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Formulation Development and Characterization of Sustained Release Matrix Tablets of Doxofylline

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ABSTRACT

The objective of this research work was to prepare sustained release matrix tablets of doxofylline. Doxofylline is a xanthine bronchodilator having reduced affinity for A_1 & A_2 adenosine receptors. Different grades of hydrophilic polymers(HPMC K4M, HPMC K15 cps, HPMC K100 M, Sodium carboxymethylcellulose) and hydrophobic polymer (ethyl cellulose) were used. FTIR study shows that drug and other excipients are compatible with each other. Tablets were prepared by wet granulation technique using non-aqueous solvent IPA and PVP K90D as a binder. Under stage I of preliminary study, tablets were formulated using polymers alone. In stage II polymers were used in combination, with an objective of sustaining release up to 12 hrs. The effect polymer concentration on drug release profile was investigated. The amounts of HPMC K100 M & NaCMC were selected as independent variables. The results of final batches indicated that a low concentration of HPMC K100 M & high amount of Sodium CMC favours sustained release of doxofylline from matrix tablets. Accelerated stability study for 8 weeks confirmed that the best selected formulation F 15 was stable

Keywords: Doxofylline , matrix tablets, HPMC, Sodium CMC, Sustained release tablets.

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INTRODUCTION

Sustained release preparations provide an immediate dose required for the normal therapeutic response, followed by gradual release of drug in amounts sufficient to maintain therapeutic response for a specific extended period of time. The major goal of designing sustained or controlled-delivery systems is to reduce the frequency of dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery.[1]

Doxofylline, a bronchodilator, is effective for the treatment of bronchial asthma and chronic obstructive pulmonary disease (COPD) in adults. It has the therapeutic properties of theophylline with lower incidence of side effects related to CNS, heart and GIT. It has a better safety profile, due to reduced affinity for adenosine A_1 and A_2 receptors. [2]After oral administration (tablets), peak plasma levels are reached after 1 hour. Absolute bioavailability is about 62.6%; at pH 7.4, plasma proteins binding the compound are about 48%. Less than 4 % of an orally administered dose is excreted unchanged in urine.[3]

Among various types of cellulose ether derivatives, HPMC polymers are popular in controlled release matrices due to their compatibility with numerous drugs[4-5]. The objective of present research work was to prepare sustained release matrix tablets of doxofylline by wet granulation using non-aqueous solvent IPA.

MATERIALS & METHODS

Materials

All the ingredients (chemicals & reagents) used were of analytical grade. The ingredients used were :Doxofylline (antiasthmatic drug), HPMC K4M, HPMC K15 cps, HPMC K 100M, Sodium CMC, ethylcellulose, PVP K90D, microcrystalline cellulose, magnesium stearate & isopropyl alcohol. HPMC, ethylcellulose & PVP k90D were purchased from Central drug house, New Delhi. Magnesium stearate and Avicel 101 were procured from Loba Chemie, Mumbai. Sodium carboxymethylcellulose was procured from Arora & co. New Delhi. Isopropanol was procured from RFCL limited, New Delhi.

Methods

Preparation of tablets

The tablets were prepared by wet granulation technique. Drug and polymers were passed through sieve no.60 except ethylcellulose which was passed through sieve no.40. Dry blend of drug was granulated with PVP K90D as a binder dissolved in isopropyl alcohol. Wet mass was dried at 50^{o}C for 30 minutes & sized through sieve 22. Magnesium stearate was mixed as

glidant ,tablet blend was compressed on rotary tablet compression machine (16 stations) using 12 mm circular flat punches.

Evaluation of tablet blends [6]

Bulk density & tapped density

Density is obtained by dividing weight of powder by volume of powder. Bulk density is determined by the bulk volume and weight of dry powder in a graduated cylinder. Bulk volume is the sum of tapped volume plus void volume. Void volume is eliminated by tapping the graduated cylinder on flat horizontal surface from constant height and by constant force. This tapped volume gives tapped density. Equations for bulk density and tapped density are as following :

$$\rho b = W/Vb$$

$$\rho t = W/Vt$$

Where, W=weight of dry blend

Vb= bulk volume

Vt= tapped volume

Hausner's ratio [7]

Hausner's ratio of the granules was determined by using following equation :

$$HR = TD/BD$$

Compressibility index [8]

Compressibility index of the granules was determined by Carr's compressibility index as given by following equation :

$$\text{Carr's index}(\%) = (TD - BD)/TD \times 100$$

Angle of repose [6, 9]

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,h (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, θ =angle of repose

h= height of heap of granules (cm)

r= radius of base of heap of granules (cm)

Evaluation of tablets [6]

Prepared tablets were evaluated for following physical properties like hardness, friability, thickness, weight variation & drug content uniformity :

Tablet hardness

The mechanical strength of tablets is an important property. It has been described by various terms including fracture resistance, hardness, bending strength and crushing strength. Tablet hardness has been defined as the force required to break a tablet in a diametral compression test. Crushing strength of compressed tablets in kg/cm^2 (n=5) was determined using Pfizer hardness tester .

Friability

Friability test was done by Roche friabilator. Six tablets were weighed & subjected to combined effect of attrition & shock by utilizing a plastic chamber that revolves at 25 rpm dropping tablets from a height of 6 inches with each revolution .Test was continued for 4 minutes , tablets dedusted & reweighed . Percent friability was calculated using equation :

$$\% \text{ friability} = [(\text{weight}_{\text{initial}} - \text{weight}_{\text{final}})/ \text{weight}_{\text{initial}}] \text{ X } 100$$

Thickness

Thickness of tablets was measured using Vernier caliper. Thickness was measured in mm.

Weight variation

Twenty tablets from each batch were selected & evaluated for weight variation (uniformity of weight).

Drug content uniformity

Ten randomly selected tablets of each batch were weighed & powdered in a pestle & mortar. The quantity of powder equivalent to 10 mg of drug was transferred to a 100 ml volumetric flask & dissolved in 40ml of distilled water in a bath sonicator for 2 hr .Solution was filtered through Whatmann paper (no.41) .Filter paper was washed with water. Washings were added to the filtrate & final volume made up to 100 ml. After suitable dilution corresponding to 20µg /ml ,absorbance of final sample was recorded at 274 nm taking distilled water as blank

***In-vitro* dissolution study**

The release rate of doxofylline SR matrix tablet was determined using USP type II dissolution apparatus. *In-vitro* dissolution study was carried out in 0.1 N HCl for 2 hours & in phosphate buffer (pH 6.8) mimicking passage of dosage form from stomach to ileum .In order to simulate pH changes along the GI tract two dissolution media with pH 1.2 & 6.8 were sequentially used referred to as sequential pH change method (method adapted by Abdalkar et.al.) [10] . When performing experiments, the pH 1.2 medium was first used for 2 h (since the average gastric emptying time is 2 h), then removed and the fresh pH 6.8 phosphate

buffer was added. 900 ml of the dissolution medium was used each time. Rotation speed was 100 rpm and temperature was maintained at 37±0.5^{0}C.The samples were filtered through 0.45 µm nylon filter and spectrophotometrically analyzed at 274 nm.

RESULTS AND DISCUSSION

Doxofylline is a xanthine bronchodilator used for the effective management of asthma & COPD. Doxofylline, a novel bronchodilator xanthine with good bioavailability, short biological half life ($t_{1/2}$) and having absorption window throughout GIT was selected for the study. It is a bronchodilator belonging to the class of methylxanthine derivatives. Doxofylline activity is mediated at least partly, by the inhibition of phosphodiesterase enzyme followed by intracellular concentrations of cyclic AMP that is likely to cause smooth muscle relaxation.[11] Due to decreased affinity towards adenosine A1 & A2 receptors ,doxofylline has less extra respiratory side effects. Theophylline has side effects like nausea ,vomiting, insomnia, epigastral pain, anxiety, restlessness, tachycardia & extrasistoles .

In the present study, HPMC(different grades),Sodium CMC & ethyl cellulose which are commonly used in hydrophilic and hydrophobic matrix drug delivery systems have been employed to formulate sustained release tablets of doxofylline. The granules for tablet preparation were prepared according to the formulae given in Table 1 & 2.

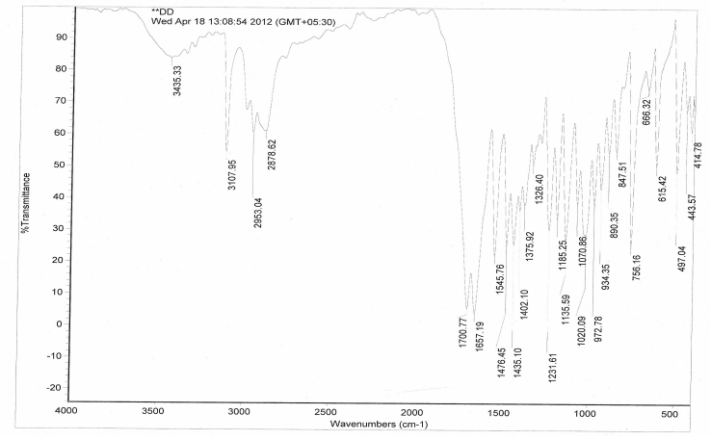

Figure 1: FTIR spectra of doxofylline

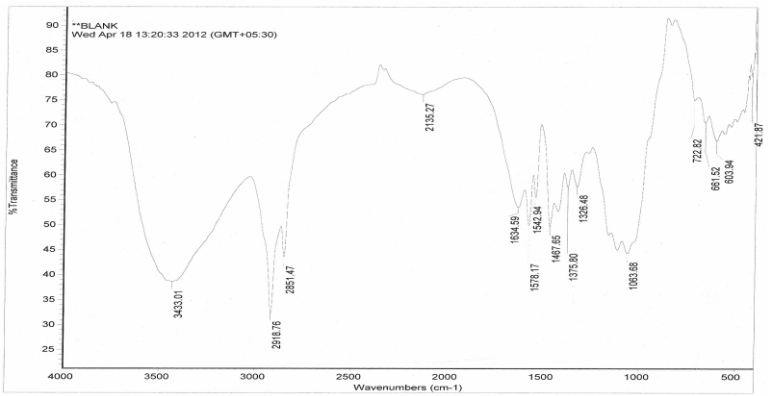

Figure 2: FTIR spectra of physical mixture of all excipients

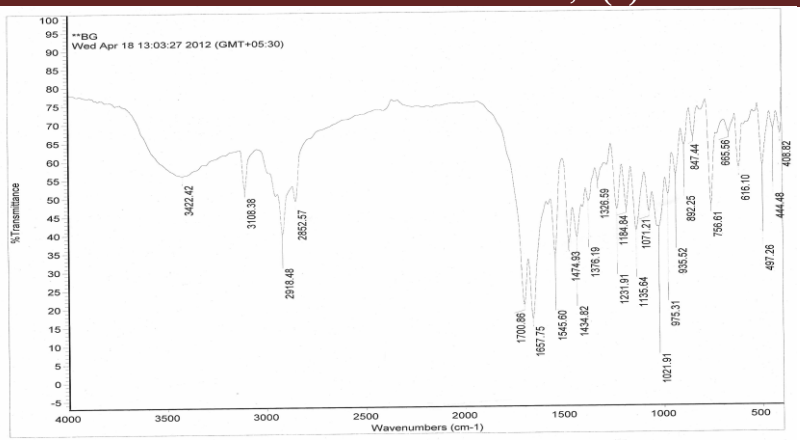

Figure 3: FTIR spectra of physical mixture of doxofylline with all excipients

Table 1: Formulation of preliminary batches.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Doxofylline	400	400	400	400	400	400	400	400	400
Hpmc k4m	100	200	100	200	-	-	-	-	-
Hpmc k15 cps	200	100	-	-	100	-	-	-	-
Hpmc k100m	-	-	200	100	200	100	200	-	100
Ethylcellulose	-	-	-	-	-	200	100	100	-
Sodiumcmc	-	-	-	-	-	-	-	200	200
Avicel 101	34	34	34	34	34	34	34	34	34
Pvp k90 d	6	6	6	6	6	6	6	6	6
Magnesium stearate	10	10	10	10	10	10	10	10	10
Ipa	qs	qs	Qs	qs	qs	qs	qs	qs	qs
Total weight/tablet	750	750	750	750	750	750	750	750	750

Table 2: Formula for final formulations F 10-F 15 .

S.No.	Ingredients	F 10	F 11	F12	F13	F 14	F 15
1	Doxofylline	400	400	400	400	400	400
2	Hpmc k100 m	200	225	250	150	75	50
3	Sodium CMC	100	75	50	150	225	250
4	Pvp k90 d	6	6	6	6	6	6
5	Avicel 101	34	34	34	34	34	34
6	Magnesium Stearate	10	10	10	10	10	10
7	Ipa	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
	total weight (mg)	750	750	750	750	750	750

A granule is an aggregation of component particles held together by the presence of bonds of finite strength. The granules of different formulations were evaluated for bulk density, tapped density, Hausner's ratio, compressibility index & angle of repose(Table 3). The results of bulk density & tapped density ranged from 0.211-0.392 & 0.289-0.49 respectively. Hausner's ratio ranged from 1.13-1.68. The results of compressibility & angle of repose ranged from 10.64-32.52 & 20.13-28.81 respectively. The results of angle of repose (<30) indicated good flow property of granules[12-13.] This was further supported by lower compressibility index values. Bulk density of granules prepared by using ethyl-cellulose was found to be lower than that of other granules.

Table 3 :Characterization of granules .

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's ratio	Carr's index(%)	Angle of repose (θ)
F 1	0.229	0.323	1.41	29.10	20.85
F 2	0.209	0.312	1.49	33.01	21.34
F 3	0.211	0.356	1.68	40.7	22.54
F 4	0.195	0.289	1.48	32.52	21.12
F 5	0.358	0.426	1.18	15.96	20.56
F 6	0.233	0.367	1.57	36.51	20.98
F 7	0.204	0.296	1.45	31.08	21.45
F 8	0.289	0.327	1.13	11.6	22.67
F 9	0.254	0.295	1.16	13.89	21.98
F 10	0.243	0.287	1.18	15.33	21.54
F 11	0.278	0.325	1.16	14.46	20.67
F 12	0.267	0.342	1.28	21.63	20.13
F 13	0.319	0.357	1.12	10.64	20.89
F 14	0.305	0.378	1.24	19.31	22.67
F15	0.39	0.49	1.26	20.40	28.81

Thickness of granules ranged from 4.3-6.2 mm. The hardness and percentage friability of tablets of all batches ranged from 10.8- 16.1 and 0.03-0.87.The average percentage deviation of 20 tablets of each formula was less than +_5%. Drug content was found to be uniform among different batches of tablets and ranged from 96-102.3 % (Table 4-5).

Table 4:Evaluation of tablets(F1-9)

Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
Hardness(kg/cm^2)n=5	12.5	13.3	12.7	11.8	12.4	13.3	12.4	14.7	15.3
Friability(%) n=6	0.57	0.80	0.31	0.59	0.86	0.65	0.64	0.47	0.58
Thickness(mm)n=10	4.9	5.0	4.9	5.1	5.2	4.8	4.8	4.9	5.3
Weight variation(mg)n=20	749.5	750.1	751.2	748.5	764.3	755.3	765.9	754.0	743.2
Assay (%)	97.96	97.4	98.9	99.6	100.4	99.7	96.7	97.8	102.3

Table 5: Evaluation of tablets(F10-15)

Physical parameter	F 10	F 11	F 12	F 13	F 14	F 15
Hardness(kg/cm^2)n=5	12.9	13.5	15.6	16.1	14.4	13.6
Friability (%) n=6	0.56	0.34	0.13	0.03	0.25	0.37
Thickness(mm) n=10	4.7	4.6	5.2	5.4	5.3	4.8
Weight variation(mg) n=20	756.8	767.3	745.7	748.6	752.5	758.1
Assay(%) n=10	96.4	99.6	98.7	97.1	100.3	98.4

The tablets of different formulations were subjected to various evaluation tests such as, hardness, friability, thickness, weight variation & drug content uniformity. The average percent deviation of all tablet formulations was found to be within limits (+_5%) and hence all formulations passed the test for uniformity of weight as per official requirements [14]. Formulation F15 showed high hardness value of 16.1 kg/cm^2. Percentage friability for all the formulations was below 1% indicating that friability is within prescribed limits.

The results of dissolution study of formulations FI, FII & FIII composed of combination (table 1) of HPMC K4 M, HPMC K15Cps, HPMC K100M are shown in figure 4. FI, FII & FIII released 83%, 79% & 68% at the end of 2 hrs and complete drug release at the end of 5,6 & 7 hrs respectively. The formulation was further modified by incorporating hydrophobic polymer ethyl cellulose to control release up to 12 hrs.FIV ,FV & F VI released 64%, 58% & 50% at end of 2 hrs and 100% drug release at the end of 5,7 & 7 hrs respectively(figure 5).F VII, FVIII & FIX (table 1) released 42%, 48% &32% at the end of 2 hrs and 100% release at the end of 8, 7 & 10 hrs (figure 6).*In-vitro* dissolution of FIX showed that combination of HPMC K100M & Sodium CMC were effective to sustain release up to 10 hrs. Therefore different combinations of these two polymers were tried (table 2). *In-vitro* dissolution study of F10-15 indicated that F15 sustained release up to 12 hrs so this formulation was selected as the best as shown in figure 7. Among all the formulations, F15 showed least deviation from theoretical release pattern. Drug release kinetics was fit to zero order, first order, Higuchi's & Korsmeyer-Peppas model, based on regression (r^2)values diffusion was found to be dominant mechanism of drug release.

In-vitro drug release characteristics were studied in 0.1 N HCl for 2 hrs & in phosphate buffer pH 6.8 for 10 hrs using USP type II dissolution apparatus. The results of dissolution study (figure 4, 5, 6 & 7) showed that release rate was increased in following polymer ratio: HPMC K4M> ethyl cellulose > HPMC K15 cps > 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 ratio. These values are in accordance with the earlier reported viscosity values for these polymers.[16] Hence, F15 is the most successful formulation among the matrix tablets developed in the present study.

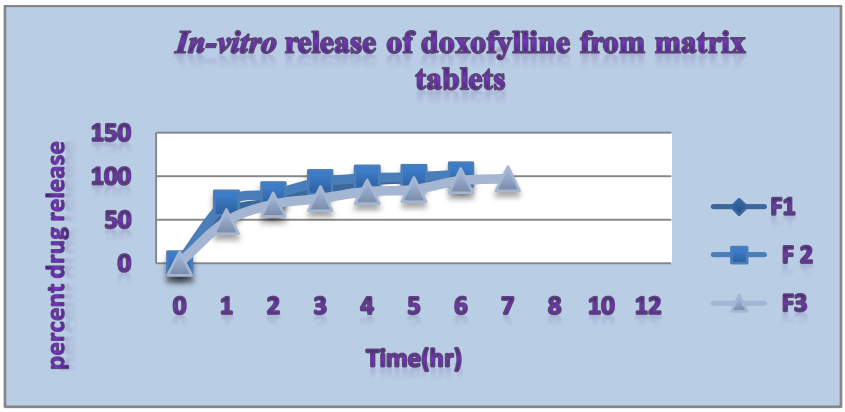

Figure 4*: In-vitro* dissolution of drug from formulations F1-3 .

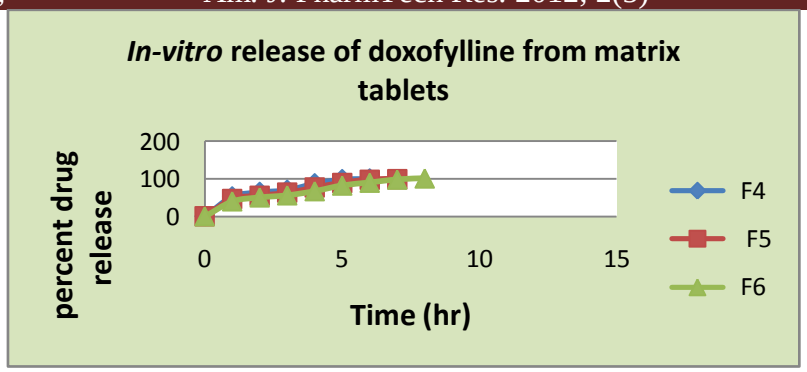

Figure 5*: In-vitro* dissolution of drug from formulations F4-6

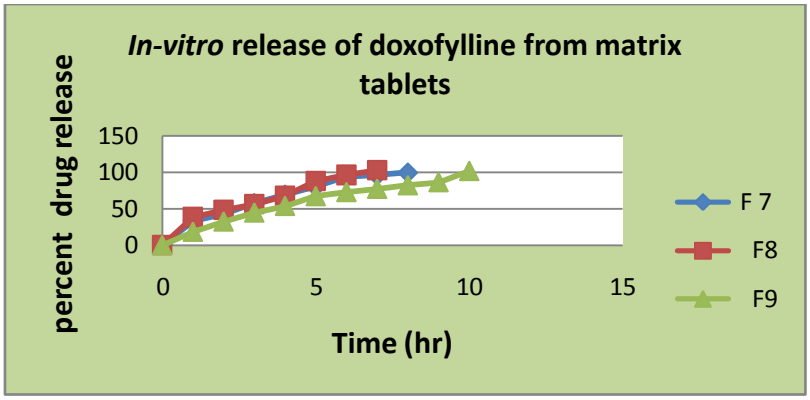

Figure 6*: In-vitro* dissolution of drug from formulations F7-9

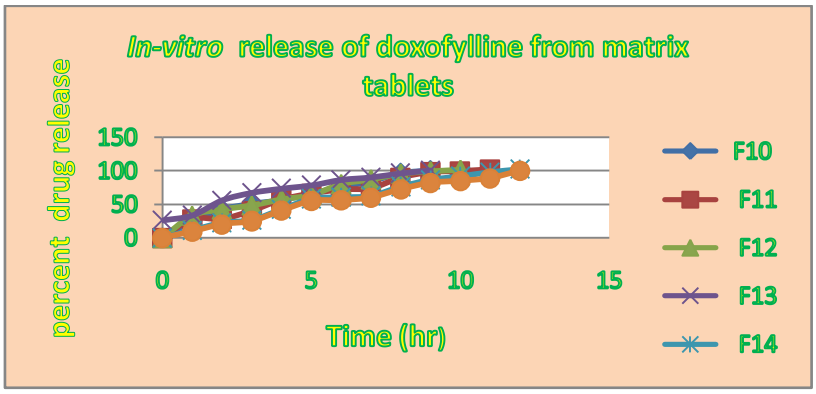

Figure 7*: In-vitro* dissolution of drug from formulations F10-15

To know the mechanism of drug release from these formulations , the data were treated according to zero order, first order, Higuchi's equation[17] & korsmeyer-peppas equation. Based on regression values, Higuchi's equation was found to be followed (table 6). Release of drug from matrix tablet containing hydrophilic polymers involves factors of diffusion. Diffusion is related to transport of drug from the dosage matrix into *in-vitro* study fluid depending on the concentration. As gradient varies, the drug is released and the distance for diffusion increases. This could explain why drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square root kinetics or Higuchi's kinetics. Accelerate stability studies carried out for 8 weeks showed that there were no significant changes in physical as well as *in-vitro* dissolution of drug from tablets.

Table 6:Regression values of formulation F15 using different kinetic models .

S.No.	Model	Regression (R^2)
1	Zero order release	0.975
2	First order release	0.848
3	Higuchi's equation	0.986
4	Korsmeyer-Peppas equation	0.985

CONCLUSION

The hydrophilic matrix of polymers alone could not control release of doxofylline for 12 hrs. It is evident from results that matrix tablet prepared by wet granulation technique using PVP K90D as a binder and combination of polymers HPMC K100 M & Sodium CMC in drug :polymer 1:0.75 ratio is a better system for sustained release of doxofylline. Based on regression values, release of drug was found to be diffusion dominated.

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