Original Research

Formulations of Doxofylline Sustained Realesed Tablets In Drug Delivery System

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INTRODUCTION:

ORAL DRUG DELIVERY SYSTEMS:

Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug through various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be due to its ease of administration and the belief that oral administration of the drug is well absorbed. All the pharmaceutical products formulated for systemic delivery through the oral route of administration irrespective of the mode of delivery (immediate sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid), must be developed within the intrinsic characteristics of GI physiology, pharmacokinetics, pharmacodynamic and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form[1].The aim of any drug delivery system is to provide therapeutic amount of drug to appropriate site in the body to achieve immediate therapeutic response and to maintain the desired drug concentration for prolonged period of time. In the recent years sustained release (SR) dosage forms continue to draw attention in the research for improved patient compliance and decreased incidence of adverse drug reactions.

Sustained release, prolonged action, extended, delayed release are the terms used to identify drug delivery system that are designed to achieve a prolog therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

Sustained release technology is relatively new field and as a consequence, research in this field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release/sustained release delivery system are constantly being developed and tested.

Table: Various Formulations of Doxofylline sustained release tablets having different components in different concentrations**.**

UV SPECTROPHOTOMETRIC METHOD FOR THE ESTIMATION OF DOXOFYLLINE:

Determination of UV absorption maxima of doxofylline:

A solution of Doxofylline containing the concentration 10 µg/ ml was prepared by using purified water in UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Method used for the estimation of doxofylline:
Doxofylline is official in IP and USP. Method of estimation of doxofylline is prescribed in IP by UV spectrophotometric method for the assay of doxofylline.

Materials:
1. Doxofylline.
2. Distilled water.

Preparation of calibration curve of doxofylline:
Take 100 mg of Doxofylline in a 100 ml volumetric flask and dissolved in 2ml of Water, and made the volume up to 100ml with 0.1N Hcl. The final solution contains 1000ug/ml. From the working standard drug solution (1000ug/ml), different concentrations (5,10,15,20,25,30ug/ml) are prepared by taking 0.5ml,1ml,1.5ml,2ml,2.5ml,3ml of secondary stock solution and the volume was made up to100ml., these solutions were estimated for the presence of doxofylline at 273nm..

6.3 STANDARD CURVE OF DOXOFYLLINE:
Table 6.1: Calibration Curve of Doxofylline in Distilled Water

Sl.no	Concentration (mcg/ml)	Absorbance at (273nm)	RSD (%)
1	0	0	0.76
2	5	0.153	0.29
3	10	0.302	0.64
4	15	0.464	0.85
5	20	0.645	0.55
6	25	0.822	0.46
7	30	0.985	0.67

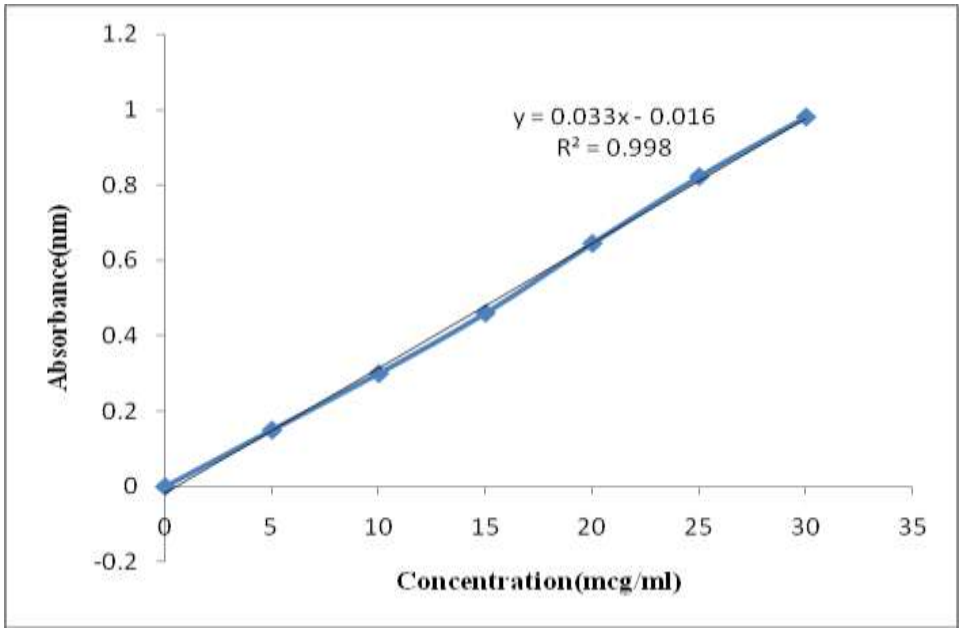

Figure 6.1: Calibration Curve of Doxofylline in Distilled Water.

6.4 PREFORMULATION STUDIES:
Preformulation studies are usually the first quantitative assessment of chemical stability of a drug as well as stability in presence of other excipients. The primary objectives of this investigation are identification of stable storage conditions for drug in the solid state and identification of compatible excipients for a formulation. Preformulation studies were performed on the drug, which include melting point determination, solubility and compatibility studies.

- **Determination of Melting Point:**

Melting point of Doxofylline was found in the range of 144- 146^{0}c, which complied with the standard, indicating purity of the drug sample.

- **Solubility:**

Doxofylline was found to highly soluble in water.

- **Loss on Drying[30]:**

Prepare the weighing bottle and cover by heating 30 minutes in the 105°C oven. Tare balance and accurately weigh both bottle and cover and record weight. Remove the cover and add 2-3 (±0.1) g of sample to the bottle. Replace cover and reweigh immediately. Record weight to the nearest 0.1 mg. Obtain the weight of the sample by difference. Heat the sample at 105°C for 1 hour. At the end of the drying time, remove the bottle and its cover from the oven (remembering to place cover over bottle but in an angled position so that bottle is not sealed) and place them in the desiccators. Allow the material to reach room temperature and then replace cover and weigh. Calculate the Loss on drying value using the following formula and it should be not more than 1.0%.

$$\text{Loss on Drying} = \frac{[\text{Sample + Bottle (Initial Wt.)}] - [\text{Sample + Bottle (Final Wt.)}]}{\text{Sample weight}} \times 100$$

- **Melting Point of Doxofylline:**

Consequently, the melting point of a compound is a criterion for purity as well as for identification. The melting point of an organic solid can be determined by introducing a tiny amount into a small capillary tube, attaching this to the stem of a thermometer centered in a heating bath, heating the bath slowly, and observing the temperatures at which melting begins and is complete.

- **Determination Of Flow Properties For Pure Drug And Excipiens[60]:**

A) 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/Vo

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_0) was measured. Then the cylinder was dropped at 2-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.

B) Tap Density:

An accurately weighed quantity of the powder (W) was carefully poured into the graduated cylinder and the volume (V_0) 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,

W= weight of sample

V_f = final volume

C) Compressibility Index and Huasners 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 inter particulate 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.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 densityX100

Hausner's 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	21 – 25	Poor
5	33 – 38	Very poor
6	>40	Extremely poor

Table 6.2: Specifications of Carr's inde

Hausner's Ratio:

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

Table 6.3: Specifications of Hausner's ratio

D) 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:

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

Where,

h = height of pile

r = radius of pile

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

Table 6.4: Specifications of angle of repose

6.5 DRUG-EXCIPENT COMPATIBILITY STUDY:

Drug-excipient compatibility was done by Fourier Transform Infrared Spectroscopy (FTIR). .

Fourier Transform Infrared Spectroscopy (FTIR):
Fourier transform infrared spectroscopy (FTIR) is a technique which is used to obtain an infrared spectrum of absorption, emission, photoconductivity or Raman scattering of a solid, liquid or gas. An FTIR spectrometer simultaneously collects spectral data in a wide spectral range which confers a significant advantage over a dispersive spectrometer which measures intensity over a narrow range of wavelengths at a time. FTIR has made dispersive infrared spectrometers all but obsolete (except sometimes in the near infrared), opening up new applications of infrared spectroscopy.
Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients. The samples were taken for FT-IR study.

Applications:
- FTIR spectrometer can be used to acquire spectrum of light emitted by the sample.
- Use of FTIR to characterize artistic materials in old master ratings.

6.5.1 Drug- Polymer Compatibility Studies:
Drug polymer compatibility studies were performed by FTIR (Fourier Transform Infrared Spectroscopy) [60]. FTIR absorption spectra of pure drug Doxofylline, HPMC K15M, HPMC K100M & PVP K90 individually and the combination of drug and excipients. 2 mg of sample mixed with 200mg of IR grade KBR in a silicon mortar and this mixture pressed into a disk. Disk was carefully kept in a position of FTIR. Infrared (IR) spectra were obtained in the scanning range of 400 to 4000 cm^{-1}.

6.6 PREPARATION OF SUSTAINED RELEASE TABLETS OF DOXOFYLLINE BY WET GRANULATION:

Preparation of tablets by wet granulation method:

Sifting and Mixing:
Doxophylline, HPMC K100M, HPMC K15M, NaCMC all the ingredients where taken in required quantities. They were sifted through # 40 mesh. Mix in HSMG for 10 min at Impeller fast speed (120rpm).

Preparation of PVP solution:
The required amount of PVP was transferred in to a stainless steel container and PVP was dissolved in the required quantity of IPA solution. Thus formed solution was filtered through the nylon cloth.

Addition:
The above solution was added to the HSMG containing material for 2-3 mins at Impeller slow speed (80rpm).

Kneading:
Kneaded the material at impeller (120rpm) and chopper (1280rpm) fast speed for formation of granules for 10 mins.

Drying:
The wet mass was dried in a rapid drier at 45-50^0 C. And at an air flow of 15, for 20 min to maintain L.O.D. below 2%. Thus formed granules after drying were passed through # 20 mesh using a vibro-sifter.

Blending:
All the sifted granules were loaded into octagonal blender, Talc (40#passed) was added and blend it for 10 mins at a speed of 6rpm.

Lubrication:
Magnesium stearate (40#passed) was taken in quantities required and added it to the blender and blending continued for 5min at 6rpm

Compression:
- Blended material was loaded in a hopper and compresses the powder into tablets by using cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm).
- Checked for weight variation, hardness, friability, thickness to meet the parameters.
- Collected the tablets in a cleaned double poly bag indicating the product and batch number.

RESULTS & DISCUSSIONS

7.1 PREFORMULATION STUDIES

7.1.1 Physico-Chemical Properties of Doxofylline:

a) Determination of wavelength maxima for Doxofylline:
The above prepared 10 mcg/ml solution was scanned in the wavelength range of 200-400nm. The wavelength was selected at 273nm.

b) Solubility studies of Doxofylline:
It was found that the of Doxofylline is more soluble in water, acetone..

c) Melting Point of Doxofylline:
Doxofylline was found to melt at 236°C.

d) Loss on Drying:
The loss on drying for doxofylline was to be 0.55%.

e) Determination of bulk density and tapped density:
Bulk density and Tapped density values for doxofylline were found to be 0.51 g/mL and 0.66 g/mL respectively.

f) Compressibility Index:
Compressibility index value for doxofylline was found to be 22.8% which reveals about poor flow property of doxofylline.

g) Hausner's Ratio:
Hausner's ratio value for Doxofylline was found to be 1.29 which reveals about poor flow property of doxofylline.

h) Angle of Repose:
Angle of repose for doxofylline was found to be 38.9° which reveals about poor flow property of doxofylline

7.2 DRUG-EXCIPENT COMPATIBILITY STUDY:

The sample was identified by FTIR spectrum is concordant with the reference spectrum of doxofylline compiles with official compendium.

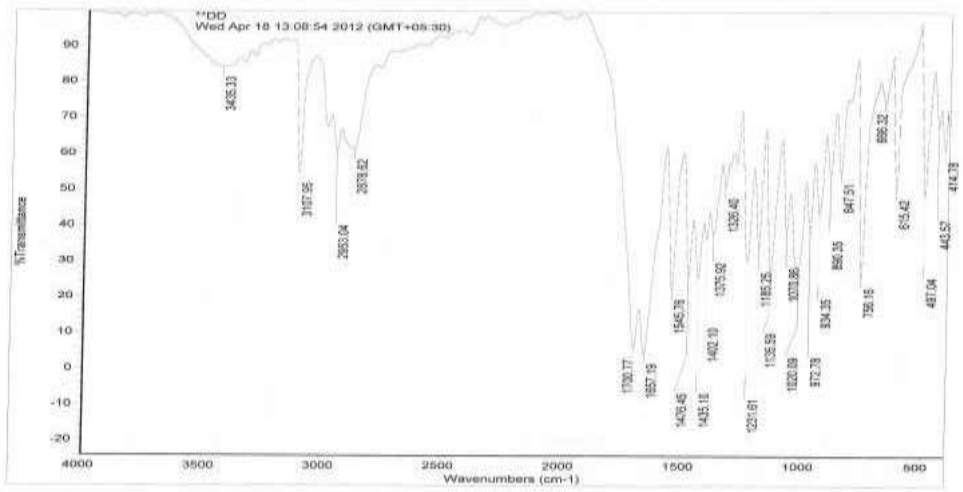

Figure 7.1: FTIR spectrum of Doxofylline

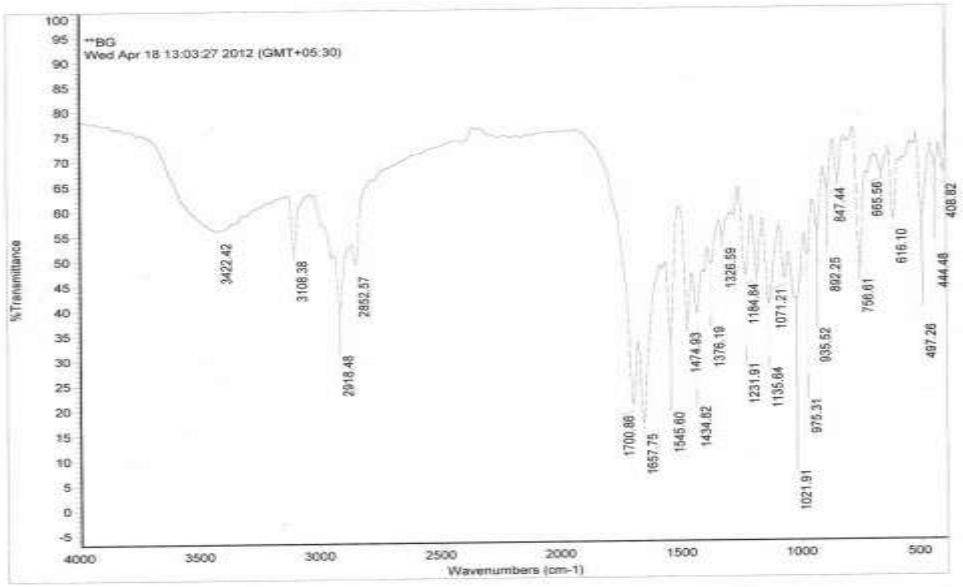

Figure 7.2: FTIR spectrum ofDrug and mixture of all excipients

Inference:
The principle peaks obtained for the combinations were almost similar to that of the drug. There was no significant difference in the IR spectra of pure Doxofylline and physical mixtures of polymer and drug**.**

Table 7.1: Drug-excipient compatibility studies at 25 ± 2^0C/60±5% RH)

Sl. No	Name of Material	Ratio (D:E)	Initial Observation	25 ± 2^0C/60±5% RH			
				Week 1	Week 2	Week 3	Week 4
1	Doxofylline	1:1	White powder	NC	NC	NC	NC
2	API + HPMC	1:1	White powder	NC	NC	NC	NC
3	API + MCC	1:1	White powder	NC	NC	NC	NC
4	API + SCMC	1:1	White powder	NC	NC	NC	NC
5	API + PVPK	1:1	White powder	NC	NC	NC	NC
6	API + Talc	1:1	White powder	NC	NC	NC	NC
7	API + Magnesium stearate	1:1	White powder	NC	NC	NC	NC
8	API + IPA	1:1	White powder	NC	NC	NC	NC

NC- No color change
D: E- Drug: Excipient

When stored the excipients with doxofylline at **25 ± 2^{0}C/60±5% RH** for one month, no changes on physical appearance was observed when checked periodically for four weeks. The results indicated that the drug, excipients were stable and compatible at the tested compositions and periods.

Table 7.2: Drug-excipient compatibility studies at 40 ± 2^{0}C/75±5% RH

Sl. No	Name of Material	Ratio (D:E)	Initial Observation	40 ± 2^{0}C/75±5% RH			
				Week 1	Week 2	Week 3	Week 4
1	Doxofylline	1:1	White powder	NC	NC	NC	NC
2	API + HPMC	1:1	White powder	NC	NC	NC	NC
3	API + MCC	1:1	White powder	NC	NC	NC	NC
4	API + SCMC	1:1	White powder	NC	NC	NC	NC
5	API + PVPK	1:1	White powder	NC	NC	NC	NC
6	API + Talc	1:1	White powder	NC	NC	NC	NC
7	API + Magnesium stearate	1:1	White powder	NC	NC	NC	NC
8	API + IPA	1:1	White powder	NC	NC	NC	NC

NC- No color change
D: E- Drug: Excipient

When stored the excipients with doxofylline at **40 ± 2^{0}C/75±5% RH** for one month, no changes on physical appearance was observed when checked periodically for four weeks. The results indicated that the drug, excipients were stable and compatible at the tested compositions and periods

Table:7.8: *In vitro* Dissolution Profile of Doxofylline Sustained Release Tablets Employing NaCMC, HPMC K100M.

Sl.no	Sampling Time (hrs)	Cumulative %drug release (Mean ± SD)	
		DSRT 7	DSRT 8
1	**1**	17.62±0.26	16.58 ±0.59
2	**2**	25.78±0.56	20.56±0.43
3	**4**	39.35±0.48	35.83±0.27
4	**6**	48.63±0.76	48.35±0.69
5	**8**	62.75±0.33	60.71±0.56
6	**10**	67.98±0.64	70.49±0.34
7	**12**	85.08±0.91	84.01±0.78
8	**15**	94.34±0.65	95.15±0.26
9	**24**	97.34±0.89	99.42±0.76

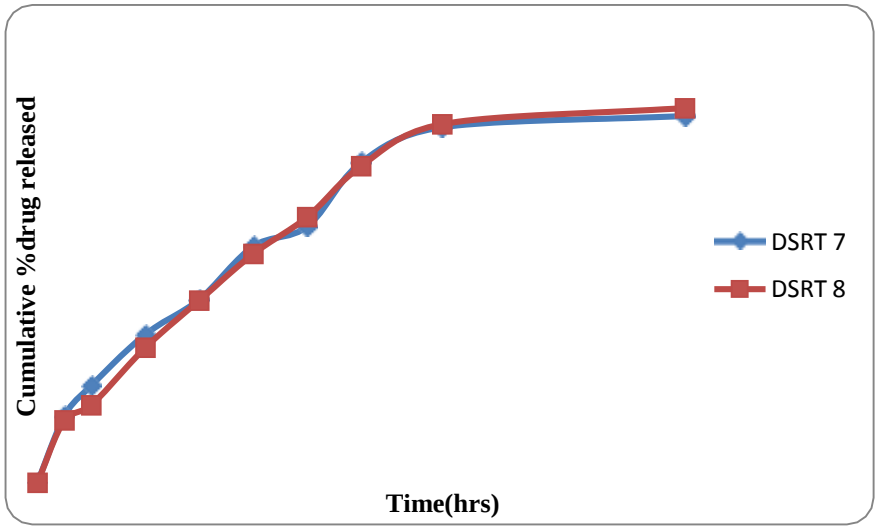

Fig7.18: Comparative dissolution profiles of Doxofylline Sustained Release Tablets employing polymers NaCMC, HPMC K100M

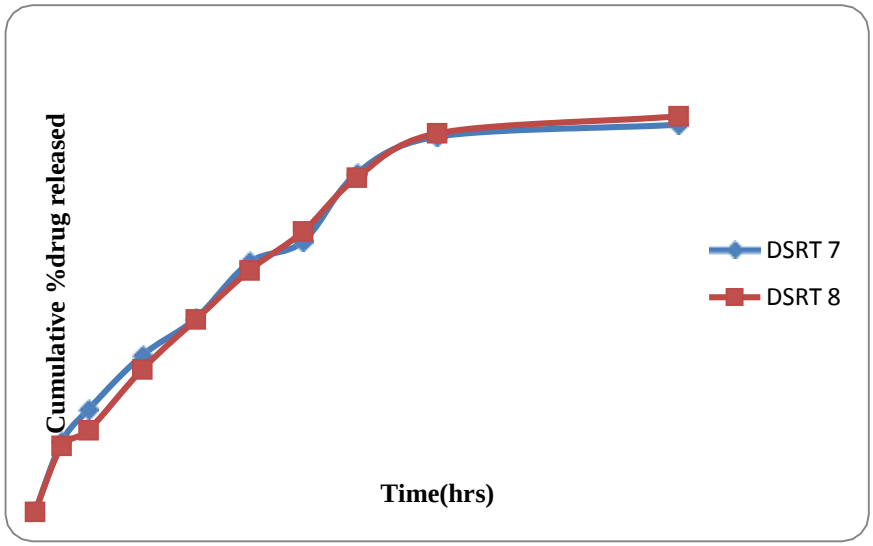

Fig7.19: Zero order plot of Doxofylline Sustained Release Tablet employing polymers NaCMC, HPMC K100M

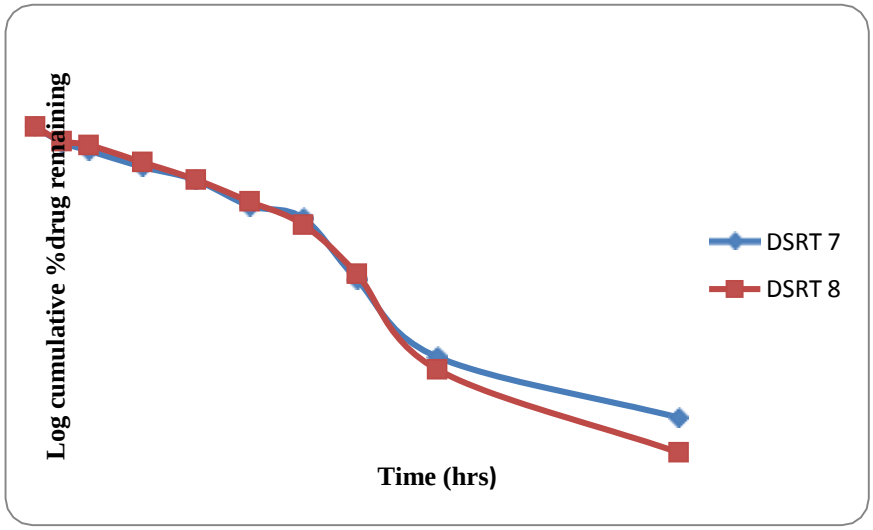

Fig7.20: First order dissolution plot of Doxofylline Sustained Release Tablet employing polymers NaCMC, HPMC K100M

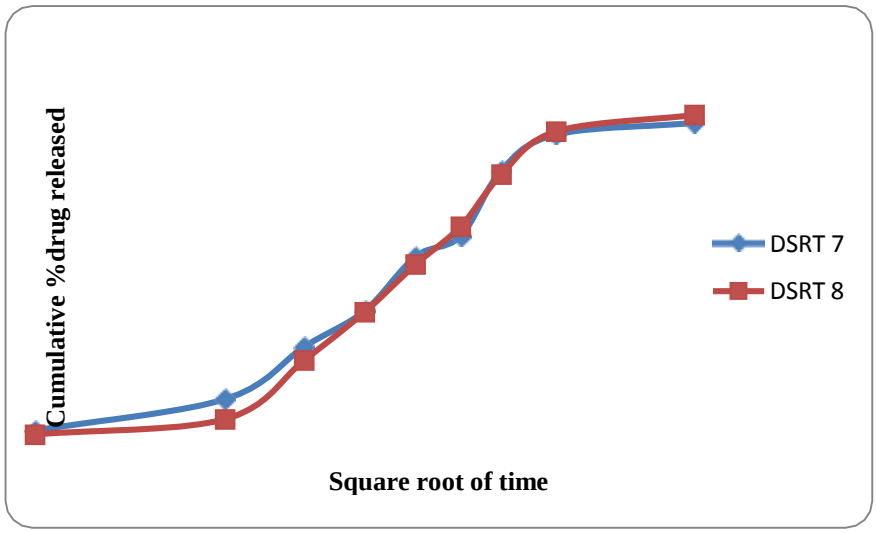

Fig7.21: Higuchi's Classical Dissolution plot of Doxofylline Sustained Release Tablet employing polymers HPMC K100m, HPMC K100M

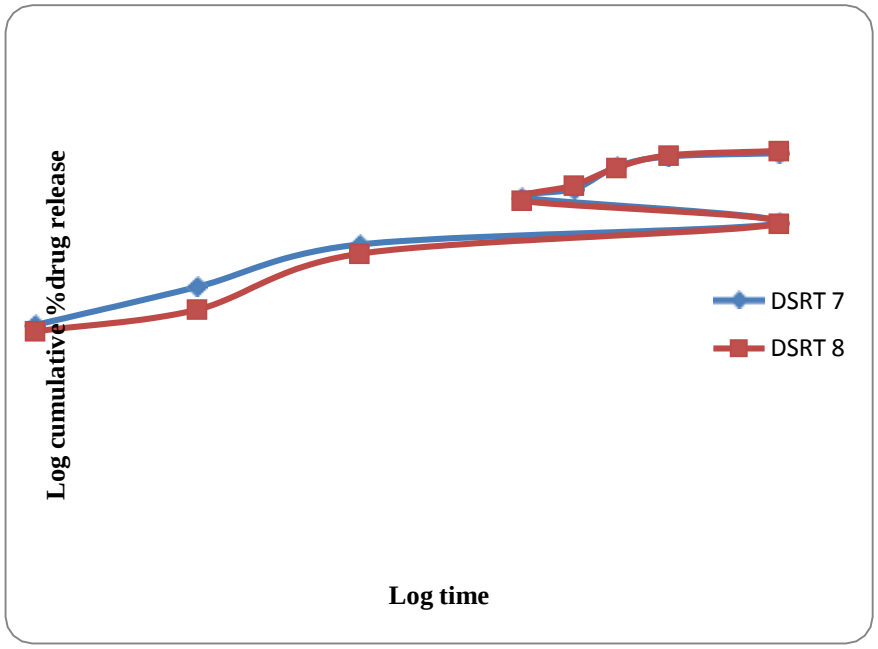

Fig7.22: Kross Meyer Peppas dissolution plot of Doxofylline Sustained Release Tablets Employing polymers HPMC K100m, HPMC K15M

7.5.5 *in-vitro* drug release studies:

In formulation F1 the Doxofylline SR tablet were prepared with 650mg of drug and 120(12%) mg of NaCMC, 100(11%) mg of HPMC K100M, 60(6%)MG OF HPMC K15M they shown drug release of 99.5% in water at end of 12th hour.

In formulation F2 the Doxofylline SR tablet were prepared with 650mg of drug and 130(13%) mg of NaCMC ,110(12%)mg of HPMC K100M, 40(4%) mg of HPMC K15M, they shown drug release of 97.50% in water at end of 12th hour.

In formulation F3 the Doxofylline SR tablet were prepared with 650mg of drug and 180mg(19%) of HPMC K100M, 100(11%)mg of SCMC, they shown drug release of 94.21% in water at end of 10th hour.

In formulation F4 the Doxofylline SR tablet were prepared with 650mg of drug and 170(18%) mg of HPMC K100M, 110(12%) mg of HPMC K15M, they shown drug release of 95.62% in water at end of 10th hour.

In formulation F5 the Doxofylline SR tablet were prepared with 650mg of drug and 170(18%) mg of SCMC, 110(12%) mg of HPMC K15M, they shown drug release of 97.8% in water at end of 12th hour.

In formulation F6 the Doxofylline SR tablet were prepared with 650mg of drug and 180(19%) mg of SCMC, 100(11%) mg of HPMC K15M, they shown drug release of 96.7% in water at end of 12th hour.

In formulation F7 the Doxofylline SR tablet were prepared with 650mg of drug and 170(18%) mg of SCMC, 110(12%) mg of HPMC K 100Mthey shown drug release of 97.34% in water at end of 24th hour.

In formulation F8 the Doxofylline SR tablet were prepared with 650mg of drug and 180(19%)mg of SCMC, 100(11%) mg of HPMC K100M, they shown drug release of 99.42% in water at end of 24th hour.

Among all the 8 formulations (DSRT 1-DSRT 8) the DSRT 8 formulation shows better drug release. The mechanism of this formulation follows zero order and non-fickian diffusion transport type.

Table:7.9 kinetic modelling of drug Release of formula DSRT 1- DSRT 8.

Formulation code	Zero order release		First order release		Higuchi's classical diffusion		Pappas exponential equation	
	K_o	R	K_1	r	K_H	r	K_P	r
DSRT 1	6.191	0.902	-0.106	0.763	19.80	0.851	0.443	0.972
DSRT 2	6.173	0.910	-0.016	0.920	19.82	0.844	0.333	0.996
DSRT 3	7.406	0.891	-0.06	0.96	19.53	0.912	0.294	0.759
DSRT 4	7.470	0.898	-0.115	0.912	20.24	0.926	0.471	0.728
DSRT 5	5.978	0.85	-0.113	0.898	19.69	0.976	0.350	0.835
DSRT 6	6.939	0.864	-0.105	0.902	25.99	0.952	0.345	0.826
DSRT 7	4.160	0.852	-0.069	0.889	19.45	0.919	0.481	0.790
DSRT 8	4.322	0.946	-0.077	0.975	20.58	0.998	0.578	0.786

CONCLUSION:

Most of the oral administered drugs, targeting is not a primary concern and it is usually intended for drugs to penetrate to the general circulation and perfuse to other tissues. For this reason more systems employed are of the sustained release variety. It is assumed that increasing concentration at the absorption site will increase circulating blood levels which in turn promote greater concentration of drug at site of action.

The present study is about the formulation and evaluation of doxofylline sustained release tablets. Doxofylline is an anti asthmatic drug. It has short halflife and efficiency of metabolism is high and having poor bioavailability. Here to increase the bioavailability and to decrease the metabolism, dosing frequency, designing of sustained release dosage form is necessary for doxofylline.

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.

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