Research Article

EFFECT OF DIFFERENT GRADES OF HPMC AND EUDRAGIT ON DRUG RELEASE PROFILE OF DOXOFYLLINE SUSTAINED RELEASE MATRIX TABLETS AND IVIVC STUDIESNiranjan Panda^{1*}, A. Venkateshwar Reddy², G.V. Subba Reddy³, Kanhu Charan Panda²¹Research scholar, Department of Pharmaceutical Sciences, JNTUA, Anantapuramu, India²PG department of Pharmaceutics, Anwarul Uloom College of Pharmacy, Hyderabad, India³Department of Chemistry, JNTUA College of Engineering, Pulivendula, YSR (Kadapa), A.P., India

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Article Received on: 11/05/15 Revised on: 13/06/15 Approved for publication: 28/07/15

DOI: 10.7897/2230-8407.068100**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 pharmacopoeia 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 (f_2) and difference factor (f_1). The formulation DSRF₁₁ containing both the grades of HPMC (*i.e* 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 f_2 value (96.41) and lowest f_1 value (0.88) was considered as optimised formulation. The hardness, friability, drug content and swelling index of DSRF₁₁ 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 DSRF₁₁ followed zero order kinetic model due to highest regression value ($R^2=0.993$) 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 conveniently used in development of Doxofylline sustained release matrix tablets. Accelerated stability studies of optimized formulation (DSRF₁₁) 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 vitro-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.³

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 ($t_{1/2}$) 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 pK_a 9.87.^{4,5}

The objective of the present study was to develop sustained release tablets of Doxofylline using hydroxyl 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 λ_{max} of pure Doxofylline and preparation of calibration curve

Primary stock solution of Doxofylline having concentration of 1000 $\mu\text{g/ml}$ was prepared using phosphate buffer pH 6.8. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10 $\mu\text{g/ml}$ 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 λ_{max} 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 $\mu\text{g/ml}$ and corresponding absorbance were measured at λ_{max} of 274nm. 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 λ_{max} was found to be 273nm 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 upto 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.⁸

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

F. No.	Doxofylline (mg)	HPMC K4M (mg)	HPMC K15M (mg)	Eudragit RSPO (mg)	Eudragit RLPO (mg)	Lactose (mg)	Starch (Insoluble) (mg)	Mg. stearate (mg)	Talc (mg)	Total wt. (mg)
DSRF ₁	400	100	-	30	-	55	45	7	13	650
DSRF ₂	400	-	100	30	-	55	45	7	13	650
DSRF ₃	400	100	-	-	30	55	45	7	13	650
DSRF ₄	400	-	100	-	30	55	45	7	13	650
DSRF ₅	400	80	-	50	-	55	45	7	13	650
DSRF ₆	400	-	80	50	-	55	45	7	13	650
DSRF ₇	400	80	-	-	50	55	45	7	13	650
DSRF ₈	400	-	80	-	50	55	45	7	13	650
DSRF ₉	400	50	50	30	-	55	45	7	13	650
DSRF ₁₀	400	50	50	-	30	55	45	7	13	650
DSRF ₁₁	400	40	40	50	-	55	45	7	13	650
DSRF ₁₂	400	40	40	-	50	55	45	7	13	650

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 (DSRF₁₁) 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 aluminium 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.^{10,11}

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).

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

Where θ 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.^{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.¹²

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

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

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.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.

$$\text{Hausner's ratio} = TD / BD$$

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.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 $\pm 5\%$ variation of standard value.^{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/cm² and average were calculated with standard deviation. According to specifications of USP; hardness values of 4-5 kg/cm² is considered as acceptable limit for sustained release tablets.¹⁴

Friability

Previously weighed ten tablets (W_i) 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 (W_f) was recorded. Friability was calculated by using following formula.

$$\% F = (W_i - W_f) / W_i \times 100$$

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.^{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%.^{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 P^H 6.8 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.^{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 P^H 6.8 as dissolution medium maintaining at $37 \pm 0.5^\circ\text{C}$. 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.¹⁸

$$\text{Swelling index (SI)} = W_f - W_i / W_i \times 100$$

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 $37 \pm 0.5^\circ\text{C}$. 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 λ_{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:

$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \right\} \times 100$$

Where R_t and T_t 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 $f_2 > 50$, 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.

$$f_1 = \left\{ \sum_{t=1}^n |R_t - T_t| \right\} / \sum_{t=1}^n R_t \times 100$$

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 having).^{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 (DSRF₁₁) into following exponential equations.

Zero order release equation is calculated by following equation.

$$Q = K_0 t$$

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.

$$\log (100-Q) = \log Q - K_1 t / 2.303$$

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.

$$Q = K_2 t^{1/2}$$

Where, K_2 is the diffusion rate constant. When the data are plotted as accumulative 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_∞ 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 $n = 0.5$ 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. Hixson-Crowell recognized that area of the particle is proportional to the cubic root of its volume, and derived an equation as follows

$$W_0^{1/3} - W_t^{1/3} = K_s t$$

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_s 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 (DSRF₁₁) 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 $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\% \text{ RH}$ (Climatic 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 marketed 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. Blood samples of 2 ml were collected in heparinised tubes at predetermined time points (0.5, 1, 2, 4, 8, 16, 24 and 36 h) using fine gauge needle alternatively from both the marginal ear vein. Collected blood samples were heparinised and stored in a freezer before analysis. Plasma samples and deproteinizing solution were mixed in a ratio of 4:1 and added to a 2 ml polypropylene micro centrifuge tube. After capping, the tube contents were vortex mixed for 30 s, and the suspension is centrifuged at 4000 rpm for 10 min and then stored at -70°C for further analysis. 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

pharmacokinetic parameters such as maximum plasma concentration ($C_{\max}$), time to reach peak plasma concentration ($t_{\max}$), plasma half-life ($t_{1/2}$), area under curve [$\text{AUC}_{(0-t)}$], elimination rate constant (K_E) and mean residence time (MRT) were calculated using by PK solver 2.0 software.^{24, 25}

RESULTS AND DISCUSSION

The FTIR spectra of pure drug Doxofylline and physical mixture used for SR tablet in optimized formulation DSRF₁₁ were obtained and shown in **figure 1**. By comparing the spectra of Doxofylline and SR tablet of optimised formulation (DSRF₁₁), the sharp peaks that appear in spectra of Doxofylline at $\sim 3110\text{ cm}^{-1}$ due to presence of aliphatic N-H stretching functional group also appears in SR tablet at $\sim 2916\text{ cm}^{-1}$ and 3110 cm^{-1} . The characteristic infrared absorption peaks of Doxofylline at $\sim 1700\text{ cm}^{-1}$ (C=O stretch), at $\sim 1656\text{ cm}^{-1}$ (C=C stretch), at $\sim 1547\text{ cm}^{-1}$ (C=N stretch), at $\sim 1477\text{ cm}^{-1}$ (C-H bend) and at $\sim 1190\text{ cm}^{-1}$ (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 DSRF₁₁ 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.

Figure 2: Compatibility studies through DSC analysis

Angle of repose is suited for particle $> 150\mu\text{m}$. Values of angle of repose $\leq 25^\circ$ generally indicates the free flowing material and angle of repose $\geq 40^\circ$ 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 $19.42^\circ \pm 0.16$ to $24.65^\circ \pm 0.21$ 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 ± 0.06 to $0.328 \pm 0.05 \text{ g/cm}^3$ and the tapped densities were found to be in between 0.344 ± 0.07 to $0.394 \pm 0.08 \text{ g/cm}^3$. 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 DSRF₄, DSRF₇ and DSRF₁₀ showed Carr's index value less than 16% that indicates good flow properties and values more than 16% indicates presences 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 (DSRF₁ – DSRF₁₂)

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

All values are expressed as mean $\pm$ SD; (n=3)

The postcompression parameters of the 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 $4.19 \pm 0.18 \text{ mm}$ 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 $5.45 \pm 0.9 \text{ kg/cm}^2$. The percentage friability of all the formulations was ranged from $0.43 \pm 0.05 \%$ to $0.66 \pm 0.04 \%$. 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 (DSRF₁ to DSRF₁₂) 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 (DSRF₁-DSRF₁₂)

F. No.	Average hardness (kg/cm ²)	Average Weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)
DSRF ₁	4.98±0.7	653.24±3.41	0.52±0.02	4.14±0.16	99.14±1.42
DSRF ₂	5.45±0.9	652.43±2.62	0.56±0.04	4.12±0.18	97.79±1.25
DSRF ₃	4.95±0.8	651.64±4.02	0.43±0.05	4.16±0.15	102.66±1.32
DSRF ₄	4.89±0.7	649.71±3.74	0.56±0.04	4.16±0.17	102.17±1.45
DSRF ₅	5.10±0.8	648.82±3.46	0.57±0.06	4.17±0.15	102.24±1.56
DSRF ₆	5.22±0.9	652.63±2.71	0.54±0.03	4.15±0.16	98.88±1.21
DSRF ₇	5.14±0.6	648.18±4.55	0.56±0.04	4.17±0.18	98.95±1.35
DSRF ₈	5.14±0.8	649.55±2.62	0.55±0.03	4.14±0.16	99.30±1.46
DSRF ₉	5.28±0.9	652.38±3.57	0.66±0.04	4.16±0.18	103.44±1.14
DSRF ₁₀	4.96±0.7	651.32±3.84	0.58±0.05	4.18±0.15	98.78±1.38
DSRF ₁₁	5.17±0.8	653.45±2.98	0.62±0.04	4.19±0.18	102.35±1.44
DSRF ₁₂	5.23±0.7	652.75±3.25	0.55±0.05	4.16±0.15	101.46±1.26

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

Swelling study was performed on all the formulations (DSRF₁ to DSRF₁₂) 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 (DSRF₉ and DSRF₁₀) containing combination of both the grade of HPMC in equal proportion, showed

higher swelling index. The formulation DSRF₁₀ that contains around 8% of HPMC K4M, 8% of HPMC K15M and 5% of Eudragit RLPO showed highest swelling indices then other formulations. Formulations DSRF₅, DSRF₆, DSRF₇, and DSRF₈ 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.

All values are expressed as mean± SD; (n=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 DSRF₁₁ 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.

Figure 4: In vitro release studies of all the formulations of Doxofylline sustained release matrix tablets

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_1 between 0 and 15 do not indicate dissimilarity. All the formulation showed dissimilarity in the dissolution profile except formulation DSRF₇, DSRF₁₁ and DSRF₁₂ that showed similarity in the dissolution profile. Among these three formulations, DSRF₁₁ 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_2) and difference factor (f_1) with dissolution profile of all formulations (DSRF₁-DSRF₁₂)

F. No.	f_1	f_2	Dissolution profiles
DSRF ₁	45.08	33.93	Dissimilar
DSRF ₂	37.36	37.64	Dissimilar
DSRF ₃	47.81	32.90	Dissimilar
DSRF ₄	54.45	30.32	Dissimilar
DSRF ₅	17.26	53.07	Dissimilar
DSRF ₆	20.54	48.09	Dissimilar
DSRF ₇	14.75	57.23	Similar
DSRF ₈	15.77	56.24	Dissimilar
DSRF ₉	21.10	48.91	Dissimilar
DSRF ₁₀	26.46	44.80	Dissimilar
DSRF ₁₁	0.88	96.41	Similar
DSRF ₁₂	8.77	67.38	Similar

The in-vitro dissolution data of optimised formulation DSRF₁₁ were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppas'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 DSRF₁₁

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 (DSRF₁₁) 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 DSRF₁₁Table 5: Regression values of in-vitro release kinetic study of optimized Doxofylline sustained release matrix tablet (DSRF₁₁)

Formulation	R ² value of Zero order	R ² value of 1 st order	R ² value of Higuchi model	R ² value of Hixon-Crowell model	R ² value of Peppas's model	'n' value of Peppas's model
DSRF ₁₁	0.993	0.922	0.954	0.717	0.991	0.732

The optimised formulation DSRF₁₁ 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 (DSRF₁₁) 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)

Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
Weight variation	653.45±2.98	653.26±2.65	653.15±2.72	653.12±2.62
Hardness	5.17±0.80	5.24±0.71	5.38±0.82	5.76±0.85
Friability	0.62±0.04	0.64±0.03	0.69±0.05	0.75±0.04
Swelling index	96 ±1.08	93 ±1.05	88 ±1.06	85 ±1.04
Drug content	102.35±1.44	99.14±1.36	96.46±1.41	93.28±1.32

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

Figure 6: In vitro release studies at accelerated stressed conditions

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_{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_{max} for test formulation indicates prolonged release of dosage form and maintenance of plasma drug concentration within therapeutic range upto 24 h. T_{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.

Figure 7: Comparative pharmacokinetic plots of optimised formulation (test) and marketed formulation (Reference)

Table 7: Pharmacokinetic parameters of optimised formulations with marketed formulation

Pharmacokinetic parameters	Marketed formulation	Test (DSRF ₁₁)
C _{max} (µg/ml)	15.68±2.21	14.54±1.74
t _{max} (h)	1.79±0.85	1.54±0.67
t _{1/2} (h)	3.88	4.25
K _E (h ⁻¹)	0.18	0.16
AUC _{0-t} (µg-h/ml)	298.66	277.4425
AUC _{0-∞} (µg-h/ml)	300.45	279.96
AUMC _{0-t} (µg-h/ml)	4122.40	3958.99
MRT (h)	13.72	14.14

In vivo-in vitro 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 equation²⁵.

$$\% \text{ Absorbed} = [(K_E \times \text{AUC}_{0-t}) + C_t / (K_E \times \text{AUC}_{0-\infty})] \times 100$$

Where K_E is the elimination rate constant for Doxofylline, AUC_{0-t} 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_{0-∞} in µg-h/ml is area under curve up to time ∞ 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 (R²=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 upto 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 upto 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*₂) and difference factor (*f*₁) 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 (R²=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.

ACKNOWLEDGMENT

The authors are thankful to Dr Reddy's laboratories Ltd., Hyderabad and Glenmark Pharma, Nasik, India for providing gift samples of drug and polymer respectively. Authors are also thankful to the chairman & principal Anwarul Uloom college of Pharmacy, Hyderabad, Telengana, for permitting to carry out research work.

REFERENCES

- Mathur V, Nagpal K, Singh SK, Mishra DN. Comparative release profile of sustained release matrix tablets of Verapamil HCl. *International Journal of Pharmaceutical Investigation* 2013;3:60-5.
- Basavaraja, Navade K, Rao BS, Kulkarni SV; Formulation and evaluation of sustained release matrix tablets of Flurbiprofen by using natural and synthetic Polymers. *Journal of Pharmaceutical Sciences & Research* 2015; 7(6): 274-281.
- Shiyani B; Formulation and evaluation of bilayer tablet of Metoclopramide hydrochloride and Ibuprofen. *AAPS Pharm Sci Tech.* 2008; 9(3):818-27.
- Bejugam NK, Parish HJ, Shankar GN; Influence of Formulation Factors on Tablet Formulations with Liquid Permeation Enhancer Using Factorial Design. *AAPS PharmSciTech.* 2009; 10 (4), 1437-1443.
- Venkataramudu TS, Firoz CY, Vikram A, Divya Sree K., & Murali Krishna T; Design and characterisation sustained release matrix tablets of Repaglinide using natural polymers. *International Journal of Pharmaceutics.* 2012; 2(2), 73-83.
- Shukla D, Chakraborty S, Singh S, Mishra B; Doxofylline: a promising methylxanthine derivative for the treatment of asthma and chronic obstructive pulmonary disease. *Expert Opinion Pharmacotherapeutics* 2009, 10(14):2343-2356.
- Chaurasiya AK, Ansary J, Md. Rahaman S and Md. Alam E: Preparation and *In-Vitro* Evaluation of Lamivudine Matrix Tablets for Oral Sustained Release Drug Delivery System Using Methocel K15m Cr Polymer. *International Journal of Pharmaceutical Science and Research* 2015; 6(1): 164-71.
- Maderuelo C, Zarzuelo A, Lanao JM. Critical factors in the release of drugs from sustained release hydrophilic matrices. *Journal of Controlled Release* 2011; 154:2-19.
- Dey S, Mahanti B, Khila S, Mazumder B & Gupta SD; Formulation development and optimization of bilayer tablets of Aceclofenac, *Expert Opinion Drug Delivery* 2012; 9(9):1041-1050.
- Naveen K. Bejugam, Helen J. Parish, and Gita N. Shankar. Influence of formulation factors on tablet formulations with liquid permeation enhancer using factorial design. *AAPS PharmSciTech* 2009; 10 (4): 1437-1443.
- Reddy BV; Formulation and characterization of extended release matrix tablets of venlafaxine hydrochloride. *Journal of Global Trends in Pharmaceutical Sciences.* 2015; 6(1): 2423 - 2428.
- Jain NK. *Controlled and Novel Drug Delivery*, 1st edn., New Delhi, CBS Publishers, 2004;236-55.
- Raval JA, Patel JK, Li N, Patel MM; Ranitidine hydrochloride floating matrix tablets based on low density powder: effects of formulation and processing parameters on drug release. *Asian Journal of Pharmaceutical Sciences.* 2007; 2 (4): 130-142.
- Navitha A, Jogala S, Krishnamohan C, Aukunuru J. Development of novel risperidone implants using blends of polycaprolactones and in vitro in vivo correlation studies. *Journal of Advanced Pharmaceutical Technology & Research* 2014; 5(2): 84-89.
- Narendra C, Srinath MS, Babu G. Optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. *AAPS PharmSciTech.* 2006; 7(2):E34.
- Islam MS, Reza S, Rahman H; In vitro release kinetics study of Diltiazem Hydrochloride from wax and kollidon SR based matrix tablets. *Iranian Journal of Pharmaceutical Research* 2008, 7: 101-108.
- Panda N, Panda KC, Reddy AV, Reddy GV; Process Optimization, Formulation and Evaluation of Hydrogel {Guargum-G-Poly(Acrylamide)} Based Doxofylline Microbeads. *Asian Journal of Pharmaceutical and Clinical Research*, 2014; 7(3): 60-65.
- Prasanth Kumar Acholu, Sudhakar Yajaman, K. N. Jayaveera. Formulation and In-vitro evaluation of novel buccal mucoadhesive tablets of Felodipine. *Int. Res. J. Pharm.* 2014; 5(11): 821-826 <http://dx.doi.org/10.7897/2230-8407.0511169>
- Wei He, Yongji Li, Rao Zhang, Zhannan Wu, Lifang Yin.; Gastro-floating bilayer tablets for the sustained release of metformin and immediate release of pioglitazone: Preparation and in vitro/in vivo evaluation. *International Journal of Pharmaceutics*, 2014; 476: 223–231.
- Patra CN, Kumar AB, Pandit HK, Singh SP, Devi MV; Design and evaluation of sustained release bilayer tablets of Propranolol hydrochloride. *Acta Pharm*, 2007, 57: 479-489.
- Ali MS, Pandit V, Jain M, Dhar KL. Mucoadhesive microparticulate drug delivery system of curcumin against *Helicobacter pylori* infection: Design, development and optimization. *Journal of Advanced Pharmaceutical Technology & Research* 2014; 5: 48-56.
- Gambhire MN, Ambade KW, Kurmi SD, Kadam VJ, Jadhav KR. Development and in vitro evaluation of an oral floating matrix tablet formulation of Diltiazem hydrochloride. *AAPS PharmSciTech*, 2007; 8(3):E73.
- Takka S, Rajbhandari S, Sakr A. Effect of anionic polymers on the release of propranolol hydrochloride from matrix tablets. *European Journal of Pharmaceutics and Biopharmaceutics* 2001; 52(1):75–82.
- Kumar P, Ganure AL, Subudhi BB, Shukla S; Design and comparative evaluation of in-vitro drug release, pharmacokinetics and gamma scintigraphic analysis of controlled release tablets using novel ph sensitive starch and modified starch-acrylate graft copolymer matrices, *Iranian Journal of Pharmaceutical Research*, 2015; 14 (3): 677-691
- Wagner J, Nelson E. Kinetic analysis of blood levels and urinary excretion in the absorption phase after single doses of drugs. *Journal of Pharmaceutical Sciences* 1964; 53(11): 1392–403.

Cite this article as:

Niranjan Panda, A. Venkateshwar Reddy, G.V. Subba Reddy, Kanhu Charan Panda. Effect of different grades of HPMC and Eudragit on drug release profile of doxofylline sustained release matrix tablets and IVIVC studies. *Int. Res. J. Pharm.* 2015; 6(8):493-504 <http://dx.doi.org/10.7897/2230-8407.068100>

Source of support: Nil, Conflict of interest: None Declared

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