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DEVELOPMENT OF MATRIX DIFFUSION CONTROLLED DRUG DELIVERY SYSTEM OF PENTOXIFYLLINE

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ABSTRACT

Background: Pentoxifylline, a theobromine derivative is used in the treatment of patients with intermittent claudification due to chronic peripheral artery disease at usual dose of 400mg, thrice a day.

Objective: In the present paper, controlled release matrix formulations of pentoxifylline were prepared with an objective to achieve development of less expensive once a day formulation using natural polymers with better control of release.

Materials and methods: Diffusion controlled matrix system of Pentoxifylline was prepared by using swellable polymers like Hydroxypropyl methyl cellulose (HPMC), Eudragit (Eudragit RS30D) as synthetic and Sodium alginate, Guar gum (Dealca P-225) as natural polymers using wet granulation technique. Combination formulations of these polymers were also tried.

Results: HPMC formulations showed very high dissolution rate releasing 70% of drug within 2 hrs but its combination formulation with Eudragit showed low dissolution rate of 0.14 hr^{-1}. Sodium alginate did not show controlled drug release pattern. Eudragit and Guar gum formulations showed low dissolution rates indicating controlled release pattern of drug but their combination formulation showed high dissolution rate of 0.73 hr^{-1}. Taking into consideration all the parameters, Eudragit and Guar gum (Dealca) individually were found to be the most suitable polymers for pentoxifylline controlled release formulations. Their release profile followed first order release kinetics in Higuchian diffusion fashion.

Conclusion: The developed matrix diffusion controlled Pentoxifylline tablet using either Eudragit or Guar gum can be administered once a day with better control of drug release. Guar gum formulation was relatively inexpensive due to use of natural polymers.

Keywords: Pentoxifylline, Eudragit, Hydroxypropyl methyl cellulose, Guar gum, Sodium alginate, Matrix diffusion.

INTRODUCTION

Pentoxifylline is a tri-substituted xanthine derivative designated chemically as 1-(5-oxohexyl)-3, 7-dimethylxanthine that, unlike theophylline, is a hemorrheologic agent, i.e. an agent that affects blood viscosity. Pentoxifylline is soluble in water and ethanol, and sparingly soluble in toluene. Pentoxifylline causes hemodynamic improvement by increasing erythrocyte flexibility and decreasing blood viscosity, thereby increasing the oxygen supply to muscles[1]. The precise mode of action of Pentoxifylline and the sequence of events leading to clinical improvement are still to be defined. In patients with chronic peripheral arterial disease, this effect increases blood flow to affected microcirculation and enhances tissue oxygenation. The usual dose of Pentoxifylline is 400 mg, taken thrice a day with meals. It is extensively absorbed after oral administration and plasma levels of the parent drug peak within 1 hour. It undergoes first pass effect. Plasma half lives of Pentoxifylline and its metabolites are 0.4 to 0.8 hours and 1 to 1.6 hours respectively. Due to short half life, daily large doses have to be given and frequent dosing is required. It has been reported that the accumulation of Pentoxifylline in plasma after repeated dosing is minimum. The pharmacokinetic data supports the need for controlled release dosage form of Pentoxifylline for therapy [1, 2].

Controlled drug delivery is described as phasing of drug administration to the needs of the condition at hand so that an optimal amount of drug is used to cure or control the condition in a minimum

time. Hydrophilic matrices containing swellable polymers are referred to as swellable controlled-release systems or hydrophilic matrix tablets. A number of polymers have been investigated to develop in situ gel-forming systems, due to the ability of these matrices to release an entrapped drug in aqueous medium and to regulate release of such drug by control of swelling and cross-linking [2, 4].

These systems draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Under ideal conditions, a controlled-release formulation maintains therapeutic blood level of a drug for a specific period of time. Oral controlled-release dosage forms have been developed and studied to restrict these systems to specific regions of the gastrointestinal tract as well as to improve the pharmacological activity and to reduce toxic effects [5]. One method of fabricating controlled-release formulations is by the incorporation of the drug in a matrix containing a hydrophilic, rate-controlling polymer [6, 7]. Hydroxypropyl methylcellulose (HPMC), Eudragit, Sodium alginate and Guar gum [8] are the polymers most widely used as gel-forming agents in the formulation of solid, liquid, semisolid and even controlled-release dosage forms. Water penetration, polymer swelling, drug dissolution, drug diffusion and matrix erosion from these dosage forms are controlled by the hydration of polymer, which forms a gel barrier through which the drug diffuses [9,10]. The adjustment of the polymer concentration, the viscosity grade and the addition of different types and levels of excipients to the polymer matrix can modify the drug release rate [11]. The influence of technological variables on drug release from various polymer matrices individually as well as in combination was reviewed [12, 13, 14]. Despite the influence of some technological variables have been already described, one goal of this study was to develop matrix tablets by the wet granulation process, evaluating the effect of various natural and synthetic polymers and their concentrations in order to develop cost effective sustained release formulation. Magnesium stearate and talc were chosen as excipients.

MATERIALS AND METHODS

Pentoxifylline BP (Menon Pharma), Eudragit RS 30D (Rohem pharma), HPMC USP, Guar gum (Dealca P-225), Sodium alginate (Signet chemicals), Magnesium stearate IP (Parag fine organic, Palghar), Talc IP (ATOZ Traden) were obtained from Menon Pharma as gift samples.

Standardization of drug and polymers

Pentoxifylline was standardized according to monograph described in BP 1993 under Oxpentifylline. It was evaluated based on its melting point, loss on drying, IR spectrum and assay (UV spectrophotometry and non-aqueous titration). Eudragit RS 30D, HPMC, guar gum, sodium alginate (IP 1996) were evaluated on the basis of pharmacopoeial monographs [15].

Preparation of Pentoxifylline matrix tablets

Development of controlled release CDDS of Pentoxifylline was attempted by designing series of formulations based on the diffusion controlled matrix systems. The detailed compositions of matrix tablet formulations are given in Table 1.

Wet granulation method was adopted as a technique for granulation. Initially the drug, polymer and excipients were passed through sieve # 60 and this mixture was kneaded with dispersion of binder solution which forms wet mass

which was then passed through sieve # 16. Different binder solutions and their concentrations for each polymer were tried out. For Eudragit, IPA was used as binder solution, as it forms sticky plastic mass, IPA was incorporated carefully.

HPMC is a swellable polymer that shows time dependant release profile when the tablet comes into contact with liquids. HPMC USP with viscosity of 3000-5600 mPas was used for matrix formulations. Formulations H1, H2, H3 and H4 were prepared by wet granulation method as described. Ethyl cellulose in ethanol was used as binder.

Formulations S1, S2, S3 and S4 were prepared by using sodium alginate polymer and starch paste as binder. PVP was also incorporated to increase the strength of granules, whereas PVP solution was used as binder for guar gum formulations.

Combination formulations, EH and ED were prepared as per the compositions described in Table 1 using IPA as binder solution. Granules thus obtained were dried at 60 °C for 15 minutes following drying in air for 1 hour. Dry granules were passed through sieve # 36. Talc and magnesium stearate were mixed in graded proportions. Tablets of all batches were compressed using capsule shaped punches at hardness of around 5-6 kg on single punch tablet compression machine.

To develop CDDS, formulations were optimized so as to release 70% of the drug at the end of 10 hr. From developed formulations, compositions D2, D3 and EH were selected as they showed the desired release pattern (Table 2).

The selected formulations D2 and D3 contained concentration dependant indigenous polymer, Guar gum (Dealca) and EH was composed of Eudragit and HPMC.

Evaluation of granules and matrix tablets

Granules obtained were evaluated for percent drug content, moisture content, particle size distribution, aerated bulk density (g/mL), packed bulk density (g/mL), compressibility, angle of repose (°) and flow rate (g/sec). Compressed tablets were evaluated for percent drug content, average weight (g), dimensions (mm) in terms of length, breadth and thickness, hardness (kg), friability and *in vitro* release profile, as depicted in Table 2, and Figure1.

Content of active ingredient was determined using BP 1993 procedure where Pentoxifylline tablet was dissolved in water and absorbance was measured at λmax of 273 nm on UV-Visible spectrophotometer (Jasco V-530- Japan).

***In-vitro* drug dissolution studies**

Drug release profiles were evaluated *in vitro* using dissolution rate test apparatus (Electrolab, India). The USP paddle method was selected to determine dissolution profiles of pentoxifylline from all the formulations using 1000 ml purified water, maintained at 37±0.5°C as dissolution medium, at a paddle rotation speed of 100 rpm. The 10 ml of release medium was withdrawn as a sample at preselected time intervals up to 10 hours to monitor the progress of dissolution and replaced by a fresh 10 ml of medium after each withdrawal. The filtered sample solutions were analyzed for pentoxifylline content by UV absorbance at 273 nm using a UV-Visible Spectrophotometer. Cumulative percentage of drug release was calculated and the mean of three

determinations was used for data analysis.

Sequential drug release of selected tablet formulations was carried out in dissolution media consisting of buffer solution, pH 1.2 for first 2 hrs, pH 5.5 for next 2 hrs and pH 7.2 for the remaining period.

Release kinetics

To study the mechanism of drug release from the matrix tablets, the release data were fitted to the following equations:

Zero-order equation: $Q = Q_0 - k_0 t$ ..... *(1)*

where Q is the amount of drug released at time t, and k_0 is the release rate;

First-order equation: $\ln Q = \ln Q_0 - k_1 t$ ..... *(2)*

where k_1 is the release rate constant;

Higuchi´s equation: $Q = k_2 t^{1/2}$ ..... *(3)*

where Q is the amount of drug released at time t, and k_2 is the diffusion rate constant.

RESULTS AND DISCUSSION

Drug and polymers were standardized and were found to comply with specifications in official compendia. Different formulations of Pentoxifylline were prepared using synthetic polymer eudragit [Eudragit RS 30D in concentration range of 15-35 % w/w (E1-E5)] and HPMC [concentration range of 15-35 % w/w (H1-H4)]. Other formulations were prepared using natural polymer sodium alginate [concentration range 12-38% w/w (S1-S4)] and Guar gum [Dealca P-225 in concentration range of 23- 30% w/w (D1-D5)] as shown in Table 1.

Further formulations using Eudragit in combination with Dealca and HPMC were also prepared. Each of the polymers in both of these formulations was used in 15% concentration. Plain conventional Pentoxifylline tablets without any release retardant were also formulated for comparison. Physicochemical parameters of all developed formulations are shown in Table 2.

Table 1: Composition of Pentoxifylline controlled release formulations

Batch code	Pentoxifylline (mg)	Eudragit (RSD 30D) (mg)	HPMC (mg)	Sodium alginate (mg)	Dealca (P-225) (mg)	Mg Stearate (mg)	Talc (mg)
E1	400	58.5	-	-	-	7.15	8
E2	400	65	-	-	-	7.15	8
E3	400	97.5	-	-	-	7.15	8
E4	400	117	-	-	-	7.15	8
E5	400	143	-	-	-	7.15	8
H1	400	-	97.5	-	-	15	15
H2	400	-	130	-	-	15	15
H3	400	-	162.5	-	-	15	15
H4	400	-	227.5	-	-	15	15
S1	400	-	-	80	-	15	15
S2	400	-	-	130	-	15	15
S3	400	-	-	162.5	-	15	15
S4	400	-	-	195	-	15	15
D1	400	-	-	-	150	7.5	15
D2	400	-	-	-	172.25	7.5	15
D3	400	-	-	-	195	7.5	15
D4	400	-	-	-	227.5	7.5	15
D5	400	-	-	-	252.25	7.5	15
EH	400	97.5	100	-	-	15	15
ED	400	97.5	-	-	100	15	15

Table 2: Physicochemical evaluation of Pentoxifylline controlled release formulations

Batch code	% content of active ingredient	Tablet weight (g)	Hardness (kg)	Friability (%)	% drug release	
					At the end of 2hrs	At the end of 8 hrs
E1	100.02(±1.43)	0.789	5.5	0.0026	48.33	96.88
E2	99.89 (±2.11)	0.795	5.6	0.0025	45.22	87.38
E3	100.21(±1.23)	0.778	5.7	0.0027	41.02	82.34
E4	99.97 (±2.10)	0.800	5.5	0.0027	39.48	70.92
E5	99.12 (±2.13)	0.897	5.7	0.0026	39.86	74.77
H1	98.99(±1.56)	0.768	6.0	0.0362	72.80	100.00
H2	99.29(±1.12)	0.865	5.8	0.0354	67.29	99.88
H3	98.97(±1.72)	0.897	5.8	0.0345	56.13	101.14
H4	98.98(±1.66)	0.788	6.0	0.0365	56.30	100.13
S1	99.95(±1.03)	0.899	5.5	0.0242	44.08	101.37
S2	98.95(±1.98)	0.876	5.7	0.0243	51.62	100.44
S3	100.40(±1.18)	0.854	5.5	0.0265	44.85	100.96
S4	102.00(±1.09)	0.786	5.6	0.0240	44.09	100.79
D1	99.07(±1.88)	0.743	6.0	0.0051	35.89	75.38
D2	99.77(±1.43)	0.766	5.9	0.0056	26.79	74.09
D3	99.43(±1.75)	0.647	6.0	0.0059	21.02	66.72
D4	99.43(±1.75)	0.647	6.0	0.0059	21.02	59.45
D5	99.43(±1.75)	0.647	6.0	0.0059	21.02	57.26
EH	98.56(±2.10)	0.873	6.5	0.0198	34.88	69.94
ED	98.78(±1.97)	0.780	6.2	0.0043	32.94	100.71

Fig. 1: *In vitro* drug release pattern of pentoxifylline matrix tablets prepared with (a) Eudragit RS. (b) HPMC, (c) Sodium alginate, (d) Dealca P-225

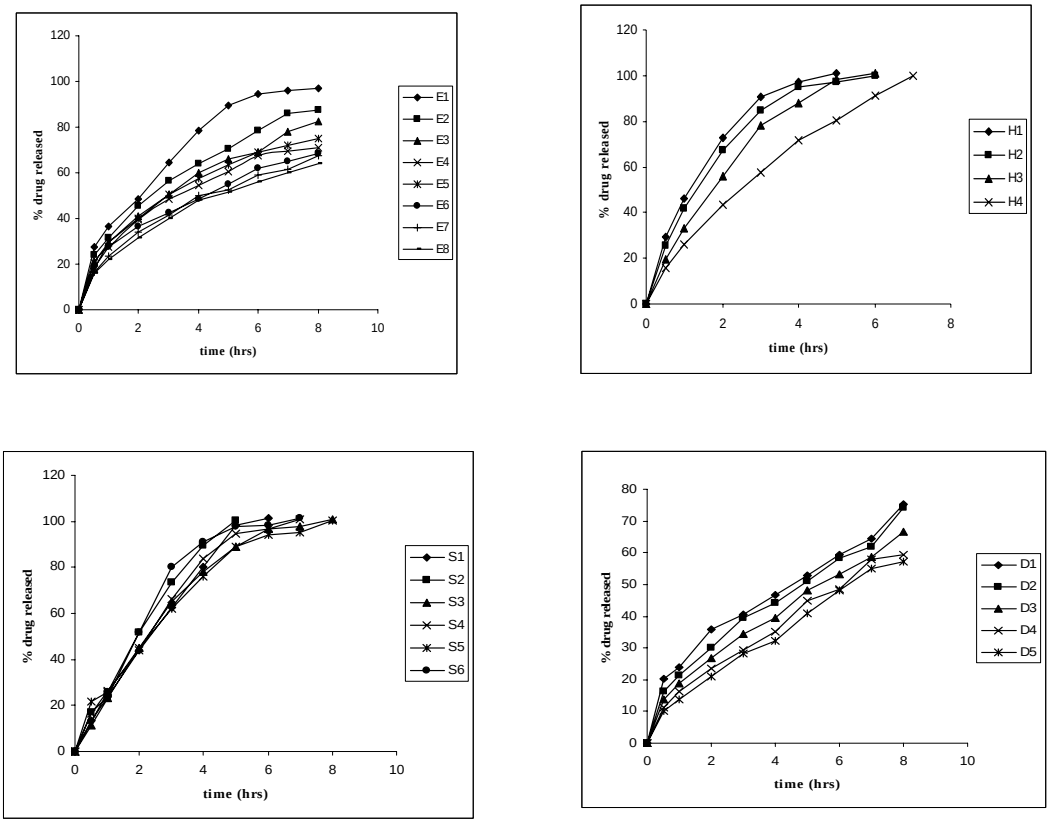
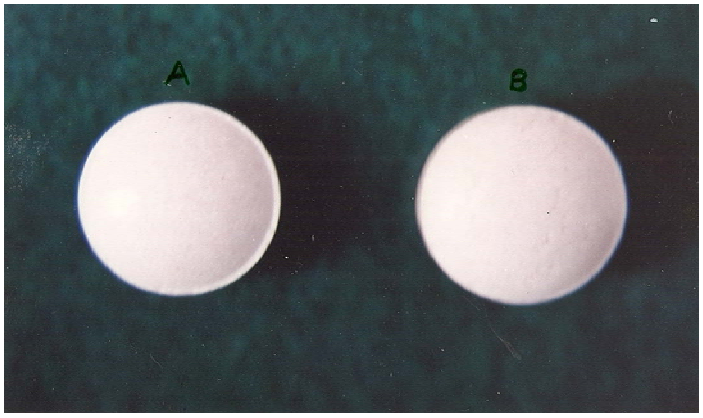


Table 3: Dissolution rates and T values of Pentoxifylline controlled release formulations

Batch code	Dissolution rate K (hrs^{-1})	T_{10} (hrs)	T_{50} (hrs)	T_{70} (hrs)
E1	0.45	0.23	1.53	2.65
E2	0.25	0.42	2.77	4.81
E3	0.19	0.53	3.47	6.02
E4	0.15	0.70	4.62	8.03
E5	0.17	0.63	4.16	7.22
D1	0.15	0.71	4.73	8.23
D2	0.13	0.85	5.61	9.75
D3	0.12	0.90	5.80	10.22
D4	0.11	0.98	6.25	10.85
D5	0.10	1.04	6.83	11.87
EH	0.14	0.77	5.07	8.81
ED	0.73	0.14	0.94	1.64

Fig. 2a: Formulation E5 remained intact after 8 hrs of dissolution.

A: Initial tablet B: After 8 hrs.



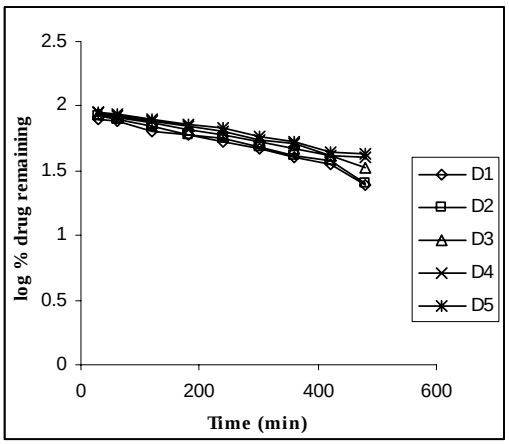
In eudragit formulations, the tablet remained intact after 8 hrs of dissolution study typical of plastic matrix system (Fig. 2a) and dissolved drug diffused through capillary network between compacted polymer particles.

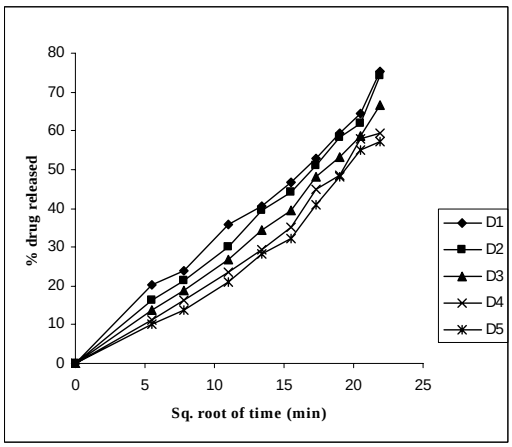
Formulations containing HPMC showed very high dissolution rate for all formulations (H1 to H4) in concentration range of 15-35 % of HPMC while 70 % of drug was released within 1-2 hrs. An increase of polymer concentration was not cost effective hence these formulations were not further investigated.

In case of formulations containing sodium alginate, use of different binders such as sodium alginate (3% w/v), starch paste (5%w/v) and PVP (5%w/v) as in compositions S1,S2,S3,S4 did not show controlled release of pentoxifylline and 70% of drug was released within 2-3 hrs. The formulation using Dealca P-225 (D5 containing 30% polymer) gave very good release pattern with dissolution rate as low as 0.1014 hr^{-1}.

The plots of percent release vs. time were not linear indicating that Pentoxifylline release did not follow the zero order release kinetics. First order plots (log % drug remaining vs. time) exhibited almost linear release pattern (Fig. 3a). In contrast, when percent drug released was plotted against square root of time (Fig. 3b). Release profile showed linear relationship. This confirms that matrix tablets released the drug in a Higuchian diffusion fashion.

Fig. 3: *In vitro* release profile of pentoxifylline formulation using Dealca as polymeric matrix. (a) First order release profile. (b) Higuchi release profile.

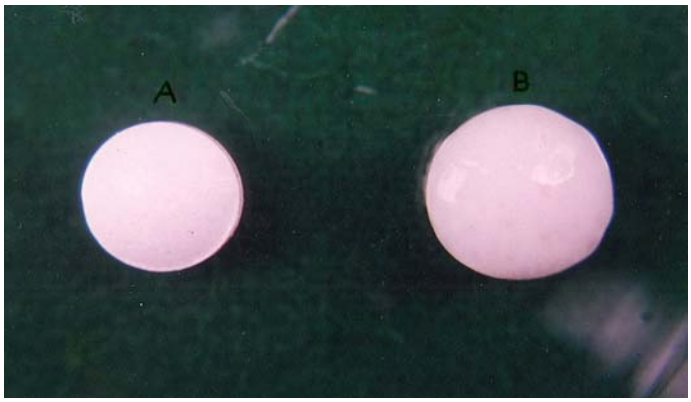




The calculated correlation coefficient (r^2) of the percent drug release versus square root of time was between 0.97-0.99 whereas those of the percent drug release versus time and log percent drug remained versus time were between 0.92-0.99 and 0.96-0.99, respectively. This implied that the best-fit release of drug from the prepared tablets accordingly followed Higuchi model. The percent release versus time plot suggests that formulation (D3) with 26.5% Dealca is the preferred proportion in the preparation of Pentoxifylline matrix tablets for the therapy, as the percent of drug released after 8 hours was nearly to 66.72% [16]. Dissolution data fit first-order kinetics and quite high correlation coefficients were obtained with Higuchi kinetic model.

The formulation D3 showed release rate of 0.12 hr^{-1} and T_{70} was 9-10 hrs. At the end of 8 hrs of dissolution, the tablets were swollen with a thick jelly layer around it indicating that the drug release was controlled by gel diffusional barrier that was formed (Fig. 2b).

Fig. 2b: Formulation D3 remained intact forming swollen thick jelly layer after 8 hrs of dissolution. A: Initial tablet B: After 8 hrs.

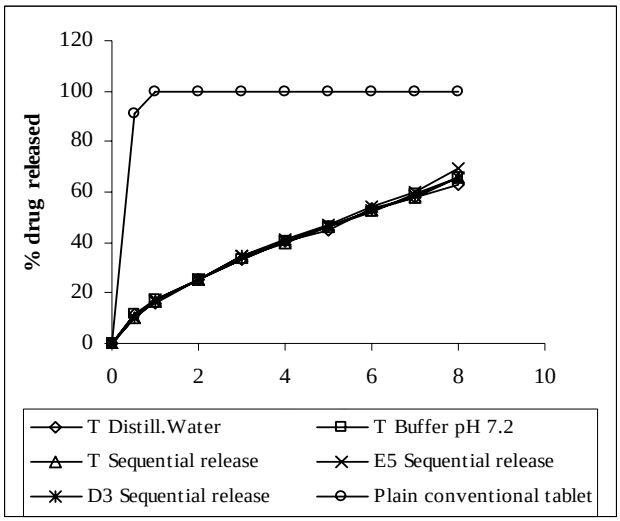


In combination formulations of Eudragit with Dealca (ED) and Eudragit with HPMC (EH), formulation ED showed high dissolution rate and T_{70} of 1.6 hrs. However, formulation EH gave a low release rate of 0.14 $hrs^{-1}$and T_{70} value of 8.8 hrs [Table 3].

Conventional formulation of Pentoxifylline using starch paste as binder released the entire drug within 1 hr. Considering all these points, formulations E5 and D3 were selected for further studies.

Sequential drug release studies of E5 and D3 in purified water, buffer with pH 1.2, 5.5 and 7.2 showed that drug release pattern is independent of the pH of the dissolution medium which was comparable to that of the marketed formulation [Fig. 4]

Fig. 4: Comparative sequential release profile of marketed formulation (T), Dealca P225 formulation D3 and Eudragit RS 30D formulation E5.



CONCLUSION

Pentoxifylline release matrices were prepared successfully utilizing Guar gum (Dealca) as a carrier. Formulations containing Dealca P-225, 26.5% w/w were found to release 70% of drug in 9-10 hrs and their T_{50} values were approximately 6hrs which was comparable to marketed controlled release formulation. The linear regression analysis showed that both the formulations followed diffusion matrix release mechanism and first order release profile.

Thus the natural polymer Dealca P-225 (guar gum) which showed release pattern similar to Eudragit RS 30D and marketed formulation which can be preferred to synthetic and more expensive polymers to give cost effective controlled release formulations.

The proposed Pentoxifylline once a day controlled release tablet could be used in place of 3-4 doses of Pentoxifylline conventional tablets for better control of drug release.

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