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FORMULATION AND EVALUATION OF VALACYCLOVIR SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The present study aimed to formulate and evaluate sustained-release matrix tablets of Valacyclovir using different polymers. Eight formulations (F1–F8) were prepared and evaluated. Pre-compression studies of the powder blends, including angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, indicated satisfactory flow and compressibility characteristics. The compressed tablets were evaluated for post-compression parameters such as weight variation, hardness, thickness, friability, drug content, and *in vitro* dissolution. Dissolution studies revealed that formulation F4 achieved complete drug release over a period of 24 hours, demonstrating effective sustained-release behavior. Drug-release kinetics were analyzed using various mathematical models, and the release mechanism of the optimized formulation was found to follow the Korsmeyer–Peppas kinetic model. The results indicate that sustained-release matrix tablets of Valacyclovir can be successfully formulated using appropriate polymer combinations.

KEYWORDS: Sustained release; Valacyclovir; spectrum scanning; FTIR; Release kinetics.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more

flexibility in dosage form design than most other routes.[1] The terms sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.[2] The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, the desire is 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.[3] Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems.[4] Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with binding agent.[5] The goal of an extended-release dosage form is to maintain therapeutic drug level in plasma for extended period of time by using slow release highly viscous type of polymers.[6]

The major drawbacks associated with conventional dosage forms are poor patient compliance, increased chances of missing the dose of a drug with short half-life for which frequent administration is necessary.[5,7] The unavoidable fluctuations of drug concentration may lead to under medication or over medication. Recently, several advancements in drug delivery system have been made to overcome the drawback of conventional drug delivery system. These techniques are capable of controlling the rate of drug delivery by sustaining the duration of therapeutic activity of drug to a tissue.[8] Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology.[9] It excludes complex production procedures such as coating and palletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer matrix is widely used for formulating an SR dosage form.[10] oral route has been one of the most popular routes of drug delivery due to its ease of administration, patience compliance, least sterility constraints and flexible design of dosage forms. Time release technology, also known as sustained release (SR) sustained action (SA), extended release (ER, XR or XL), time-release or timed-release, controlled-release (CR), modified release (MR) or continuous-release (CR) is a mechanism used in pill tablet or capsules to dissolve slowly and release a drug over a prolong period of time. It is by far the most

commonly used oral extended-release technology and the popularity of the matrix systems can be attributed to several factors. The release from matrix type formulations is governed by Fick's first law of diffusion.[11] In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a hydrophobic polymer (such as wax, polyethylene, polypropylene, and ethyl cellulose) or hydrophilic polymer (such as hydroxy propyl cellulose, hydroxy propyl methyl cellulose, methylcellulose, sodium carboxy methylcellulose, and alginates). In this sense, the term "matrix" indicates the three-dimensional network containing the drug and other substances such as solvents and excipients required for the specific preparation.[12] Matrix drug delivery systems release the drug in continuous manner. These release the drug by both dissolutions controlled as well as diffusion-controlled mechanisms.[11] Initially, drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter, drug particles at successively increasing distances from the surface of the release unit will be dissolved and released by diffusion in the pores to the exterior of the release unit. In this system the drug reservoir is prepared by homogeneously dispersing drug particles in a rate controlling polymer matrix fabricated from either a lipophilic or a hydrophilic polymer. The drug is dispersed in the polymer matrix either by blending a therapeutic dose of finely ground drug particles with a liquid polymer or a highly viscous base polymer, followed by cross-linking of the polymer chain, mixing drug and polymer at an elevated temperature. It can also be fabricated by dissolving the drug and the polymer in a common solvent, followed by solvent evaporation at an elevated temperature and/or under a vacuum. The rate of drug release from this polymer matrix diffusion-controlled drug delivery system.[13]

Sustained release drug delivery system.[14] The term sustained release has been constantly used to describe a pharmaceutical dosage form formulated to retard the release of a therapeutic agent such that its appearance in the systemic circulation is prolonged and its loading dose, polymer solubility of drug and its diffusivity in the polymer matrix and the porosity of the release unit plasma profile is sustained in duration.[15] Hence present study aimed to develop sustained release dosage form for Valacyclovir in order to prolong drug release, maintain therapeutic plasma concentration for an extended period and to reduce dosing frequency.

MATERIAL AND METHODS

MATERIALS

Drug (API) is a gift sample from Aurobindo pharma Hyderabad, HPMCK-100M, guar gum, lactose, talc and magnesium stearate. Matrix-forming polymers is used Hydroxypropyl K100M were purchased from S.D. Fine Chem Mumbai. Suspending agent, guar gum acts as binding agent in tablet preparation was obtained from Kepra Industries Mumbai. Diluents Lactose monohydrate, Lubricant magnesium stearate and Glidant talc were purchased from SD. Fine chem. Mumbai.

METHODOLOGY

Preformulation studies

Preformulation studies are a crucial stage in the drug development process, aimed at developing and evaluating the physicochemical properties of a drug substance before formulating it into a sustained-release dosage form. These studies help in understanding factors such as solubility, stability, and drug–excipient compatibility, which are essential for designing an effective sustained-release system.[16] The information obtained during preformulation ensures the selection of suitable polymers, excipients, and formulation strategies to achieve sustained drug release, improved therapeutic efficacy, and consistent product performance.[17]

UV spectroscopy

UV spectroscopy is used to identify and estimate Valacyclovir by measuring its absorbance at a specific wavelength scanned between 200-400 nm (λmax). A solution of the drug is prepared in a suitable solvent and scanned in a UV–visible spectrophotometer. The obtained λmax is used for quantitative analysis, helping in drug content estimation.

Preparation of standard graph of API

To prepare a standard graph of Valacyclovir, a known quantity of the drug is accurately weighed and dissolved in a suitable solvent to make a stock solution of known concentration. From this stock solution, a series of dilutions are prepared to obtain different concentrations. The absorbance of each dilution is then measured at the drug's λmax using a UV–visible spectrophotometer. A graph is plotted with absorbance on the y-axis and concentration on the x-axis. The resulting linear graph, which follows Beer–Lambert's law, can be used for the quantitative estimation of Valacyclovir in formulations.

Method of Preparation

Valacyclovir sustained-release matrix tablets were prepared by the wet granulation method. Accurately weighed quantities of Valacyclovir hydrochloride, matrix-forming polymer (HPMC), lactose and guar gum were passed through a #40 mesh sieve and blended uniformly to ensure homogenous distribution of the drug. A binder solution was prepared by dissolving HPMC K-100M in a suitable solvent such as isopropyl alcohol. The binder solution was added gradually to the powder blend with continuous mixing to obtain a coherent wet mass. The wet mass was passed through a #16 mesh sieve to form granules, which were then dried in a tray dryer at 40–50°C until the moisture content was within acceptable limits(2%). The dried granules were resized through a #20 mesh sieve and blended with magnesium stearate for lubrication. The final blend was compressed into tablets using a rotary tablet compression machine fitted with suitable punches to obtain sustained-release matrix tablets of Valacyclovir. A detail list of drug excipients were given in table 1.

Formulation Details

Table 1: Composition of formulations (F1-F8).

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Valacyclovir (mg)	500	500	500	500	500	500	500	500
HPMC K-100M (mg)	25	50	75				25	50
Guar gum (mg)				25	50	75	25	50
Lactose (mg)	95	70	45	95	70	45	65	20
Talc (mg)	3	3	3	3	3	3	3	3
Magnesium Stearate (mg)	2	2	2	2	2	2	2	2
Total (mg)	625	625	625	625	625	625	625	625

PRE-COMPRESSION PARAMETERS

Angle of repose (θ)

It is a direct measure of flow property of granules. It is the maximum angle that can be obtained between the free-standing surface of a powder heap and the horizontal.

Procedure

Angle of repose was determined using funnel to pour the granules on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of

base of a pile was measured at 5 different points and average was taken for calculating angle of repose using following formula:

$$\theta=\tan^{-1} h/r$$

Where, h = height of a pile (2 cm) r = radius of pile base.

Bulk density(ρ_b)

It is the ratio of given mass of granules and its bulk volume determined by measuring the volume of known mass of granules sample that has been passed through the screen in to graduating cylinder.

Procedure

Bulk density was determined according to USP method I, the prepared granules sample of 100g was accurately weighed and filled in a 100ml graduated cylinder and the powder was leveled and the unsettled volume (Vo) was noted. Bulk density (Db) was calculated in g/ml by the formula:

$Db= M/V_o$, Where, M = mass of granules taken, Vo= unsettled apparent volume

Normally expressed as g/ml. The total volume includes particle volume, inter particle void volume and internal pore volume. The bulk density of granules depends greatly on degree of compaction

Tapped density(ρ_t)

Procedure

Tapped density was determined by USP method II. The granules of 100g was filled in 100ml graduated cylinder of tap density tester (electrolab, ETD 1020). The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (V_0) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated. Initial tapped volume and final tapped volume.

Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until differences between volumes of subsequent tapping was less than 2%. Therefore, the tapped density of a material can be used to predict both its flow properties and its compressibility. This volume was noted as, the final tapped volume (Vt). The tapped density (Dt) was calculated in g/ml by the formula:

Dt= M/Vt,

Where, M = mass of granules taken, Vt= final tapped volume.

Carr's index (Compressibility Index)

Carr's compressibility index i.e., % compressibility indicates the flow property and packing ability of the tablet. It is determined by measuring both the bulk and tapped density of granules. Compressibility Index was calculated using following equation:

CI (%) = Dt-Db/Dt x 100

Where, Dt = tapped density, Db = bulk density.

Hausner's ratio

The Hausner ratio indicates the flowability and packing ability of the tablet. When the Hausner ratio is close to 1, materials have acceptable flow and packing ability. Hausner Ratio was calculated using the formula:

HR = Dt/Db

Where, Dt = tapped density, Db = bulk density.

POST-COMPRESSION PARAMETERS

Hardness

Hardness is the mechanical strength of the tablets was evaluated for determine crushing of tablet.[18] Tablet hardness was measured using six tablets selected randomly from each batch with a Monsanto hardness tester to ensure adequate resistance to breaking during handling and transportation it is expressed in kg/cm^2.

Friability

Friability testing was performed on twenty tablets using an friabilator (Electrolab, India) to assess the ability of the tablets to withstand abrasion and mechanical stress. The percentage weight loss after the test was calculated, and the results were used to confirm that the tablets possessed sufficient mechanical integrity for sustained-release applications.[19] Friability can be calculated.

Friability=initial weight – final weight / initial weight × 100

Thickness

Tablet thickness was measured to ensure uniformity among the compressed tablets. The test was carried out using a thickness gauge (Campbell Electronics, India). Five tablets were

randomly selected from each batch, and the thickness of each tablet was recorded individually by using screw gauge it is expressed in mm.[20]

Weight variation

Weight variation test was carried out to assess the uniformity of tablet weight within each formulation. Twenty tablets from each batch were individually weighed using an electronic balance. The test was conducted in accordance with the official procedure described in the British Pharmacopoeia.[21] The individual tablet weights were compared with the average weight, and the results were used to ensure compliance with pharmacopoeia limits, indicating consistent die filling and uniform tablet production it is expressed in mg.

Drug content

The drug content of the tablets was determined to ensure uniform distribution of the active pharmaceutical ingredient in each formulation. twenty tablets were randomly selected, accurately weighed, and finely powdered. An amount of the powder equivalent to the required dose of the drug was dissolved in a suitable solvent and analyzed using an appropriate analytical method, UV-visible spectrophotometry. The results were expressed as percentage drug content, and compliance with pharmacopoeial limits confirmed the uniformity and accuracy of drug loading in the sustained-release tablets.

***In vitro* drug dissolution**

The *in vitro* drug dissolution study was carried out to evaluate the drug release behavior of the sustained-release tablet formulations. The test was performed using a USP dissolution apparatus (Type II) under specified experimental conditions. A suitable dissolution medium was maintained at a controlled temperature of 37 ± 0.5 °C and agitated at 100 rpm speed to simulate physiological conditions.[22] At different time intervals (1,2,4,6,8,10,12,24) predetermined time intervals, samples of 2 ml withdrawn from the dissolution medium and replaced with an equal volume of fresh medium to maintain sink conditions. The collected samples were filtered and analyzed using an appropriate analytical technique, such as UV-visible spectrophotometry, to determine the amount of drug released. The cumulative percentage of drug release was calculated and plotted against time to assess the sustained-release characteristics of the formulation.

Drug-excipient compatibility studies

Drug–excipient compatibility studies were performed to evaluate possible physical or chemical interactions between the active pharmaceutical ingredient and the excipients used in the formulation.[23] These studies are essential to ensure the stability, safety, and efficacy of the sustained-release tablets. The drug and optimized formulation were then analyzed using suitable analytical techniques, such as Fourier Transform Infrared (FTIR) spectroscopy, to detect any changes in characteristic peaks of the drug. The absence of significant shifts indicated compatibility between the drug and excipients, used in formulation development.[24]

RELEASE KINETICS

Zero Order[25]

Zero order release would be predicted by the following equation:

$At = A_0 - K_{0t}$ Where,

At = Drug release at time 't'

A_0 = Initial drug concentration.

K_0 = Zero-order rate constant (hr^{-1})

When the data is plotted as cumulative percent drug release *versus* time, if the plot is linear then the data obeys Zero order kinetics and its slope is equal to zero order release constant K_0.

First Order

First order release could be predicted by the following equation:

$Log\ C = \log C_0 - K_t / 2.303$ Where,

C = Amount of drug remained at time 't'

C_0 = Initial amount of drug.

K = First order rate constant (hr^{-1}).

A straight line obtained by plotting log cumulative percent of drug remaining to be released *versus* time indicates first-order release, with the rate constant K_1 calculated as 2.303 times the slope.

Higuchi square root law

Higuchi's model drug release from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation:

$Q = [DЄ / \tau(2A – ЄCs)\ Cst]1/2$

Where,

Q = Amount of drug release at time 't'

D = Diffusion coefficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

Cs = Solubility of drug in the matrix.

Є = Porosity of the matrix.

τ = Tortuosity.

t = Time (hrs at which q amount of drug is released).

Above equation can be simplified as if we assume that 'D', 'Cs' and 'A' are constant. Then equation becomes:

$Q = Kt_{1/2}$

When the data is spited according to equation i.e. cumulative drug release *versus* square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer-peppas equation

To study the mechanism of drug release from the matrix system the release data was also fitted to the well-known exponential equation (Korsmeyer equation/ Peppa's law equation), which is often used to describe the drug release behavior from polymeric systems.

$$Mt / M\alpha = Kt_n$$

Where, Mt/Mα = The fraction of drug released at time 't'. K = constant incorporating the structural and geometrical characteristics of the drug / polymer system. n = Diffusion exponent related to the mechanism of the release as shown in table 2.

$$Log\ Mt / M\alpha = Log\ K + n\ Log\ t$$

Hixson–Crowell cube root law

The Hixson–Crowell cube root law describes the drug release behavior of dosage forms in which the surface area and particle diameter decrease with time during dissolution. As the drug dissolves uniformly from the surface, the volume of the tablet or particle gradually reduces, and the cube root of the remaining drug amount becomes proportional to time.[6] Based on this concept, Hixson and Crowell established a mathematical relationship between drug release and time, which is expressed by the following equation:

$$W_0^{1/3} - Wt^{1/3} = k_4 t$$

where W_0 represents the initial amount of drug present in the dosage form, Wt is the amount of drug remaining at time t and k_4 is the Hixson–Crowell rate constant, which reflects the relationship between the surface area and volume of the dissolving system, t represents time.

Mechanism of drug release

Table 2: Diffusion exponent and mechanism.

S. No	Diffusion	Exponent (n) Overall solute diffusion mechanism
1.	0.45	Fickian diffusion
2.	0.45<n<0.89	Anomalous (non-Fickian) diffusion
3.	0.89	Case-II transport
4.	n>0.89	Super case-II transports

RESULTS AND DISCUSSION

Spectrum scanning

A standard solution of Valacyclovir (10µg/mL) was prepared using 0.1 N HCl as the solvent. The solution was scanned in the wavelength range of 200–400 nm using a Shimadzu UV–visible spectrophotometer, with 0.1 N HCl serving as the blank. The maximum absorbance was observed at 255 nm, which is in agreement with the reported λmax, as illustrated in the figure 1.

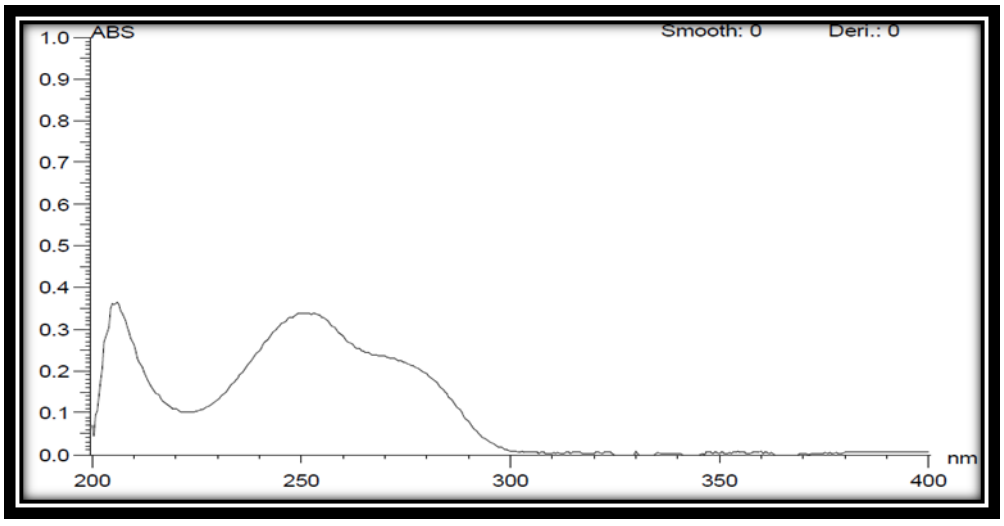

Figure 1: Spectrum scanning.

Construction of standard graph

A stock solution of Valacyclovir was prepared by dissolving 1 mg of the drug in 1 mL of 0.1 N HCl. From this stock solution, serial dilutions were prepared to obtain concentrations of 2, 4, 6, 8, 10, and 12 µg/ml. The absorbance of each solution was measured at 255 nm. As shown in table 3. A calibration curve was constructed by plotting concentration *versus* absorbance, and linear regression analysis of the data demonstrated good linearity, as shown in the figure 2 with R^2 value of 0.9983.

Table 3: Standard curve data of Valacyclovir.

Concentration (µg/mL)	Absorbance
0	0
2	0.0687
4	0.1344
6	0.1805
8	0.2435
10	0.3083
12	0.3744

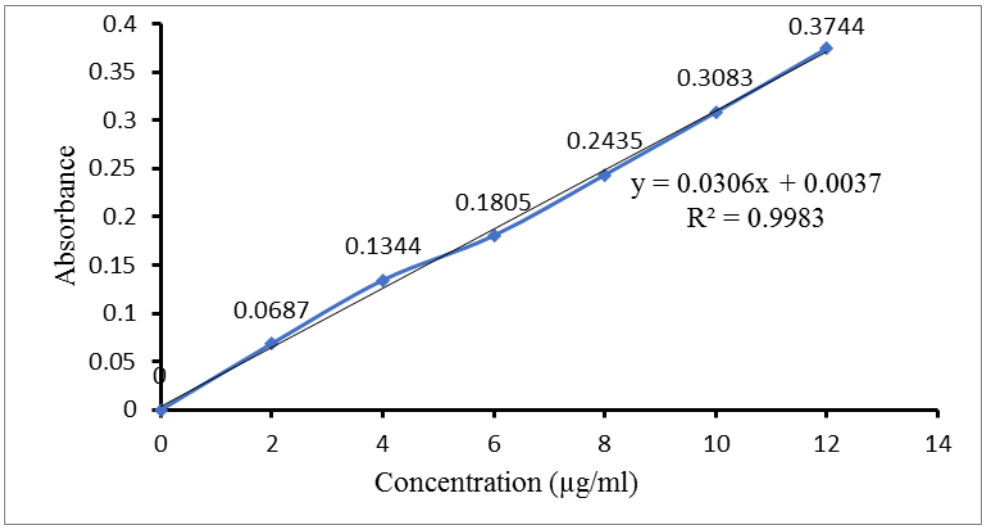

Figure 2: Standard graph of pure drug (Valacyclovir).

Pre-compression parameters

Pre-compression studies were performed to evaluate the flow and packing characteristics of all powder blends. The angle of repose ranged from 24.94 ± 0.26° to 28.81 ± 0.34°, with formulation F4 showing an angle of 27.03 ± 0.42° (θ), indicating satisfactory flow properties suitable for further processing. The bulk density of the powders varied between 0.37 ± 0.03 and 0.40 ± 0.03 g/cm³, reflecting its packing behavior under gravity. The tapped density measurements ranged from 0.38 ± 0.02 to 0.48 ± 0.03 g/cm³, suggesting moderate

compressibility. The Carr's compressibility index, an indicator of powder flowability, was found between 4.3 ± 0.021 and 20.0 ± 0.030, implying good compressibility. Finally, the Hausner's ratio values ranged from 1.02 ± 0.04 to 1.26 ± 0.04, and confirming excellent flow characteristics for all batches of powder blends. The all results are as shown in Table 4.

Table 4: Results of pre-compression parameters.

F Code	Angle of repose ± SD (θ)	Bulk Density ± SD (gm/cc)	Tapped Density ± SD (gm/cc)	Carr's index ± SD %	Hausner's ratio ± SD
F1	24.94±0.26	0.37±0.032	0.38±0.023	4.3±0.021	1.02±0.04
F2	26.56±0.27	0.38±0.028	0.40±0.032	5.2±0.033	1.04±0.03
F3	28.81±0.34	0.39±0.038	0.41±0.028	4.8±0.016	1.05±0.02
F4	27.03±0.42	0.36±0.042	0.39±0.034	7.69±0.038	1.08±0.05
F5	27.47±0.16	0.40±0.033	0.44±0.052	9±0.022	1.1±0.06
F6	25.64±0.20	0.38±0.036	0.48±0.033	20±0.030	1.26±0.04
F7	27.92±0.28	0.37±0.032	0.44±0.012	15±0.028	1.18±0.09
F8	28.20±0.34	0.38±0.026	0.43±0.022	11.62±0.042	1.31±0.06

(n=3 Avg ± SD)

Post-compression parameters

Hardness

The hardness of all batch's formulations from F1 to F8 found in the ranges of 6.32±0.22 to 7.39±0.53kg/cm^2, All the formulations were found within the limits as per IP. That implies the tablet withstand the mechanical shock as shown in table 5.

Friability

The friability of all formulation batches, F1 to F8, ranged from 0.12 ± 0.14% to 0.44 ± 0.35% as shown in table 5. These values are well within the limits specified by the Indian Pharmacopoeia (IP), indicating that the tablets possess sufficient mechanical strength and can withstand handling, packaging, and transportation without significant breakage or chipping.

Thickness

The thickness of the tablets from all formulation batches (F1–F8) was measured and found to range from 4.29 ± 0.07 mm to 4.53 ± 0.06 mm as shown in table 5. These results indicate consistent tablet dimensions across all batches, reflecting uniformity in the compression process and ensuring reproducible dosing.

Weight variation

The tablet weight for all formulation batches (F1–F8) ranged from 622.26 ± 3.16 mg to 628.38 ± 5.43 mg as shown in table 5. These results demonstrate minimal variation in weight across the batches, indicating uniformity in the manufacturing process and ensuring consistent dosing of the active ingredient, in line with Pharmacopoeial standards.

Drug content

The drug content of tablets from all formulation batches (F1–F8) was found to range from 97.0 ± 0.082% to 99.67 ± 0.08% as shown in table 5. These values fall within the acceptable pharmacopoeial limits, indicating uniform distribution of the active pharmaceutical ingredient in each tablet and confirming the accuracy and consistency of the formulation process.

Table 5: Results of post-compression parameters.

F Code	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Weight variation (mg)	Drug content (%)
F1	7.39 ±0.53	0.12±0.14	4.42±0.06	625.68±2.13	98±0.061
F2	7.10±0.58	0.28±0.11	4.53±0.04	628.28±4.13	99.32±0.08
F3	7.55±0.63	0.29±0.12	4.29±0.07	627.48±3.13	98.42±0.05
F4	6.32±0.22	0.25±0.17	4.43±0.03	626.48±6.23	98.98±0.09
F5	6.44±0.12	0.35±0.22	4.53±0.06	628.38±5.43	99.56±0.08
F6	6.62±0.54	0.27±0.71	4.42±0.05	622.26±3.16	97.0±0.082
F7	6.80±0.83	0.44±0.35	4.45±0.07	624.34±5.43	99.67±0.08
F8	6.72±0.18	0.34±0.58	4.52±0.03	625.64±3.44	98.92±0.06

(n=3 Avg ± SD)

***In-vitro* dissolution studies**

The *in vitro* release study of the prepared sustained release tablets of Valacyclovir was determined in phosphate buffer pH 7.4 as dissolution medium, drug release from all eight formulations (F1–F8) was monitored over 24 hours, with results expressed as cumulative percentage released (mean ± SD). F1 to F3 tablets were prepared by using HPMCK100M different concentrations but it shows the poor sustained release. At the beginning (0 hr), no drug was released in any formulation. After 1 hour, drug release ranged from 16.92 ± 2.0% in F3 to 29.24 ± 1.8% in F4. From F4 to F8 tablets were prepared by using different concentration of Guar gum and Lactose and observed change in the drug release from formulations. Over time, all formulations showed a gradual increase in release. At 4 hours, cumulative release varied between 24.26 ± 1.0% (F8) and 47.43 ± 2.9% (F4). By 8 hours, F4 released the highest amount (66.68 ± 2.2%), while F8 released 44.27 ± 1.5%. At the 12-hour mark, F4 again exhibited the fastest release at 88.63 ± 2.6%, whereas F8 released 50.74 ±

3.0%. At the end of 24 hours, drug release was nearly complete, ranging from 75.68 ± 1.1% (F3) to 95.57 ± 3.0% (F4). as shown in figure 3 and table 6. Overall, F4 showed the most rapid and extensive release, whereas the other formulations demonstrated slower, sustained release over the study period. This is due to higher concentration of polymer used in preparation of formulation, in contrary the formulation contains combination of polymer.

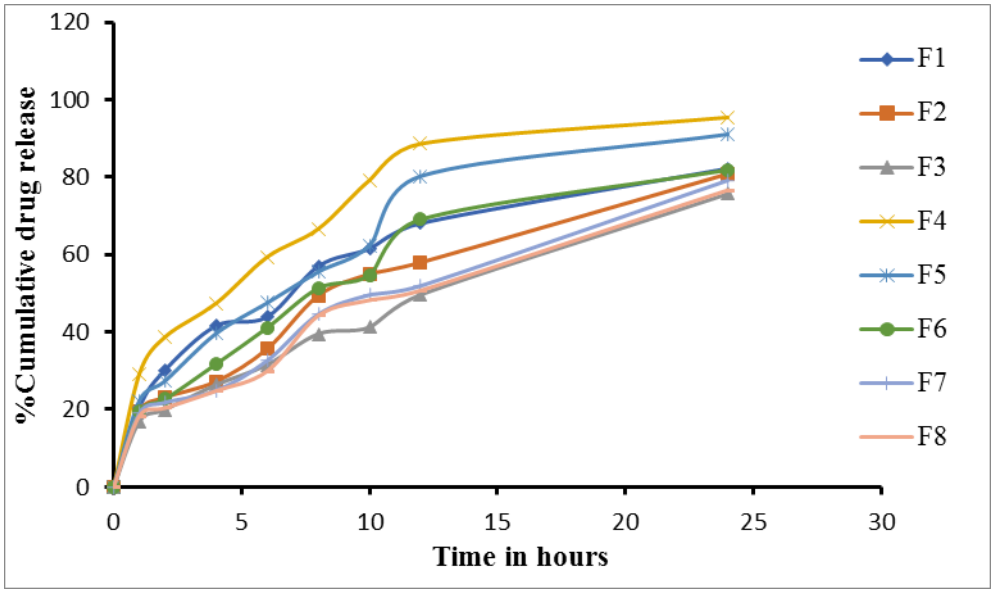

Figure 3: *In vitro* drug release.

Table 6: Results of *In Vitro* Dissolution.

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	**0**	0	0	0	0
1	20.48±2.4	19.52±2.0	16.92±2.0	**29.24±1.8**	22.28±0.4	19.34±0.8	19.04±1.2	18.13±0.5
2	30.17±3.7	23.12±1.2	19.98±2.2	**38.72±2.4**	27.37±1.4	22.66±1.2	21.82±1.3	20.38±0.9
4	41.63±2.6	25.46±0.7	26.38±2.8	**47.43±2.9**	39.62±2.1	31.73±2.3	24.89±1.0	24.26±1.0
6	43.95±3.5	35.69±1.8	31.56±2.3	**59.40±1.4**	47.52±1.3	41.14±1.5	32.64±2.3	29.92±1.1
8	57.02±4.8	49.44±2.2	39.54±2.4	**66.68±2.2**	55.56±3.4	51.33±3.5	44.61±1.4	44.27±1.5
10	61.52±3.4	54.98±3.0	41.25±2.3	**79.24±2.1**	62.35±1.3	54.73±1.6	49.61±1.5	48.24±3.5
12	68.09±1.5	57.40±2.2	49.64±1.3	**88.63±2.6**	80.25±3.2	69.09±3.0	51.96±1.3	50.74±3.0
24	82.64±2.4	80.84±1.6	75.68±1.1	**95.57±3.0**	91.08±2.8	81.86±2.4	79.16±2.7	76.64±3.6

(n=3, Avg±SD)

Drug excipient compatibility studies

The Fourier Transform Infrared (FTIR) analysis was conducted to confirm the presence of characteristic functional groups in the pure drug (Valacyclovir) and the formulated batch F4. The N–H stretching vibration was observed at 3326.99 cm^{-1} in the pure drug and 3327.57 cm^{-1} in formulation F4, indicating no significant shift. The C–H stretching of the

alkyl group appeared at 2835.89 cm^{-1} in the pure drug and 2876.45 cm^{-1} in F4. Similarly, the ester carbonyl (C=O) stretching was found at 1723.40 cm^{-1} in the pure drug and 1724.46 cm^{-1} in F4 as shown in table 7. These minor variations confirm that there is no significant chemical interaction between the drug and excipients, as shown in figure 4 and 5. Suggesting compatibility between two or more chemical company used in the formulation development.

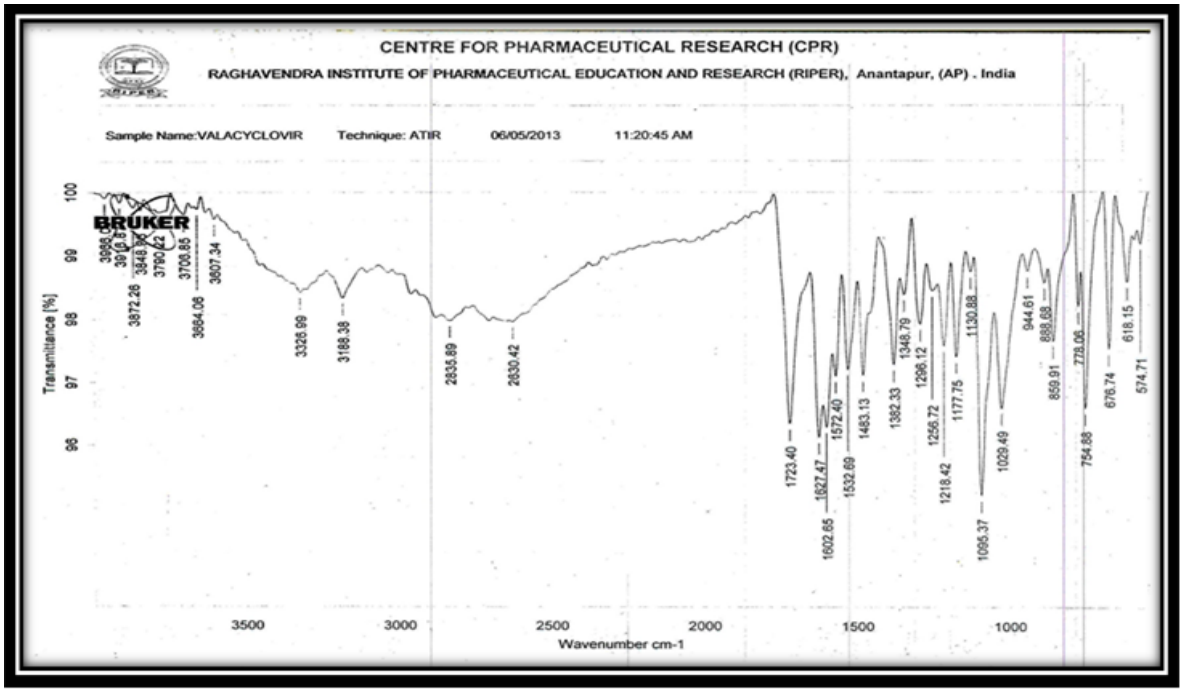

Figure 4. FTIR of pure drug (Valacyclovir)

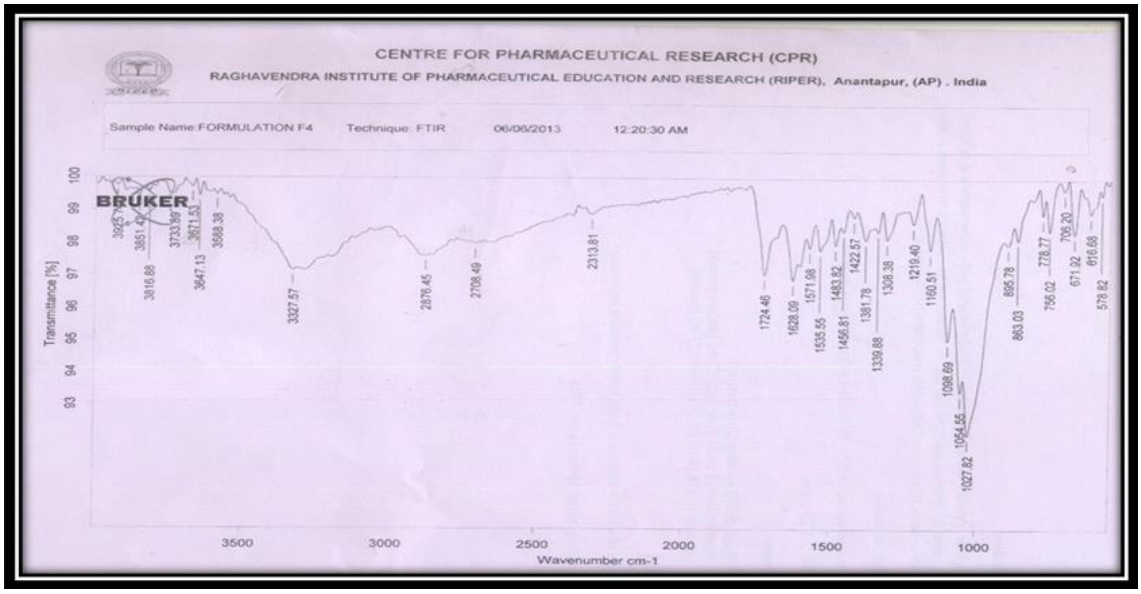

Figure 5. FTIR of formulation F4.

Table 7: FTIR spectra data.

Functional group	Range (cm^{-1})	Pure drug (Valacyclovir) (cm^{-1})	Formulation F4 (cm^{-1})
N-H Stretching	3400	3326.99	3327.57
C-H Stretching (alkyl group)	2900	2835.89	2876.45
C=O Stretching (ester carbonyl	1730	1723.40	1724.46

Release kinetics

The *in vitro* drug release data of all formulation batches (F1–F8) were analyzed using various kinetic models. The coefficient correlation (R^2) values indicate that the release of Valacyclovir from all batches. Showed zero order drug release ranging from 0.746-0.940 as shown in table 8. First-order kinetics, with from 0.963 to 0.991, suggesting that the release rate is concentration dependent. The Higuchi model also showed high linearity (R^2 = 0.951–0.982), indicating that diffusion is a major mechanism of drug release. The Korsmeyer–Peppas model exhibited R^2 values between 0.9333 and 0.9848, and the calculated *n* values ranged from 0.403 to 0.488, suggesting that the drug release follows Fickian diffusion (n < 0.5). Hixson-Crowell model showed linearity with all the formulation ranging R^2 value ranging from 0.9141-0.9828, and suggesting the drug release from solid dosage form changes in both surface area and particle diameter significantly. Overall, the data confirm a controlled and predictable release profile across all formulations. The formulation F4 showed maximum of drug release that is 95.75% of drug release within 24 hr and its follows zero order kinetics with higher R^2 value of 0.964 as shown in table 8.

Table 8: Release kinetics.

F Code	Zero order (R^2)	First order (R^2)	Higuchi model (R^2)	Hixson–Crowell model (R^2)	Korsmeyer-Peppas model (R^2)	n-value
F1	0.802	0.975	0.977	0.9215	0.9848	0.444
F2	0.893	0.991	0.973	0.9689	0.9541	0.473
F3	0.940	0.990	0.982	0.9828	0.9715	0.483
F4	**0.746**	**0.964**	**0.951**	**0.9141**	**0.9745**	**0.403**
F5	0.838	0.963	0.974	0.9441	0.9783	0.477
F6	0.858	0.970	0.980	0.9423	0.9733	0.488
F7	0.923	0.988	0.981	0.9796	0.9373	0.467
F8	0.920	0.987	0.975	0.9758	0.9333	0.468

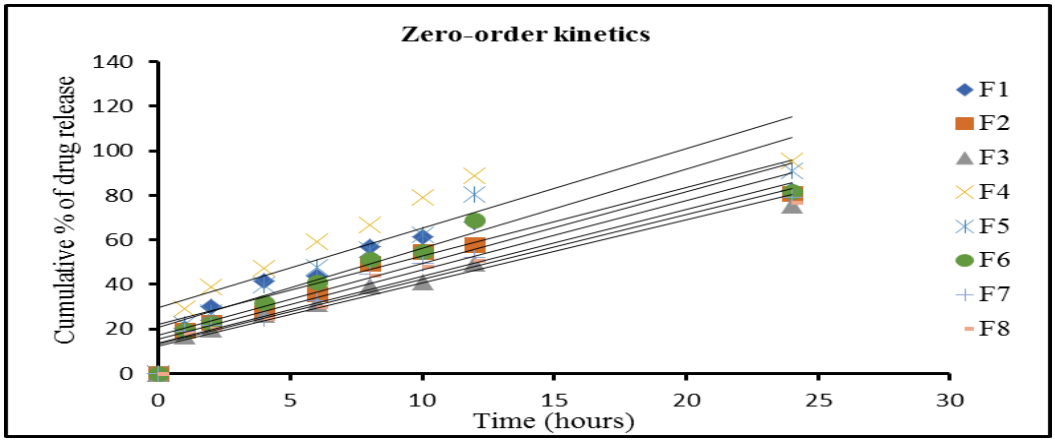

Figure 6. Zero order kinetics plot (F1-F9).

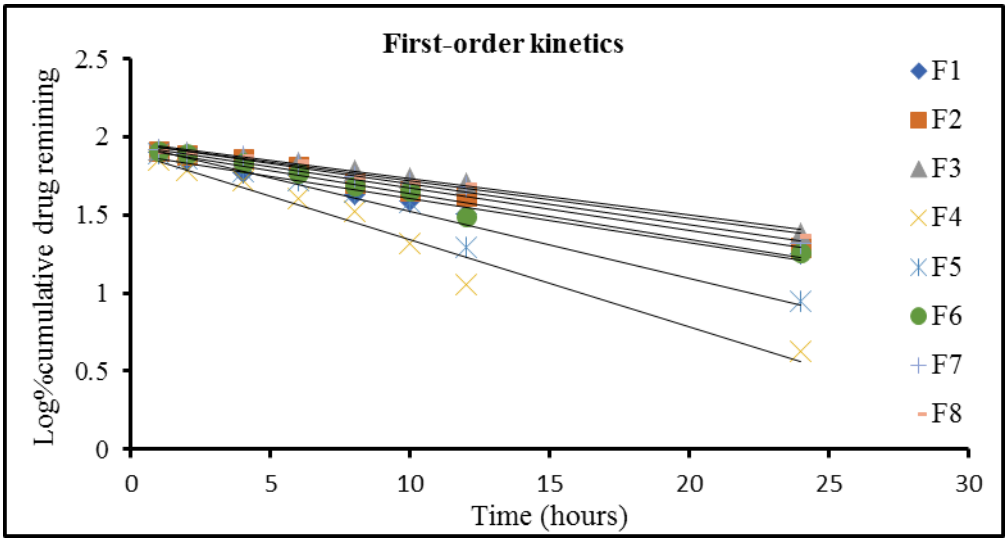

Figure 7. First order kinetics plot (F1-F9).

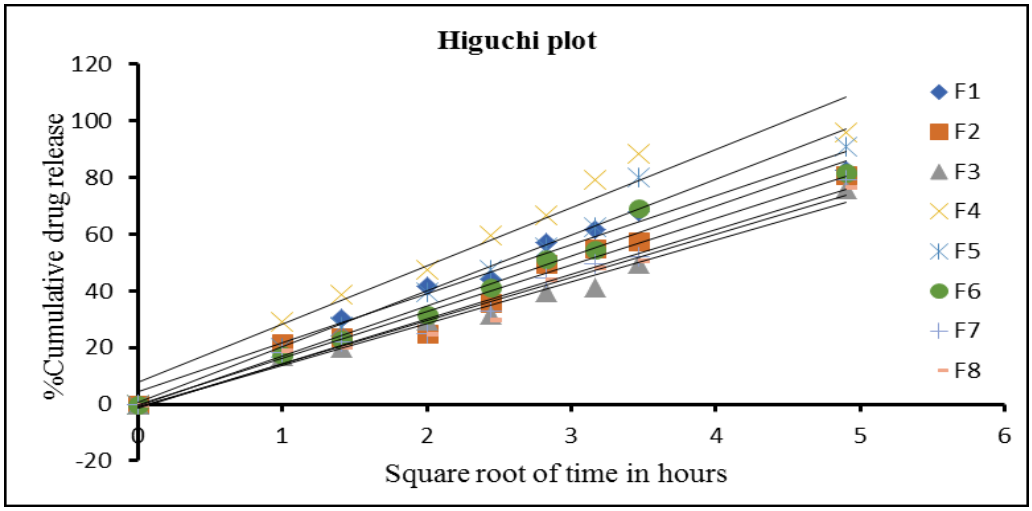

Figure 8. Higuchi's kinetics plot (F1-F9).

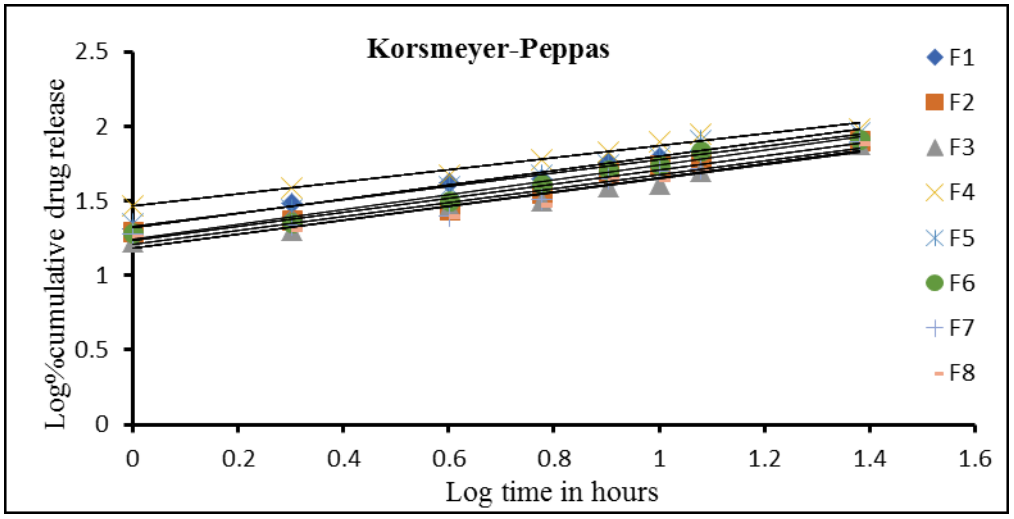

Figure 9. Korsmeyer-Peppas kinetics plot (F1-F9).

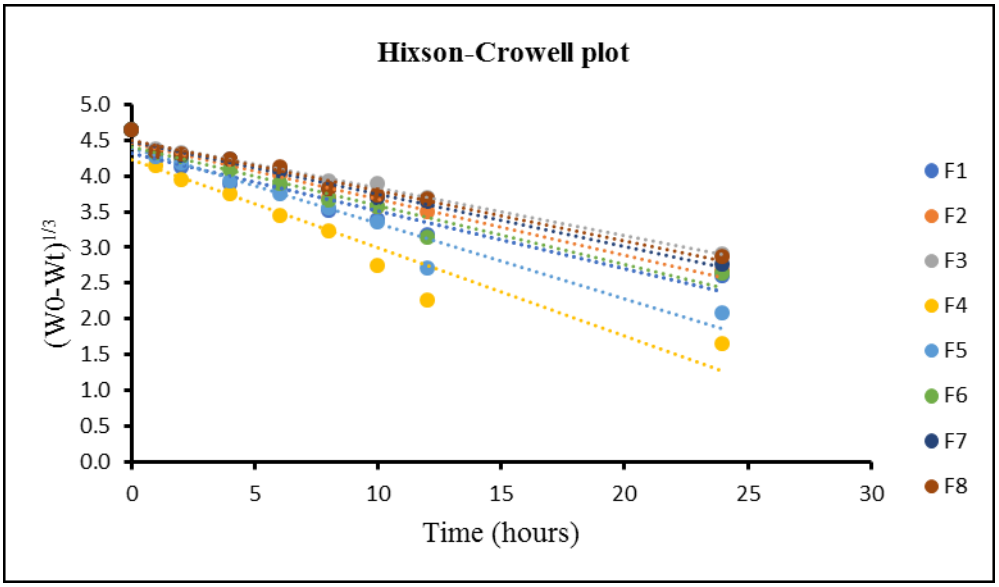

Figure 10. Hixson-Crowell plot (F1-F9).

DISCUSSION

All Valacyclovir sustained-release tablet formulations (F1–F8) showed satisfactory pre- and post-compression characteristics. The powder blends exhibited good flow properties, while the tablets demonstrated uniform thickness, weight variation, friability, and drug content, meets pharmacopoeial standards. FTIR analysis confirmed no significant interaction between the drug and excipients. *In vitro* release studies indicated that drug release followed first-order kinetics and Fickian diffusion. Overall, the formulations were uniform, mechanically stable, and suitable for sustained release drug delivery, with F4 showing optimal performance.

CONCLUSION

The present study was carried out with an aim to design sustained release tablets of Valacyclovir for once daily administration for anti-viral therapy. It can be concluded that successful release of drug for 24 hours which helped in improving patient compliance. This finding offers a basis for conducting further *in vivo* studies to conform the drug release behavior and pharmacokinetic performance.

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CONFLICT OF INTEREST

The authors have no conflict of interest to publish this article in this journal.

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