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A Study On Evaluations Of Doxofylline Tablets In Sr-Ds

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Abstract

The main objective of present research investigation is to formulate the sustained release tablet of Doxofylline using 3 2 factorial design. Doxofylline, an anti-Asthmatic agent, belongs BCS class-III agent. The SR tablets of Doxofylline were prepared employing different concentrations of HPMC K100M and Chitosan in different combinations by Direct Compression technique using 3 2 factorial design. The concentration of Polymers, HPMC K100M and Chitosan required to achieve the desired drug release was selected as independent variables, X 1 and X 2 respectively whereas, time required for 10% of drug dissolution (t 10%), 50% (t 50%), 75% (t 75%) and 90% (t 90%) were selected as dependent variables. Totally nine formulations were designed, Formulated and are evaluated for hardness, friability, thickness, % drug content, In-vitro drug release. From the Results it was concluded that all the formulation were found to be with in the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept, slope & regression coefficient were calculated. Polynomial equations were developed for t 10% , t 50% , t 75% , t90%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C 1 , C 2). According to SUPAC guidelines the formulation

Key words: Doxofylline, HPMC K100M and Chitosan, hardness, friability, thickness etc.

INTRODUCTION:

FACTORS AFFECTING THE FORMULATION OF ORAL SUSTAINED RELEASE DRUG DELIVERY SYSTEM[27]:

There are two factors affecting the formulation of oral sustained drug delivery system. They are

- Physicochemical factors
- Biological factor

1Physicochemical factors:

a) Aqueous Solubility:

Most of the drugs are weak acids or weak bases Drugs with low water solubility will be difficult to incorporate into sustained release mechanism. For a drug with high solubility and rapid dissolution rate, it is often quite difficult to retard its dissolution rate. A drug of high water solubility can dissolve in water or gastrointestinal fluid readily and tends to release its dosage form in a burst and thus is absorbed quickly leading to a sharp increase in the blood drug concentration compared to less soluble drug. It is often difficult to incorporate a highly water soluble drug in the dosage form and retard the drug release especially when the dose is high. The pH dependent solubility particularly in the physiological pH range would be another problem for Sustained release formulation because of the variation in the pH throughout the gastrointestinal tract and variation in the dissolution rate. The biopharmaceutical classification system (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral absorption[22].

Class III (High solubility- Low permeability) & Class IV (Low solubility- Low permeability) drugs are poor candidates for Sustained release dosage form compound with solubility < 0.1 mg/ml face significant solubilisation obstacles and often compounds with solubility 10 mg/ml present difficulties to solubilisation dosing formulation. In general, highly soluble drugs are undesirable for formulation in to a Sustained release product.

b) Partition Coefficient (K (o/w)) :

Partition coefficient is defined as the fraction of drug in an oil phase to that of an adjacent aqueous phase. Drugs that passes though biological membrane, if partition coefficient of drug influences shows very much bioavailability because lipophilic nature of biological membrane. Drugs that have lower partition coefficient are not suitable for oral CR drug delivery system and drugs that have higher partition co-efficient are also not suitable for oral SR drug delivery system because they will not partition out of the lipid membrane once it gets in the membrane.

c) Drug pKa and ionization at physiological pH :

Drugs existing largely in ionized form are poor candidates for oral Sustained release drug delivery system. Absorption of the unionized drugs are well whereas permeation of ionized drug is negligible because the absorption rate of ionized drug is 3-4 times less than that of the unionized drug. The pKa range for acidic drug whose ionization is P^H sensitive is around 3.0-7.5 and pKa range for basic drug whose ionization is P^H sensitive is around 7.0-11.0 are ideal for optimum positive absorption. Drug shall be unionized at the site to an extent 0.1-5.0%.

d) Drug Stability:

Drugs undergo both acid/base hydrolysis and enzymatic degradation when administered oral route. If the drug in the solid state the degradation will occur in reduced rate, for the drugs that are unstable in stomach that prolong delivery to the entire GI tract are beneficial. If drug is administered in extended release dosage form that are unstable in small intestine may demonstrate decreased bioavailability. This occurs due to the fact that a greater quantity of drug is delivered in small intestine and is being subjected to more degradation[12].

e) Molecular size and Diffusivity:

Drugs in many sustained release systems must diffuse through a rate controlling membranes or matrix. The ability of a drug to diffuse through membranes, it's so called diffusivity (diffusion coefficient), is a function of its molecular size (or molecular weight). An important influence upon the value of the diffusivity. 'D', in polymers is the molecular size for molecular weight of the diffusing species. Diffusivity depends on size & shape of the cavities of the membrane. The diffusion co-efficient of intermediate molecular weight drug is 100-400 Daltons; through flexible polymer range is 10-6-10-9 cm2/sec. For drugs having molecular weight >

500 Daltons, the diffusion coefficient in many polymers are very less i.e. less than 10-12 cm2/sec. The examples of drugs which are difficult to control release rate of medicament from dosage form are proteins and peptides.

1.4.2 Biological Factors[28]:

The absorption behavior of a drug can affect its suitability as an extended release product. The aim of formulating Sustained release product is to place a control on the delivery system. It is essential that the rate of release is much slower than the rate of absorption. If we assume the transit time of dosage forms in the absorptive areas of GI tract is about 8-12 hours, the maximum half-life for absorption should be approximately 3-4 hours. Otherwise the dosage form will pass out of absorptive regions before drug release is complete. Therefore, the compounds with lower absorption rate constants are poor candidates. Some possible reasons for low extent of absorption are poor water solubility, small partition co-efficient, acid hydrolysis and metabolism or its site of absorption. The distribution of drugs in tissues can be important factor in the overall drug elimination kinetics. Since it not only lowers the concentration of circulating drug but it also can be rate limiting in its equilibrium with blood and extra vascular tissue, consequently apparent volume of distribution assumes different values depending on time course of drug disposition. Drugs with high apparent volume of distribution, which influence the rate of elimination of the drug are poor candidate for oral SR drug delivery system. A drug which extensively metabolizes is not suitable for SR drug delivery system.

a) Half-life:

The half-life of a drug is an index of its residence time in the body. If the drug has short half life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. On the other hand, drug with elimination half-life of 8 hours or more are sufficiently controlled in the body, when administered in conventional dosage from and Sustained release drug delivery system is generally not necessary in such cases. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system

b) Therapeutic Index (TI):

Drugs with low therapeutic index are unsuitable for incorporation in Sustained release formulations. If the system fails in the body, dose dumping may occur, which leads to toxicity.

c) Dose:

If the dose of a drug in the conventional dosage form is high, then it is less suitable for SRDDS. This is because the size of a unit dose Sustained release oral formulation would become too big to administer without difficulty.

d) Absorption Window:

Certain drugs when administered orally are absorbed only from a specific part of gastrointestinal tract. This part is referred to as the *'absorption window'.* These candidates are also not suitable for SRDDS

e) Plasma Concentration Response Relationship:

Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral Sustained release drug delivery system

f) Concentration dependency on transfer of drug :

Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics.

METHODOLOGY:

EVALUATION OF GRANULES[61]:

6.7.1 Bulk Density:

Bulk density is defined as the mass of powder divided by bulk volume, it is calculated using the following equation:

Bulk density = W/V_o

Where,

W= Weight of Sample

V_0 = initial volume.

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the cylinder was dropped at 2-6 second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

6.7.2 Tapped Density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (v_o) was measured. Then the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume (V_f) after 50 taps on wooden surface from 6 inch height and was expressed in g/cm3.

Tapped density = W/V_f
Where,
V_0 = initial volume.
V_f = final volume

6.7.3 Compressibility Index and Hausner's Ratio:

The Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. As such, they are measures of the relative importance of interparticle interactions in a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the compressibility Index and the Hausner's Ratio. The compressibility index and Hausner's ratio may be calculated using measured values for bulk density (bulk) and tapped density (tapped) as follows:

Carr's index (%) = (Tapped density –Bulk density)/Tapped density X100
Hausners ratio = Tapped density/Bulk density

Carr's Index :

Sl.no	Cars index	Type of flow
1	5 – 15	Excellent
2	12 – 16	Good
3	18 – 21	Fair
4	23 – 25	Poor
5	33 – 38	Very poor
6	>40	Extremely poor

Table 6.6: Specifications of Carr's Index

Hausner's ratio:

Sl.no	Hausners ratio	Type of flow
1	< 1.25	Good flow
2	>1.25	poor

Table 6.7: specifications of Hausner's Ratio

6.7.4 Angle of repose:

Flow properties of granules are evaluated by determining the angle of repose. Angle of repose was measured according to the fixed funnel & free standing cone method of Banker & Anderson .A funnel with the end of stem cut perpendicular to the axis symmetry was secured with its top at a given height (2 cm) above graph paper placed on a flat horizontal surface. The granules were carefully poured through funnel until the apex of conical pile so formed just reached tip of funnel. Thus with r being radius of base of granules of conical pile ,angle of repose was calculated by using following equation :

$\tan\theta = h/r$
Where,

h = height of pile of granules
r = radius of pile of granules

Sl.no	Angle of repose	flow
1	25 – 30	Excellent
2	31 – 35	Good
3	36 – 40	Fair
4	41 – 45	Passable
5	46 - 55	poor

Table 6.8: Specifications of Angle of repose

6. 8 EVALUATION OF TABLETS:

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters[6].

a) Weight Variation
b) Thickness
c) Hardness Test
d) Friability Test
e) Assay
f) *In-vitro* Release Study

a) Weight variation:

It was performed as per the method given in the Indian Pharmacopoeia. Tablets were randomly checked to ensure that proper tablets were being made. 20 tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Avg. Weight(mg)	Maximum % difference allowed
130 or less	10
130-324	7.5
More than 324	5

Table: 6.9 weight variation

b) Thickness:

Three tablets were randomly selected from each batch and there thickness was measured by using vernier calipers. Thickness of three tablets from each batch was measured and mean was calculated.

c) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kp. It measures the pressure required to break diametrically placed matrix tablet, by a coiled spring. Three tablets were randomly picked and hardness of the tablets was determined.

d) Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Five tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not lose more than 1% of their weight.
The percentage friability was measured using the formula,

$\% F = \{1-(W_0/W)\} \times 100$
where
% F = friability in percentage
W_0 = Initial weight of tablet
W = weight of tablets after revolution

e) **Assay:**

Buffer preparation:

Accurately weigh and transfer about 1.7 g of Potassium dihydrogen orthophosphate in to a 1000 ml of water and sonicate to dissolve. Adjust the pH 3.0 with phosphoric acid.

Mobile phase preparation:

Prepare a filtered and degassed mixture of Buffer and Acetonitrile in the ratio of 80 : 20 (v/v) respectively.

Chromatographic Conditions:

Column	: C18; 150 mm x 4.6 mm, 5µm
Flow	: 1.0 ml/minute
Wavelength	: 275 nm
Injection volume	: 20 µl
Column Temperature	: Ambient
Runtime	: About 10 minutes

Diluent: Mobile phase

Standard preparation:

1. Accurately weigh and transfer about 80 mg of Doxofylline working standard in to a 50 ml volumetric flask. Add 20 ml of methanol, and sonicate to dissolve. Make up to volume with methanol, and mix well.
2. Take 5 ml of above solution in to a 50 ml volumetric flask, and make up to volume with diluent and mix well.

Sample preparation:

1. Take not fewer than 20 tablets in to a dry mortar and crush the tablets in to a fine powder. Accurately weigh a portion of the powder equivalent to about 650 mg of Doxofylline into a 200 ml volumetric flask, add 60 ml of methanol and sonicate for 15 minutes to dissolve. Make up to volume with methanol and mix well. Filter through 0.45 µm filter paper; discard the first few ml of the filtrate.
2. Take 5 ml of above filtered solution in to a 100 ml volumetric flask, and make up to volume with diluent and mix well.

System Suitability:

1. The tailing factor from standard preparation should be not more than 2.0.
2. The relative standard deviation from the five replicate standard preparation injections should be not more than 2.0 %.
3. Theoretical plates from standard preparation should be not less than 2000.
4. The retention time of Doxofylline is about 4.1 minutes.

Procedure:

Separately inject the Blank (diluent), standard solution (5 times) and the sample solution into the liquid chromatography and record the peaks

Calculation:

$$\frac{At}{As} \times \frac{Ws}{50} \times \frac{5}{50} \times \frac{200}{Wt} \times \frac{100}{5} \times \frac{P}{100} \times \frac{Avg}{LC} \times 100$$

Where,

At = Area of Doxofylline peak in the chromatogram of sample solution,

As = Average area of five replicate injections for Doxofylline peak in the Chromatograms of standard solution,

Ws = Weight of Doxofylline working standard taken, in mg,

Wt = Weight of sample taken, in mg,

LC = Label Claim of Doxofylline in mg, per tablet,

P = Purity of Doxofylline working standard, (on as is basis)

Avg = Average weight of tablet, in mg

f) *In-vitro* dissolution studies

Dissolution parameters:

Apparatus : USP Apparatus I (Basket)
Medium : Water
Volume : 900 ml
RPM : 100 RPM
Temperature : 37°C ± 0.5°C
Sampling Interval : $1^{st,}$ 2^{nd}, $4^{th,}$ $6^{th,}$ 8^{th}, 10^{th}, 12^{th}, 15^{th} and 24^{th} Hour.

Diluent: Dissolution medium

Standard preparation:

1. Accurately weigh and transfer about 100 mg of Doxofylline working standard in to a 100 ml volumetric flask. Add 5 ml of methanol and 60 ml of diluent, and sonicate to dissolve. Make up to volume with diluent and mix well.
2. Take 2 ml of above solution in to a 100 ml volumetric flask, and make up to volume with diluent and mix well.

Sample preparation:

1. Place 900 ml of the dissolution medium in all the vessel assemble the apparatus equilibrate the dissolution media to 37±0.5°C. Place one tablet in each vessel and immediately operates the apparatus for above mentioned time.
2. Withdraw the 5 ml of specimen from each vessel after the above mention time form a zone midway between the surface of dissolution media and top of rotating basket and not less than 10 mm from the vessel, and replace with an equal volume of fresh dissolution medium (temperature 37±0.5°C) at the specified time intervals. Filter the solution through a 0.45 µm filter paper. Reject first few ml of the filtrate.
3. Transfer 2 ml of the filtered solution in to a 100 ml volumetric flask and make up to volume with diluent and mix well.

Procedure:

Measure the absorbance of the standard solution and sample solution in a UV - Visible spectrophotometer at 273 nm using dissolution medium as a blank.

Calculations:

Calculate the drug release with the formula given below

$$\% \text{ drug release} = \frac{At}{As} \times \text{dilution factor} \times \frac{}{LC} \times 100$$

Where,

At = Absorbance of Doxofylline peak in the spectrum of sample solution,
As = Absorbance of Doxofylline peak in the spectrum of standard solution,
LC = Label Claim of Doxofylline in mg, per tablet,

6.8 IN-VITRO DISSOLUTION STUDY AND KINETIC MODELLING OF DRUG RELEASE:

The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data[62].

Mathematical models are

1) Zero order release model
2) First order release model
3) Higuchi Release Equation
4) Krossmeyer-Peppas Equation

6.8.1 Zero order release equation:

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$Q_t = Q_0 + K_0 t$

Where,

Q_0 = initial amount of drug

Q_t = cumulative amount of drug release at time "t"

K_0 = zero order release constant

t = time in hours

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal systems, as well as matrix tablets of low soluble drugs (Varelas et al., 1995), coated form, osmotic systems, etc.

6.8.1 First order release equation:

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman. The following relation can express this model:

$\text{Log } Q_t = \text{Log } Q_0 + K_t /2.303$

Where ,

Q_0 = initial amount of drug

Q_t = cumulative amount of drug release at time "t"

K = first order release constant

t = time in hours

Here, the drug release rate depends on its concentration

A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line

6.8.2 Higuchi Release Equation :

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by the equation:

$Q=K_H\ t\ 1/2$

Where ,

Q = cumulative amount of drug release at time "t"

K_H = Higuchi constant

t = time in hours

Higuchi describes drug release as a diffusion process based on the Fick's law, dependent on square root of time. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems (Costa et al., 1996) and matrix tablets of water soluble drugs.

6.8.3 Krossmeyer-Peppas Equation:

Korsmeyer – peppas equation is

$F = (M\ t /M) = K\ m\ t\ n$

Where,

F = Fraction of drug released at time 't'

M t = Amount of drug released at time 't'

M = Total amount of drug in dosage form

K m = Kinetic constant

n = Diffusion or release exponent

t = Time in hours

'n' is estimated from linear regression of log (M t /M) versus log t.

Release exponent (n)	Drug transport mechanism
0.5	Fickian diffusion
0.5 < n < 1.0	Non-Fickian diffusion
1.0	Case-II transport
n> 1.0	Super case II transport

Table 6.10: Drug transport mechanism

6.9 STABILITY STUDIES:

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. Real time and accelerated (and intermediate) studies undertaken on primary and commitment batches according to a prescribed stability protocol to establish or confirm the re-test period of a drug substance or shelf life of a drug product.

6.9.1 Stability Testing:

Is an integral and critical part of pharmaceutical product development for successful registration and commercialization.

- **Accelerated Stability:**

Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated conditions as part of formal stability studies.

- **Real Time Testing:**

Stability studies under the recommended storage condition for the re-test period or shelf life proposed for labeling.

- **Purpose of stability testing:**

Stability Testing permits the establishment of recommended pack, storage condition, retest periods and shelf life. During Development of the product. During Registration of application, Post Registration.

6.9.2 ICH GUIDELINES:

q1 – Stability:

- Q1A: Stability Testing of New Drug Substances & Products.
- Q1B: Stability Testing: Photo stability testing of New Drug Substances & Products.
- Q1C: Stability Testing for New Dosage Forms.
- Q1D: Bracketing & Matrixing Designs for Stability Testing of Drug Substances & Products.
- Q1E: Evaluation of Stability Data.
- Q1F: Stability Data Package for Registration Applications in Climatic Zones III

Type of Study	Storage condition	Time period
Long term	25°c±2°c/60% RH±5% RH	12 month
Intermediate	30°c±2°c/65% RH±5% RH	6 month
Accelerated	40°c±2°c/75% RH±5% RH	6 month

Table 6.11: ICH guide lines for Stability Study

6.14 Method for Stability Estimation of Doxofylline Sustained Release Tablets:

Sustained release matrix tablets of Doxofylline formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at40oc ± 20C 75% RH and 2-80c for a period up to 30 days. The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, friability, drug content and in vitro drug release.

EVALUATION OF MICROMERITIC PROPERTIES OF GRANULES:

The physical properties like bulk density, Tap density, Carr's Compressibility Index angle of repose and Hausner's ratio are given in the following table.

Table 7.3: Micromeritic properties of Doxofylline sustained release granules

Formulation code	Derived properties		Flow properties		
	Bulk density (mean±SD) (g/ml)	Tapped density (mean±SD) (g/ml)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
DSRT 1	0.424±0.03	0.590±0.012	31.9±0.25	12.93±1.82	1.361±0.05
DSRT 2	0.436±0.018	0.597±0.01	32.1±0.32	14.03±1.74	1.352±0.07
DSRT 3	0.471±0.021	0.614±0.01	31.7±0.64	10.11±1.61	1.341±0.03
DSRT 4	0.454±0.018	0.586±0.015	30.9±0.91	15.29±2.12	1.353±0.01
DSRT 5	0.412±0.011	0.562±0.02	30.5±0.69	14.52±2.32	1.360±0.03
DSRT 6	0.434±0.03	0.591±0.012	31.9±0.25	12.93±1.82	1.351±0.05
DSRT 7	0.436±0.018	0.592±0.01	32.1±0.32	14.03±1.74	1.358±0.07
DSRT 8	0.451±0.021	0.604±0.01	31.7±0.64	10.11±1.61	1.341±0.03

Discussion:
The flow properties and other derived properties evaluated for all the 8 formulations were proved to be within limits showing good flow properties.

7.4 EVALUATION OF PHYSICAL PARAMETERS OF DOXOFYLLINE SUSTAINED RELEASE TABLETS :

All the eight formulations were tested for Physical parameters like hardness, thickness, weight variation, friability. The results of the tests are tabulated.

Table 7.4: Evaluation of the prepared tablets for physical parameters

Sl.no	Formulation code	Average weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Assay (%)
1	DSRT 1	974.5mg	5.89mm	6.9kg/cm^2	0.6%	85.6%
2	DSRT 2	975.0mg	6mm	6.1kg/cm^2	0.7%	92.02%
3	DSRT 3	975.0mg	5.80mm	6.1kg/cm^2	0.8%	89.9%
4	DSRT 4	975.0mg	5.83mm	6.6kg/cm^2	0.8%	91.3%
5	DSRT 5	974.5mg	5.9mm	6.7kg/cm^2	0.6%	93.32%
6	DSRT 6	975.0mg	5.7mm	6.3kg/cm^2	0.8%	100.22%
7	DSRT 7	975.0mg	5.73mm	6.2kg/cm^2	0.6%	95.6%
8	DSRT 8	975.0mg	6.2mm	6.3kg/cm^2	0.6%	99.8%

Discussion:
The prepared 8 Sustained release tablet formulations were evaluated for physic chemical parameters and were proved to be within limits (As per USP).

7.5 *In-Vitro* CHARACTERIZATION OF DOXOFYLLINE SR TABLETS

Table:7.5. *In vitro* dissolution profile of Doxofylline Sustained Release Tablets Employing polymers NaCMC,HPMC K100m, HPMC K15M.

Sl.no	Sampling Time (hrs)	Cumulative %drug released (Mean ± SD)	
		DSRT 1	DSRT 2
1	**1**	32.80±0.56	31.60±0.54
2	**2**	36.90± 0.34	35.84±0.42
3	**4**	47.80±0.56	45.60±0.54
4	**6**	56.90± 0.34	54.84±0.42
5	**8**	67.85±0.76	65.79± 0,29
6	**10**	81.79± 0.45	80.75±0.86
7	**12**	99.50± 0.85	97.50±0.96
8	**15**	102.2±0.43	101.8±0.45
9	**24**	----	----

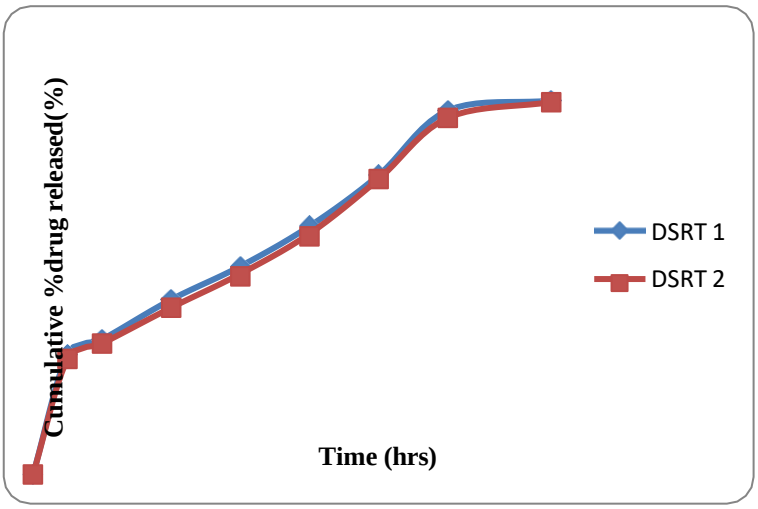


Fig7.3: Comparative dissolution profiles of Doxofylline Sustained Release Tablets employing polymers NaCMC,HPMC K100m, HPMC K15M

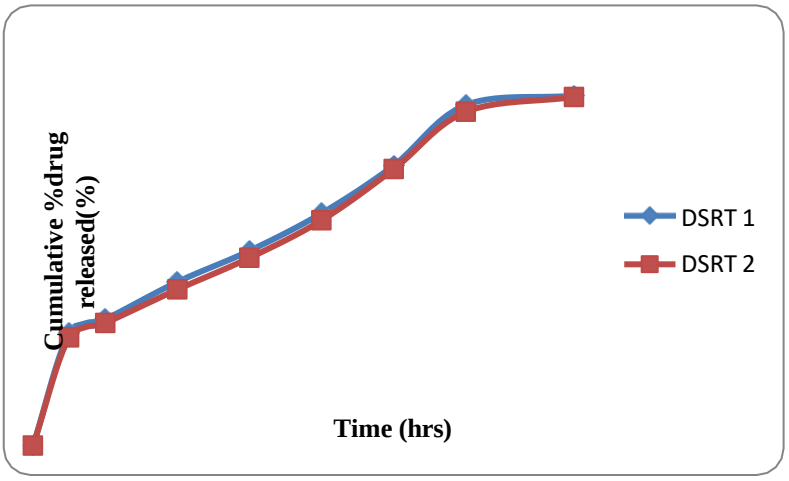


Fig7.4: Zero order rate kinetics of Doxofylline Sustained Release Tablet employing polymers NaCMC,HPMC K100m, HPMC K15M

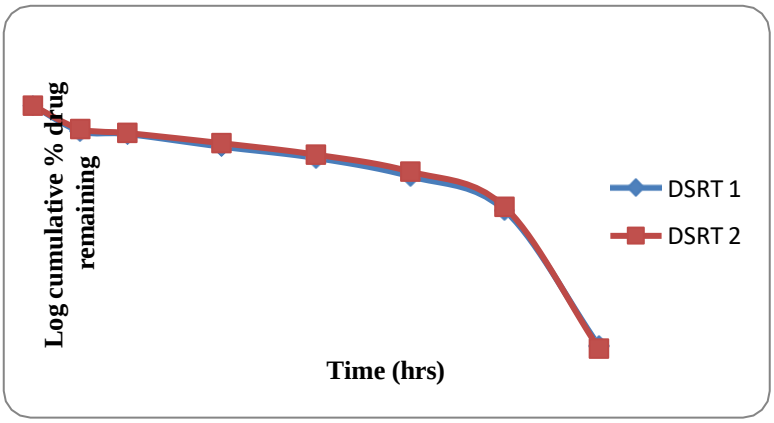


Fig7.5: First order dissolution plot of Doxofylline Sustained Release Tablet employing polymers NaCMC,HPMC K100m, HPMC K15M

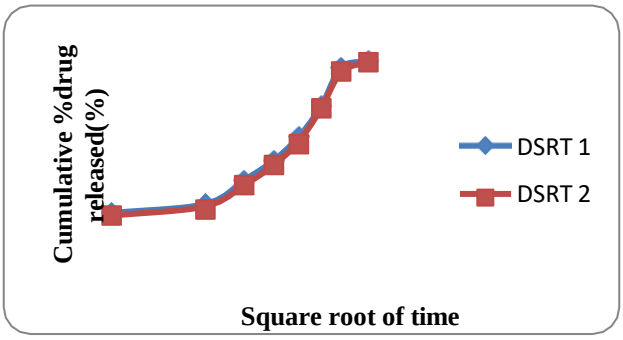


Fig7.6: Higuchi's Classical Dissolution plot of Doxofylline Sustained Release Tablet employing polymers NaCMC,HPMC K100m, HPMC K15M

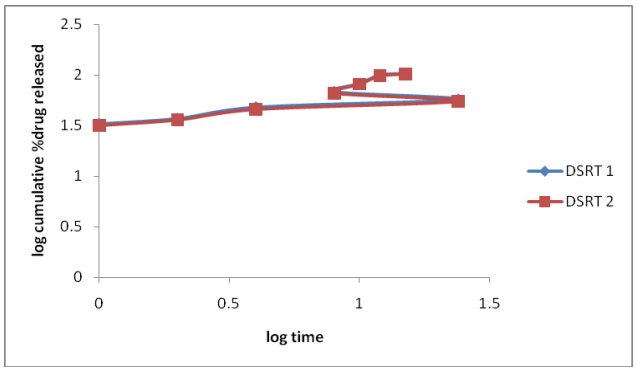


Fig7.7: Kross Meyer Peppas dissolution plot of Doxofylline Sustained Release Tablets employing polymers NaCMC,HPMC K100m, HPMC K15M

Table:7.6: *In vitro* Dissolution Profile of Doxofylline Sustained Release Tablets Employing HPMC K100M, HPMC K15M.

Sl.no	Sampling Time (hrs)	Cumulative %drug released (Mean ± SD)	
		DSRT 3	DSRT 4
1	1	36.80±0.65	36.51±0.69
2	2	49.01±0.45	48.69±0.91
3	4	58.70±0.73	62.51± 0.46
4	6	76.50± 0.91	72.70±0.73
5	8	85.62± 0.48	83.40±0.65
6	10	94.21± 0.82	95.62±0.34
7	12	104.2±0.28	106.2±0.82
8	15	----	----
9	24	----	----

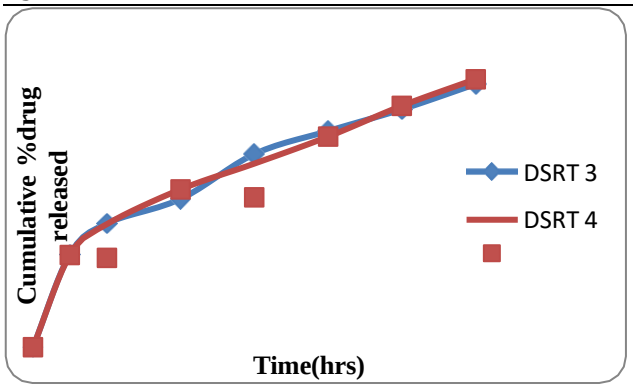


Fig7.8: Comparative dissolution profiles of Doxofylline Sustained Release Tablets employing polymers HPMC K100m, HPMC K15M

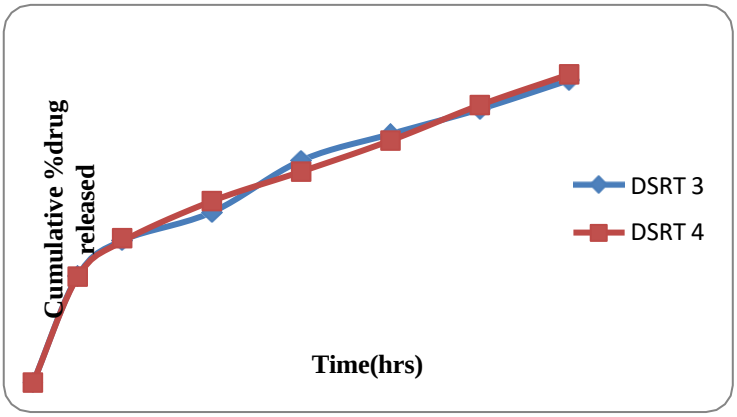


Fig7.9: Zero order dissolution plot of Doxofylline Sustained Release Tablets Employing polymers HPMC K100m, HPMC K15M

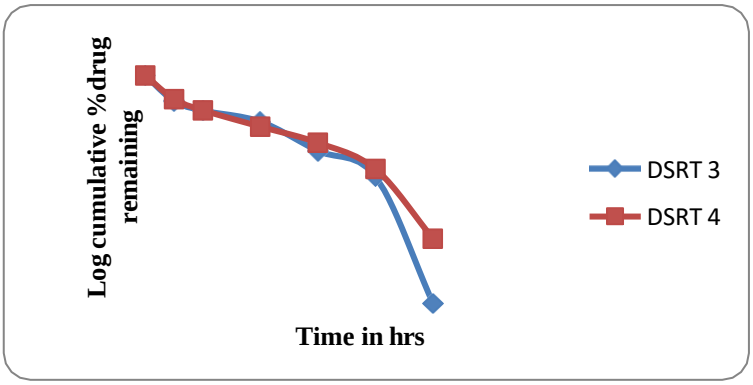


Fig7.10: First order dissolution plot of Doxofylline Sustained Release Tablets Employing polymers HPMC K100m, HPMC K15M

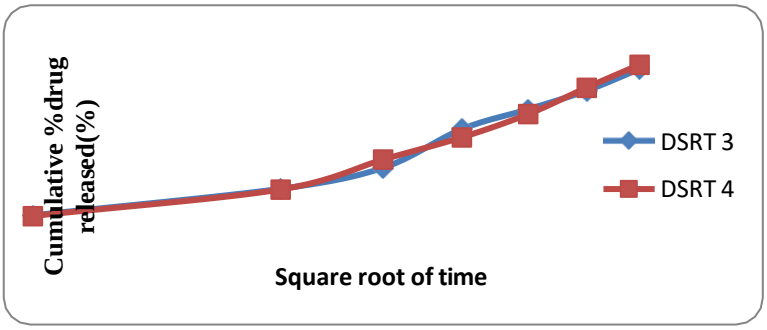


Fig7.11: Higuchi's Classical Dissolution plot of Doxofylline Sustained Release Tablet employing polymers HPMC K100m, HPMC K15M

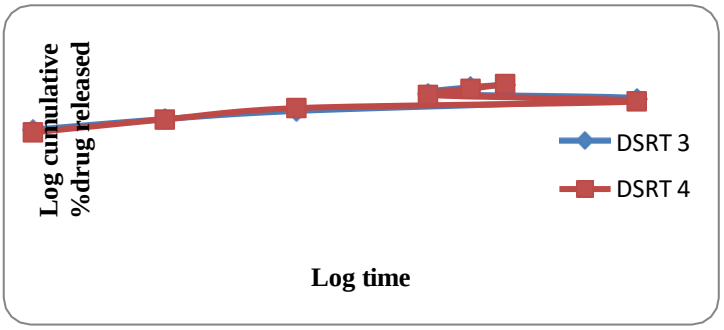


Fig7.12: Kross Meyer Peppas dissolution plot of Doxofylline Sustained Release Tablets employing polymers HPMC K100m, HPMC K15M

Table:7.7. *In vitro* Dissolution Profile of Doxofylline Sustained Release Tablets Employing NaCMC, HPMC K15M.

Sl.no	Sampling Time (hrs)	Cumulative %drug released (Mean ± SD)	
		DSRT 5	DSRT 6
1	1	30.57±0.45	30.96±0.53
2	2	46.54±0.53	47.85±0.48
3	4	62.60±0.29	60.76±0.54
4	6	76.74±0.76	75.89±0.59
5	8	81.60±0.38	82.70±0.43
6	10	86.50±0.84	87.43±0.23
7	12	97.80±0.56	96.70±0.76
8	15	102.3±0.86	103.6±0.34
9	24	----	----

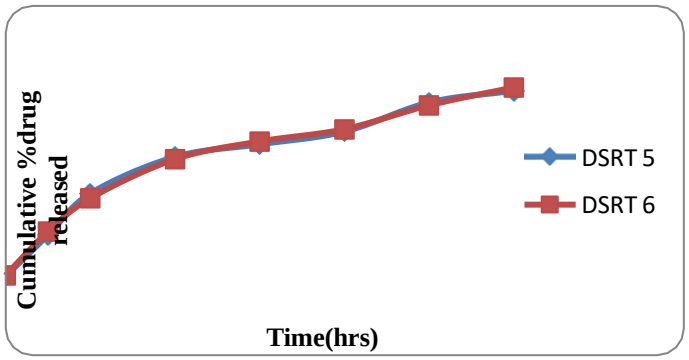


Fig7.13: Comparative dissolution profiles of Doxofylline Sustained Release Tablets employing polymers NaCMC, HPMC K15M

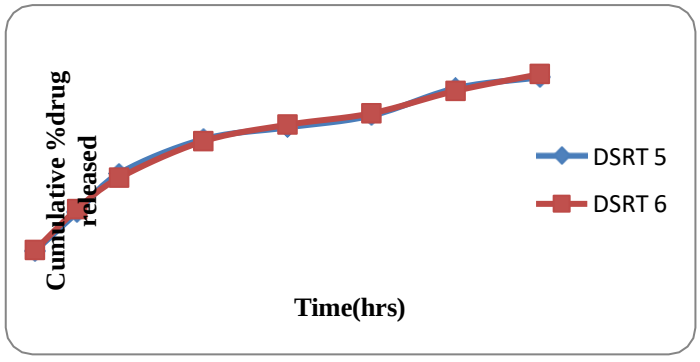


Fig7.14: Zero order dissolution plot of Doxofylline Sustained Release Tablet employing polymers NaCMC, HPMC K15M

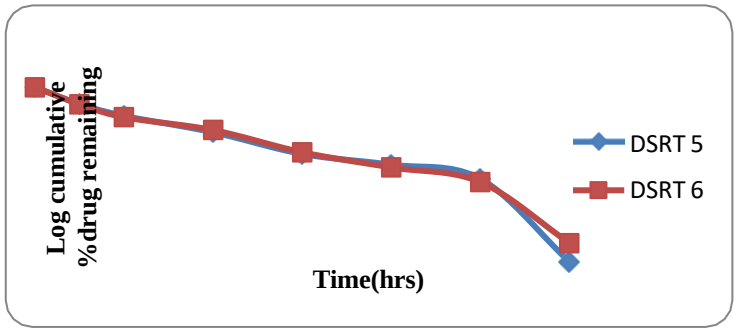


Fig7.15: First order dissolution plot of Doxofylline Sustained Release Tablet employing polymers NaCMC, HPMC K15M

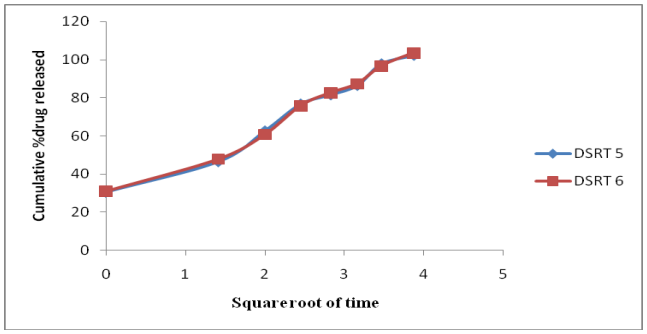
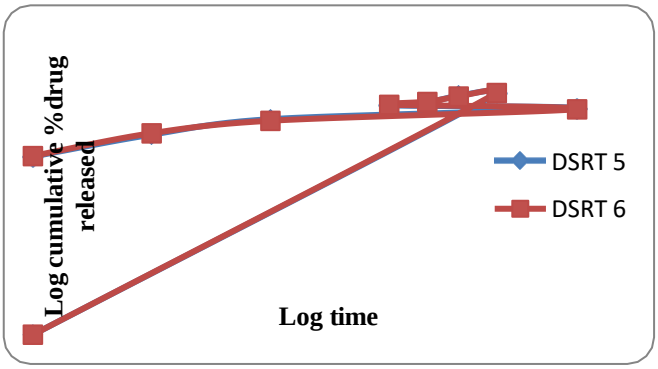


Fig7.16: Higuchi's Classical dissolution plot of Doxofylline Sustained Release Tablet employing polymers HPMC K100m, HPMC K15M



STABILITY STUDIES:

Table 7.10: Evaluation of physic chemical properties of DSRT 8 at room temperature:

Formulation Code	Time (days)	Hardness (kg/cm^2)	Drug content(%)	Friability (%)	Cum%drug release
DSRT 8	15	6.4 kg/cm^2	99.6%	0.63%	98.72%
DSRT 8	30	6.3 kg/cm^2	99.4%	0.58%	98.64%
DSRT 8	60	6.3 kg/cm^2	99.22%	0.56%	98.59%
DSRT 8	90	6.3 kg/cm^2	99.05%	0.54%	98.32%

Table 7.11 Evaluation of physic chemical propertites of DSRT 8 at temperature $40^0C \pm 2^0C$ & 75% RH:

Formulation code	Time (days)	Hardness kg/cm^2	Drug content(%)	Friability (%)	Cum%drug release
DSRT 8	15	5.9 kg/cm^2	100.1%	0.6%	100.1%
DSRT 8	30	6 kg/cm^2	99.6%	0.6%	99.8%
DSRT 8	60	5.8kg/cm^2	99.6%	0.59%	99.6%
DSRT 8	90	5.7kg/cm^2	99.56%	0.55%	99.5%

Table 7.12 Evaluation of physic chemical propertites of DSRT 8 at temperature ($2\text{-}8^0C$):

Formulation code	Time (days)	Hardness kg/cm^2	Drug content(%)	Friability (%)	Cum%drug release
DSRT 8	15	6.7 kg/cm^2	99.6%	0.58%	99.85%
DSRT 8	30	6.9 kg/cm^2	99.4%	0.57%	98.8%
DSRT 8	60	7.0 kg/cm^2	99.39%	0.56%	97.65%
DSRT 8	90	7.4 kg/cm^2	99.22%	0.56%	97.21%

DISCUSSION:

The results revealed that there is no significant change in appearance, drug content, hardness, friability, and in- vitro release for DSRT 8 formulation, so that it is stable for longer period of time.

The wavelength maxima for doxofylline is determined are determined at 273nm. The drug excipient compatibility studies also performed. The UV spectrophotometer showed reduced absorption bands. The

reduced absorption bands suggest a hydrophilic polymer physical interaction. Since there is no total disappearance of the bands it may be concluded that is no chemical interaction between the drugs and polymers. The physical properties of drug doxofylline were found. The flow properties for drug and excipients are very poor hence the tablets were prepared by wet granulation technique. The prepared granules are evaluated for physical characteristics. The tablets were prepared and evaluated to determine the quality of the pharmaceutical product.

Though all preparations exhibited higher rates of dissolution. The formulation DSRT 8 shows higher dissolution rate when compared to other formulations. The tablets prepared by various polymers like HPMC K15M, HPMC K100M, NaCMC. The higher dissolution rate exhibited by formula DSRT 8 contains two polymers and the formulations DSRT 3 and DSRT 4 are shows less dissolution rate than other all formulations due to the lack of NaCMC. The formulations DSRT 1, DSRT 2, DSRT 5, DSRT 6 shows drug release maximum due to the presence of NaCMC. The results of dissolution studies of all formulations showed that release rate was increased in following order like HPMC K15M > HPMC K100M >Sodium CMC. These polymers have been well known to retard drug release by swelling in aqueous media[15.]Sodium CMC & HPMC K100 M controlled release more than other polymers used at same drug to polymer. These values are in accordance with the earlier reported viscosity values for these polymers. Hence, DSRT 8 is the most successful formulation among the matrix tablets developed in the present study.

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