

Preparation and Evaluation of *In Vitro* Release Kinetics of Theophylline Loaded Matrix Tablet Based on Eudragit NE 30 D and Eudragit RS 30 D

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ABSTRACT: In the present study efficiency of Eudragit NE 30 D and RS 30 D as matrix forming materials was investigated. It was found that theophylline loaded granules prepared with these two polymers could not sustain drug release for a significant period of time. However, compression of these granules into tablets retarded drug release for up to 7 hours. Release was similar with both of the polymers. Effects of fillers and rate modifiers on drug release have been assessed. Incorporation of lactose and starch caused substantial release of theophylline from both the polymeric systems. Avicel PH 101 intensified the retardation effect of both NE 30 D and RS 30 D on theophylline release. Hydrophobic excipients also show retardation of release from both NE 30 D and RS 30 D.

Key words: Eudragit RS 30 D, Eudragit NE 30 D, Theophylline, Matrix system, Controlled release

INTRODUCTION

The fluctuating drug concentrations in blood and tissues caused by conventional dosage forms lead to an insufficient influence on the pathological conditions of diseases and are related to the excessive use of a drug. Various oral dosage forms able to control the rate of drug delivery into the systemic circulation have been prepared and studied.¹ In spite of the recent technological advances in the fabrication of oral controlled-release dosage forms, particular attention has been paid to the regulation of drug release rate by means of monolithic devices, whereby prior dispersion of the drug in a polymer matrix is carried out.² Embedding a drug within an

insoluble matrix provides a convenient means of controlling the drug release. In such a system, drug release is preceded by penetration of the dissolution medium into the porous matrix to dissolve the drug, followed by diffusion/leaching of the dissolved molecules out of the matrix. Solid drug on the matrix surface will be dissolved and released first. Upon exhaustion of the surface drug, the depletion zone will then increase progressively as the solid drug front recedes into the matrix.³

A wide array of polymers has been employed as drug-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. Liquid penetration into the matrix is the rate-limiting step in such systems

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unless channeling agents are used.⁴ Utilization of acrylic polymer as plastic rate-retarding matrix has been reported previously.⁵

In the present study, the comparative potentiality of Eudragit NE 30 D (ethyl acrylate-methyl methacrylate based copolymer in the 2:1 ratio) and Eudragit RS 30 D (poly ethyl acrylate, methyl acrylate, trimethyl ammonio ethyl methacrylate chloride in the 1:2:0.02 ratio) as matrix material for controlling the release of active ingredient has been investigated. Wet granulation process with aqueous dispersion of NE 30 D and RS 30 D was carried out to prepare the controlled-release tablets. Effect of excipients with differential physico-chemical property on theophylline release from RS 30 D and NE 30 D systems have been evaluated.

MATERIALS AND METHODS

Materials. Materials used in this experiment are theophylline, which was a generous gift from Square Pharmaceuticals Ltd., Bangladesh. Eudragit NE 30 D and Eudragit RS 30 D (Rohm), Avicel PH 101 (FMC Biopolymer, USA), Stearic acid (BDH, UK), carnauba wax (Loba, India), Lactose (The Lactose Co. of New Zealand, New Zealand), starch (Loba

Chemie pvt. Ltd), Aerosil 200 (Degussa, Germany), and Magnesium Stearate (Wilfrid Smith Ltd, UK) were in the study. All the other chemicals used were of analytical grade.

Preparation of wet mass granules. For the preparation of theophylline loaded granules, 10 ml of polymer dispersion (Eudragit NE 30 D/ Eudragit RS 30 D) was added part by part to 20 g of theophylline with continuous blending. The wet mass was passed through 10 mesh sieve followed by 20 mesh. Finally the granules were passed through 1 mm sieve. These granules were subjected to dissolution studies.

Preparation of compressed tablets. For each batch of matrix formulation 300 mg of prepared granules were measured in an electronic balance and mix with previously measured 100 mg of fillers/release modifier in a blender. A mixing time of 15 minutes was used to produce homogenous granules-exciipient mixture. The formulation code of tablets and granules are presented in Table 1. The appropriate amount of mixture were then compressed using a Perkin-Elmer laboratory hydraulic press equipped with 13 mm flat faced punch and die set. The compression force and compression time were 5 ton and 30 seconds respectively.

Table 1. Composition of different formulations (mg) of matrix tablets

	Theophylline	Eudragit NE 30 D	Eudragit RS 30 D	Starch	Lactose	Avicel PH101	Carnauba wax	Stearyl alcohol
NE-S	260	40	-	100	-	-	-	260
NE-L	260	40	-	-	100	-	-	-
NE-A101	260	40	-	-	-	100	-	40
NE-CAR	260	40	-	-	-	-	100	-
NE-SA	260	40	-	-	-	-	-	100
RS-S	260	-	40	100	-	-	-	-
RS-L	260	-	40	-	100	-	-	-
RS-A101	260	-	40	-	-	100	-	-
RS-CAR	260	-	40	-	-	-	100	-
RS-SA	260	-	40	-	-	-	-	100

Dissolution studies. *In vitro* drug release studies from the prepared matrix tablets were conducted using a six stations USP XXII type 1 apparatus at $37 \pm 0.5^\circ\text{C}$ and 50 rpm speed. 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 theophylline present in the samples were calculated with the help of appropriate calibration curves constructed from reference standard. Drug dissolved at specified time periods was plotted as percent release versus time (hours) curve.

Kinetic modeling of drug release. After completing *in vitro* dissolution of all the batches for eight hours, the data were treated with zero order equation ⁶ and Higuchi equations ⁷ (equation 1-2 respectively).

$$M_t = M_0 + k_0t \dots\dots\dots (1)$$

$$M_t = M_0 - k_H t^{1/2} \dots\dots\dots (2)$$

In these equations, M_t is the cumulative amount of drug released at any specified time (t) and M_0 is the dose of the drug incorporated in the delivery system. k_0 and k_H are rate constants for zero order and Higuchi model respectively. These models failed to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix. Therefore the dissolution data were also fitted to well-known Korsmeyer kinetic equation ⁸ to ascertain the mechanism of drug release.

$$\log (M_t/M_\infty) = \log k + n \log t \dots\dots\dots (3)$$

Where M_∞ is the amount of drug release after infinite time; k is the release rate constant which considers structural and geometric characteristics of the tablet; and n is the diffusional exponent or release exponent; indicative of the mechanism of drug release. For a tablet having cylindrical shape, when n is below 0.45, the Fickian diffusion phenomenon dominates, and n between 0.45 and 0.89 is an anomalous transport (non-Fickian diffusion), often termed as first-order release. After the n value reaches 0.89 and above, the release can be

characterized by case II and super case II transport, which means the drug release rate does not change over time and the release is characterized by zero order. In this case, the drug release is dominated by the erosion and swelling of the polymer.⁹⁻¹⁰

Statistical analysis. The data was subjected to ANOVA for analyzing the statistical difference.

RESULTS AND DISCUSSION

Theophylline granules were prepared with two different polymers, Eudragit NE 30 D and Eudragit RS 30 D. Compressed tablets of the granules were also prepared with different types of release modifier such as Starch, Lactose, Avicel PH 101, Carnauba wax and Stearyl alcohol. Both granules and compressed tablet were then evaluated for *in vitro* dissolution study in distilled water.

The tablets of different formulations were subjected to various evaluation tests, such as weight variation, friability, hardness, and content uniformity according to procedure specified in Indian Pharmacopoeia. The weight variation and friability was less than 6% and 0.5%, respectively. Good uniformity in drug content was found among different batches of the tablets, and the drug content was more than 95% (Table 2). A linear relationship was observed between the hardness and the disintegration time (Figure 1). Maximum disintegration time was found 130 minutes in case carnauba wax containing batches of both NE 30 D and S 30 D where the hardness values were also found maximum as 11.1 ± 0.2 and 10.2 ± 0.3 respectively.

Table 2. Characterization of matrix tablet of Theophylline*

Parameter	NE-S	NE-L	NE-A 101	NE-CAR	NE-SA	RS-S	RS-L	RS-A 101	RS-CAR	RS-SA
Weight variation	401 ± 4.0	402 ± 2.0	399 ± 3.0	405 ± 2.0	402 ± 3.0	403 ± 4.0	402 ± 2.0	401 ± 5.0	401 ± 2.0	402 ± 4.0
Friability (%)	0.33	0.42	0.18	0.17	0.23	0.44	0.36	0.31	0.17	0.33
Hardness (kg/cm ²)	5.4 ± 0.3	5.7 ± 0.2	9.4 ± 0.1	11.1 ± 0.2	9.3 ± 0.2	5.6 ± 0.2	5.8 ± 0.1	9.1 ± 0.3	10.2 ± .3	9.6 ± 0.2
Content Uniformity (%)	98.2 ± 2.1	99.3 ± 3.3	99.1 ± 3.3	98.1 ± 2.4	98.4 ± 3.5	99.1 ± 4.1	97.1 ± 1.1	99.3 ± 2.2	98.2 ± 3.1	98.1 ± 4.4
Disintegration Time (min))	25	15	35	130	125	20	10	30	130	145

*All values represent mean ± SD (n=3)

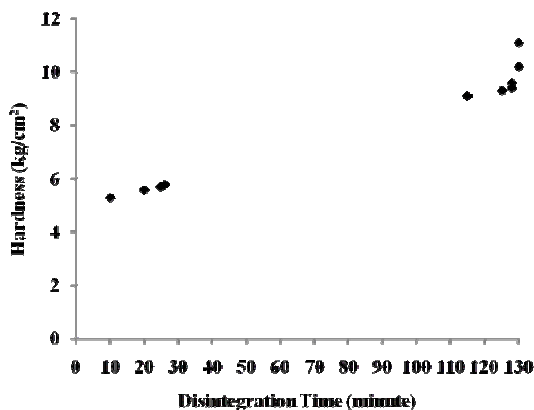


Figure 1. Hardness versus disintegration time relation.

The effects of NE 30 D and RS 30 D polymers on drug release from granules as well as from compressed tablet are presented in Figure 1. Both the polymers could not impart significant sustaining action on drug release from matrix granules ($P < 0.5$). More than 80% of theophylline was released from granules prepared with NE 30 D and RS 30 D within 2 hours. Compression of the granules into tablets at 5-ton compression pressure significantly prolonged the dissolution period for more than 8 hours. Reduction of surface area presented to dissolution fluid is the attributable factor for this observation. Figure 2 also reveals that drug release was almost similar with both of the polymers.

Figure 2 also shows that, after 3 hours 90.21% of theophylline was released from NE 30 D granules whereas 48 % of theophylline was released from NE 30 D matrix tablet. About 91% of the active ingredient was released after 3 hour of dissolution from RS 30 D granules whereas 48 % was released from RS 30D matrix tablet.

Eudragit RS 30 D is a copolymer based on ethyl acrylate and methyl methacrylate with plastic characteristics. These polymers are devoid of gel formation and swelling property. The higher rate and extent of theophylline released from NE 30 D is due to greater extraction of theophylline from the vicinity of matrix surface since NE 30 D do not hydrate quickly to form gelatinous surface barrier around the tablet. With the release of surface drug, numerous pores and channels are generated through which

dissolution fluid enters into the matrix structure and further elevates the rate and extent of theophylline release.

Figure 3 illustrates the effect of starch, lactose, Avicel PH 101, carnauba wax and stearyl alcohol on release behavior of theophylline from Eudragit NE 30 D and RS 30 D compressed tablets. Figure 3a summarizes the effect of the excipients on drug release from NE 30 D polymer based matrix while Figure 3b shows the effect of the excipients on drug

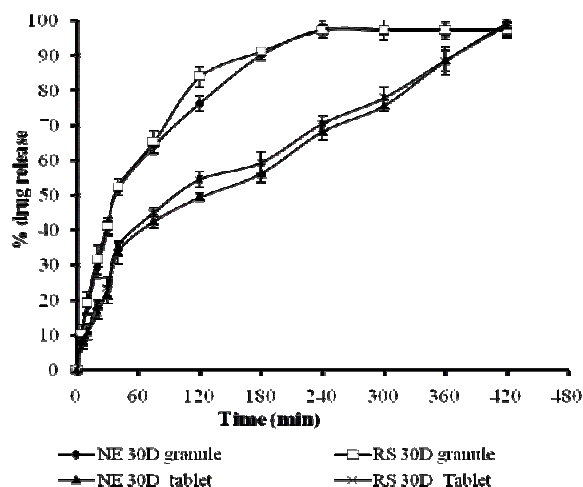


Figure 2. Zero order release profile of theophylline from Eudragit NE 30D and Eudragit RS 30 D. Data are represented as mean \pm SD (n=3).

release from RS 30 D polymer based matrix. In case of both of the polymers, incorporation water soluble and water insoluble fillers influenced the release of theophylline significantly from matrix tablet ($P < 0.01$). Generally, incorporation of water-soluble excipients results in an increase in the drug release rate due to an increment in total porosity of the matrices due to swelling of starch and lactose (initial porosity plus porosity due to the dissolution of the drug). Lactose is water soluble in nature (1 in 4.63 at room temperature).¹¹ Though starch is practically insoluble in cold water, it swells instantaneously in water by about 5-10% at 35°C¹²⁻¹³. This is the reason why starch retarded few more drug than lactose. Both carnauba wax and Stearyl alcohol are water insoluble excipients. Carnauba wax is practically insoluble in water and showed good release retarding capacity. Stearyl alcohol is also practically insoluble in water

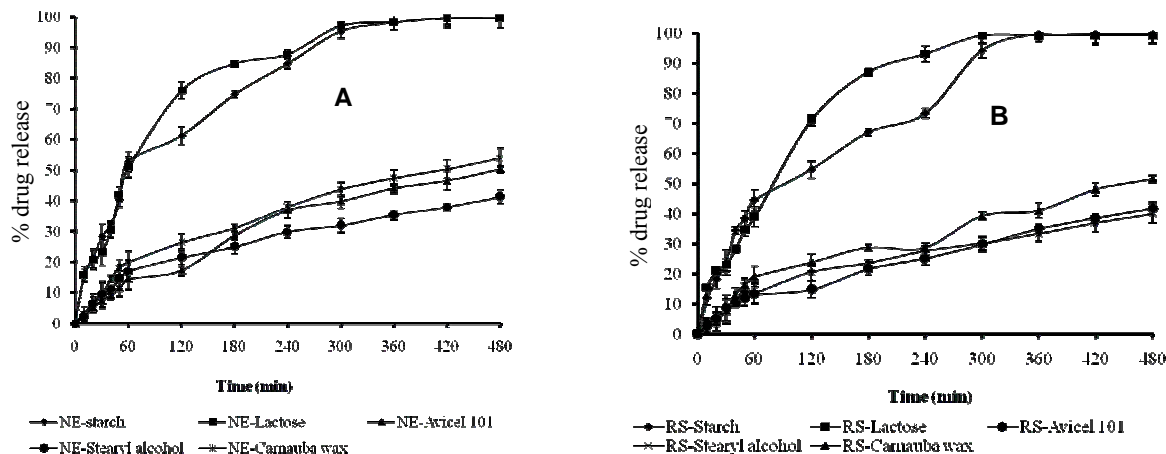


Figure 3. Zero order release profile of theophylline showing effect of excipients on drug release from (a) Eudragit NE 30 D (b) Eudragit RS 30 D. Data are represented as mean \pm SD (n=3)

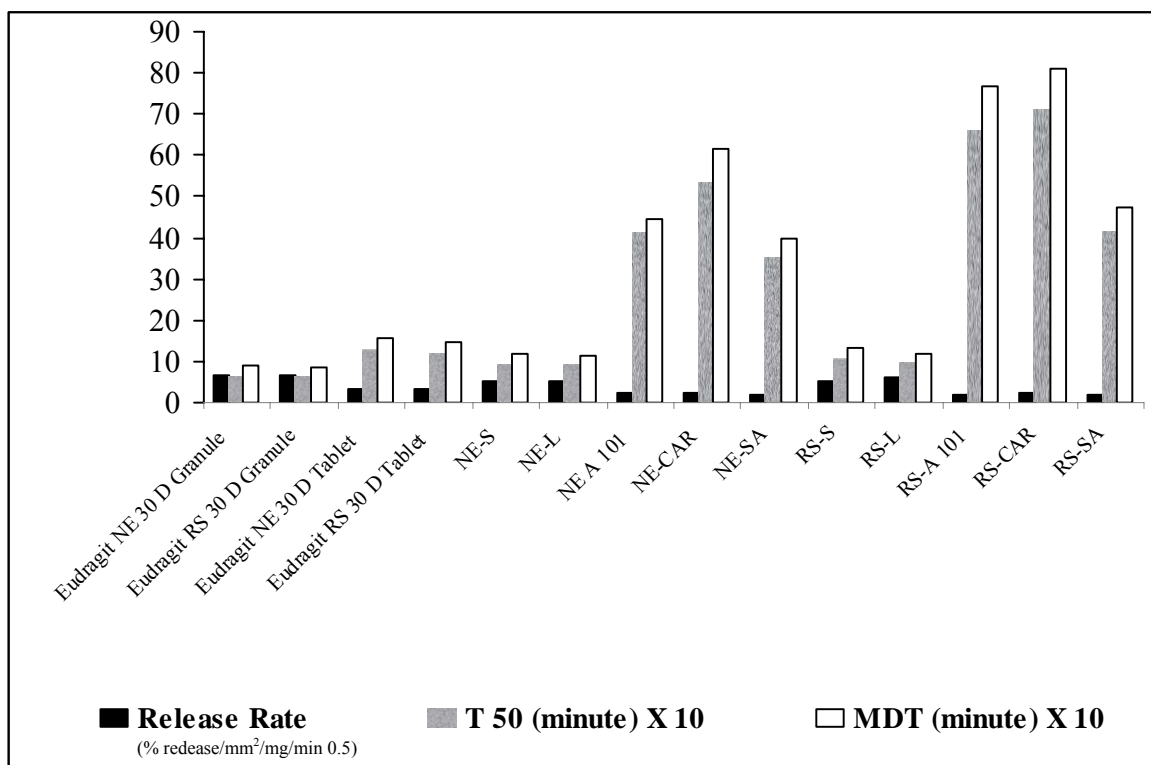


Figure 4. Drug release parameters of different formulas.

and for this reason it has been used in controlled release tablet preparation.¹⁴⁻¹⁵ Similar controlled release behavior of stearyl alcohol is also seen in case of theophylline matrix tablet in this experiment. But amongst all, Avicel PH 101 released lowest amount of drug from both NE 30 D and RS 30 D matrix systems. Incorporation of Avicel PH 101 which is

microcrystalline cellulose retarded drug release. Only 46.5% of drug was released after 7 hours. This might be due to the water insoluble nature of microcrystalline cellulose. Avicel PH 101 is a highly hydrophilic and gel forming excipient which may have formed gel structure at the pores, reducing hydrodynamic activity at the pores and thereby

causing delay in the drug leaching out of the matrix tablets. Hydrophobic excipients retard drug release more effectively compared to hydrophilic excipients. It was observed that 37.88 % and 50.4 % theophylline was released after 7 hours from

formulation containing carnauba wax and stearyl alcohol respectively. Hydrophobicity of both of these excipients is due to the presence of long chain alkyl group in their structures.

Table 3. Mathematical Modeling and Drug Release Kinetics of Theophylline Conventional and Sustained-Release Matrix Tablets*

Batch	r^2 †				n	Order of Release
	Zero Order	First Order	Korsmeyer	Higuchi		
Eudragit NE 30 D granule	0.761	0.879	0.939	0.926	0.491	Non-Fickian
Eudragit RS 30 D granule	0.734	0.888	0.931	0.909	0.481	Non-Fickian
Eudragit NE 30 D tablet	0.942	0.961	0.98	0.989	0.551	Non-Fickian
Eudragit RS 30 D tablet	0.925	0.961	0.989	0.989	0.68	Non-Fickian
NE-S	0.860	0.966	0.974	0.971	0.492	Non-Fickian
NE-L	0.808	0.967	0.950	0.94	0.521	Non-Fickian
NE-A 101	0.960	0.983	0.985	0.982	0.748	Non-Fickian
NE-CAR	0.933	0.975	0.924	0.99	0.635	Non-Fickian
NE-SA	0.916	0.953	0.955	0.988	0.672	Non-Fickian
RS-S	0.900	0.911	0.975	0.981	0.542	Non-Fickian
RS-L	0.825	0.955	0.965	0.943	0.543	Non-Fickian
RS-A 101	0.971	0.985	0.978	0.983	0.619	Non-Fickian
RS-CAR	0.943	0.977	0.930	0.978	0.685	Non-Fickian
RS-SA	0.923	0.945	0.953	0.984	0.67	Non-Fickian

NE and RS indicate Eudragit NE 30 D and Eudragit RS 30 D based formulations respectively. S-Starch, L-Lactose, A 101-Avicel PH 101, CAR-Carnauba wax, and S-Stearyl alcohol. *Analyzed by Regression co-efficient method. † Correlation coefficient

Table 4. Dissolution parameters of Theophylline matrix tablet

Batch	$t_{25\%}$ (minute)	$t_{50\%}$ (minute)	$t_{75\%}$ (minute)	MDT* (minute)
Eudragit NE 30 D granule	15.9 ± 0.1	65.25 ± 0.2	149.01 ± 0.4	88.16 ± 0.5
Eudragit RS 30 D granule	14.6 ± 0.2	61.65 ± 0.6	143.23 ± 0.5	84.60 ± 0.2
Eudragit NE 30 D tablet	35.76 ± 0.1	125.82 ± 0.2	262.63 ± 0.1	157.26 ± 0.7
Eudragit NE 30 D tablet	34.34 ± 0.2	119.47 ± 0.1	247.73 ± 0.1	148.51 ± 0.5
NE-S	21.53 ± 0.4	88.11 v	200.89 ± 0.3	118.87 ± 0.4
NE-L	23.25 ± 0.2	87.95 ± 0.1	191.54 ± 0.1	113.96 ± 0.2
NE-A 101	163.61 ± 0.4	413.30 ± 0.2	710.69 ± 0.2	446.76 ± 0.3
NE-CAR	179.24 ± 0.5	533.96 ± 0.4	1011.162 ± 0.5	617.77 ± 0.3
NE-SA	125.35 ± 0.2	351.63 ± 0.1	642.87 ± 0.1	396.44 ± 0.2
RS-S	29.41 ± 0.2	105.66 ± 0.2	223.26 ± 0.6	133.42 ± 0.1
RS-L	26.40 ± 0.5	94.62 ± 0.4	199.66 ± 0.3	119.34 ± 0.2
RS-A 101	214.32 ± 0.1	656.74 ± 0.5	1264.375 ± 0.1	769.41 ± 0.5
RS-CAR	248.33 ± 0.2	712.09 ± 0.2	1318.72 ± 0.4	810.34 ± 0.5
RS-SA	148.95 ± 0.2	419.12 ± 0.4	767.655 ± 0.1	473.1514 ± 0.2

*MDT indicates mean dissolution time. All values represent mean ± SD (n=3).

Release data were then fitted in different model. Most of the release curves followed Korsmeyer and Higuchi model (Table 3). Non-fickian type release mechanism was observed from all the tablets (n < 0.85). This means theophylline from matrix tablets of all the formulations were released following diffusion as well erosion⁹. Release rate (% release

/mm²/mg/min^{1/2}) of drug were calculated from the slope values of the straight line of the Higuchi plot. The values of release rate of different formulations are shown in Figure 4. Release rate for formulation NE-S, NE-L, NE-A101, NE-CAR, NE-SA were 5.15, 5.38, 2.53, 2.60 and 1.99 respectively which shows that release rate is higher with hydrophilic excipients

and lower than hydrophobic excipients. On the other hand release rates of RS-S, RS -L, RS -A101, RS -CAR, RS -SA formulations were 5.28, 6.36, 1.91, 2.41 and 1.88 respectively. T50% and mean dissolution time (MDT) of different formulas were plotted in Figure 4.

Formulations containing Eudragit NE 30 D granules, RS 30 D granules, NE 30 D tablets, RS 30 D tablets have shown better fitting with korsmeyer equation than zero order or first order equation. The R^2 values of korsmeyer equation for the above mentioned formulations were 0.9399, 0.9316, 0.983, and 0.9826 respectively. Release exponent (n) values of the above mentioned formulation were 0.491, 0.481, 0.551, and 0.681 respectively which indicates that release pattern of the drug was anomalous. The R^2 value of korsmeyer equation for formulation NE-S, NE-L, NE-A101, NE-CAR, NE-SA formulations were 0.9746, 0.9505, 0.985, 0.924, and 0.955 respectively. The R^2 values of first order equation for the above mentioned formulations were 0.9669, 0.9677, 0.9831, 0.975, and 0.9535 respectively. Release exponent (n) values of the above mentioned formulation were 0.492, 0.521, 0.748, 0.635, and 0.6721 respectively. The R^2 value of korsmeyer equation for formulation RS-S, RS -L, RS -A101, RS -CAR, RS -SA formulation were 0.975, 0.9659, 0.978, 0.9309 and 0.953 respectively. Release exponent (n) values of the above mentioned formulation were 0.542, 0.543, 0.6195, 0.685, and 0.67 respectively.

CONCLUSION

The experiment reveals that, it is possible to design controlled release drug delivery systems with Eudragit RS 30 D and RS 30 D polymers by wet granulation method. Fabrication of pellets / granules entails the incorporation of stronger rate-retarding agents. Drug release from compressed tablets prepared with NE 30 D and RS 30 D system was found to be critically governed by the excipients present in the system. 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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