Research Article

EFFECT OF DIFFERENT GRADES OF HPMC AND EUDRAGIT ON DRUG RELEASE PROFILE OF DOXOFYLLINE SUSTAINED RELEASE MATRIX TABLETS AND IVIVC STUDIES

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ABSTRACT

Present studies aimed for design of sustained release matrix tablets of Doxofylline through in vitro as well as pharmacokinetic studies that will reduce the frequency of dosing and improve patient compliance and to establish in vitro-in vivo correlation. Wet granulation methods were adopted using different grade of release retarding polymers HPMC and Eudragit in various proportion to optimise the release profile. Different precompression and post compression characterization of tablet was carried out and the results satisfied according to the pharmacopeia specifications. In-vitro release studies were carried out in USP II paddle type dissolution apparatus for different formulations and the dissolution profiles of all the formulations were compared with standard marketed formulation by calculating the similarity factor (f2) and difference factor (f1). The formulation DSRF1: containing both the grades of HPMC (6%, HPMC K4M and HPMC K15M) having 7% each and 8% of Eudragit RSPO was considered as optimised formulation as the initial release was 18% and maximum release (99.19%) upto 12 h and showed highest f2 value (96.41) and lowest f1 value (0.88) was considered as optimised formulation. The hardness, friability, drug content and swelling index of DSRF1, found as 5.17±0.8 kg/cm², 0.62±0.04, 102.35±1.44 and 96.29±2.16 respectively. The kinetic of in-vitro drug release profile of DSRF1, followed zero order kinetic model due to highest regression value (R²=0.993) having drug release mechanism as anomalous diffusion coupled with erosion (n=0.732). FTIR and DSC analysis revealed that there was no interaction between the drug and the polymers, thus these polymers can be used in development of Doxofylline sustained release matrix tablets. Accelerated stability studies of optimized formulation (DSRF1) showed a little change in physicochemical properties as well as drug release profiles at the end of 90 day indicating the stability of formulations. In vivo pharmacokinetic studies of optimised formulation and marketed standard formulation were carried out in New Zealand white rabbit and in vivo-in vivo correlation was established. Thus the current study clearly indicate a promising potential of the Doxofylline sustained release matrix tablets system as an alternative to the conventional dosage form as it control in vitro burst effect of the highly water-soluble drug, Doxofylline hydrochloride and can prevent in-vivo dose dumping.

Key Words: Sustained release tablet, Similarity factor, Difference factor, Doxofylline, HPMC, Eudragit, In vitro-in vivo correlation (IVIVC)

INTRODUCTION

Oral drug delivery is the most preferred and convenient choice as the oral route provides maximum active surface area and hence increase residence time of the drug among all drug delivery system for administration of various drugs. Usually conventional dosage form produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. This factor such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. Such dosage forms exhibit better pharmacological effect and prolonged therapeutic activity. Matrix tablets are one of the most commonly used controlled release dosage forms as they release the drug in a controlled manner.1,2 Such type of dosage form will be beneficial for the chronic disease like asthma, diabetes, hypertension and inflammation that require constant plasma level for maintenance therapy.1

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant monitoring. Doxofylline, a methylxanthine derivative that works by inhibition of phosphodiesterase IV activities, has recently drawn attention because of its better safety profile and similar efficacy over the most widely prescribed analogue, theophylline, indicated for asthma and chronic obstructive pulmonary disease due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is chemically designated as 7-(1, 3 dioxolone-2-yl methyl) theophylline. Presence of a dioxolane group in position C-7 differentiates it from theophylline, Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) and is extensively metabolized in liver by demethylation and oxidation to an extent of 80-90% and 48% plasma protein bound. Elimination half life (t1/2) is around 6-7 h and < 4% of an administered dose of Doxofylline is excreted unchanged in the urine. The daily dose is 200-400 mg two to three times in a day. Doxofylline is coming under class III of BCS classification and oral absorption is 62.2%. It is having solubility of 12 mg/ml in water and having pH 9.87.3,4

The objective of the present study was to develop sustained release tablets of Doxofylline using hydroxy propyl methylcellulose K4M, K15M (HPMC K4M, K15M) and Eudragit RSPO, RLPO as polymeric retardant materials to reduce the frequency of dosing and to improve the therapeutic efficacy. Different proportion of HPMC K4M, K15M and Eudragit RSPO, RLPO were selected to form different sustained release tablets formulation for optimization of drug release rate.5,6 Optimised formulation and marketed standard formulation were tested with in-vivo pharmacokinetic studies in New Zealand white rabbit and in vitro-in vivo correlation was established.
MATERIALS AND METHODS

Materials

Doxofylline was procured as a gift sample from Dr. Reddy’s Laboratories Hyderabad, India. HPMC K4M, HPMC K15M and Eudragit RSPO, RLPO polymers were received as gift sample from Glenmark Pharma, Nasik, India. The diluent Micro crystalline cellulose (MCC) and lactose were purchased from Otto Manufacturers. PVP K30, Talc and magnesium Stearate were purchased from S.D. fine chemicals Pvt. Ltd. Mumbai, India. All the ingredients were of laboratory grade. The distilled water used in the process of research work was prepared by double distillation process in the laboratory.

Methods

Determination of λmax of pure Doxofylline and preparation of calibration curve

Primary stock solution of Doxofylline having concentration of 1000 µg/ml was prepared using phosphate buffer pH 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10 µg/ml was prepared using same phosphate buffer pH 6.8. The prepared secondary stock solution was then scanned by a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400 nm to 200 nm, and the λmax for solution was determined and it was found to be 274 nm. The secondary stock solution was then diluted using same phosphate buffer pH 6.8 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at λmax of 274 nm. For obtaining the calibration curve of pure Doxofylline, the measured absorbencies were plotted against corresponding concentrations. The same procedure was followed for preparation of standard calibration curve in HCl buffer pH 1.2. For HCl buffer pH 1.2 the λmax was found to be 273 nm after scanning 6-7.

Formulation of sustained release matrix tablets of Doxofylline

For preparation of sustained release matrix tablets of Doxofylline wet granulation methods were adopted. Accurate quantities of all ingredients were weighed and passed through sieve no #80 before their use in formulations. For each formulation specific and accurate quantities of powder like Doxofylline, HPMC, Eudragit, starch (insoluble), and lactose were blended uniformly and passed through #20. Here starch (insoluble) was used as binder and lactose was used as diluent. A lump wet mass was produced by adding required quantity of distilled water as granulating agent. The aggregates formed were initially dried for 10 min to reduce moisture level and to prevent sticking with sieve. The aggregates were passed through sieve # 20 to get granules. The granules were dried at 40°C for 20 min to reduce moisture content up to 2-5 %. After lubrication with magnesium stearate and talc the formulations were evaluated for angle of repose, bulk density, compressibility; prior to compression. The evaluated granules were compressed on a 10-station rotary tablet punching machine (SAIMACH India, ltd) using 10 mm concave punches. Each tablet contains 400 mg of Doxofylline as sustained release matrix formulation. The compositions for different formulations are given in Table 1 and same method was followed for all the formulations. Then the prepared tablet formulations were evaluated for various post compression parameters like average thickness, weight variation, hardness, friability, swelling studies, drug content and in-vitro dissolution studies.

Table 1: Composition of different excipients used for sustained release matrix tablets of Doxofylline

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Doxofylline (mg)</th>
<th>HPMC K4M (mg)</th>
<th>HPMC K15M (mg)</th>
<th>Eudragit RSPO (mg)</th>
<th>Eudragit RLPO (mg)</th>
<th>Lactose (mg)</th>
<th>Starch (Insoluble) (mg)</th>
<th>Mg. stearate (mg)</th>
<th>Talc (mg)</th>
<th>Total wt. (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSDF1</td>
<td>400</td>
<td>100</td>
<td>-</td>
<td>30</td>
<td>-</td>
<td>55</td>
<td>45</td>
<td>7</td>
<td>13</td>
<td>650</td>
</tr>
<tr>
<td>DSDF6</td>
<td>400</td>
<td>-</td>
<td>100</td>
<td>30</td>
<td>-</td>
<td>55</td>
<td>45</td>
<td>7</td>
<td>13</td>
<td>650</td>
</tr>
<tr>
<td>DSDF1</td>
<td>400</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>30</td>
<td>55</td>
<td>45</td>
<td>7</td>
<td>13</td>
<td>650</td>
</tr>
<tr>
<td>DSDF6</td>
<td>400</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>55</td>
<td>45</td>
<td>7</td>
<td>13</td>
<td>650</td>
</tr>
<tr>
<td>DSDF12</td>
<td>400</td>
<td>100</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>55</td>
<td>45</td>
<td>7</td>
<td>13</td>
<td>650</td>
</tr>
</tbody>
</table>

EVALUATION

Drug excipients compatibility studies

Drug excipients compatibility studies were done by FTIR and DSC analysis.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transform infrared (FTIR) study was carried out to verify any physical or chemical interaction between the drug and the excipients used in the formulation. The FTIR studies of pure drug Doxofylline and optimised formulation (DSDF1) were carried out by comparing the obtained spectra for the presence of functional groups. It was performed by potassium bromide (KBr) pellet method. The samples were triturated with KBr and pellet was prepared by setting the pressure to 100 kg/cm² for 2 min. The obtained pellet was analyzed in FTIR 8400S, Shimadzu, Japan. KBr background was obtained initially before analysis of test samples. The same procedures were repeated for the analysis of drug and for physical mixture of drug and excipients 9,10.

Differential Scanning Calorimetric (DSC) analysis

The DSC analysis of Doxofylline and physical mixture of drug with excipients used for formulations were carried out using a Shimadzu DSC 60, Japan; to evaluate any possible polymer drug thermal interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminum crucible and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.9,11
Evaluation of precompression parameters

Angle of Repose (θ)

The angle of repose was then calculated by measuring the height and radius of the heap of granules formed that were allowed to flow through the funnel fixed to a stand at definite height (h).

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

Where $\theta$ was called as angle of repose that indicates flow properties of granules, h and r were height and radius of the granule heap respectively. According to the specifications the angle of repose value less than 25° indicates excellent flow whereas angle greater than 40° indicates poor flow.\textsuperscript{10,11}

Bulk density

For the determination of both the bulk density (BD) and tapped density (TD) of prepared Doxofylline sustained release granules of all the formulations following formula were adopted:\textsuperscript{12}

\[ BD = \text{Weight of the granule taken / volume of the packing} \]

\[ TD = \text{Weight of the granule taken / tapped volume of the packing} \]

Compressibility Index (Carr’s index)

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of powder and the rate at which it packed down. Compressibility index (Carr’s index) of prepared Doxofylline sustained release granules were calculated by following formula

\[ \text{Carr's index (\%) = TD – BD / TD} \times 100 \]

According to the specification the Carr’s index values ranging between 5-15 indicates excellent flow and between 12-16 indicates good flow whereas Values between 33-38 indicates very poor and greater than 40 indicates extremely poor flow.\textsuperscript{13}

Hausner’s ratio

Another method used for the determination of flow properties of granules is by calculating the Hausner’s ratio and for all the formulations of prepared Doxofylline sustained release granules; it was determined by using following formula.

\[ \text{Hausner's ratio} = \frac{TD}{BD} \]

According to specifications values less than 1.25 indicate good flow (=20% of Carr’s index), where as greater than 1.25 indicates poor flow (=33% of Carr’s index). Between 1.25 and 1.5, glidant need to be added to improves flow.\textsuperscript{14}

Evaluation of postcompression parameters of Doxofylline sustained release tablets formulations

Average thickness

From each formulation of Doxofylline sustained release tablets; ten tablets were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial thickness Gauge, Japan) and the results were expressed as mean values of ten readings, with standard deviations. According to specification tablet thickness should be controlled within a ± 5% variation of standard value.\textsuperscript{12,13}

Tablet Hardness

The hardness of all the formulations of prepared Doxofylline sustained release tablets were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten sustained release tablets with known weights were recorded in kg/cm\textsuperscript{2} and average were calculated with standard deviation. According to specifications of USP; hardness values of 4-5 kg/cm\textsuperscript{2} is considered as acceptable limit for sustained release tablets.\textsuperscript{14}

Friability

Previously weighed ten tablets (W) from each batch of Doxofylline sustained release tablets were taken in Roche friabilator (Roche friabilator, Secor India, Delhi, India). After hundred revolutions of friabilator; tablets were recovered with cleaning to make free from dust and the total remaining weight (Wf) was recorded. Friability was calculated by using following formula.

\[ % \, F = \left( \frac{W_i - W_f}{Wi} \right) \times 100 \]

For any compressed uncoated tablet; friability lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.\textsuperscript{13,14}

Weight variation test

All the formulations of Doxofylline sustained release tablets were evaluated for weight variation as per USP monograph. Twenty tablets from each batch were weighed collectively and individually using an electronic balance. The average weight was calculated with percent variation of each tablet and the process is repeated thrice to calculate standard deviation. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130 mg or less is 10% whereas for average weight between 130-324 mg is 7.5% and for average weight more than 324 mg is 5%. For the tablet to be accepted, the weight of not more than two tablets deviate from the average weight by not more than 7.5% and no tablet deviates by more than 15%.\textsuperscript{15,16}

Content uniformity

For determination of content uniformity of the all formulations of Doxofylline sustained release tablets; twenty tablets from each batch were triturated to form powder. Powder equivalent to one tablet was taken and dissolved in 100 ml of phosphate buffer \textsuperscript{P6.8} and heated at 37 °C for 60 min with constant stirring. The solution was cooled, filtered and after suitable dilution the Doxofylline content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 274 nm. Each measurement was carried out in triplicate and the average drug content in each formulation was calculated.\textsuperscript{16,17}

Swelling Index (SI)

The swelling behaviour of all formulations of Doxofylline sustained release tablets were measured by studying its weight gain in the dissolution medium under study. The swelling index were determined by placing the tablets in the basket of dissolution apparatus containing 100 ml of phosphate buffer \textsuperscript{P6.8} as dissolution medium maintaining at 37 ± 0.5 °C. After every one hour interval and upto 12 h, each dissolution basket containing tablet was withdrawn and blotted with tissue paper to remove the excess water and weighed on the analytical balance (Shimadzu, AX 120). The experiment was performed in triplicate for each time point. Swelling index was calculated by using the following formula.\textsuperscript{18}
Swelling index (SI) = \( W_f - W_i / W_i \times 100 \)

Where \( W_f \) and \( W_i \) is called as wet and dry weight of the tablet respectively.

In-vitro drug release study

The in-vitro release studies were conducted for all Doxofylline sustained release matrix tablet formulations using eight stations USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India) maintaining at 37 ± 0.5 °C. To simulate the physiological conditions of GIT, first 2 h of dissolution was carried out in 900 ml of simulated gastric fluid (SGF, 3.2 mg/ml pepsin in 0.05M HCl, \( pH \ 1.2 \)) and the rest of the time in 900 ml of simulated intestinal fluid (SIF, 10 mg/ml pancreatic fluid in phosphate buffer, \( pH \ 6.8 \)). At regular intervals of time, the aliquots were withdrawn and analyzed for drug using the UV-Visible spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at \( \lambda_{max} \ 273 \ nm \) and 274 nm for HCl buffer \( pH \ 1.2 \) and phosphate buffer, \( pH \ 6.8 \) respectively. After each sampling an equal volume of fresh dissolution media was added to the dissolution medium. All the dissolution studies were repeated thrice.\(^{16, 19} \)

Calculation of similarity and difference factors

The best formulation was chosen according to comparative dissolution study with a reference marketed product of Doxovent SR-TAB (Glenmark, Majesta) containing Doxofylline 800mg, calculating the similarity factor equation \( (f_2) \) and difference factor \( (f_1) \) introduced by Moore and Flanner. The similarity factor \( (f_2) \) adopted by the U.S. Food and Drug Administration (FDA) was used to evaluate the similarity in release profiles between the two pharmaceutical preparations. The similarity factor, which is a logarithmic transformation of the sum squared error of differences between the test preparation and reference preparation, was calculated by the following equation:

\[
f_2 = 50 \times \log \left[ \left( \frac{1}{n} \sum_{i=1}^{n} (R_i - T_i)^2 \right)^{0.5} \right] \times 100
\]

Where \( R_i \) and \( T_i \) are the accumulated release rates of the reference preparation and test preparation at the predetermined time points, respectively, and \( n \) represents the number of the time points. The value of the similarity factor is between 0 and 100. The value 100 indicates that the test and reference profiles are identical; the more it approaches 0, the more dissimilarity of the two preparations occurs. Generally, if \( f_2 \geq 50 \), the release profiles are considered to be similar, and the larger the \( f_2 \) value, the higher the similarity. Difference factor \( (f_1) \) measures the percent error between two drug release curves over all time points.

\[
f_1 = \left( \frac{\sum_{i=1}^{n} |R_i - T_i|}{\sum_{i=1}^{n} R_i} \right) \times 100
\]

Dissolution profile was considered satisfactory if \( f_1 \) values lies below 15 (nearing zero, more it approaches towards zero more similarity between the products is being has).\(^{19, 20} \) In the present study three time point were taken i.e. 1st, 5th, and 8th hour for the calculation of similarity and difference factors of all the formulations.

In-vitro drug release kinetic studies

The rate and mechanism of release of Doxofylline from prepared sustained release tablets were analyzed by fitting the dissolution data of optimised formulation (DSRF\(_{11} \)) into following exponential equations.

Zero order release equation is calculated by following equation.

\[
Q = K_0t
\]

Where \( Q \) is the amount of drug released at time \( t \) and \( K_0 \) is the zero order release rate constant.

The first order equation is calculated by following equation.

\[
\log (100-Q) = \log Q - K_1t/2.303
\]

Where, \( K_1 \) is the first order release rate constant. When the data are plotted as logarithm of cumulative percent drug remaining versus time, it yields a straight line, indicating that the release follows first order kinetics. The constant \( K_1 \) can be obtained by multiplying 2.303 with slope.

The dissolution data was fitted to the following Higuchi’s equation.

\[
Q = K_{Ht}^{1/2}
\]

Where, \( K_2 \) is the diffusion rate constant. When the data are plotted as cumulative drug released versus square root of time, it yields a straight line, indicating that the drug released by diffusion mechanism. The slope is equal to \( K_2 \).

The dissolution data was also fitted to the Korsmeyer-Peppas equation, which is often used to describe the drug release behaviour from polymeric systems.

\[
\log (M_t/M_\infty) = \log K + n \log t
\]

Where \( M_t \) is the amount of drug released at time \( t \), \( M_\infty \) is the amount of drug release after infinite time, \( K \) is a release rate constant and \( n \) is the diffusion exponent indicative of the mechanism of drug release.

For matrix tablets, if the exponent \( n \ < \ 0.5 \), then the drug release mechanism is quasi-fickian diffusion (If \( n = 0 \) then fickian diffusion and if the value is \( 0.5 < n < 1 \), then it is anomalous diffusion coupled with erosion. An exponent value of 1 is indicative of Case-II Transport or typical zero-order and \( n \ > \ 1 \) non-fickian super Case II). The diffusion exponent was based on Korsmeyer-Peppas equation. Hixon-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

\[
W_0^{1/3} = W_t^{1/3} = Kdt
\]

Where \( W_0 \) is the initial amount of drug, \( W_t \) is the remaining amount of drug in dosage form at time \( t \) and \( K_d \) is a constant incorporating the surface volume relation. The graphs are plotted as cube root of percent drug remaining versus time \(^{18, 20} \).

Stability studies of optimised formulation

The tablets of optimized batch (DSRF\(_{11} \)) were packed in air tight bottles and subjected to accelerated stability studies according to ICH guidelines. The accelerated condition that chosen for stability study was 40 °C ± 2 °C / 75% ± 5% RH(Climate zone III condition for accelerated testing) using humidity control oven NEC 210R10 (Newtronic Instruments, India) for 90 days. The optimised formulation of Doxofylline sustained release matrix tablets were withdrawn from the humidity control oven at interval of 30 days, 60 days and 90 days for evaluation of physicochemical parameters i.e. physical appearance, weight variation, hardness, friability, swelling index, drug content and in-vitro drug release characteristics.\(^{20, 22} \)

In-vivo Pharmacokinetic study in male New Zealand white rabbits

Based on in-vitro dissolution profile, the optimized sustained release matrix tablets of Doxofylline were further subjected to in-vivo...
pharmacokinetic studies after getting approval from IAEC. Six male healthy New Zealand white rabbits weighing 2.5±0.5 kg were selected for these studies and divided into two groups. These studies were performed by using parallel design. One group was administered standard marked innovator formulation and another was administered with optimised formulation. All rabbits were housed in an animal house as per CPCSEA norms. All the rabbits are fasted overnight on the penultimate day before actual experimentation. The sustained release matrix tablet formulations of innovator and test formulations containing 400mg of Doxofylline were orally administered to second and third group of rabbits respectively by using an oral tube. Few ml of distilled water was pushed through a syringe (without needle) to ascertain that all the content reached the stomach. The FTIR spectra of pure drug Doxofylline and physical mixture used for SR tablet in optimized formulation DSRF₁ were obtained and shown in figure 1. By comparing the spectra of Doxofylline and SR tablet of optimised formulation (DSRF₁), the sharp peaks that appear in spectra of Doxofylline at 3110 cm⁻¹ due to presence of aliphatic N-H stretching functional group also appears in SR tablet at 2916 cm⁻¹ and 3110 cm⁻¹. The characteristic infrared absorption peaks of Doxofylline at -1700 cm⁻¹ (C=O stretch), at -1656 cm⁻¹ (C=C stretch), at -1547 cm⁻¹ (C=N stretch), at -1477 cm⁻¹ (C-H bend) and at -1190 cm⁻¹ (C-N vibration) were also present in the physical mixture (drug and excipients of SR tablet) with no shifting in the major peaks that indicated that there were no interaction occurred between the Doxofylline and excipients used in the preparation of different sustained release tablet formulations. Therefore the drug and excipients are compatible to form stable formulations under study.

Figure 1: Compatibility studies through FTIR analysis

DSC thermogram of pure drug Doxofylline and physical mixture used for SR tablets in optimized formulation DSRF₁ were obtained and shown in Figure 2. It was observed that the endothermic peak appeared at 146 °C for pure drug Doxofylline also appeared at 148 °C and 151 °C in optimised formulation of SR tablet respectively. The prominent endothermic peak found at 76 °C in HPMC was also clearly noticed at 83 °C in SR layer of formulations. In case of Eudragit the endothermic peaks that are found 214 °C and 234 °C were also prominently found in SR formulation layer at 215 °C and 235 °C respectively. The endothermic peak that found at 83 °C in SR layer was an intermediate peak found in HPMC and Eudragit at 76 °C and 86 °C respectively. These studies indicated that the formulation is thermodynamically stable because the formulation required slightly more heat than pure drug due to presence of various excipients. Appearance of extra peaks were due to presence of other excipients in the formulations. The DSC thermogram of pure drug and the formulations showed there was no major shifting i.e from endothermic to exothermic with appearance of major thermal peaks in the optimised formulation.

RESULTS AND DISCUSSION

The pharmacokinetic parameters such as maximum plasma concentration (Cmax), time to reach peak plasma concentration (tmax), plasma half-life (t½), area under curve [AUC(0-t)],elimination rate constant (Ke) and mean residence time (MRT) were calculated using by PK solver 2.0 software. The plasma was separated using micropipette for further quantitative evaluation. The supernatant liquid was collected and diluted with the mobile phase; was analyzed by RP HPLC method. The
Angle of repose is suited for particle > 150μm. Values of angle of repose ≤ 25° generally indicates the free flowing material and angle of repose ≥ 40° suggest a poor flowing material. The angle of repose is indicative of the flowability of the material. The angle of repose of all formulations fell within the range of 19.42±0.16 to 24.65±0.21 i.e. granules of Doxofylline sustained release tablets showed good flow properties. The bulk densities of Doxofylline sustained release granules of all formulations were found to be in the range of 0.295±0.04 to 0.328±0.05 g/cm³ and the tapped densities were found to be in between 0.344±0.07 to 0.394±0.08 g/cm³. This indicates good packing capacity of granules. Measurements of bulk density and tapped density found that density of granules depends on particle packing and density changes as the granules consolidates. All the formulations except DSRF_{9}, DSRF_{10} and DSRF_{11} showed Carr’s index value less than 16% that indicates good flow properties and values more than 16% indicates presence of more fines with lack of uniformity in particles. Hausner’s ratio is simple method to evaluate stability of power and granule column and to estimate flow properties. In all formulations the Hausner’s ratios values were found ‘between’ 1.10 to 1.22 that indicates good flow characteristics. The precompression characterizations of different batches of sustained released granules are given in Table 2.

Table 2: Evaluation of precompression parameters of Doxofylline Sustained release granules (DSRF_{1} – DSRF_{12})

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Bulk density (gm/ml)</th>
<th>Tapped density (gm/ml)</th>
<th>Angle of repose (°)</th>
<th>Carr’s Index (%)</th>
<th>Hausner’s ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSRF_{1}</td>
<td>0.310±0.04</td>
<td>0.352±0.06</td>
<td>22.52±0.20</td>
<td>11.93</td>
<td>1.14</td>
</tr>
<tr>
<td>DSRF_{2}</td>
<td>0.318±0.05</td>
<td>0.364±0.08</td>
<td>23.63±0.16</td>
<td>12.64</td>
<td>1.14</td>
</tr>
<tr>
<td>DSRF_{3}</td>
<td>0.324±0.04</td>
<td>0.381±0.07</td>
<td>23.44±0.15</td>
<td>14.96</td>
<td>1.18</td>
</tr>
<tr>
<td>DSRF_{4}</td>
<td>0.325±0.07</td>
<td>0.394±0.08</td>
<td>24.65±0.21</td>
<td>17.51</td>
<td>1.21</td>
</tr>
<tr>
<td>DSRF_{5}</td>
<td>0.306±0.05</td>
<td>0.365±0.06</td>
<td>23.82±0.16</td>
<td>16.16</td>
<td>1.19</td>
</tr>
<tr>
<td>DSRF_{6}</td>
<td>0.298±0.04</td>
<td>0.344±0.07</td>
<td>21.63±0.17</td>
<td>13.37</td>
<td>1.15</td>
</tr>
<tr>
<td>DSRF_{7}</td>
<td>0.295±0.06</td>
<td>0.360±0.05</td>
<td>24.21±0.17</td>
<td>18.05</td>
<td>1.22</td>
</tr>
<tr>
<td>DSRF_{8}</td>
<td>0.322±0.04</td>
<td>0.354±0.06</td>
<td>19.85±0.14</td>
<td>9.04</td>
<td>1.10</td>
</tr>
<tr>
<td>DSRF_{9}</td>
<td>0.328±0.05</td>
<td>0.389±0.07</td>
<td>21.14±0.18</td>
<td>15.68</td>
<td>1.19</td>
</tr>
<tr>
<td>DSRF_{10}</td>
<td>0.320±0.03</td>
<td>0.387±0.08</td>
<td>22.09±0.19</td>
<td>17.31</td>
<td>1.21</td>
</tr>
<tr>
<td>DSRF_{11}</td>
<td>0.308±0.05</td>
<td>0.355±0.07</td>
<td>19.42±0.16</td>
<td>13.24</td>
<td>1.15</td>
</tr>
<tr>
<td>DSRF_{12}</td>
<td>0.314±0.06</td>
<td>0.362±0.08</td>
<td>20.61±0.12</td>
<td>13.26</td>
<td>1.15</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD; (n=3)

The postcompression parameters of all the formulations of Doxofylline sustained released matrix tablets were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The average thicknesses of the tablets were ranged from 4.12±0.18 to 4.19±0.18mm and the variation observed were within prescribed limits. Weight variations for different formulations were ranged between 653±2.98 to 648±3.46 mg. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Doxofylline sustained released matrix tablets formulations were ranged from 4.89±0.7 to 5.45±0.9 kg/cm². The percentage friability of all the formulas was ranged from 0.43±0.05 % to 0.66±0.04 %. In the present study, the percentage friability for all for
formulations was within the prescribed limits. The percentages of drug content for Doxofylline sustained released matrix tablet formulations (DSRF$_1$ to DSRF$_{12}$) were found to be in between 98.78±1.38% to 103.44±1.14% which were within the acceptable limits. The physicochemical characterizations of different batches of sustained released tablets are given in Table 3.

Table 3: Evaluation of postcompression parameters of Doxofylline sustained release matrix tablets (DSRF$_1$-DSRF$_{12}$)

<table>
<thead>
<tr>
<th>F. No.</th>
<th>Average hardness $^2$ (kg/cm)</th>
<th>Average Weight Variation (%)</th>
<th>Average friability (% w/w)</th>
<th>Average thickness (mm)</th>
<th>Drug content uniformity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSRF$_1$</td>
<td>4.98±0.7</td>
<td>653.24±3.41</td>
<td>0.52±0.02</td>
<td>4.14±0.16</td>
<td>99.14±1.42</td>
</tr>
<tr>
<td>DSRF$_2$</td>
<td>5.45±0.9</td>
<td>652.43±2.62</td>
<td>0.56±0.04</td>
<td>4.12±0.18</td>
<td>97.79±1.25</td>
</tr>
<tr>
<td>DSRF$_3$</td>
<td>4.95±0.8</td>
<td>651.64±4.02</td>
<td>0.43±0.05</td>
<td>4.16±0.15</td>
<td>102.66±1.32</td>
</tr>
<tr>
<td>DSRF$_4$</td>
<td>4.89±0.7</td>
<td>649.71±3.74</td>
<td>0.56±0.04</td>
<td>4.16±0.17</td>
<td>102.17±1.45</td>
</tr>
<tr>
<td>DSRF$_5$</td>
<td>5.10±0.8</td>
<td>648.82±3.46</td>
<td>0.57±0.06</td>
<td>4.17±0.15</td>
<td>102.24±1.56</td>
</tr>
<tr>
<td>DSRF$_6$</td>
<td>5.22±0.9</td>
<td>652.63±2.71</td>
<td>0.54±0.03</td>
<td>4.15±0.16</td>
<td>98.88±1.21</td>
</tr>
<tr>
<td>DSRF$_7$</td>
<td>5.14±0.6</td>
<td>648.18±4.55</td>
<td>0.56±0.04</td>
<td>4.17±0.18</td>
<td>98.95±1.35</td>
</tr>
<tr>
<td>DSRF$_8$</td>
<td>5.14±0.8</td>
<td>649.55±2.62</td>
<td>0.55±0.03</td>
<td>4.14±0.16</td>
<td>99.30±1.46</td>
</tr>
<tr>
<td>DSRF$_9$</td>
<td>5.28±0.9</td>
<td>652.38±3.57</td>
<td>0.66±0.04</td>
<td>4.16±0.18</td>
<td>103.44±1.14</td>
</tr>
<tr>
<td>DSRF$_{10}$</td>
<td>4.96±0.7</td>
<td>651.32±3.84</td>
<td>0.58±0.05</td>
<td>4.18±0.15</td>
<td>98.78±1.38</td>
</tr>
<tr>
<td>DSRF$_{11}$</td>
<td>5.17±0.8</td>
<td>653.45±2.98</td>
<td>0.62±0.04</td>
<td>4.19±0.18</td>
<td>102.35±1.44</td>
</tr>
<tr>
<td>DSRF$_{12}$</td>
<td>5.23±0.7</td>
<td>652.75±3.25</td>
<td>0.55±0.05</td>
<td>4.16±0.15</td>
<td>101.46±1.26</td>
</tr>
</tbody>
</table>

All values are expressed as mean± SD; (n=3)

Swelling study was performed on all the formulations (DSRF$_1$ to DSRF$_{12}$) upto 12 hours. The formulation containing more concentration of HPMC K4M, HPMC K15M showed higher swelling indices due to higher hydrophilicity and more water uptake of the polymers. But reverse is observed with the formulations containing higher percentage of Eudragit RSPO and RLPO, as it is a hydrophobic polymer. The formulations (DSRF$_9$ and DSRF$_{10}$) containing combination of both the grade of HPMC in equal proportion, showed higher swelling index. The formulation DSRF$_{10}$ that contains around 8% of HPMC K4M, 8% of HPMC K15M and 5% of Eudragit RLPO showed highest swelling indices then other formulations. Formulations DSRF$_5$, DSRF$_6$, DSRF$_7$, and DSRF$_8$ that contain more percentage of Eudragit RSPO and RLPO had lower swelling index as compare to other formulations as Eudragit is a hydrophobic polymer. The comparative swelling index for all the formulations were shown as histogram in Figure 3.

Figure 3: Swelling studies of all the formulations of Doxofylline matrix tablet formulations
In order to optimise the in-vitro drug release profile of Doxofylline sustained released matrix tablets; different hydrophilic matrix polymers viz., HPMC K4M, HPMC K15M and hydrophobic matrix polymer viz., Eudragit RSPO and Eudragit RLPO were used and twelve different formulations were prepared. Between the two grades of HPMC used, HPMC K15M having better controlled release profile than HPMC K4M. It was observed that using HPMC polymer alone causes initial burst release because drug is hydrophilic in nature and maximum of drug was released upto 8 hours. So one more hydrophobic polymer i.e. Eudragit was added to reduce the initial burst release of drug and to maintain sustained release effect for required period of time. Among the two grade of Eudragit used, Eudragit RSPO showed better sustained release effect than Eudragit RLPO. By increasing the concentration of HPMC the prolong release effect increased and it was found optimum at HPMC polymer concentration of 16%. The formulation DSRF_{11} that contained combination of two grades of HPMC (i.e both HPMC K4M and HPMC K15M) having 7% each and 8% of Eudragit RSPO was considered as optimised formulation as the initial release was 18% and maximum release upto 12 hours. This release profile complies with the release profile of marketed formulation. Further increase in the concentration of Eudragit; the initial release rate was much slower which was not desirable. So 8% of Eudragit RSPO was considered as optimum. Further to compare the release profile of all the formulations with marketed formulation; similarity and difference factor were calculated. The drug release profiles of different formulations were shown in Figure 4.

The similarity factors ($f_2$) and difference factor ($f_1$) play a very important role in comparing the test formulations release profile with standard marketed formulation. When the two dissolution profiles are identical, the value of $f_2$ is 100 and when the dissolution of one product (test or reference) is completed before the other begins, $f_2$ can be rounded to zero. Thus, the value of $f_2$ ranges from 0 to 100. If a difference between the test and the reference products is 10%, and this average absolute difference is substituted in the equation, $f_2$ becomes 50. Two dissolution profiles are considered "similar" when the $f_2$ value is between 50 and 100. A higher $f_2$ value indicates closeness between the two dissolution profiles. However, the equation is only applicable in comparing curves in which the average differences between the reference and the test formulation profiles is less than 100 and the amount of drug released in percent. The percent error is zero when the test and the drug reference profiles are identical, and increases proportionally with the dissimilarity between the two dissolution profiles. It is generally accepted that values of $f_2$ between 0 and 15 do not indicate dissimilarity. All the formulation showed dissimilarity in the dissolution profile except formulation DSRF_{7}, DSRF_{11} and DSRF_{12} that showed similarity in the dissolution profile. Among these three formulations, DSRF_{11} showed highest $f_2$ value (96.41) and lowest $f_1$ value (0.88) was considered as best formulation. The dissolution profiles of all the batches of sustained release tablet prepared in the present investigation were presented in Table 4.
Table 4: Similarity factor ($f_1$) and difference factor ($f_2$) with dissolution profile of all formulations (DSRF$_1$-DSRF$_{12}$)

<table>
<thead>
<tr>
<th>F. No.</th>
<th>$f_1$</th>
<th>$f_2$</th>
<th>Dissolution profiles</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSRF$_1$</td>
<td>45.08</td>
<td>33.93</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_2$</td>
<td>37.36</td>
<td>37.64</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_3$</td>
<td>47.81</td>
<td>32.90</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_4$</td>
<td>54.45</td>
<td>30.32</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_5$</td>
<td>17.26</td>
<td>53.07</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_6$</td>
<td>20.54</td>
<td>48.09</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_7$</td>
<td>14.75</td>
<td>57.23</td>
<td>Similar</td>
</tr>
<tr>
<td>DSRF$_8$</td>
<td>15.77</td>
<td>56.24</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_9$</td>
<td>21.10</td>
<td>48.91</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_{10}$</td>
<td>26.46</td>
<td>44.80</td>
<td>Dissimilar</td>
</tr>
<tr>
<td>DSRF$_{11}$</td>
<td>0.88</td>
<td>96.41</td>
<td>Similar</td>
</tr>
<tr>
<td>DSRF$_{12}$</td>
<td>8.77</td>
<td>67.38</td>
<td>Similar</td>
</tr>
</tbody>
</table>

The in-vitro dissolution data of optimised formulation DSRF$_{11}$ were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppa’s kinetic model equation and the graphs were plotted (Figure 3). The zero order release plot was found fairly linear as indicated by its highest regression (0.993) values. The release exponent ‘$n$’ for optimised formulation DSRF$_{11}$ was found to be 0.732 ($0.5 < n < 1$), which appeared to indicate an anomalous diffusion coupled with erosion. So in present study in-vitro drug release kinetic of optimised formulation of Doxofylline sustained release matrix tablets (DSRF$_{11}$) followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion.

![Figure 5: In-vitro release kinetic studies of optimised formulations DSRF$_{11}$](image)

Table 5: Regression values of in-vitro release kinetic study of optimized Doxofylline sustained release matrix tablet (DSRF$_{11}$)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>$R^2$ value of Zero order</th>
<th>$R^2$ value of 1st order</th>
<th>$R^2$ value of Higuchi model</th>
<th>$R^2$ value of Hixon-Crowell model</th>
<th>$R^2$ value of Peppa’s model</th>
<th>‘$n$’ value of Peppa’s model</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSRF$_{11}$</td>
<td>0.993</td>
<td>0.922</td>
<td>0.954</td>
<td>0.717</td>
<td>0.991</td>
<td>0.732</td>
</tr>
</tbody>
</table>

The optimised formulation DSRF$_{11}$ of Doxofylline sustained release matrix tablets was selected for the accelerated stability studies. It did not show any significant change in physicochemical characteristics i.e. physical appearance, weight variation, hardness, friability, swelling studies drug content and in-vitro drug release characteristics. More than 90% of the drug had been retained after in-vitro dissolution studies stored under stressed condition for 3 months. Thus, it was found that the sustained release matrix of Doxofylline (DSRF$_{11}$) were stable under accelerated storage conditions for at least 3 month. The results of change in physicochemical characteristics and in-vitro release profile of optimised formulation at different time interval in
accelerated stability conditions were shown in table 6 and figure 6 respectively.

### Table 6: Comparative physicochemical characterization of optimized batch (DSRF11) at accelerated conditions (40 °C ± 2 °C / 75% ± 5% RH)

<table>
<thead>
<tr>
<th>Physical characteristics</th>
<th>Initial</th>
<th>After 30 days</th>
<th>After 60 days</th>
<th>After 90 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical appearance</td>
<td>Pale white, circular, concave smooth surface without any cracks</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Weight variation</td>
<td>653.45±2.98</td>
<td>653.26±2.65</td>
<td>653.15±2.72</td>
<td>653.12±2.62</td>
</tr>
<tr>
<td>Hardness</td>
<td>5.17±0.80</td>
<td>5.24±0.71</td>
<td>5.38±0.82</td>
<td>5.76±0.85</td>
</tr>
<tr>
<td>Friability</td>
<td>0.62±0.04</td>
<td>0.64±0.03</td>
<td>0.69±0.05</td>
<td>0.75±0.04</td>
</tr>
<tr>
<td>Swelling index</td>
<td>96 ±1.06</td>
<td>93 ±1.05</td>
<td>88 ±1.06</td>
<td>85 ±1.04</td>
</tr>
<tr>
<td>Drug content</td>
<td>102.35±1.44</td>
<td>99.14±1.36</td>
<td>96.46±1.41</td>
<td>93.28±1.32</td>
</tr>
</tbody>
</table>

All values are expressed as mean±SD; (n=3)

The in-vivo pharmacokinetic parameters for the optimized sustained release matrix tablets containing Doxofylline were performed in New Zealand white rabbits. The formulations DSRF11 were selected for in-vivo studies along with the marketed formulation and in-vivo data were compared. $C_{\text{max}}$ for marketed formulation and test (DSRF11) were found 15.68±2.21 and 14.54±1.74 µg/ml respectively. These results showed that less $C_{\text{max}}$ for test formulation indicates prolonged release of dosage form and maintenance of plasma drug concentration within therapeutic range upto 24 h. $T_{\text{max}}$ for test formulation (DSRF11) was also found to be less in comparison to standard that clearly indicates rapid onset of action of the test formulation. Higher value of both the AUC$_{0-t}$ and AUC$_{0-\infty}$ for marketed formulation denoted the extent of absorption is more but lesser value of plasma half-life ($t_{1/2}$) and MRT indicated rapid elimination of the drug. In-vivo pharmacokinetic studies on Doxofylline matrix tablets showed prolonged release effect and were able to sustain the therapeutic effect over a prolonged period of time up to 24 h. Pharmacokinetic plots of optimised formulation and marketed formulation is shown in figure 7 and table 7.
compartment model. Therefore

**CONCLUSION**

For an extended release formulation, the in vitro drug release was a limiting step for absorption; establishing in vitro–in vivo correlation (IVIVC) was needed. After calculation, the drug followed a one-compartment model. Therefore IVIVC for the formulation DSRF11 was carried out by using the most meaningful level A correlation by deconvolution method. Wagner–Nelson method was adopted that is presented in following equation:\(^2\):

\[
\text{% Absorbed} = \left[ \frac{(K_e \times \text{AU}C_{t,0}) + C_t}{(K_e \times \text{AU}C_{t,0})} \right] \times 100
\]

In vitro–in vivo correlation

For an extended release formulation, the in vitro drug release was a limiting step for absorption; establishing in vitro–in vivo correlation (IVIVC) was needed. After calculation, the drug followed a one-compartment model. Therefore IVIVC for the formulation DSRF11 was carried out by using the most meaningful level A correlation by deconvolution method. Wagner–Nelson method was adopted that is presented in following equation:\(^2\):

\[
\text{% Absorbed} = \left[ \frac{(K_e \times \text{AU}C_{t,0}) + C_t}{(K_e \times \text{AU}C_{t,0})} \right] \times 100
\]

**Table 7: Pharmacokinetic parameters of optimised formulations with marketed formulation**

<table>
<thead>
<tr>
<th>Pharmacokinetic parameters</th>
<th>Marketed formulation</th>
<th>Test (DSRF11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C_{max}</strong> (µg/ml)</td>
<td>13.68±2.21</td>
<td>1.54±0.67</td>
</tr>
<tr>
<td><strong>t_{max}</strong> (h)</td>
<td>1.79±0.85</td>
<td></td>
</tr>
<tr>
<td><strong>t_1/2</strong> (h)</td>
<td>3.88</td>
<td>4.25</td>
</tr>
<tr>
<td><strong>K_e</strong> (h(^{-1}))</td>
<td>0.18</td>
<td>0.16</td>
</tr>
<tr>
<td><strong>AU_{C,0}</strong> (µg-h/ml)</td>
<td>298.66</td>
<td>277.4425</td>
</tr>
<tr>
<td><strong>AU_{C,∞}</strong> (µg-h/ml)</td>
<td>300.45</td>
<td>279.96</td>
</tr>
<tr>
<td><strong>AUMC&lt;sub&gt;0&lt;/sub&gt;</strong> (µg-h/ml)</td>
<td>4122.40</td>
<td>3958.99</td>
</tr>
<tr>
<td><strong>MRT</strong> (h)</td>
<td>13.72</td>
<td>14.14</td>
</tr>
</tbody>
</table>

Where \(K_e\) is the elimination rate constant for Doxofylline, \(AUC_{t,0}\) in µg-hour/ml is area under curve up to time \(t\), \(C_t\) in µg/ml is plasma concentration at time \(t\) in h and \(AUC_{t,∞}\) in µg-h/ml is area under curve up to time \(\infty\) in h. This was done by a two-stage procedure: deconvolution followed by comparison of the % of Doxofylline absorbed to the cumulative % of Doxofylline releases. In this, % of Doxofylline absorbed (in-vivo) as dependent factor was plotted against the independent factor cumulative % of Doxofylline released in dissolution medium (in-vitro) under study. The graphical representation is shown in figure 8 and the correlation coefficient \(R^2=0.821\) denotes a good correlation between the two observed parameters. Therefore, the test of in vitro drug release could provide prediction for in-vivo behaviour.

**Figure 8: IVIVC of Doxofylline sustained release matrix tablets**

**CONCLUSION**

In the present investigation Doxofylline sustained release matrix tablet were successfully developed. The major challenge in these studies was to design a sustained release matrix tablet of Doxofylline that can provide sustained release effect up to 12 hour by using different grade of hydrophilic polymer HPMC and hydrophobic polymer Eudragit. The main objective of using hydrophobic polymer Eudragit with HPMC was to prevent the burst release effect the hydrophilic drug under study which was successfully developed. Formulation DSRF11 that contained 7% of both the grade of HPMC and 8% of Eudragit RSPO in SR layer showed 16% of drug release within first hour that may be essential to elicit pharmacological response and sustained release up to 12 h with almost complete release (99.19%) emerged as optimised formulation. Increase in proportion of hydrophilic polymer caused initial burst release effect where reverse was noticed by increasing the concentration of hydrophobic polymer. The similarity factors (\(f_1\)) and difference factor (\(f_2\)) were calculated to compare the release profile of test formulations with standard marketed formulation. Among all the formulations, DSRF11 showed highest \(f_2\) value (96.41) and lowest \(f_1\) value (0.88) was considered as best formulation that was considered for kinetic studies. Kinetic of in-vitro drug release of DSRF11 followed zero order release kinetic models and drug release mechanism is anomalous diffusion coupled with erosion. FTIR and DSC studies revealed that there is no chemical and thermal interaction between drug and excipients used in the present studies. The accelerated stability studies were carried out for the optimised formulation and were found to be stable without any remarkable physicochemical changes. In-vivo pharmacokinetic studies on Doxofylline matrix tablets showed prolonged release effect and were able to sustain the therapeutic effect over a prolonged period of time up to 24 hr. The IVIVC coefficient \(R^2=0.821\) denotes a good correlation between the two observed parameters. Thus the results of the current study clearly indicate a promising potential of the Doxofylline sustained release matrix tablets system as an alternative to the conventional dosage form as it enhance bioavailability of the Doxofylline by producing a sustained release effect and can be therapeutically beneficial for sustainable asthma. However, further clinical studies are needed to assess the utility of this system for patients suffering from asthma.
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