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Investigation of the effects of different physicochemical parameters on *in vitro* release kinetics of theophylline from Eudragit NE 30 and Eudragit RS 30D matrix tablets

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Abstract:
The present study was considered out to investigate the effects of various physicochemical factors such as compression force, pH of dissolution medium, amount of HPMC (hydroxyl propyl methyl cellulose) on Eudragit NE 30D and Eudragit RS 30D based matrix tablet of Theophylline. Here tablets were prepared using hydraulic press at different compression pressure and using varying concentration of HPMC. *In vitro* dissolution the studies were carried out using a USP dissolution tester at different pH to observe the effects of pH on release from matrix tablets. The study showed that the compression pressure (2, 3, 4, 5, 6 and 8 tons) had a significant influence on the release behavior of the matrix disks and the release rate was found to be higher with decreased compression pressure. It was found that the release rate markedly increased with the addition of HPMC in the matrices. The effect of pH on drug release is insignificant when Eudragit NE 30D and RS 30D based theophylline matrix tablet was prepared. Theophylline matrix tablet can be successfully prepared using Eudragit NE 30D and Eudragit RS 30D. Optimum Compression pressure should be used for drug release retardation. Using a judicious amount of HPMC with Eudragit NE 30D and RS 30D sustained release matrix tablet can be prepared.

Key words: *Eudragit RS 30D, Eudragit NE 30D, Theophylline, compression force, HPMC, pH*

Introduction

The Biopharmaceutical Classification System (BCS) was developed primarily in the context of immediate release (IR) solid oral dosage forms. It is the scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability [1].The BCS takes into account the three major factors governing bioavailability viz. dissolution, solubility and permeability. The BCS class I drugs exhibit low solubility and high permeability characteristics [2]. Their oral absorption is mostly governed by *in vivo* dissolution; the solubility and the dissolution rate are therefore key determinants for the oral bioavailability of these drugs. This implies that a small increase in the dissolution rate will result in a multi-fold increase in bioavailability [3].

A wide array of polymers has been employed as drug release retarding agents each of which presents a different approach to the matrix concept. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the release of drug. Plastic polymers, e.g., ethyl cellulose and acrylates, which are capable of forming insoluble or skeleton matrices, have been widely used for controlled release of drugs due to their inertness and drug embedding ability. Liquid penetration into the matrix is the rate- controlling step in such systems, unless channeling agents are used [4]. Acrylic polymers are widely used as tablet coatings and as retardants of drug release in sustained released formulations [5].

Probably the simplest and least expensive way to control the release of an active agent is to disperse it in an inert polymeric matrix [6]. In polymeric system, the active agent is physically blended with the polymer powder and then fused together by compression moulding, which is a common process in the pharmaceutical industry [7-9]. These dosage forms are designed to deliver the drug at a controlled and predetermined rate, to maintain a therapeutically effective concentration of the drug in the systemic circulation for a longer period of time

reducing the frequency of dosing to improve patient compliance [10-11].

Anhydrous theophylline being a xanthine bronchodilator, is used in the treatment of both chronic and acute asthmatic attacks. Due to its low therapeutic index, careful control of its release from dosage forms has to be ensured. Faulty formulation may result in the release of large amounts of theophylline, i.e., dose dumping, and hence could produce toxic effects [12].

In the present study, the comparative potentiality of Eudragit NE 30D (ethyl acrylate-methyl methacrylate based copolymer 2:1 in the ratio) and Eudragit RS 30D (poly ethyl acrylate, methyl acrylate, trimethyl ammonio ethyl methacrylate chloride in the 1:2:2 ratio) [13] as matrix material for controlling the release of active ingredient has been investigated. Effect of various physiochemical factors such as compression pressure, pH of dissolution medium, and effect of different concentration of HPMC on Eudragit polymers were studied.

Materials and methods

Materials used in this experiment are theophylline, which was a generous gift from Square Pharmaceuticals Ltd., Eudragit NE 30D and Eudragit RS 30D (BASF, Germany), Aerosil (BASF, Germany) and Magnesium stearate (BDH, UK) and all other solvents and chemicals used, were of reagent grade.

Study of compression pressure on Theophylline release from Eudragit NE 30D & Eudragit RS 30D matrix tablets:

Six batch of matrix tablets were prepared using previously prepared 80% Theophylline loaded granules, at different compression pressures (*viz*. 2 tons, 3 tons, 4 tons, 5 tons, 6 tons and 8 tons). "Perkin Elmer", hydraulic press was used for compression. Theophylline and Eudragit polymer were used in the ratio of 8:2 in every tablet. Weight of each disk was 300mg containing 240 mg of Theophylline and 60 mg of Eudragit polymer (Eudragit NE 30D & Eudragit RS 30D). Stainless still die and punch with 13 mm diameter were used in hydraulic press for compression. Tablets prepared with 2, 3, 4, 5, 6 and 8 ton pressure using Eudragit NE 30D were coded as NEP-2T, NEP-3T, NEP-4T, NEP-5T, NEP-6T, NEP-8T respectively and Tablets prepared with 2, 3, 4, 5, 6 and 8 ton pressure using Eudragit RS 30D were coded as RSP-2T, RSP -3T, RSP -4T, RSP -5T, RSP -6T, RSP -8T respectively.

The release kinetics from disks at different pH (2, 3, 4, 5, 6 and 7) media was studied. For study of the effect of pH on drug release tablet prepared with 5 ton pressure was used and the formulation was same as the previous. Results of dissolution from Eudragit NE 30D based matrix tablet at 2, 3, 4, 5, 6 and 7 pH were coded as NEP-2, NEP-3 NEP-4, NEP-5, NEP-6, NEP-7 respectively and Results of dissolution from Eudragit NE 30D based matrix tablet at 2, 3, 4, 5, 6 and 7 pH were coded as RSP-2, RSP -3 RSP -4, RSP -5, RSP -6, RSP -7 respectively.

***Study of Theophylline release kinetics from Eudragit NE30D & Eudragit RS 30D matrix tablets using different amount of HPMC*:**

Six batches of matrix tablets were prepared using previously prepared granules and different amounts of HPMC at 5 compression pressures. "Perkin Elmer", hydraulic press was used for compression. Theophylline and Eudragit polymer were used in the ratio of 8:2 (240 mg theophylline and 60 mg Eudragit) in every tablet.

Evaluation of tablets

a) In vitro release studies

In vitro drug release studies from the prepared matrix tablets were conducted using a six station USP XXII type-1 apparatus at 37 ± 0.5°C and 50 rpm speed.

Table1: Amount of granules & HPMC following by total weight of tablet belonging to each batch.

Batch No.	Granules (mg)	HPMC (mg)	Total (mg)
NE 1/ RS 1	300	50	350
NE 2 / RS 2	300	100	400
NE 3 / RS 3	300	150	450
NE 4 / RS 4	300	200	500
NE 5 / RS 5	300	250	550
NE 6 / RS 6	300	300	600

NE = Eudragit NE 30D based and RS = Eudragit RS 30D based formulation

The dissolution studies were carried out in duplicate for 8 hours in distilled water under sink condition. At specific time interval samples of 10 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solution was analyzed at 271 nm for theophylline by an UV spectrophotometer (Shimadzu, Japan). The amounts of drug present in the samples were calculated with the help of appropriate calibration curves constructed from reference standards. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

b) Data treatment:

Different kinetic equations (zero-order, higuchi equation) were applied to interpret the release rate from matrix system. Table-2 summerizes the values of n, K and the correlation-coefficient (R2) obtained with all the experimental batches prepared with NE 30D and RS 30D polymer.

Results and discussion

In vitro dissolution data showed that after 8 hr 95.44%, 89.11%, 81.21%, 78.44%, 74.65% and 70.21% drug were released when 2 ton, 3 ton, 4 ton, 5 ton, 6 ton and 8 ton pressure were used to prepare tablet using Eudragit NE 30D as a rate controlling polymer. In case of Eudragit RS 30D after 8 hr 93.66%, 85.66%, 78.88%, 75.0%, 70.99% and 67.49% drug were released when 2 ton, 3 ton, 4 ton, 5 ton, 6 ton and 8 ton pressure were used to prepare tablet.

Dissolution data at different pH showed pH independent release profile. When Eudragit NE 30D is used after 8 hr of dissolution 77.0%, 78.88%, 75.47%, 78.44%, 77.65% and 78.66% drug were released at 2, 3, 4, 5, 6 and 8 pH. In case Eudragit RS 30D is used after 8 hr of dissolution 73.57%, 74.54%, 76.21%, 75.0%, 75.58% and 76.12% drug were released at 2, 3, 4, 5, 6 and 8 pH.

It was also revealed from the investigation that release rate was increased with increase in the amount of HPMC. When Eudragit NE 30D is used after 8 hr of dissolution 76.2%, 77.7%, 78.6%, 86.02%, 88.54% and 88.98% drug were released from NE 1,NE 2, NE 3, NE 4, NE 5, NE 6 . In case of Eudragit RS 30D is used after 8 hr of dissolution 72.0%, 74.2%, 76.1%, 76.4%, 77.46% and 96.0% drug were released from RS 1, RS 2, RS 3, RS 4, RS 5, RS 6. Release rate of all the formulation were calculated from the slop values of the straight line portion of Higuchian plot.

It is also revealed from the dissolution curves that the release from the matrix formulation compiled to Higuchi's matrix dissolution model. Higuchi plot shows that the release pattern was diffusion controlled. Here the release of Theophylline decreased as the pressure increased but zero order release of Theophylline showed a curve release pattern. This indicates that the Theophylline did not follow zero order kinetics. R^2 values of different formulation are mentioned in Table 2.

Table 2: Drug release after 480 minutes from various conditions used in the experiment

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Code	% release after 480 min	Zero-order		Higuchi		Release rate (% release/min)
		Ko (min^{-1}	R^2	k_H ($min^{-1/2}$)	R^2	
NEP-2T	95.44	0.165	0.783	4.159	0.932	4.159
NEP-3T	89.11	0.153	0.798	3.82	0.940	3.820
NEP-4T	81.21	0.150	0.896	3.63	0.987	3.630
NEP-5T	78.44	0.140	0.932	3.32	0.985	3.327
NEP-6T	74.65	0.136	0.937	3.21	0.988	3.212
NEP-8T	70.21	0.127	0.955	2.97	0.984	2.972
RSP-2T	93.66	0.163	0.791	4.09	0.935	4.092
RSP-3T	85.66	0.152	0.808	3.8	0.948	3.805
RSP-4T	78.88	0.148	0.913	3.55	0.990	3.552
RSP-5T	75.0	0.140	0.937	3.312	0.991	3.312
RSP-6T	70.99	0.131	0.950	3.084	0.987	3.084
RSP-8T	67.49	0.125	0.973	2.886	0.978	2.886
NEP- 2	77.0	0.125	0.728	3.190	0.895	3.191
NEP- 3	78.88	0.13	0.744	3.294	0.905	3.294
NEP- 4	75.47	0.145	0.877	3.537	0.981	3.538
NEP- 5	78.44	0.140	0.932	3.327	0.985	3.327
NEP- 6	77.65	0.142	0.948	3.329	0.984	3.329
NEP- 7	78.66	0.146	0.974	3.362	0.97	3.362
RSP-2	73.57	0.119	0.673	3.078	0.852	3.079
RSP-3	74.54	0.130	0.765	3.275	0.919	3.275
RSP-4	76.21	0.146	0.905	3.509	0.989	3.509
RSP-5	75.0	0.140	0.937	3.312	0.991	3.312
RSP-6	75.58	0.141	0.960	3.271	0.976	3.271
RSP-7	76.12	0.145	0.982	3.294	0.954	3.294
NE 1	76.2	0.157	0.996	3.575	0.929	3.576
NE 2	77.7	0.172	0.923	4.140	0.955	3.684
NE 3	78.6	0.162	0.997	3.696	0.929	3.824
NE 4	86.02	0.187	0.993	4.305	0.945	4.208
NE 5	88.54	0.177	0.966	4.208	0.978	4.306
NE 6	88.98	0.194	0.990	4.491	0.953	4.344
RS 1	72.0	0.157	0.985	3.663	0.964	3.664
RS 2	74.2	0.168	0.975	3.949	0.96	3.850
RS 3	76.1	0.17	0.978	3.936	0.943	4.020
RS 4	76.4	0.166	0.981	3.824	0.927	4.036
RS 5	77.46	0.176	0.964	4.096	0.934	4.073
RS 6	96.0	0.218	0.978	4.976	0.914	4.977

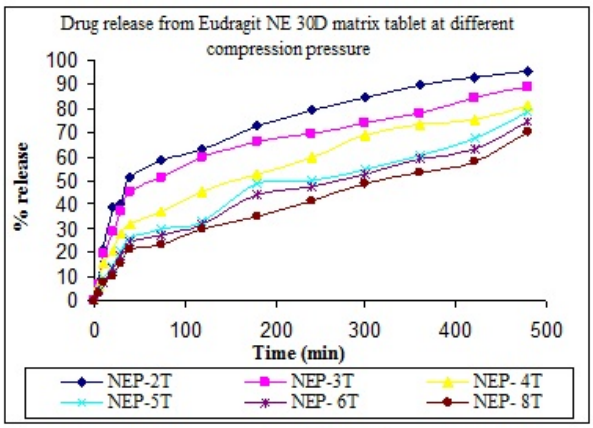


Figure 1

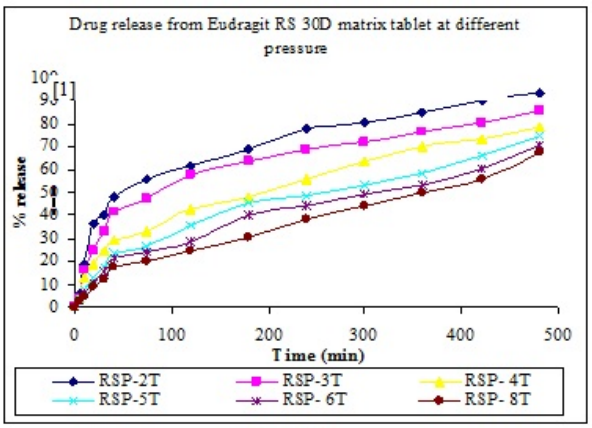
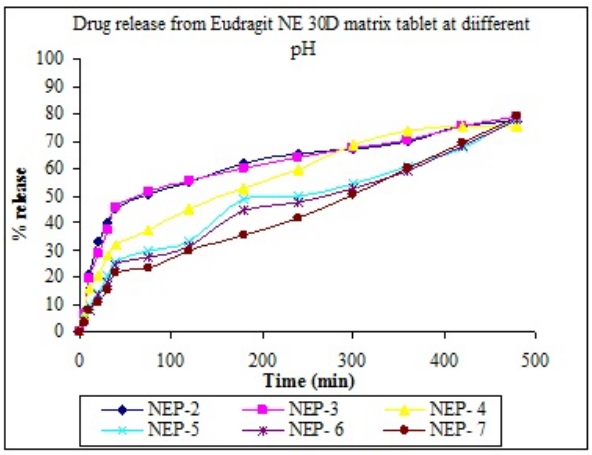


Figure 2



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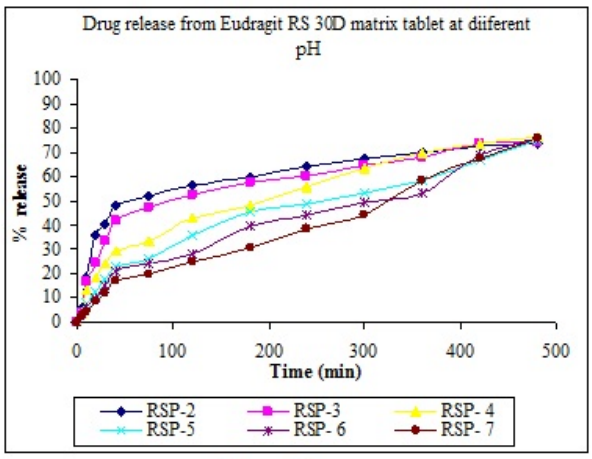

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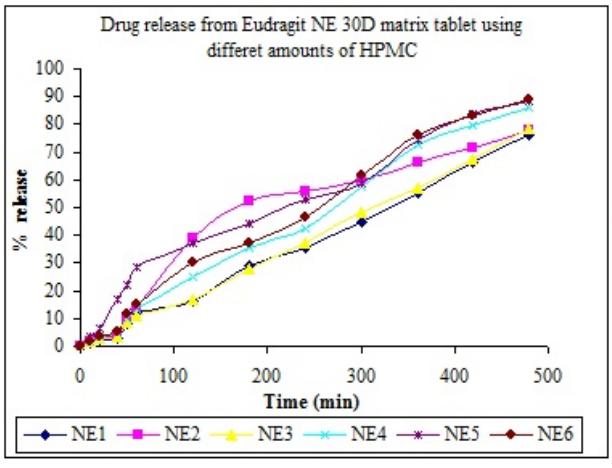

Figure 5

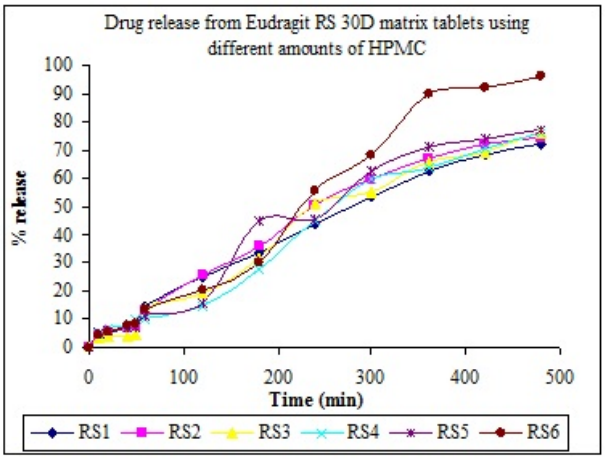

Figure 6

Figure 1 and 2 shows % of drug release at different time interval with tablets compressed at different compression pressure using Eudragit NE 30D and

Eudragit RS 30D respectively. Figure showed that release rate decreased as the pressure increased. This was due to more compaction of the materials in the tablets. As the compression pressure was increased, the thickness of the tablet was decreased and thereby the dissolution of the drug decreases due to decrease in surface area and increase in hardness. This may be related to the low porosity resulted from the hardness of the tablets. Release rate of drug from all matrix tablets were calculated from the slop values of Higuchian plot.

Effect of pH on drug release: Eudragit RS 30D is an aqueous dispersion of copolymers of acrylic acid and methacrylic acid esters with a low content of quaternary ammonium groups. Eudragit RS 30D is less permeable to water and give pH independent release of active substance. Eudragit NE 30D is an aqueous dispersion of neutral copolymer consisting of polymethacrylic acid esters. Films prepared from the lacquer swell in water to which they become permeable. Thus films produced are insoluble in water but give pH-independent drug release. So the effect of pH in the release mechanism of Eudragit coated theophylline matrix tablets is insignificant.

Effect of HPMC on drug release: Figure 3 and 4 shows % of drug release at different time interval with tablets prepared with varying concentration of HPMC using Eudragit NE 30D and Eudragit RS 30D respectively. It was also revealed from the investigation that release rate was increased with increase in the amount of HPMC which can be explained by the fact that the presence of increased amount of HPMC itself caused the matrix to be more hydrophilic in nature. So during dissolution studies the percent of water into the matrix increased manifold which also increased the release rate of water soluble Theophylline.

From the investigation it is found using Eudragit NE 30D and RS 30D can retard drug release and hence suitable for controlled release drug delivery system preparation. Tablet compression pressure has impact on drug release and drug release was inversely proportional with compression pressure. Usually dissolution media influences drug release pattern as solubility of a drug changes with changes in pH. In this investigation it was found that Eudragit based theophylline matrix tablet showed pH independent drug release. Inclusion of hydrophilic binder such as HPMC has impact on drug release. Other factors such as different types of excipients can influence release pattern. Thus a formulation requires a judicious combination of various factors that influence drug release for optimum efficacy of drug. However, further investigation is required to establish *In-vivo-In-vitro* correlation to reveal the accurate pattern of drug release in vivo environment from these polymeric systems.

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