Research Article

Formulation Design and Study the effect of Polyplasdone-XL and AC-Di-Sol on Release Profile of Doxofylline Immediate Release Tablets

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ABSTRACT

Doxofylline is an anti-tussive and bronchodilator used for maintenance therapy in patients suffering with asthma and chronic obstructive pulmonary disease (COPD) that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives due to decreased affinities towards adenosine A1 and A2 receptors. Doxofylline is coming under class III of BCS classification and freely water soluble. Present work studies were carried on the formulation and design of immediate release tablets of Doxofylline using super disintegrant like Polyplasdone-XL And AC-Di-Sol with a view to obtain rapid disintegration in gastric P^H and to achieve quick action for acute conditions for therapeutic benefits to patient. Different Precompression and post compression characterization of tablet was carried out and the result 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 formulation containing 4% of Polyplasdone-XL giving best release profile because of highest similarity factor and lowest difference factor. *In-vitro* release kinetic studies were carried out for zero order, first order, Higuchi, Hixon-Crowell and Korse-Meyer Peppa's kinetic model. The optimised formulation followed Peppa's kinetic model with drug release mechanism was anomalous diffusion coupled with erosion. FTIR studies were carried out for pure drug Doxofylline, superdisintegrants and for optimised formulation to confirm that there is no interaction between drug and different excipients used in the formulation. DSC studies were carried out to know the thermal stabilities of drug and optimised formulation. Accelerated stability studies were carried out to confirm the stability of dosage forms.

Keywords: Doxofylline, Immediate release tablets, Polyplasdone-XL, AC-Di-Sol, Antiasthmatic

INTRODUCTION

The tablets are still the most popular and accepted dosage forms due to its continuous development and implementation of innovative ideas to overcome the basic drawbacks of the existing formulations. A rapid disintegrating drug delivery system is the novel concept of drug delivery system which was developed to overcome the basic drawbacks of conventional tablets. Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques. Immediate release dosage forms are most commonly formulated when the half life of the drug is more and there is no necessity of frequent dosing.

This also serves as an advantage for patient compliance. Other reason for formulating immediate release dosage form is rapid response. Sometimes immediate release dosage forms are used as one of layer in a bilayer tablet as loading dose for quick on set of action. Superdisintegrant is the vital component along with various common excipients like diluents, binder, lubricants, glidant etc used for the preparation of immediate release tablets. The immediate release tablets are usually prepared by using various superdisintegrant like sodium starch glycolate (Primojel^{TM}), crosscarmellose (AC-Di-Sol^{TM}) and different grade of crosspovidone (Polyplasdone- XL^{TM}) etc for quick and easy disintegration of tablets.[1]

Asthma and COPD (Chronic Obstructive Pulmonary Disease) are the most common life threatening pulmonary disease that requires constant monitoring. Xanthine derivatives are used since a long period of time for treatment of Asthma and COPD. Doxofylline is a new generation xanthine derivative that works by inhibition of phosphodiesterase activities with no cardiovascular side effects that usually seen in case of theophylline and other xanthine derivatives 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 50% plasma protein bound Elimination half life ($t_{½}$) is around 6-7 hour and daily dose is 200-400 mg two to three times in a day. Doxofylline is coming under class III of BCS classification and well absorbed orally. It is having solubility of 12 mg/ml in water and having P^{Ka} 9.87.[2]

The basic objective of present studies were to formulate and to carry out *in vitro* evaluation studies of immediate

release tablets of Doxofylline using super disintegrant like crosscarmellose (AC-Di-Sol™) and crosspovidone (Polyplasdone-XL™) with a view to obtain rapid disintegration when taken through oral route, permitting a rapid onset of action during sudden asthma attack.[3]

MATERIALS AND METHODS

Materials

Doxofylline was procured as a gift sample from Dr. Reddy's Laboratories Hyderabad, India.

The superdisintegrant crosscarmellose (AC-Di-Sol™) and crosspovidone (Polyplasdone- XL™) were also obtained as a gift sample from Dr. Reddy's laboratories Pvt. Ltd. The diluent Micro crystalline cellulose (Avicel 101) was purchased from Otto Manufacturers. Lactose, 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 1000µg/ml was prepared using HCl buffer P^H 1.2. From the primary stock solution after necessary dilution secondary stock solution having concentration of 10µg/ml was prepared using same HCl buffer P^H 1.2.

The prepared secondary stock solution was then scanned by a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400nm to 200nm, and the λmax for solution was determined and it was found to be 273 nm.

The secondary stock solution was then diluted using same HCl buffer P^H 1.2 to form a series of concentration of 2, 4, 6, 8, and 10 µg/ml and corresponding absorbance were measured at λmax of 273nm. For obtaining the calibration curve of pure Doxofylline, the measured absorbencies were plotted against corresponding concentrations.[3]

Formulation of Doxofylline Immediate Release Tablets

For the preparation of immediate release tablets of Doxofylline wet granulation method 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, MCC, crosscarmellose sodium, lactose, starch (insoluble), PVP K30 and starch (soluble) were blended uniformly and passed through #20. PVP K30 and starch (insoluble) were used as binder. The aggregates formed after addition of binder were initially dried 5-10 minutes to reduce moisture level and to prevent sticking with sieve. The aggregates were passed through sieve # 20 to get granules.

The granules are dried at 40° C for 20 minutes to reduce moisture content upto 2-5 %. Magnesium Stearate and talc were used as lubricants and the required quantities are mixed with dried granules for 2-3 minutes. After lubrication the formulations were evaluated for angle of repose, bulk density, tapped density, compressibility index, Hausner's ratio; prior to compression. The evaluated granules were compressed into tablets on a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.) using 12mm concave punches. Each tablet contains 200 mg of Doxofylline. The formulas 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, drug content study and in-vitro dissolution studies.[3,4]

Table 1: Compositions of different excipients used for Doxofylline Immediate Release Tablets

F. No.	Doxofylline (mg)	Avicel 101 (mg)	Lactose (mg)	PVP K30 (mg)	Starch (Soluble) (mg)	AC-Di-Sol (mg)	Polyplasdone- XL (mg)	Mg. stearate (mg)	Talc (mg)	Total wt. (mg)
$DIRF_1$	300	20	20	40	8	-	-	4	8	400
$DIRF_2$	300	20	12	40	16	-	-	4	8	400
$DIRF_3$	300	20	04	40	24	-	-	4	8	400
$DIRF_4$	300	20	20	40	-	8	-	4	8	400
$DIRF_5$	300	20	12	40	-	16	-	4	8	400
$DIRF_6$	300	20	04	40	-	24	-	4	8	400
$DIRF_7$	300	20	20	40	-	-	8	4	8	400
$DIRF_8$	300	20	12	40	-	-	16	4	8	400
$DIRF_9$	300	20	04	40	-	-	24	4	8	400
$DIRF_{10}$	300	20	12	40	-	8	8	4	8	400
$DIRF_{11}$	300	20	04	40	-	8	16	4	8	400
$DIRF_{12}$	300	20	04	40	-	16	8	4	8	400

Evaluation of Pre-compression parameters of Doxofylline Immediate Release Granules of all Formulations

Angle of Repose (ϑ)

Angle of repose is an important parameter that is used to find out the flow properties of granule and it is indicated as maximum angle possible between the surface of a pile of granules and the horizontal plane. The granules were allowed to flow through the funnel fixed to a stand at definite height (h).

The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where θ is called as angle of repose, h and r were height and radius of the granule heap respectably. According to the specifications the angle of repose value less than 25^0 indicates excellent flow whereas angle "between" 25^0-30^0 indicates good flow. The angle "between" 30^0-40^0 indicates passable flow whereas angle greater than 40^0 indicates very poor flow.[5]

Bulk Density

Both the loose bulk density (LBD) and tapped bulk density (TBD) of prepared Doxofylline immediate release granules of all the formulations were determined. The quantity of 2 gm of granules from each formula, previously lightly shaken to break any agglomerates formed; were introduced into a 10 ml measuring cylinder.

After the initial volume was observed, the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second interval. The tappings were continued until no further changes in volume were noted. LBD and TBD of prepared granules were calculated using the following formulas.[3,6]

$$LBD = \frac{weight\ of\ the\ granule}{volume\ of\ the\ packing}$$

$$TBD = \frac{weight\ of\ the\ granule}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's Index)

The flow ability of granules can be evaluated by comparing the loose bulk density (LBD) and tapped bulk density (TBD) of granules and the rate at which it packed down. Compressibility index (Carr's index) of prepared Doxofylline immediate release granules were calculated by following formula:

$$Carr's\ index\ (\%) = \frac{TBD-LBD}{TBD} \times 100$$

According to the specification the Carr's index values "between" 5-15 indicates excellent flow where as between 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable where as between 23-25 indicates poor flow. Between 33-38 indicates very poor and greater than 40 indicates extremely poor flow.[3,5]

Hausner's Ratio

The Hausner's ratios of prepared Doxofylline immediate release granules were determined by following formula:

$$Hausner's\ ratio = \frac{TBD}{LBD}$$

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, added glidant normally improves flow.[3,6]

Evaluation of Postcompression parameters of Doxofylline Immediate Release Tablets of all Formulations

Thickness

Ten Doxofylline immediate release tablets from each formulation were randomly selected and used for thickness determination. Thickness of each tablet was measured by using digital Vernier Callipers (Mitutoyo dial Thickness Gauge, Mitutoyo, 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.[7]

Tablet Hardness

All the formulations of Doxofylline immediate release tablets hardness were measured by using Monsanto hardness tester (Cad Mach). From each formulation the crushing strength of ten immediate release tablets with known weights were recorded in kg/cm^2 and average were calculated and presented with standard deviation. According to specifications of USP hardness values of 3-3.5 Kg for immediate release tablets is considered as acceptable limit.[8]

Friability

Previously weighed ten Doxofylline immediate release tablets from each batch were taken in Roche friabilator (Roche friabilator, Secor India, Delhi, India). After hundred revolutions of friabilator tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula:

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

Where W_i and W_f were the initial and final weight of the tablets before and after friability test. For compress tablet that lose less than 0.1 to 0.5 % and maximum upto 1% of the tablet weigh are consider acceptable.[9]

Weight Variation Test

All formulated Doxofylline immediate release tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each

tablet was calculated. According to USP monograph, the weight variation tolerance limit for the uncoated tablet having average weight 130mg or less is 10% whereas for average weight between 130-324mg is 7.5% and for average weight more than 324mg 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%.[9,10]

Content Uniformity

Twenty Doxofylline immediate release tablets were taken and triturated to form powder and powder equivalent to one tablet was taken and dissolved in 100 ml of HCl buffer P^H 1.2 and heated at 37 ^{0}C for 15 to 20 minutes with stirring.

The solution was filtered, suitably diluted and the Doxofylline content was measured by using UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 273 nm. Each measurement was carried out in triplicate and the average drug content in the Doxofylline immediate release tablets was calculated.[7]

Wetting Time and Water Absorption Ratio

Twice folded tissue paper was placed in a petri dish having an internal diameter of 6.5 cm containing 10 ml of HCl buffer P^H 1.2 containing methylene blue (0.1% w/v).

A tablet from each formulation of Doxofylline immediate release tablets was carefully placed on the surface of the tissue paper in the petri dish. The time required for the dye to reach the upper surface of the tablet was recorded as wetting time. Measurements were carried out in triplicate and standard deviations were also determined.

Water absorption ratio (R), can be estimated by simple procedure include weighing (W_b) of the tablet prior to the placement on the petri dish, then after recording the wetting time. The wetted tablet was removed and reweighed (W_a), the water absorption ratio (R) was determined according to the following equation.[3,10]

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

In-vitro Disintegration Time (D_t)

According to USP (United States Pharmacopoeia) disintegration test for immediate release tablets, the disintegration apparatus is used without the covering plastic disks and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for immediate release dosage form. The test was carried out using tablet disintegration apparatus (model EI D-16, Electrolab, Mumbai, India).

In-vitro disintegration test was carried out using a modified disintegration method (n = 6) using disintegration tester maintained at 37°C ± 0.5°C in HCl buffer P^H 1.2. The tablets were kept in the basket and noted the time taken for the tablet to disintegrate completely into smaller particles.[11]

In-vitro Drug Release Study

The *in-vitro* dissolution study was conducted for all the formulations using an eight station USP dissolution rate test apparatus type-II (LABINDIA DS 8000, Mumbai, India). A total volume of 900 ml of HCl buffer P^H 1.2 was taken as dissolution medium, which was maintain at 37°C ± 0.5°C at 50 rpm. 5ml of aliquots were periodically withdrawn and the sample volume was replaced with an equal volume of fresh dissolution medium. Samples were collected at 5 min intervals and filtered by Whatmann filter paper. Samples were analyzed spectrophotometrically at 273 nm for determination of Doxofylline that were released from immediate release tablets.[12]

Calculation of Similarity and Difference Factors

The optimized formulation was chosen according to comparative dissolution study with a reference marketed product of DOXOBRON TAB (Invision) containing Doxofylline 400mg, employing the similarity factor (f_2) and difference factor (f_1) equation introduced by Moore and Flanner.[13]

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:[14]

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

Where,

n = Number of time points at which percent dissolved was determined,

R_t = percent dissolved of reference (marketed) formulation at a given time point

T_t = percent dissolved of the test formulation to be compared at the same time point.

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.[15]

Difference factor (f_1) measures the percent error between two drug release curves over all time points.

$$f_1 = \frac{\sum_{t=1}^{n}|Rt - Tt|}{\sum_{t=1}^{n} Rt} \times 100$$

Similarly dissolution profile was considered satisfactory if f_1 values lie below 15 (nearing zero), more it approaches towards zero more similarity is the product.

Characterization of the in vitro drug release profile

The rate and mechanism of release of Doxofylline from prepared immediate release tablets were analyzed by fitting the dissolution data into following exponential equations.

Zero order release 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:

$$\log(100 - Q) = log100 - K_1 t$$

Where, K_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

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

Where, K_2 is the diffusion rate constant.

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

$$\log\left({}^{M_t}/_{M_\infty}\right) = \log K + n\, logt$$

Where Mt 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_o 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.[17,18]

Drug Excipients Compatibility Studies

Drug excipients compatibility studies were done by FTIR and DSC

Fourier Transform Infrared (FTIR) Spectroscopy

Fourier transform infrared (FTIR) study was performed to verify any physical or chemical interaction between the pure drug and the excipients used. The FTIR studies of pure drug Doxofylline, Avicel 101, PVP K30, AC-Di-Sol, Polyplasdone- XL and physical mixture of drug and all excipients (optimised formulation) were carried out. 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/cm^2 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, individual excipients and for physical mixture of drug and excipients.[19,20]

Differential Scanning Calorimetric (DSC) Analysis

Another method of estimating the physical interaction between drug and polymers used for the formulation of different dosage form is thermal analysis by DSC or TGA techniques.

In the present studies the DSC analysis of Doxofylline and physical mixture of drug with excipients (optimised formulation) used for formulation of Doxofylline immediate release tablets 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^o C/min over a temperature range of 40 to 300^{o}C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50 ml/min.[21]

Stability Studies of Optimised Formulation

The stability studies of optimised formulation of Doxofylline immediate release tablet were carried out according to ICH guidelines. The optimized formulation was subjected to accelerated stress condition at 40 ^{o}C ± 2 ^{o}C/75% ± 5% RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content and in vitro drug release study.[22]

RESULTS AND DISCUSSION

The loose bulk densities of Doxofylline immediate release granules of all formulations were found to be in the range of 0.399 to 0.541 g/cm^3 and the tapped densities were found to be in between 0.475 to 0.589 g/cm^3.

This indicates good packing capacity of granules. Bulk density and tapped density measurements found that density of granules depends on particle packing and that density changes as the granules consolidates.

Values of Carr's index for all the formulations were found below 16% that usually indicates good flow characteristics except the formulations $DIRF_1$, $DIRF_2$ and $DIRF_{12}$ which may indicate lake of uniformity in granule sizes and presences of more fine particles in those formulations.

Hausner's ratio is simple method to evaluate stability of power and granule column and to estimate flow properties.

Low range was observed of Hausner's ratio that indicates good flow ability. In all formulations the Hausner's ratios values were found "between" 1.07 to 1.21 that indicates good flow characteristics.

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 18.62±0.12 to 22.65±0.12 *i.e.* dry granules of Doxofylline immediate release layer showed good flow properties. The results of precompression parameters for all the formulations were given in **Table 2**.

The physical parameters such as average hardness, average weight variation, average friability and average thickness of all the formulations of Doxofylline immediate release tablets were found to be satisfactory.

Typical tablet defects, such as capping, chipping and picking, were not observed. The physicochemical characterizations of different batches of Doxofylline immediate release tablets are given in **Table 3**.

The thickness of the tablets were ranged between 4.12±0.10 to 4.36±0.12mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 397±1.85 to 404±3.26mg.

The acceptable average percentage variation for tablet formulations having weight 400mg is 5% and all the formulations fall within the limit, and hence passed the test for uniformity of weight as per official requirement.

The average hardness of all the Doxofylline immediate release tablet formulations was ranged from 2.47±0.6 to 3.82±0.8 kg/cm^2. By increasing the concentration of superdisintegrant concentration the hardness usually decreased that noticed in case of formulation $DIRF_6$, $DIRF_9$, $DIRF_{11}$ and $DIRF_{12}$.

The percentage friability of all the formulations were ranged from 0.35±0.05% to 0.78±0.07% and also the % friability were found more by increased concentration of superdisintegrant concentration.

In the present study, the percentage friability for all for formulations was within the prescribed limits.

The percentages of drug content for $DIRF_1$ to $DIRF_{12}$ were found to be in between 98.45±1.6 to 102.59±1.3 of Doxofylline immediate release tablet formulations which were within the acceptable limits.

Disintegration time were determined for all the formulations and it was found that by increasing concentration of superdisintegrant, the disintegration time decreases; but increase in concentration above 6% the hardness value didn't fall in the acceptable range.

The wetting time of all the formulations were found between 28±0.30 to 168±0.43. For the case of wetting time by increasing the concentration of superdisintegrant the wetting time decreases those were noticed in case of formulations of $DIRF_6$, $DIRF_9$, $DIRF_{11}$ and $DIRF_{12}$.

Between cross carmellose and cross povidone the later having less wetting time than former at equal concentrations. The water absorption ratio of formulations $DIRF_1$ to $DIRF_{12}$ was found in the range of 10.41±0.24 to 39.31±0.29.

By increasing the concentration of superdisintegrant the water absorption ratio increases that might be due to increase in the porosity of the formulation with increase in superdisintegrant concentration.

Table 2: Evaluation of precompression parameters of Doxofylline Immediate release Granules ($DIRF_1$ – $DIRF_{10}$)

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's Index (%)	Hausner's ratio
$DIRF_1$	0.432±0.05	0.521±0.06	22.41±0.11	17.08	1.21
$DIRF_2$	0.490±0.06	0.584±0.05	21.53±0.10	16.09	1.19
$DIRF_3$	0.465±0.08	0.502±0.06	20.91±0.14	7.37	1.07
$DIRF_4$	0.501±0.06	0.573±0.08	19.62±0.16	12.57	1.14
$DIRF_5$	0.423±0.05	0.492±0.07	22.84±0.18	14.02	1.16
$DIRF_6$	0.399±0.08	0.475±0.05	18.62±0.12	16.01	1.19
$DIRF_7$	0.482±0.09	0.521±0.08	21.52±0.11	7.48	1.08
$DIRF_8$	0.541±0.07	0.589±0.07	20.63±0.13	8.15	1.09
$DIRF_9$	0.477±0.05	0.524±0.06	19.49±0.14	8.97	1.10
$DIRF_{10}$	0.472±0.06	0.525±0.08	22.28±0.15	10.10	1.11
$DIRF_{11}$	0.482±0.03	0.521±0.06	19.46±0.14	7.48	1.08
$DIRF_{12}$	0.490±0.08	0.584±0.09	22.65±0.12	16.09	1.19

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

Table 3: Evaluation of Post-compression parameters of Doxofylline immediate release tablets

Formulation code	Average hardness (kg/cm^2)	Average Weight Variation (%)	Average Friability (% w/w)	Average thickness (mm)	Drug content uniformity (%)	D_t (Sec)	Wetting time (Sec)	Water absorption ratio
$DIRF_1$	3.82±0.8	401±2.44	0.35±0.05	4.12±0.10	102.29±1.8	360±1.12	168±0.43	10.41±0.24
$DIRF_2$	3.64±0.4	404±3.26	0.58±0.02	4.25±0.12	99.48±1.5	342±1.09	132±0.62	12.42±0.35
$DIRF_3$	3.12±0.5	402±3.18	0.62±0.06	4.36±0.14	101.26±1.6	306±0.95	114±0.54	14.30±0.28
$DIRF_4$	3.35±0.4	401±2.46	0.42±0.02	4.30±0.10	99.36±1.6	214±0.69	98±0.60	19.28±0.27
$DIRF_5$	3.12±0.3	403±2.34	0.66±0.05	4.34±0.16	98.66±1.5	128±0.78	60±0.25	25.52±0.34
$DIRF_6$	2.81±0.5	398±2.52	0.78±0.03	4.28±0.18	102.59±1.3	74±0.92	32±0.36	32.46±0.30
$DIRF_7$	3.40±0.4	397±1.85	0.53±0.07	4.25±0.12	100.42±1.6	242±0.82	89±0.32	18.38±0.42
$DIRF_8$	3.26±0.5	402±2.58	0.68±0.02	4.35±0.15	101.81±1.1	126±0.88	76±0.37	22.35±0.35
$DIRF_9$	2.47±0.6	397±2.32	0.75±0.06	4.18±0.19	99.72±1.5	66±0.94	44±0.36	36.39±0.27
$DIRF_{10}$	3.18±0.4	398±2.46	0.58±0.04	4.25±0.15	98.45±1.6	112±0.86	58±0.45	32.43±0.39
$DIRF_{11}$	2.82±0.7	403±2.56	0.78±0.07	4.22±0.19	99.56±1.2	46±0.91	30±0.21	37.56±0.35
$DIRF_{12}$	2.78±0.5	404±3.15	0.72±0.05	4.26±0.20	101.82±1.4	56±0.72	28±0.30	39.31±0.29

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

The *in-vitro* drug release characteristics of Doxofylline immediate release tablets were studied in HCl buffer P^H 1.2 dissolution medium for a period of 45 minutes using USP type-II paddle type dissolution apparatus.

The rate of dissolution increased by increasing the concentration of superdisintegrant upto an optimum concentration of 6%.

By increasing the concentration of starch (soluble) upto 6% ($DIRF_3$) the percentage cumulative drug release was 99.86% in 45 minute.

The formulation $DIRF_6$ having 6% of AC-Di-Sol^{TM} released 99.86% of the drug in 35 minute whereas formulation $DIRF_8$ having 4% of Polyplasdone-XL released 99.12% of the drug in 35 minute and was looking similar with marketed formulation and at 6% concentration ($DIRF_9$) the cumulative percentage drug release was 99.45% at 30 minute.

When both the superdisintegrants were used in combination in total concentration of 4% it shows some better dissolution profile and release almost all the drug within 35 minute.

Formulation $DIRF_{11}$ having superdisintegrant concentration of 6% (2% AC-Di-Sol^{TM} and 4% Polyplasdone-XL) release the drug upto 99% within 30 minutes.

Combination of MCC (Avicel 101) and lactose worked good as diluents so it was used in all the formulations.

The dissolution profiles of all the formulations (DIRF1 to DIRF12) were shown in **Figure 1**.

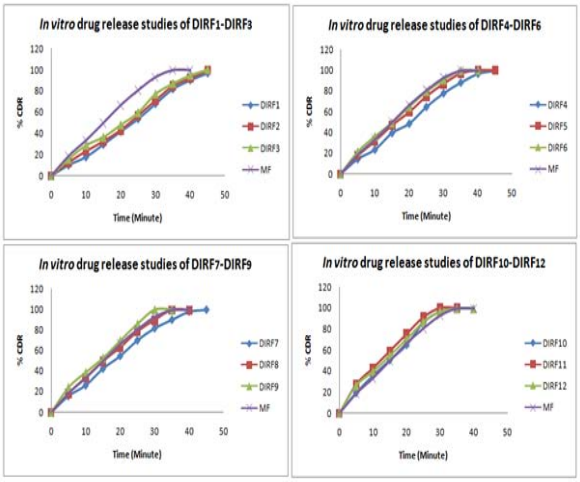


Figure 1: *In vitro* dissolution studies of formulation $DIRF_1$-$DIRF_{12}$

The similarity factors (f_1) and difference factor (f_2) 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 doesn't indicate dissimilarity. Thus, the dissolution profiles of all the batches of immediate release tablet prepared in the present investigation were presented in **Table 4**.

Formulation $DIRF_1$ to $DIRF_4$ showed dissimilarity in the dissolution profile whereas formulation $DIRF_5$ to $DIRF_{12}$ showed similarity in the dissolution profile. Among all the formulations, $DIRF_8$ showed highest f_2 value (82.78) and lowest f_1 value (2.4) was considered as best formulation.

On the basis of highest f_2 and lowest f_1 value, the formulation $DIRF_8$ was chosen for drug release kinetic and mechanism of drug release studies. The *in vitro* dissolution data of Doxofylline immediate release tablets ($DIRF_8$) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixson-Crowell and Korse Meyer-Peppas equation and the graphs were plotted **Figure 2**. The Korse-Mayer Peppa's kinetic plots were found to be fairly linear as indicated by their highest regression values (0.999) for $DIRF_8$ formulation. The release exponent 'n' for optimised formulation $DIRF_8$ was found to be 0.869 ($0.5 < n < 1$), that appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study *in vitro* drug release kinetic of Doxofylline immediate release tablet followed zero order release kinetic model and the drug release mechanism was said to be anomalous diffusion coupled with erosion.

Table 4: Similarity factor (f_2) and difference factor (f_1) with dissolution profile of all formulations

F. No.	f_1	f_2	Dissolution Profiles
$DIRF_1$	33.55	35.67	Dissimilar
$DIRF_2$	27.95	39.23	Dissimilar
$DIRF_3$	20.17	45.5	Dissimilar
$DIRF_4$	18.39	48.14	Dissimilar
$DIRF_5$	6.46	68.74	Similar
$DIRF_6$	3.44	81.5	**Similar**
$DIRF_7$	13.33	54.46	Similar
$DIRF_8$	2.4	82.78	**Similar**
$DIRF_9$	9.29	63.58	Similar
$DIRF_{10}$	3.36	79.50	**Similar**
$DIRF_{11}$	15.49	53.48	Similar
$DIRF_{12}$	10.18	61.79	Similar

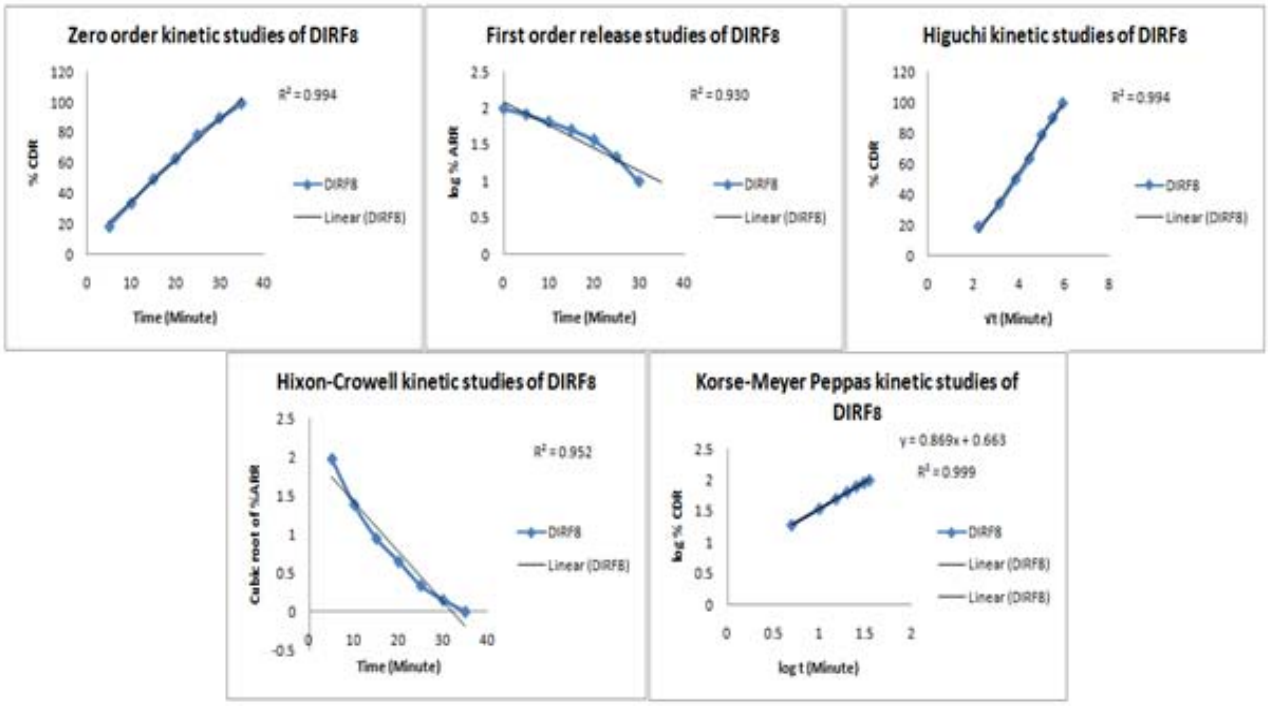


Figure 2: *In vitro* release kinetic studies of optimised formulation DIRFs

Table 5: Regression values of *in-vitro* release kinetic study optimized Doxofylline immediate release Tablet ($DIRF_8$)

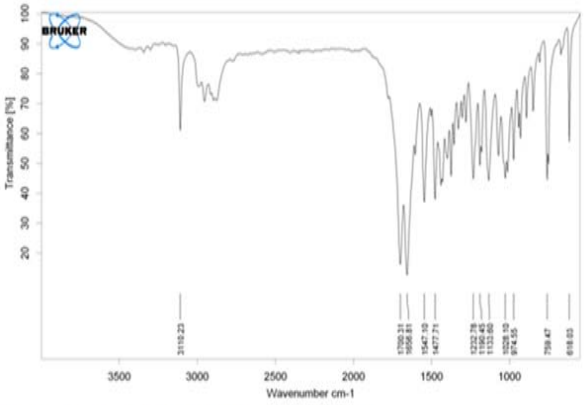
Formulation	R^2value of Zero order	R^2 value of 1st order	R^2value of Higuchi model	R^2value of Hixon-Crowell model	R^2value of Peppa's model	'n' value of Peppa's model
$DIRF_8$	0.994	0.930	0.994	0.952	0.999	0.933

Compatibility Studies by FTIR and DSC

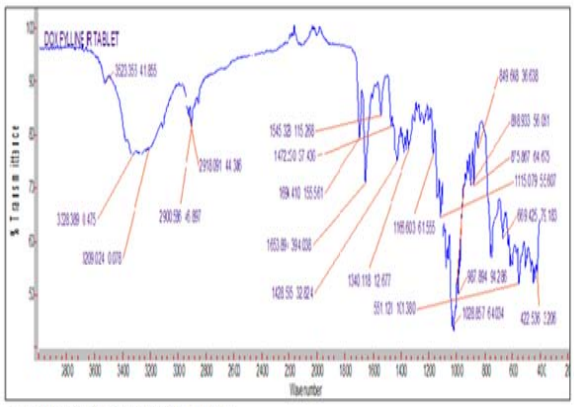
The FTIR spectra of pure drug Doxofylline, and physical mixture (optimised formulation: $DIRF_8$) of drug with all excipients used were shown in **Figure 3**.

By comparing the spectra of Doxofylline and optimised formulation ($DIRF_8$), the sharp peaks that appear in spectra of Doxofylline at~ 3110 cm^{-1} also appears in physical mixture (drug and excipients) at~ 2916 cm^{-1}.

The characteristic IR 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) with no shifting in the major peaks that indicate there were no interaction occurred between the Doxofylline and excipients used in the preparation of different immediate release formulations.



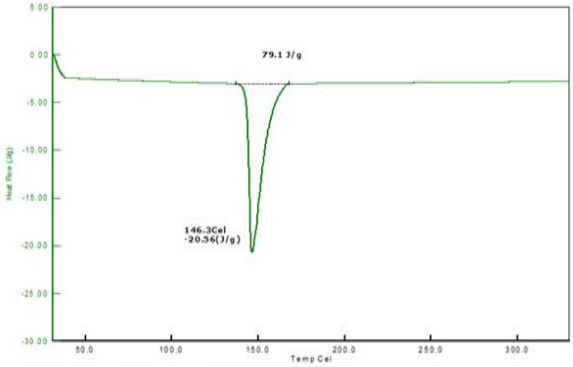
FTIR SPECTRA OF DOXOFYLLINE PURE DRUG



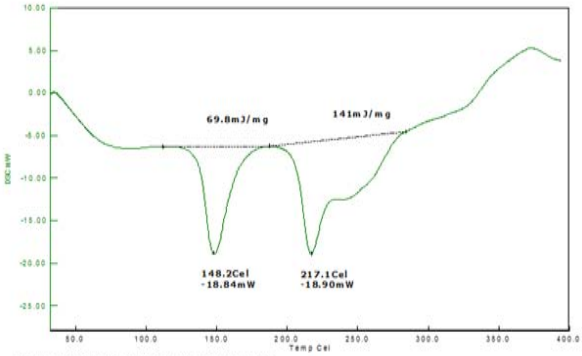
FTIR SPECTRA OF DOXOFYLLINE IR LAYER

Figure 3: FTIR spectra of pure drug and optimised formulation (DIRF8)

DSC thermogram of pure drug Doxofylline and physical mixture (drug and excipients) were obtained and it was observed that the endothermic peak appeared at 146 °C and 148 °C respectively which indicate that the physical mixture (drug and excipients) is thermodynamically stable because the formulation required slightly more heat than pure drug due to presence of various excipients like MCC, lactose, cross carmellose, cross povidone, PVP K30, magnesium Stearate, talc. The DSC thermogram of pure drug and physical mixture of drug and excipients used in the formulations were given in **Figure 4.**



DSC THERMOGRAM OF DOXOFYLLINE PURE DRUG



DSC THERMOGRAM OF DOXOFYLLINE IR LAYER

Figure 4: DSC thermogram of pure drug and optimised formulation DIRF8

The optimised formulation ($DIRF_8$) of Doxofylline immediate release tablets was selected for accelerated stability studies. The optimised formulation ($DIRF_8$) Doxofylline immediate release tablets did not show any significant changes in physicochemical parameters and *in vitro* drug release characteristics. More than 90% of the drug had been retained in the *in vitro* dissolution studies after 90days of exposure to accelerated stress condition. Thus, it was found that the immediate release tablets of Doxofylline ($DIRF_8$) were stable under short term accelerated storage conditions for at least 3 months.

CONCLUSION

In the present work Doxofylline immediate release tablets were successfully developed. The major challenge in this work was to study the effect of Polyplasdone- XL and AC-Di-Sol on *in vitro* release rate of immediate release tablet of Doxofylline. The immediate release drug delivery system was a promising approach to achieve quick release of drug and beneficial for acute diseases like asthma and COPD. FTIR and DSC studies revealed that the drug and excipients were compatible with each other and formulation is thermally stable. Wet granulation methods were adopted for the preparation of Doxofylline immediate release granules and the evaluation results of all the precompression parameters were satisfied the acceptance criteria that showed excellent flow properties of granules. All the postcompression parameters like average thickness, hardness, friability, weight variation and disintegration also fall within acceptable limit. Lactose along with MCC (Avicel 101) were used both as diluents for all the formulations for better drug release profile. Formulation $DIRF_{11}$ containing 2% of AC-Di-Sol

and 4% of Polyplasdone-XL showed complete drug release within 30 minute (>99%) emerging as optimised formulation and using both the superdisintegrant in combination showed better drug release profile. But the formulation $DIRF_8$ having 4% of Polyplasdone-XL shows highest similarity factor and lowest difference factor when it was compared with the standard marketed formulation and considered as best formulation with dissolution profile point of view. By increase in superdisintegrant concentration the drug release profile became faster but the hardness and friability of the formulation were severely affected. Kinetic of *in vitro* drug release of optimized formulation $DIRF_8$ found to follow Peppa's kinetic model having highest R^2 value with drug release mechanism as anomalous diffusion coupled with erosion.

The stability studies were carried out according to ICH guideline and selected $DIRF_8$ formulation were stable at 40°C/75% RH up to 3 months with a little change in physicochemical as well as drug release characteristics of the formulations.

Thus from the results of the current study clearly indicate, a promising potential of the Doxofylline immediate release tablets drug delivery system can be used as an alternative to the conventional dosage form because it release the drug quickly and useful for the acute condition of asthma and COPD diseases. However, further clinical studies are needed to assess the utility of this system for patients suffering from asthma and COPD.

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