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Research Study

Diltiazem Hydrochloride For Chronotherapeutic Drug Delivery System: Formulation, Optimization, and Evaluation.

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ABSTRACT

The objective of this research was to develop and evaluate the extended-release (ER) tablet designed for chronobiology of increased blood pressure. Diltiazem Hydrochloride (Dil HCL) ER tablets have been developed for chronotherapeutic drug delivery. Dil HCL was initially granulated with Eudragit L30 D55 dispersion using top spray on FBP. Further, the ER tablets were prepared using opadry enteric polymer. ER tablets were prepared using 3^2 full factorial design with dependent variables selected as t10%, t25%, t75% and t90% of cumulative drug release. Pre- and post-compression parameters, differential calorimeter scanning, and in vitro dissolution were evaluated for the prepared tablets. Using kinetic models, specifically first order, Higuchi, Hixon-Crowell, Baker – Lonsdale and Korsmeyer-Peppas model, the drug release profile was studied and kept for stability. Parameters of pre and post-compression showed good flow and compressibility. Extended-release profile exhibited pH dependency of the coat applied and pH of dissolution media. During the stability study period of 3 months, the formulation did not show any significant changes. The integrated delivery system helps patients with blood pressure by delivering the drug in the right place and the right doses at the right time.

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INTRODUCTION

The traditional pharmaceutical goal is becoming obsolete due to advances in chronopharmacokinetic and chronopharmacodynamic and drug delivery systems that synchronize the circadian clock [1,2,3]. There is a need for chronological delivery because it makes a therapeutic agent available at a predetermined lag after administration to meet the therapeutic requirement. It also meets the therapeutic requirement that may occur during a patient's circadian cycle for therapeutic effects [4]. The demand can arise during the circadian cycle of a patient for producing the therapeutic effect. Conditions where diabetes, myocardial infarction, cancer, bronchial asthma, peptic ulcer, arthritis, and hypercholesterolemia are promising. Many functions such as blood pressure (BP), heart rate, volume of stroke, cardiac production, cardiovascular system blood flow are subjected to circadian rhythms with higher morning capillary resistance and vascular reactivity. Most circadian-related diseases show symptoms at early morning hours. Blood pressure pathophysiology is lowest during sleep and increases in the early morning. Many patients with critical high blood pressure have a similar circadian BP pattern. [5,6,7].

Different approaches have been used for colon-targeted delivery systems, together with prodrugs, microbial induced, pH-sensitive, osmotic controlled, pressure-dependent, and timed release systems. Of all the formulations for colon-specific drug delivery systems, the use of pH-sensitive systems (enteric-coated systems) has much more influence due to the simplicity of their design. The rationale for these systems is that human gastrointestinal (GIT) pH increases gradually from the stomach (pH 1–3) to colon (pH 7–8) [8].

Enteric-coated systems shields the formulation in the stomach against drug release. Alternatively, provides a delayed drug release. This delayed drug release step is adjusted to suit the transit time of the intestine. Nevertheless, the dosage form pass through the upper GIT intact without showing a drug release. Instead, certain agents that help to retard drug release may be included in the formulation [9].

The present research article targets to develop chronotherapeutic drug delivery system of Diltiazem Hydrochloride (Dil HCl) to enable the release with the circadian biorhythm [10]. It has a short half-life and undergoes extensive first-pass hepatic metabolism and bioavailability of 40% [12-14]. ER tablets containing Dil HCl and other excipients were formulated using different weight ratios of hydrophilic polymers like Xanthan gum [15,16] Sodium alginate. Eudragit L30 D55 is an anionic copolymer-based aqueous dispersion of methacrylic acid copolymer and ethyl acrylate [19,20].

MATERIALS AND METHODS:

Materials:

Diltiazem Hydrochloride was procured from Piramal Health Care, Ltd (Mumbai). Eudragit L30 D55 was supplied by Evonik, Xanthan gum of grade Xanthural 75 was obtained from Kelco, Sodium Alginate of Keltone grade was kindly donated by ISP Corporation, and Opadry Enteric was used as enteric coating polymer from Piramal Health Care, Ltd (Mumbai). All the other materials and reagents were of analytical grade.

Methods:

Preparation of matrix tablets

Dil HCl was properly mixed with an adequate amount of diluent and granulated with Eudragit L30 D55 dispersion using FBP top spray (Fluid Bed Processor PAM GLATT 1.1). Tray drier at a temperature of 50ºC ± 5ºC for 12 hrs was used to dry the wet granules. # 20 (ASTM) mesh retained granules were obtained by sizing through # 60 mesh (ASTM). The excipients were then mixed with the drug-dilute granules. Granules were then sieved thoroughly under # 22 mesh (ASTM). Magnesium stearate was used to lubricate the blend and was compressed to form oval shaped standard concave tablets by using punch 22.5 x 9.6 mm.

Opadry coating of tablets

Tablets were coated using the disperse solution of 20% w/v Opadry enteric in purified water with vigorous mixing on an overhead stirrer for 45 minutes. The solution was filtered through a muslin cloth. The tablets were coated 5 – 7 % w/w of a tablet with a coating solution using a pan coater (Ideal Cure, Pharma R&D coater).

Factorial Design

A 3^2 full factorial design, each at 3 levels and 9 experimental trials were performed with different combinations. Independent variables selected were concentration of xanthan gum (X_1) and concentration sodium alginate (X_2). The time required for 10%, 25%, 75% and 90% of cumulative drug release were chosen as dependent variables. An interactive and polynomial statistical model was used to evaluate the response [22,23].

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \text{……..(1)}$$

Where,

Y = the dependent variable, b_0 = the arithmetic mean response of 9 runs and b1 = estimated coefficient for factor X_1. The main effects (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction terms (X_1X_2) show how the response changes when two factors are changed simultaneously.

Characterization of enteric-coated tablets

Tablet weight variation test

Randomly 20 tablets were selected and accurately weighed using analytical balance (Mettler–Toledo, Greifensee, Switzerland). The results were expressed as mean values of 20 determinations.

Tablet thickness test

The thickness of the tablets was determined using a caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations.

Hardness determination

10 tablets were sampled and individually subjected to test hardness. The tablet hardness was expressed in kilogram (kg) unit.

Friability determination

The friability of uncoated tablets was determined using Electrolab friabilator in the laboratory. This device subjects several tablets to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm, dropping the tablets a distance of six inches with each operation for 100 revolutions. The tablets were then dusted and reweighed [24-27].

Assay

20 coated tablets were weighed and crushed to form a fine and uniform powder. The quantity equivalent to 420 mg of Dil HCl was taken in 100 ml volumetric flask and methanol were added to it. It was mixed well and kept for sonication for 20 - 30 min. After sonication, the solution was filled to make up the volume. 2 ml of solution was filtered through a 0.45µ filter from the solution to a 10 ml volumetric flask to make suitable dilution. The absorbance of the filtrate was measured at 236 nm.

Differential scanning calorimetry (DSC)

DSC was carried out using a Perkin-Elmer (DSC-7) instrument to obtain the melting endotherms of a drug, optimized formulations and placebo. An empty aluminum pan was used as a reference. Formulations containing approximately 5 mg of Dil HCl scanned in sealed aluminum pans from 100°C to 180°C at a rate of 10°C/min under nitrogen atmosphere. Before overlapping, all DSC curves were normalized and autoscaled.

***In-vitro* Dissolution Studies**

The dissolution studies were executed with USP apparatus II, paddle, 75 rpm (Electrolab, model TDT-06T, Mumbai, India) using 900ml of 0.1N HCl, 37± 0.5ºC for 2hrs. The same tablets were detached and placed in 900 ml of phosphate buffer pH 6.8, 37± 0.5ºC for the remaining study. Samples (5 ml) were drawn at every 1, 2, 4, 6, 8, 10, 12, 16, 20 and 24 hours, filtered through 0.45µ membrane, diluted appropriately and analyzed by UV-Visible spectrophotometer (Perkin Elmer Lambda 20 model) at 236 λ max. Fresh medium, was added after removing each sample to maintain sink condition.

Kinetic modeling of drug release

In order to study release kinetics from ER tablets, release data in dissolution media was fitted to the exponential equation. These are often used to describe the drug release behaviour from polymeric systems when the mechanism is not well understood or when more than one type of release phenomenon is involved.

$$Mt / M\infty = k. t^{n} \quad \cdots(2)$$

where $Mt/M\infty$ is the drug released fraction at a time, where Mt corresponds to the amount of drug released in time t, $M\infty$ is the total amount of drug that must be released at infinite time, K is a constant and "n" is the release exponent indicating the type of drug release mechanism.

In Fickian release, "n" has the limiting values of 0.45 for release. The non-Fickian release is when the n values are between 0.45 and 0.89. Non-Fickian kinetics correspond to coupled diffusion / polymer relaxation. The dissolution profile of all the batches was fitted to first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas and Bekker and Lonsdale to ascertain the kinetic modeling of drug release [28-30].

RESULTS AND DISCUSSION:

Pre-compression and post-compression parameters were observed within the acceptable limits for the batch D7 and are outlined in Table 1 and 2. The prepared tablets contained DIL HCl equivalent to 101.90 % of the labeled content.

Table 1: Pre - compression parameters:

Parameters	**Blend D7**
Bulk Density (g/ml)	0.655
Tapped Density (g/ml)	0.874
Compressibility index (%)	25
Hausner's ratio	1.333

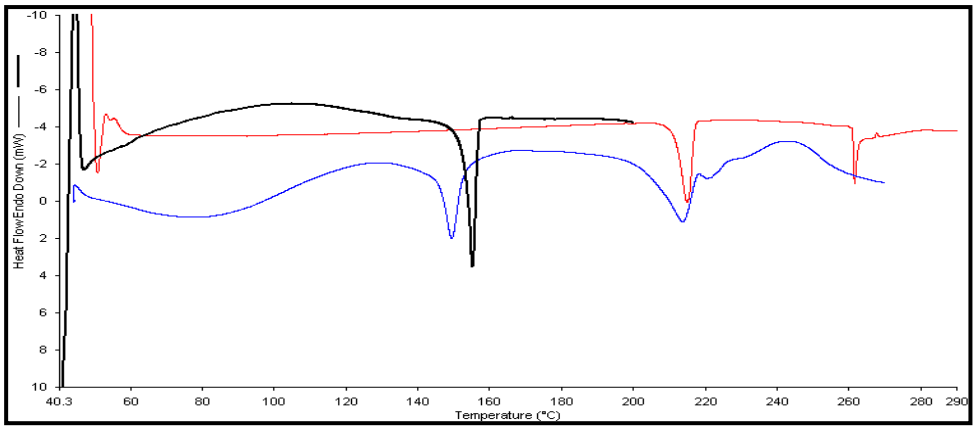
Table 2: Post- compression parameters

Parameters	**Final batch (Batch D7)**
Tablet weight (mg)	1000 ± 5
Hardness (kg/cm^2)	8.55
Friability (%)	0.8
Thickness (mm)	6.19
Diameter (mm)	9.6
Assay (%)	101.90

Differential Scanning Calorimetry (DSC)

DSC results of DIL HCl (red), batch D 7 (blue) and placebo (black) showed sharp melting endothermic peak temperature at 214.97^{o}C (Figure.1). It showed the high purity of the DIL HCl. No interference in peaks was found that suggested no incompatibility with the excipients.

Figure 1: DSC spectra of Dil HCl, Placebo, Blend of the preliminary trial (Batch D7)



In vitro drug dissolution studies

Preliminary batch D7 was found as the ideal batch as it showed the desired % cumulative drug release of 97.20 % as shown in Figure. 2. Batch D7 was selected for optimization using a Factorial design based on the desirable lag time and release profile composition of formulation. The drug release of the optimized batches (Batch A- I) is shown in Figure 3. Batch E from the optimized batches was selected for choosing the suitable model.

Figure 2: Dissolution profile of Batch D7

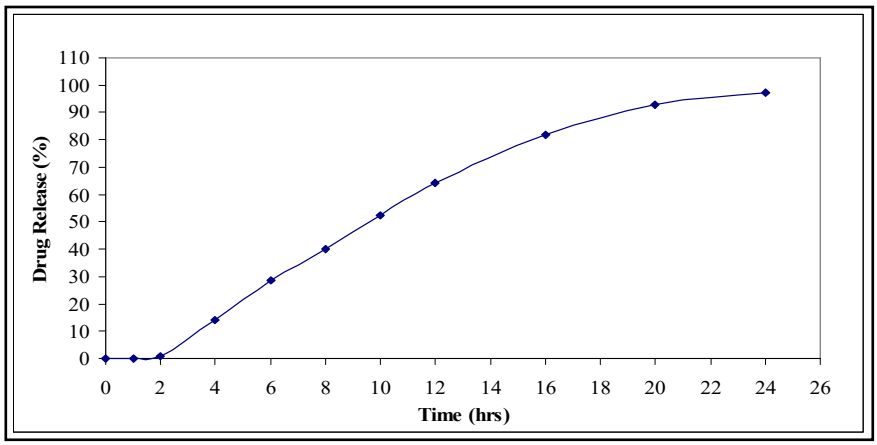
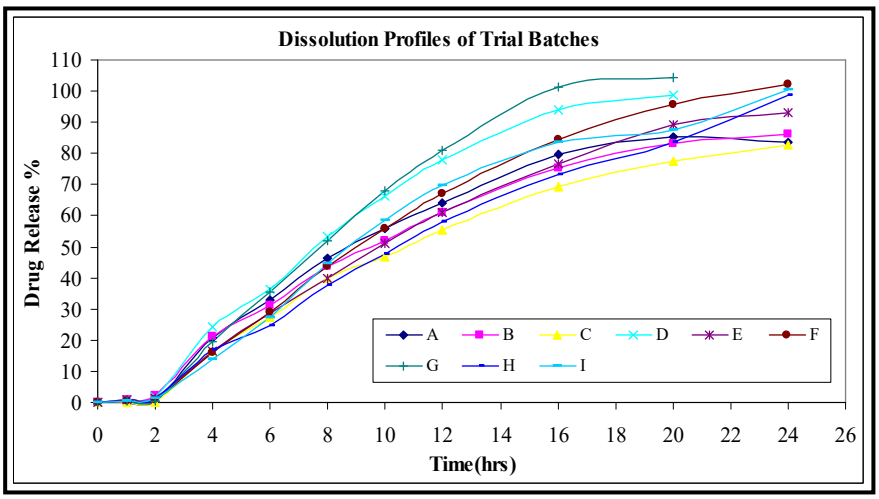


Figure-3: Dissolution profiles of Optimized Batches A – I



Optimization of formulation

The concentration of xanthan gum (X_1) and sodium alginate (X_2) were selected as independent variables. The time required for 10%, 25%, 75% and 90% of cumulative drug release were the dependent variables. In order to investigate nonlinearity, the polynomial terms were included. Multi-linear regression analysis using Systat was conducted for statistical analysis of factorial design batches. The t_{10}, t_{25}, t_{75} and t_{90} for the 9 batches showed wide variations were compiled in Table 3.

Table 3: Optimization Batches as per 3^2 Full Factorial Design

Batch No.	Levels of Xanthan Gum	Levels of Sodium Alginate	t_{10} (hrs)	t_{25} (hrs)	t_{75} (hrs)	t_{90} (hrs)
A	-1	-1	3	4.6	14.7	-
B	0	-1	2.8	4.6	16	-
C	+1	-1	3.2	5.6	18.4	-
D	-1	0	2.8	4.2	11.4	14.8
E	0	0	3.2	5.4	15.6	20.4
F	+1	0	3.2	5.4	13.8	17.8
G	-1	+1	3.1	4.7	11	13.6
H	0	+1	3.1	6	16.6	21.8
I	+1	+1	3.4	5.6	13.4	21.5

The fitted equations relating the response, time required for 10%, 25%, 75%, and 90% are shown in the following equations 4, 5, 6 and 7 respectively. The multiple regression analysis for the responses of factorial batches revealed the good fit as shown in the following equations:

$$t_{10} = 3.536 - 0.085X_1 - 0.035X_2 + 0.001X_1X_2 + 0.003X_1^2 + 0.001X_2^2 \quad R^2 = 0.999 \quad (3)$$

$$t_{25} = 1.486 + 0.498X_1 - 0.155X_2 - 0.001X_1X_2 - 0.013X_1^2 + 0.007X_2^2 \quad R^2 = 0.997 \quad (4)$$

$$t_{75} = 4.197 + 3.218X_1 - 1.775X_2 - 0.013X_1X_2 - 0.091X_1^2 + 0.057X_2^2 \quad R^2 = 0.995 \quad (5)$$

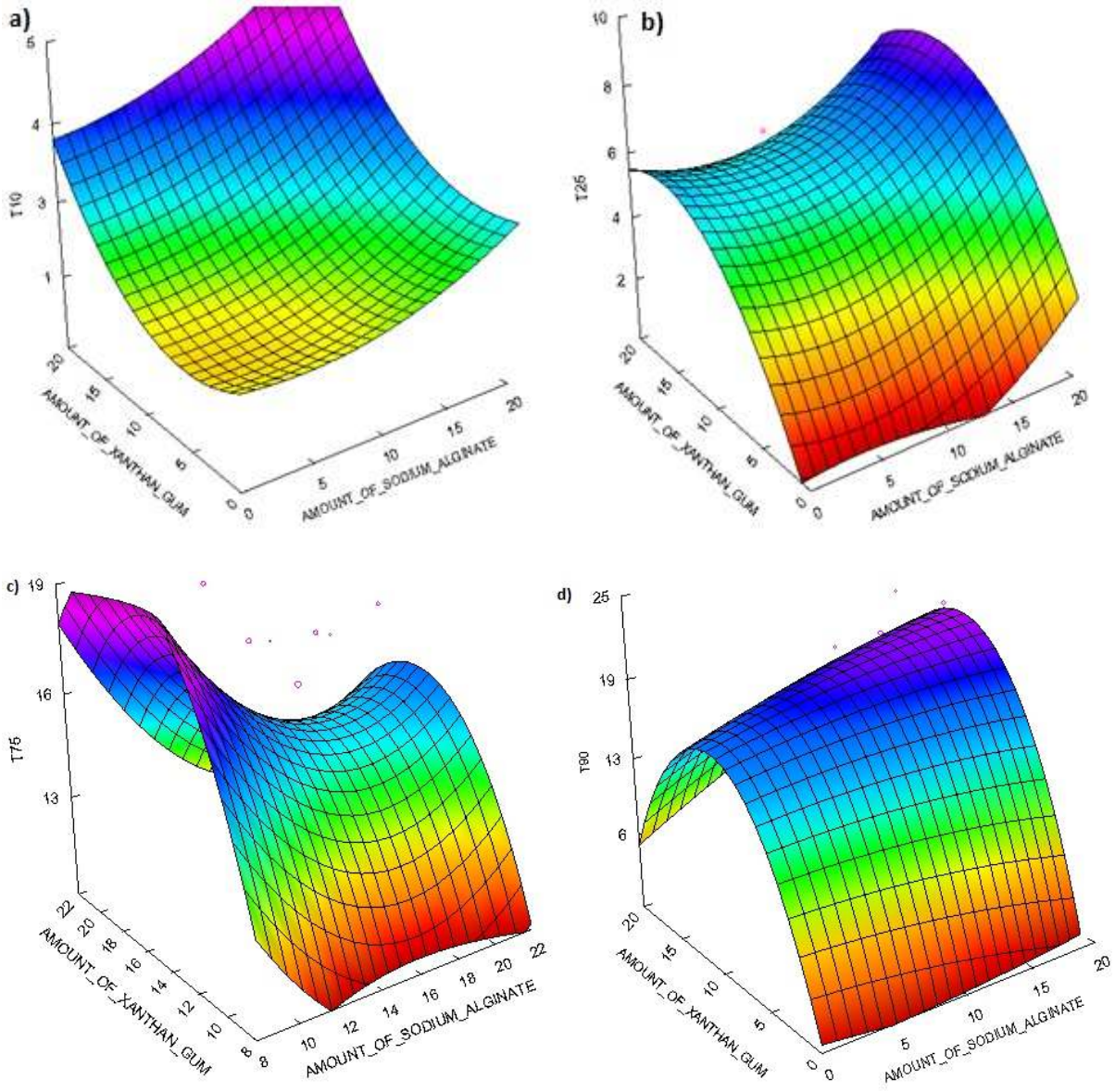
$$t_{90} = 13.935 + 3.840X_1 + 0.010X_2 + 0.098X_1X_2 - 0.167X_1^2 - 0.035X_2^2 \quad R^2 = 0.993 \quad (6)$$

The data demonstrated that the factor X_1 had a more pronounced effect on t_{75} and t_{90}. It is a general observation that, as the polymer increases the retard in drug release is observed. The drug hindrance was observed on the responses when the concentration of X_1 was increased which is also supported by the positive value of X_1. These may be in line with a high degree of swelling due to water absorption and a small amount of erosion due to polymer relaxation of xanthan gum. Xanthan gum is used as a suspending agent in sustained release matrix tablets and has viscosity over a wide pH range. Literature also suggests xanthan gum have been reported to sustain the drug release predictably, and the drug release profiles of these tablets were not influenced by pH and agitation. Hence, it was clinched that the low level of X_1 (amount of xanthan gum) and the higher level of X_2 (amount of sodium alginate) favors the preparation of DIL HCl ER tablets. The low value of the X_1X_2 coefficient also suggested that the interaction between X_1

and X_2 has no substantial effect on the responses t_{10}, t_{25}, t_{75} and t_{90}.

Below figures show the plot of the amount of xanthan gum (X_1) and sodium alginate (X_2) versus t_{10}, t_{25}, t_{75} and t_{90} respectively.

Figure 4. Response Surface Plots of (a) time required for 10%, (b) time required for 25%, (c) time required for 75% and (d) time required for 90%



Kinetic modeling of drug release

The drug release profile of all the optimized batches were fitted to first-order, Higuchi, Hixon Crowell, Baker–Lonsdale and Korsemeyer- Peppas models. The model that best fitted the release data was evaluated by the correlation coefficient (R^2). Coefficient of Determination (R^2), slope (k) and release exponent (n) for all formulations in various models are given in Table 2.The release profile of the optimized Batch E, best fitted to the Korsemeyer- Peppas model with a coefficient of determination, (R^2 = 0.974) and release exponent (n = 0.877) indicating non-fickian diffusion or anomalous transport with the release by diffusion and swelling mechanism with the combination of both diffusion and erosion controlled release.

Table 2: Kinetic modeling of drug release

Curve Fitting with model equation	R^2 (Coefficient of Determination)	k (Slope)	n (release exponent)
First-order	0.948	0.076	-
Hixon Crowell	0.972	0.021	-
Higuchi	0.865	17.03	-
Baker–Lonsdale	0.803	0.006	-
Korsmeyer–Peppas	0.974	6.28	0.877

CONCLUSION

The present study described that Dil HCl ER tablets based on controlled release pattern can be intended for chronopharmacotherapy in hypertension. Uses of hydrophilic polymers were essential for achieving the desired release pattern. The combination of enteric polymer (Eudragit L30 D55), the pH-dependent hydrophilic polymer (divalent cation-Sodium alginate) and hydrophilic polymer (Xanthan gum) gave optimum release profile by providing initial swelling in acidic pH followed by controlled erosion. The study found that adequate balance between the different levels of the two polymers was necessary for the acquiring desirable controlled release and floating patterns. It can be concluded that the drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. The drug release mechanism was non-fickian diffusion.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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