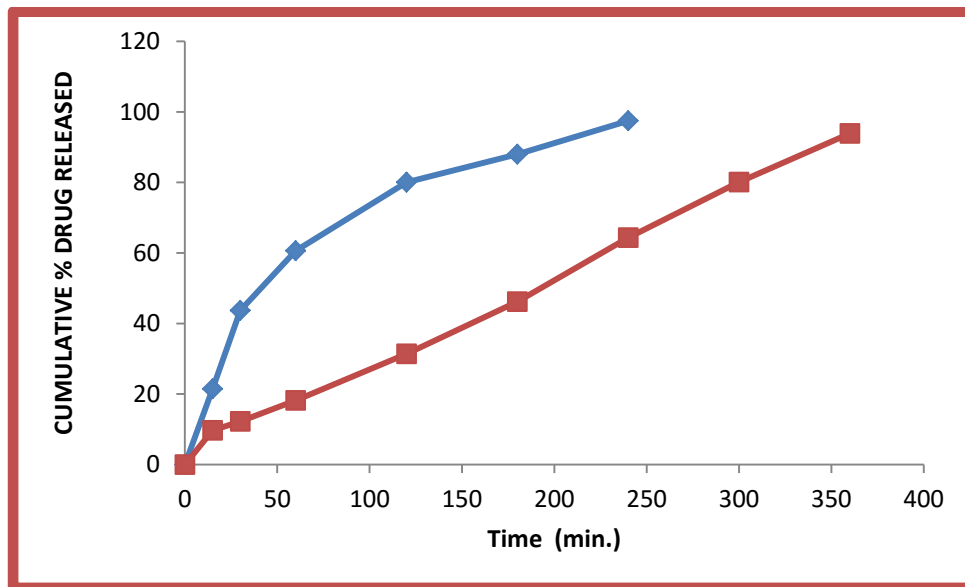


Table 3 Drug release kinetic of paracetamol micropellets

Sr.No.	Time (min.)	Square root of Time	Log time	Cumulative %Drug Release \pm SD	Log Cumulative % Drug Release	Cumulative % Drug Remaining	Log Cumulative % Drug Remaining
1	0	0	0	0 \pm 0.00	0	100	2
2	15	3.872	1.176	9.692 \pm 0.180	0.986	90.308	1.955
3	30	5.47	1.47	12.223 \pm 0.180	1.087	87.77	1.943
4	60	7.74	1.77	18.161 \pm 0.227	1.25	81.83	1.912
5	120	10.9	2.07	31.392 \pm 0.271	1.496	68.608	1.836
6	180	13.41	2.25	46.191 \pm 0.227	1.664	53.809	1.730
7	240	15.49	2.38	64.334 \pm 0.227	1.808	35.666	1.552
8	300	17.32	2.47	80.067 \pm 0.138	1.903	19.93	1.299
9	360	18.97	2.55	93.871 \pm 2.39	1.972	6.129	0.787

Comparison of R² Value for above models

R ² Value	
Zero order	0.996

First order	0.880
Higuchi Plot	0.934
Koresmeyer and Peppas Model	0.991

The R^2 values of Zero and Koresmeyer and Peppas Model were the maximum and comparable. But Zero order was the best fit compared to other Models and even the R^2 value for Zero order is more close to one. Therefore based on above data and observations we recommend that our formulation F2 has followed zero order type release kinetics.

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