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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF DOXOFYLLINE

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ABSTRACT

Doxofylline is a new generation methyl xanthine derivative used to treat asthma. Doxofylline belongs to a group of medicines known as phosphodiesterase inhibitors. Doxofylline have decreased affinity towards adenosine A1 and A2 receptors, which may account for better safety profile of drug. The aim of present work was to formulate and evaluate sustained release tablets of Doxofylline by using hydrophilic polymers such as HPMC K100M and HPMC K15M in different ratios. Drug-excepients interactions were studied by FTIR. Different sustained release granules were prepared by slugging and wet granulation methods, the granules were evaluated for their derived properties and flow properties. The prepared granules were compressed by using rotary tablet punching machine and evaluated for weight variation, assay, *In-vitro* drug release profile and stability. *In-vitro* drug release studies were compared among the different SR formulations and F7 releases 98.85% of drug at the end of 12^{th} hour and were considered as a best formulation. The obtained data was fitted into different kinetic models and the formulation F7 was best explained Peppas kinetic model. The release was follows Non-Fickian diffusion transport mechanism.

Key words: Doxofylline, Asthma, HPMC K100M, Sustained release tablets, In-vitro drug release, Drug release kinetics.

INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed [1]. All the pharmaceutical products formulated for systemic delivery via 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, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form [2].

The concept of sustained release drug delivery has been explored for the delivery of drugs for prolonged period of time for the past few years. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs. Utilizing the concept of incorporating drug in to the polymer system and extend the drug release for prolonged period of time, an attempt was made to design and evaluate sustained release tablets of Doxofylline.

The sustained drug release system provide a slow release of drug over an extended period of a time and can provide some control, whether this be of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug levels in the target tissue or cells [3].

Doxofylline is a new generation methyl xanthine derivative used to treat asthma. Doxofylline belongs to a

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group of medicines known as phosphodiesterase inhibitors [4]. Doxofylline have decreased affinity towards adenosine A1 and A2 receptors, which may account for better safety profile of drug. The aim of present work was to formulate and evaluate sustained release tablets of Doxofylline by using hydrophilic polymers such as HPMC K100M and HPMC K15M in different ratios [5].

MATERIALS AND METHODS

Materials

Doxofylline was obtained from Suven life sciences, Micro crystalline cellulose from hiranya cellulose, HPMC K15M, HPMC K100M and magnesium stearate from janani pharma Pvt.ltd., PVPK90 was purchased from BASF Mumbai, and talc was obtained from Sreemahalakshmi Pharma Pvt.Ltd,.

Methods for preparation of Doxofylline sustained release tablets

Method 1: Preparation of tablets by Direct compression (Slugging)

The formulations (F1-F4) of Doxophylline sustained release tablets were prepared by passing drug, polymer, Mcc101 through a no.30 mesh sieve. And dry mix for 10mins and blend with talc no.40 mesh sieve for 2mins. Finally lubricate with Mg. Stearate through a no.40 mesh sieve. The blend was compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). And then collect the tablets, mill through 1.2mm screen in multi-mill and further the milled granules was compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). Finally the tablet weight was adjusted to 975mg. The composition of core tablet is given in table-1.

Method 2: Preparation of tablets by wet granulation method

The formulations (F5-F9) of Doxophylline sustained release tablets were prepared by passing drug, polymer, Mcc101 through a no.40 mesh sieve, and dry mix for 10mins. Then granulated with pvpk90 solution and dried. The dried granules were sifted through no.20 mesh sieve and lubricated with HPMC K100M, talc, magnesium stearate. The granules were compressed in a cadmach tablet compressing machine filled with biconvex punches (19.5mm+8.2mm). Finally the tablet weight was adjusted to 975mg. The composition of core tablet is given in table-1

Construction of Calibration Curve for Doxofylline

The Calibration curve of Doxofylline was constructed by preparing three stock solutions.

Preparation of 0.1M HCL 1.2 pH[6].

Accurately measured 8.5ml of concentrated HCl was added to 1000ml to make 0.1M HCL. The resulting solution pH was measured by pH meter and it was recorded as 1.2 pH.

Step-1: Preparation of standard stock solution

Accurately weighed 100mg of Doxofylline was dissolved in 10 ml of methanol taken in volumetric flask and volume was made up to 100ml with 0.1M HCl. This is called stock solution I. It contains 1000µg/ml of Doxofylline. From the stock solution I 10 ml of solution was pipette out and made up to the 100ml with the 0.1M HCl. This is called stock solution II. It contains 100µg/ml of Doxofylline. From the stock solution II 10 ml of solution was pipette out and made up to the 50 ml with the 0.1 M HCl. This is called stock solution III. It contains 20µg/ml of Doxofylline.

Step-2: Preparation of sample solution

The aliquots were prepared from stock solution III whose concentration ranging from 2 to 20 µg/ml. The absorbance was measured at 273nm by using UV spectrophotometer against the blank. [7]

Pre compression evaluation parameters

Drug- Polymer Compatibility Studies

Drug polymer compatibility studies were performed by FTIR (Fourier Transform Infrared Spectroscopy). FTIR absorption spectra of pure drug Doxofylline, MCC PH101, HPMC K100M & PVP K90 individually and the combination of drug and excipients. Two 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 4000 to 400 cm^{-1}. The obtained spectras were shown in figure 2-5.

Angle of repose

This is the maximum angle possible between the surface of the pile or powder and horizontal plane. Angle of repose was determined by using funnel method. The frictional forces in the lose powder can be measured by Angle of repose. The tangent of Angle of repose is equal to the coefficient friction between the particles [8].

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

Where**,** θ is the angle of repose, h is the height in cm and r is the radius in cm.

Bulk Density

It was determined by pouring pre-sieved drug excipients blend into a graduated cylinder and measuring the volume and weight "as it is". It is generally expressed in g/mL and is given by,

$Db = M / V_O$

Where, M is the mass of powder and V_O is the Bulk volume of the powder.

Tapped density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipients blend, on mechanical tapping apparatus.

$D_T = M / V_T$

Where, M is the mass of powder and V_T is the tapped volume of the powder.

The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL.

Compressibility index

It is an important measure that can be obtained from the bulk and tapped densities. A material having values less than 20 to 30% is defined as the free flowing material. Based on the apparent bulk density and tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$I = D_T – D_b / D_T \times 100$

Where, I is the Compressibility index,

Dt is the tapped density of the powder; D_b is the bulk density of the powder.

Hausner's ratio

It indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density

$H = D_t / D_b$

Where, H is the Hausner's ratio, Dt is the tapped density of the powder and Db is the bulk density of the powder.

Post-compression evaluation parameters

After compression of desired doses of drug and its excipients into suitable tablet dosage form, each batch was subjected to the following evaluation parameters which includes [9],

Thickness

The thickness of the each Tablet was measured by using Vernier calipers and the average thickness was calculated.

Weight variation

Formulated Tablets were tested for weight uniformity, 20 Tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\%\ \text{Weight Variation} = \frac{\text{Average Weight - Individual Weight}}{\text{Average Weight}} X 100$$

Hardness

The hardness of Tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm^2.

Friability

The Roche friability test apparatus was used to determine the friability of the Tablets. Ten pre-weighed Tablets were placed in the apparatus and operated for 100 revolutions and then the Tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\%\ \text{Friability} = \frac{\text{Initial Weight - Final Weight}}{\text{Initial Weight}} X 100$$

Determination of drug content (By HPLC) [10]

The mobile phase was prepared by using phosphate buffer pH 3 and acetonitrile in the ratio of (80:20). And it was used as diluents [11].

Step-1: Standard preparation:

80 mg of Doxofylline working standard was accurately weighed and transfered in to a 50 ml volumetric flask. Added 20 ml of methanol, and sonicated to dissolve. Make up to volume with methanol, and mix well. From the above solution 5 ml was taken and added to a 50 ml volumetric flask, and make up to volume with diluent and mixed well.

Step-2: Sample preparation:

20 tablets was taken in to a dried mortar and crushed in to a fine powder. Accurately weighed a portion of the powder equivalent to about 650 mg of Doxofylline into a 200 ml volumetric flask, to this 60 ml of methanol was added and sonicated for 15 minutes to dissolve. Volume was marked up with methanol and mixed well. Filtered through 0.45 µm filter paper; the first few ml of the filtrate was discarded. From the above solution 5 ml was taken and was added into a 100 ml volumetric flask, and make up to volume with diluent and mixed well.

Procedure:

The Blank (diluent), standard solution (5 times) and the sample solution were separately injected into the liquid chromatograph and recorded 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

***In vitro* dissolution studies**

The USP dissolution apparatus I(Basket) was used with 900 ml of water as dissolution medium, and maintained a bowl temperature at 37±0.5°C; the apparatus was run at 100 rpm. Samples of the dissolution medium were withdrawn at a specified time intervals and compensated by fresh dissolution medium. Samples were properly diluted and doxofylline concentrations were analyzed UV-spectrophotometrically at 273 nm. The percentage drug released at time different intervals was calculated and plotted against time [10].

Calculate the drug release with the formula given below

$$\% \text{ drug release} = \frac{At}{As} \times \frac{Ws}{100} \times \frac{2}{100} \times \frac{900}{1} \times \frac{100}{2} \times \frac{100}{LC} \times \frac{P}{100}$$

Where,

At = Absorbance of Doxofylline peak in the spectrum of sample solution,

As = Average Absorbance of five replicate injections for Doxofylline peak in the spectrum of standard solution,

Ws = Weight of Doxofylline working standard taken, in mg

LC = Label Claim of Doxofylline in mg per tablet,

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

Drug release kinetics for prepared sustained release tablets

To study the release kinetics, data obtained from *In vitro* release were plotted in various kinetic models.

a) Zero order equation

The graph was plotted as % drug release Vs time in days.

$C=K_0 t$

Where, K_O -Zero order rate constant in conc/time

t- Time in days.

The graph would yield a straight line with a slope equal to K_O and intercept the origin of the axis. The results were tabulated and graph was shown [11].

b) First order equation

The graph was plotted as log cumulative % drug remaining Vs time in days [12].

$\text{Log } C=\log C_O - Kt/2.303$

Where, C_O-Initial concentration of drug.

K – First order constant.

T – Time.

C) Higuchi kinetics

The graph was plotted as cumulative % drug release Vs square root of time

$$Q=Kt^{1/2}$$

Where, K- Constant reflecting design variable of system. (Differential rate constant)

t- time in days.

Hence drug release rate is proportional to the reciprocal of square root of time. If the plot yields a straight line, and the slope is one, then the particular dosage form is considered to follow Higuchi kinetics of drug release. The results were tabulated [13].

e) Korsmeyer – Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs time.

$M_t/M\alpha = Kt^n$

$\text{Log } M_t/M\alpha = \log K + n \log t$

Where, $M_t/M\alpha$-fraction of drug released at time t

t – Release time

K – Kinetic constant (incorporating structural and geometric characteristics of Preparation) [14,15]

n – Diffusional exponent indicative of the mechanism drug release.

RESULTS

Calibration curve for Doxofylline

Drug- Polymer Compatibility Studies

Table 1. Composition of Doxofylline SR tablet formulations

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Doxofylline	650	650	650	650	650	650	650	650	650
MCCPH101	-	-	-	-	150	150	195	165	145
MCCPH102	150	90	120	150	-	-	-	-	-
HPMC K15M	-	90	60	50	50	100	-	-	-
HPMC K100M	150	120	120	100	100	50	85	115	135
PVPK90	-	-	-	-	-	-	20	20	20
I.P.A.	-	-	-	-	Q.S	Q.S	Q.S	Q.S	Q.S
TALC	18	18	18	18	18	18	18	18	18
Mg Stearate	07	07	07	07	07	07	07	07	07
Total (Mg) Wt.	975	975	975	975	975	975	975	975	975

Table 2. Micrometric properties for Doxofylline SR 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)
F1	0.424±0.03	0.590±0.012	31.9±0.25	12.93±1.82	1.361±0.05
F2	0.436±0.018	0.597±0.01	32.1±0.32	14.03±1.74	1.352±0.07
F3	0.471±0.021	0.614±0.01	31.7±0.64	10.11±1.61	1.341±0.03
F4	0.454±0.018	0.586±0.015	30.9±0.91	15.29±2.12	1.353±0.01
F5	0.412±0.011	0.562±0.02	30.5±0.69	14.52±2.32	1.360±0.03
F6	0.434±0.03	0.591±0.012	31.9±0.25	12.93±1.82	1.351±0.05
F7	0.436±0.018	0.592±0.01	32.1±0.32	14.03±1.74	1.358±0.07
F8	0.451±0.021	0.604±0.01	31.7±0.64	10.11±1.61	1.341±0.03
F9	0.434±0.018	0.576±0.015	30.9±0.91	15.29±2.12	1.357±0.01

Table 3. Post compression results for Doxofylline SR tablets

S.No	Weight Variation(mg)	Thickness (mm)	Hardness Kg/cm^2	Friability (%)	Drug content (%)
F1	975.2 ± 0.13	5.82 ± 0.03	10.5 ± 0.11	0.20 ± 0.04	99.7±0.36
F2	972± 0.45	5.79 ± 0.31	11.0 ± 0.07	0.30 ± 0.02	99.5±0.61
F3	978.8± 0.16	5.84 ± 0.23	10.0 ± 0.14	0.41 ± 0.05	100.2±0.15
F4	975.6± 0.21	5.81 ± 0.08	10.5± 0.16	0.41 ± 0.01	99.7±0.99
F5	980± 0.17	5.85 ± 0.16	12.5± 0.04	0.30 ± 0.03	100.2±0.30
F6	972.2± 0.32	5.78 ± 0.12	13.5± 0.02	0. 20± 0.04	99.3±0.45
F7	975.4± 0.45	5.8 ± 0.31	13.0± 0.11	0.20± 0.02	99.7±0.91
F8	978.2± 0.21	5.83 ± 0.08	12.5± 0.14	0.30± 0.01	99.6±0.99
F9	980.4± 0.32	5.85 ± 0.12	13.0± 0.04	0.10 ± 0.04	100.1±0.45
Limits	975±5%mg	5.8±0.2mm	NLT6kg/cm^2	NMT 1%	100±10%

Table 4. *In-vitro* drug release data for Doxofylline SR tablets

Time (hr)	Cumulative % drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	12.99	10.38	14.79	19.77	18.01	9.83	20.56	19.58	17.2
2	20.15	15.52	25.7	35.44	31.72	15.93	35.83	33.09	30.35
4	29.36	22.69	32.09	43.9	40.81	22.65	49.35	45.63	49.05
6	32.31	29.66	44.23	51.12	49.21	37.64	60.71	54.75	56.80
8	34.86	33.58	53.86	59.71	52.44	45.66	70.49	66.15	62.58
10	38.06	40.61	62.69	62.44	57.50	54.10	84.01	71.29	69.33
12	40.46	46.96	68.33	70.19	61.09	66.13	98.85	82.21	73.25

Table 5. In-vitro drug release kinetics data for best formulation F7

Zero order		First order		Higuchi's data		Korsemayer-Peppas data	
Time (h)	Cum. % drug release	Time (h)	log cum. % of drug remaining	SQRT of time	Cum. % drug release	Log time	Log Cum. % drug release
1	20.56	1	1.900	1	20.56	0	1.313
2	35.83	2	1.807	1.414	35.83	0.301	1.554
4	49.35	4	1.705	2.00	49.35	0.602	1.693
6	60.71	6	1.594	2.44	60.71	0.778	1.783
8	70.49	8	1.470	2.828	70.49	0.903	1.848
10	84.01	10	1.204	3.162	84.01	1	1.924
12	98.15	12	0.267	3.464	98.15	1.079	1.992

Figure 1. Standard Plot for Doxofylline in 0.1N Hcl at 273nm

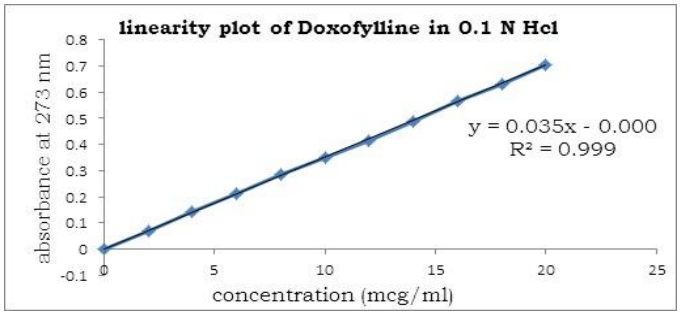


Figure 2. FT-IR Spectra of Doxofylline

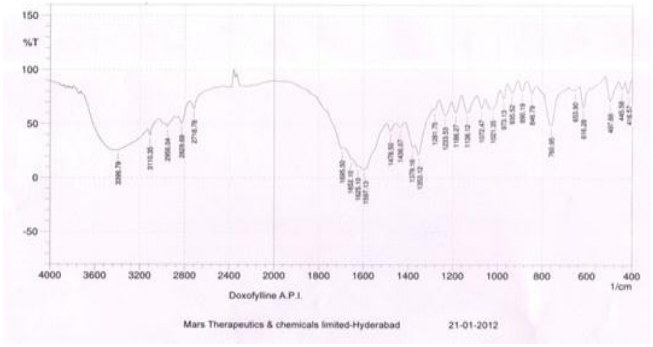


Figure 3. FTIR Spectrum Of Doxophylline and HPMC K100M(1:1)

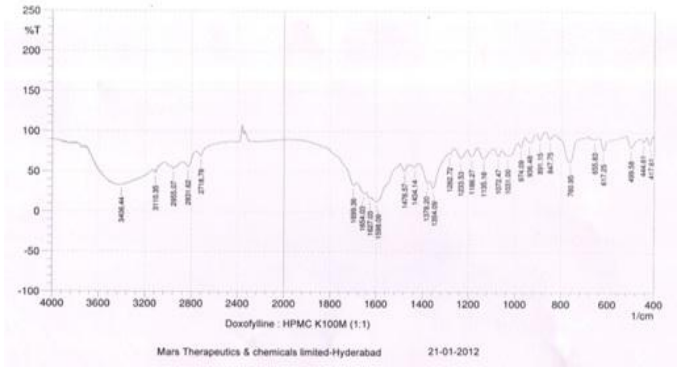


Figure 4. FTIR Spectrum Of Doxophylline and MCCPH101(1:1)

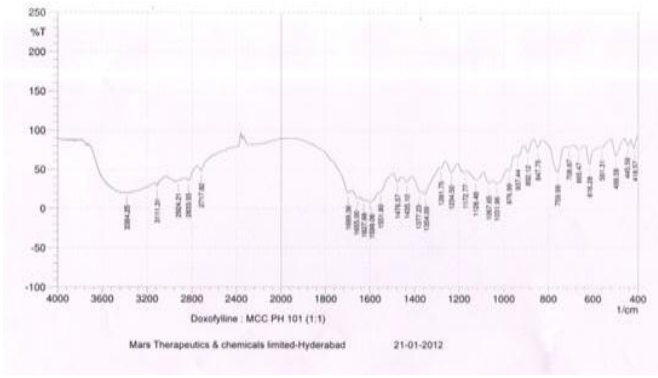


Figure 5. FTIR Spectrum Of Physical mixture

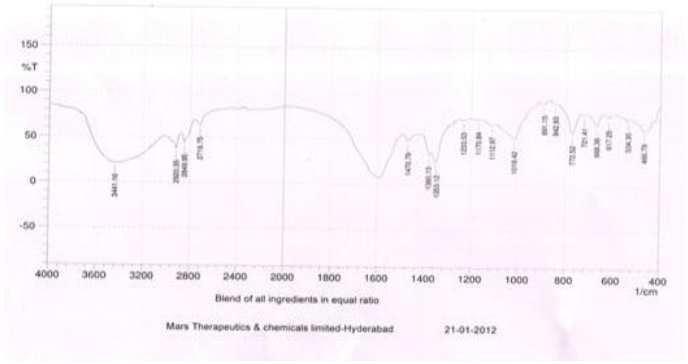
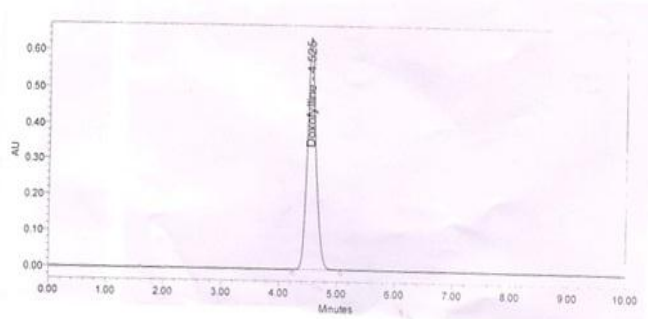
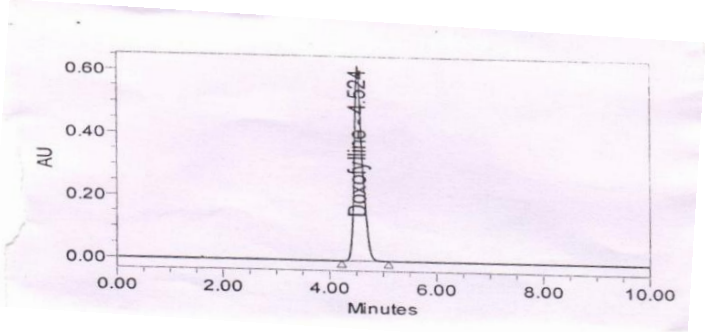


Figure 6. HPLC peak of standard drug



Peak name	RT	Area	Drug content
Doxofylline	4.525	639656	100%

Figure 7. HPLC peak of F7 for drug content estimation



Peak name	RT	Area	Drug content
Doxofylline	4.524	638188	99.77%

Figure 8. comparative in-vitro drug release plot for F1-F9

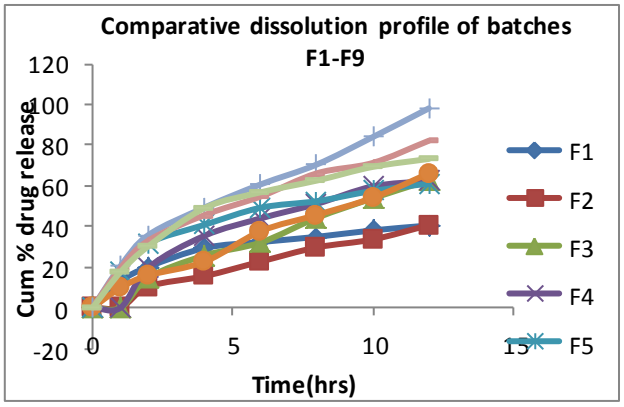
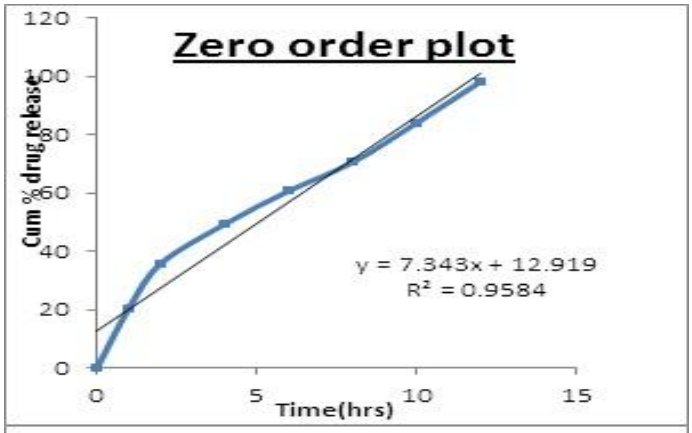
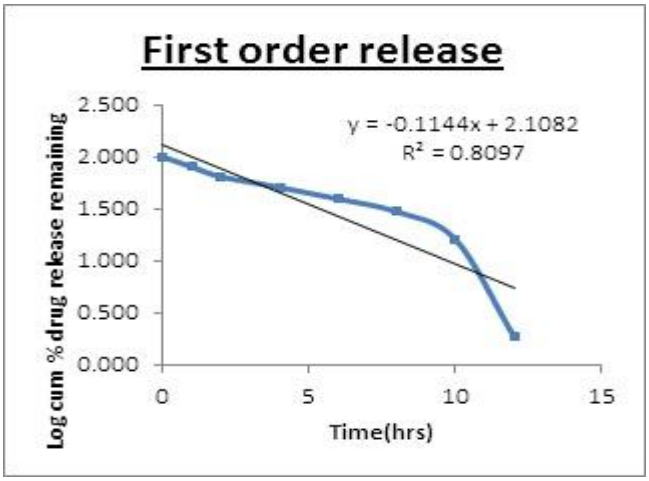
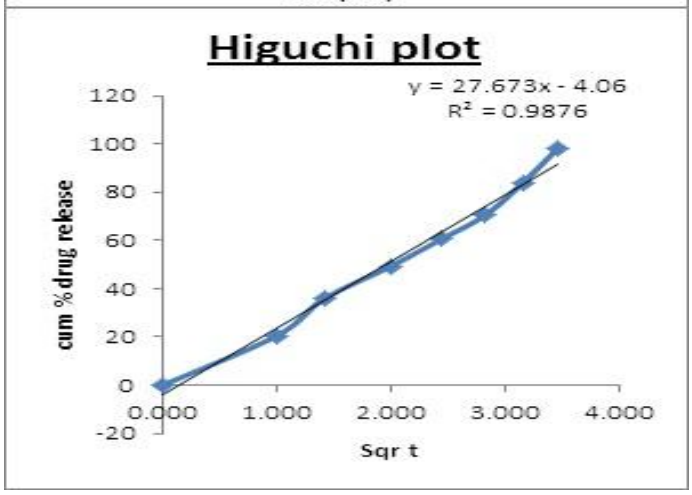
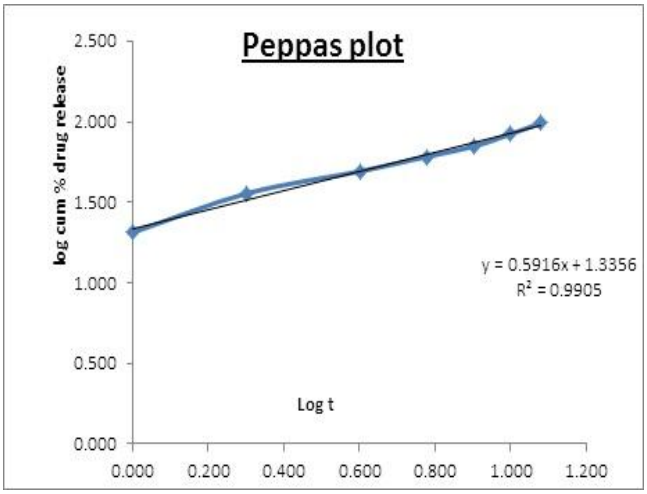


Figure 9 (a,b,c&d). drug release kinetics plots for F7 formulation









DISCUSSION

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. So, it was confirmed that the drug and polymers are compatible with each other.

The flow properties and other derived properties evaluated for all the 9 formulations were proved to be within limits showing good flow properties.

The tablets were evaluated for Appearance, Weight variation, Thickness, Diameter, Hardness, Friability, Assay and Dissolution to meet the Pharmacopoeias standards. And it was found to be within the limits.

Hence different model dependent approaches (Zero order, First order, Higuchi, Korsemayer- Peppas plots) were performed for dissolution profile comparison of best formulation F7. The results of these models indicate the formulation F7 follow Peppas model as "best fit model". This is due to previously proved fact depending on R^2 value obtained from model fitting. Korsemayer - Peppas release exponent (n) value of formulation F7 is greater than 0.45 indicating non - Fickian diffusion.

CONCLUSION

Doxophylline sustained release tablet formulations were prepared successfully using HPMC as polymer to retard release and achieve required dissolution profile. From the results it was concluded that, percent drug release was increased with decrease in the concentrations of HPMCK100M. The 12 hour drug release profile may improve patient compliance and better therapeutic effect in treatment of asthma. Based on the *in-vitro* drug release studies, the data were fitted into different kinetic models shows zero order release pattern followed by non-fickian transport mechanism. Drug release profiles on model fitting follow Peppas model as best fit model which indicates drug diffusion in hydrated matrix.

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