RESEARCH ARTICLE

Effect of acrylic polymers on physical parameters of spheronized pellets using an aqueous coating system

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The aim of this study was to develop ambroxol hydrochloride sustained release pellets by an extrusion-spheronization technique and subsequent coating with acrylic polymers. Acrylic polymers like Eudragit RL 30 D, Eudragit RS 30 D and Eudragit NE 30 D were used as release retarding coating polymers. The release retarding capability of these polymers was also investigated. In each case, 10% polymer on dry basis was loaded. The flow property, surface roughness as well as the drug release behavior of the pellets was found to be the subject of types of polymers. About 35% drug was released at the first hour in 0.1N HCl media (pH 1.2) from Eudragit RL 30 D-coated pellets but from Eudragit RS 30 D and Eudragit NE 30 D-coated pellets, only 13.75 and 2.43% drug was released, respectively. In buffer media (pH 6.8), about 54% drug was released at the first hour from Eudragit RL 30 D-coated pellets but only 64% drug was released at 10 h. From Eudragit RL 30 D- and Eudragit NE 30 D-coated pellets only 7.28 and 1.14% drug was released at 1 h, respectively, but about 5.14 and 5.86 h was required for 50% drug release from these two polymers and about 80% drug was released at 10 h. The functional groups present in the polymeric films played a significant role on *in vitro* release kinetics of the drug from the coated pellets. Different kinetic models like zero order, first order and Higuchi were used for fitting the drug release pattern. The Higuchi model was the best fitted for ambroxol release from the coated pellets. The drug release mechanism was derived with Korsmeyer equation.

Key words: *Ambroxol hydrochloride, pellets, extrusion-spheronization, aqueous coating, acrylic polymer, physical properties*

INTRODUCTION

Pelletization is increasingly applied currently for the preparation of solid oral controlled-release dosage forms. The production of the particles, which are regular in shape and size, can be achieved with the application of the proper polymer auxiliary materials and new pharmaceutical technological methods (extrusion, spheronization). Regularity in shape and size, attained by the optimization of several production parameters, can promote the coating procedure. Under optimal conditions, particles were prepared for coating in a high-shear mixer, which is used to produce uniform particles.[1-3] Using a marketed microcrystalline cellulose (Avicel PH 101) excipient, optimum extrusion and spheronization conditions for less-soluble drugs required more water, a longer wet mixing time and prolonged spheronizing times.[4] The successful spheronization of extrudates requires the correct water content. This water content is different for the formulations as well as for the extruders. Pellet sphericity was also strongly dependent on the correct water content of the formulations.[5,6]

Aqueous film-coating dispersions generally consist of polymeric colloidal particles, a plasticizer, a pigment and an anti-adherent agent.[7] Polymethacrylates are primarily used in oral capsule and tablet formulations as film-coating agents[8,9] Depending on the type of polymer used, films of different solubility characteristics can be produced. Eudragit RL 30 D and Eudragit RS 30 D are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with a low content of quarternary ammonium groups.[10,11] The quarternary groups occur as salts and are responsible for the permeability of films made from these polymers. Film coatings prepared from both polymers give a pH-independent release of the active substance. Plasticizers are usually added to improve the film properties.[10] The most widely used aqueous polymer dispersions for sustained-release coating

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applications are either ethylcellulose-based (Aquacoat ECD, Surelease) or acrylate-based (Eudragit RL 30 D-ammonio methacrylate copolymer Type A; Eudragit RS 30 D-ammonio methacrylate copolymer Type B; Eudragit NE 30 D and others) products. Eudragit® NE 30 D is the aqueous dispersion of a neutral copolymer based on ethyl acrylate and methyl methacrylate. On aging, an endogenous surfactant (nonoxynol 100) of Eudragit NE 30 D was recently found to be prone to gradual precipitation from the cast-free film, thereby creating pores in the film and potentially affecting product dissolution.[12,13]

Ambroxol is a metabolite of bromhexine with similar actions and uses.[14] It is chemically described as trans-4-[(2-Amino-3,5-dibromobenzyl)amino]-cyclohexanol. It is an expectorant and a mucolytic agent used in the treatment of acute and chronic disorders characterized by the production of excess or thick mucous. It has been successfully used for decades in the form of its hydrochloride as a secretion-releasing expectorant in a variety of respiratory disorders.[15] The biological half life of this drug is 4 h,[16-17] which facilitates its frequent daily dosing (two to three times). For this, the therapeutic use in chronic respiratory diseases necessitates its formulation into a sustained release dosage form. The aim of the present study is to prepare ambroxol hydrochloride sustained-release pellets as well as to investigate the effect of acrylic polymers like Eudragit RL 30 D, Eudragit RS 30 D and Eudragit NE 30 D on the release kinetics of drug from the coated pellets and to assess the release rate retarding properties.

MATERIALS AND METHODS

Materials used in this experiment are ambroxol hydrochloride (Alchymars ICM Pvt. Ltd., Kancheepuram District, Tamil Nadu, India), maize starch (Cerestar, Coenhavenweg, Amsterdam, The Netherlands), lactose (The Lactose Co. of New Zealand Ltd., Hawera, New Zealand), avicel pH 101 (Ming Tai Chemical Co., Bah-Der City, Taiwan), HPMC 6cps (Shin-etsu, Chioda-Ku, Tokyo, Japan), purified talc (Asian Mineral, Bangkok, Thailand), titanium dioxide (Warner Jenkinson, Italy), triethyl citrate (Morflex Inc., Greensboro, North Carolina, USA), Eudragit RL 30 D (Rohm Pharma., Darmstadt, Germany), Eudragit RS 30 D (Rohm Pharma., Darmstadt, Germany) and Eudragit NE 30 D (Rohm Pharma., Darmstadt, Germany). All other chemicals were analytical grade.

Preparation of ambroxol hydrochloride sustained-release pellets

Extrusion-spheronization technology was followed to prepare the ambroxol hydrochloride sustained-release pellets. For the preparation of drug-loaded pellets, a wet mass was prepared with ambroxol hydrochloride, lactose, maize starch, avicel pH 101, HPMC 6 cps and purified water [Table 1]. The wet mass was passed through a 0.8-mm aperture screen (SS) of the screen type Extruder (Extruder 35, Caleva, UK) to prepare the extrudates. The extrudates were loaded on the specially designed pan of the spheronizer (Spheronizer 500, Caleva, UK) and the pan was rotated at 550-570 rpm for 2-3 min to prepare the spherical pellets. Then, all the pellets were dried at 55-60°C for 6-7 h and sieved through 20 and 24 mesh to get the desired size (20/24) of the drug-loaded pellets [Figure 1]. Then, to prepare the sustained-release coating suspension, a paste was prepared using purified talc, titanium dioxide and purified water. Then, Eudragit RL 30 D (10% polymer on dry basis) and triethyl citrate were added respectively and diluted with purified water to make the final weight of suspension according to Table 1. Then, 300.00 g of drug-loaded pellets was taken in the bottom-spray Lab coater (Wurster column) and coating suspension was sprayed according to Table 2. After completion of spraying, the coated pellets were dried at 55-60°C for 5-6 h and sieved through 18 and 24 mesh to get the desired size (16/24) of the final coated pellets and the lot is termed as F1 [Table 1]. The same process was applied in case of Eudragit RS 30 D and Eudragit NE 30 D (10% polymer load on dry basis in each case) and the lots were termed as F2 and F3, respectively [Table 1].

Moisture content

Table 1: Formula of ambroxol hydrochloride sustained-release pellets (weights in g)

Materials	Formulation code		
	F1	F2	F3
Core			
Ambroxol hydrochloride	109.091	109.091	109.091
Maize starch	16.364	16.364	16.364
Lactose	38.182	38.182	38.182
Avicel pH 101	121.363	121.363	121.363
HPMC 6 cps	15.000	15.000	15.000
Water	150.000	150.000	150.000
Coating			
Eudragit RL 30 D*	100.000	-	-
Eudragit RS 30 D*	-	100.000	-
Eudragit NE 30 D*	-	-	100.000
Talc	3.000	3.000	3.000
Titanium dioxide	1.500	1.500	1.500
Triethyl citrate	4.500	4.500	4.500
Water	200.000	200.000	200.000

*30% dispersion commercial grade used

Table 2: Machine parameters set up during coating in the fluid bed coater

Parameters	Setting
Inlet air temperature	50-55°C
Outlet air temperature	29-32°C
Product temperature	35-40°C
Chamber humidity	55%
Air flow	90 m^3/h
Spraying pressure	1.20 bar
Spraying rate	3.0 g/min

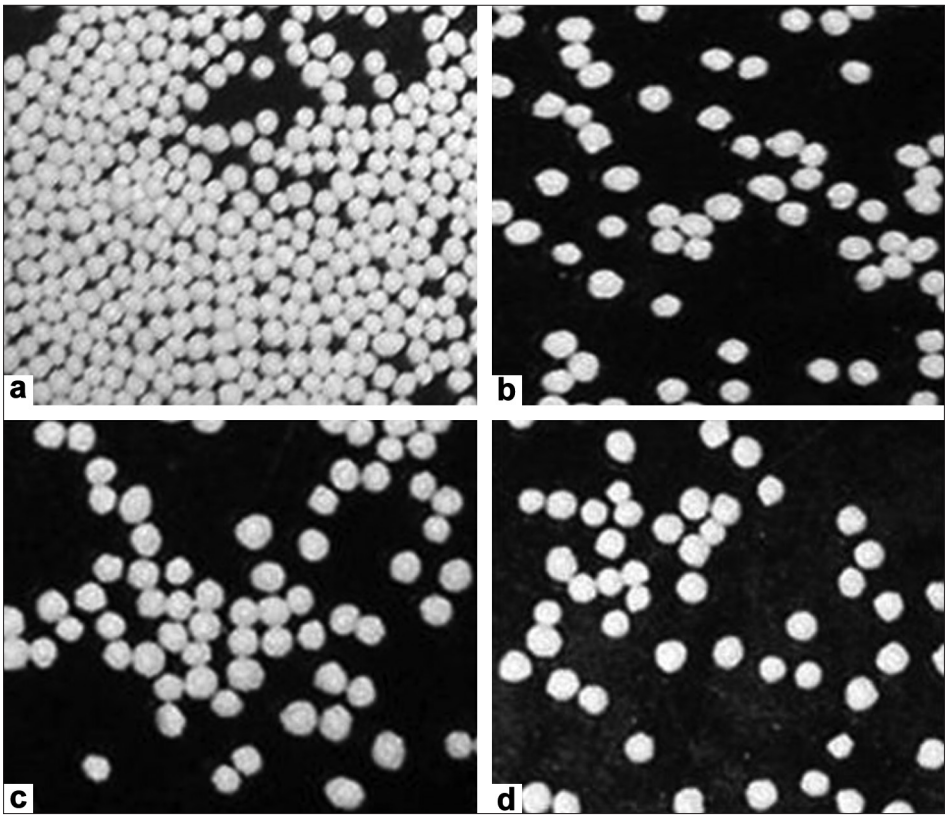

Figure 1: Drug loaded beads (dried, 18/24 size) prepared by extrusion-spheronization technique (a: Core beads; b: Eudragit RL 30 D, c: Eudragit RS 30 D, d: Eudragit NE 30 D coated pellets)

The moisture content (% loss on drying) of the dried and sieved pellets (18/24) was determined using Mettler Toledo Halogen Moisture Analyzer (Model HB43, Mettler Toledo Inc., Columbus, Ohio, USA) where the working temperature was 105°C.

Friability

Friability test of the drug-loaded beads (18/24) was performed for 10 min at 24 rpm using the Electrolab EF-2 Friabilator [Goregaon (East), Mumbai, India].

Bulk density

Bulk density of the dried and sieved pellets (18/24) was determined using bulk density detector (Stampfvolumeter, STAV 2003, Jel, Ludwig-schafen, Germany) after performing 100 strokes to measure a cylinder containing 10 g of the sample.

Assay

Pellets (18/24) were crushed to powder and then 60 mg of the powder was taken in a 100 ml volumetric flask and the required amount of 0.1N HCl was added. This was then sonicated for 10 min in an ultrasonic water bath and filtered. The filtrate was suitably diluted with 0.1N HCl. The quantity of ambroxol hydrochloride in the prepared pellets was determined spectrophotometrically using 0.1N HCl as blank and the absorbance was measured at 244 nm with Shimadzu UV-Visible spectrophotometer (Shimadzu Corporation, Nakagyo-Ku, Kyoto, Japan).

***In vitro* dissolution study**

The dissolution of the prepared ambroxol hydrochloride sustained-release pellet was studied by Erweka (Germany) dissolution tester USP (XXVIII) using USP apparatus II (Paddle method). Ambroxol hydrochloride sustained-release pellets equivalent to 75 mg of ambroxol hydrochloride were used in 900 ml of dissolution medium (0.1N HCl, pH 1.2) at 370 ± 0.5°C with 50 rpm for 1h.[18,19] At the end of 0.5 and 1 h, drug content of the sample solution was determined spectrophotometrically at 244 nm using a UV-Visible spectrophotometer (Shimadzu). After 1 h, by replacing the acid media, 900 ml dissolution media (KH_2PO_4 buffer, pH 6.8) was added in each vessel and the machine was run at 50 rpm for the next 10 h. Samples were drawn at every 1-h interval and the drug content of the collected samples were determined spectrophotometrically at 244 nm using a UV-Visible spectrophotometer (Shimadzu).

RESULTS AND DISCUSSION

The ambroxol hydrochloride pellets were prepared following the extrusion-spheronization technique and then coated with polymers in the fluid bed coater (Wurster column). The cumulative percent of drug release was plotted in different fashions in Figures 4-6. It was revealed that the release

kinetics of the drug is a function of the physicochemical properties of the polymers.

No significant difference was found among moisture content values and bulk density of the prepared pellets from three different formulations [Table 3]. The Eudragit NE 30 D polymer-coated pellets showed an agglomeration and twinning tendency [Figure 2] during coating and storage and this problem was solved by the addition of a small amount of purified talc, but this type of problem was not observed while core pellets were coated with Eudragit RL 30 D and Eudragit RS 30 D. The mean drug content was found to be maximum for pellets coated with Eudragit NE 30 D and minimum drug content was found for Eudragit RS 30 D-coated pellets [Figure 3]. The maximum yield was found from Eudragit RL 30 D-coated pellets and the converse was obtained from Eudragit NE 30 D-coated pellets due to agglomeration behavior of the Eudragit NE 30 D polymer. But, Eudragit NE 30 D-coated pellets showed the least friability [Table 3]. The aesthetic view and surface smoothness of Eudragit RS 30 D-coated pellets seemed to be better than that of the other polymer-coated pellets. Better flow property was exhibited by Eudragit RL 30 D- and Eudragit RS 30 D-coated beads [Table 3]. The potency of the finished pellets of all batches was found to be close to the theoretical value (32.18%), indicating a better efficiency of the spheronization as well as the coating process.

The best release rate retarding properties was attributed in case of Eudragit RS 30 D and Eudragit NE 30 D but Eudragit RL 30 D failed to express the sustaining effect. While dissolution was performed in the acid media, about 21 and 35% of the drug was released at 0.5 and 1 h, respectively, when ambroxol hydrochloride-loaded pellets were coated with Eudragit RL 30 D [Figure 4]. Films prepared from Eudragit RL 30 D are readily permeable to water and dissolve active substances,[10,11,20] which can be attributed to higher percentage of drug release within a short time. But, in case of Eudragit RS 30 D-coated pellets, 13.75% drug was released at the first hour [Figure 4], which might be due to low permeability properties as well as the presence of quaternary

Table 3: Physical properties of the prepared pellets of three different formulations

Parameters	Formulation codes		
	F1	F2	F3
% Yield (after coating)	96.51	94.16	89.32
% LOD	1.93 ±1.25	1.94 ± 1.12	1.93 ± 0.67
% Potency	30.17 ± 1.65	28.86 ± 1.44	31.02 ± 2.03
True density (g/cc)	1.18 ± 0.01	1.21 ±0.00	1.19 ± 0.01
Bulk density (g/cc)	0.88 ± 0.02	0.86 ± 0.01	0.91 ± 0.03
Friability (%)	0.36 ± 0.04	0.28 ± 0.15	0.22 ± 0.07
Flow property	++	++	+
Surface roughness	+	+	++
% Agglomeration	-	-	++

LOD - Loss on drying; (mean ± SD, *n* = 3); F1: Eudragit RL 30 D; F2: Eudragit RS 30 D; F3: Eudragit NE 30 D coated pellets

Figure 2: Twinned and agglomerated pellets coated with Eudragit NE 30 D

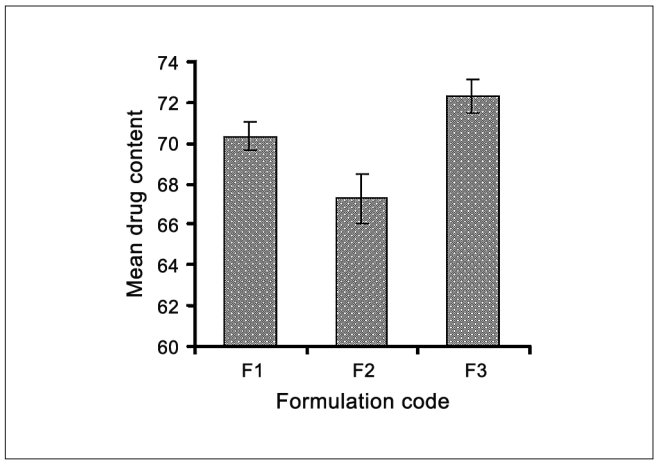

Figure 3: Mean drug content (mg/230 mg of pellets) of different polymer coated pellets (F1: Eudragit RL 30 D, F2: Eudragit RS 30 D, F3: Eudragit NE 30 D coated pellets)

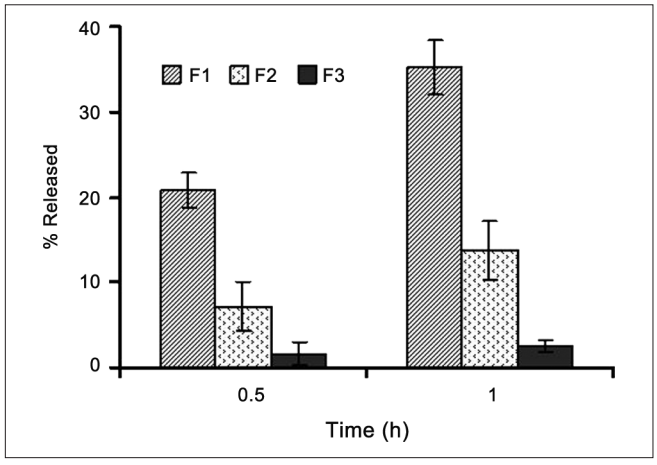

Figure 4: Release of ambroxol hydrochloride from coated pellets in 0.1N HCl at 0.5h and 1h (F1: Eudragit RL 30 D, F2: Eudragit RS 30 D, F3: Eudragit NE 30 D coated pellets)

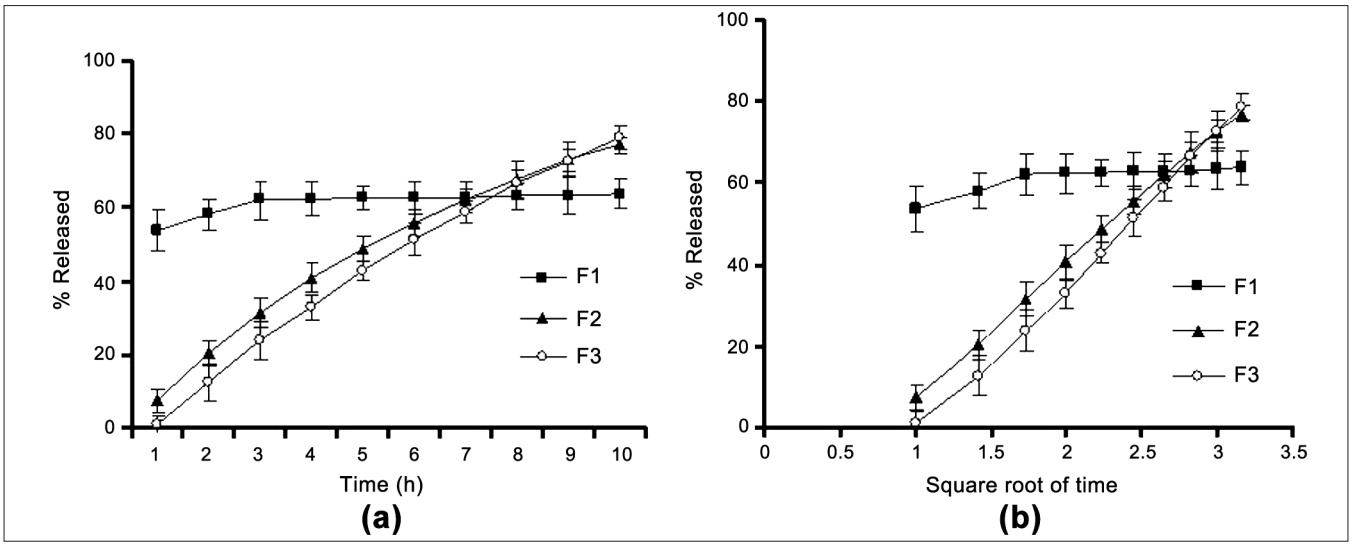

Figure 5: Release kinetics of ambroxol hydrochloride from coated pellets in buffer media. (F1: Eudragit RL 30 D, F2: Eudragit RS 30 D, F3: Eudragit NE 30 D coated pellets and A-Zero order, B-Higuchi release)

ammonium groups in the film of Eudragit RS 30 D.[11,20] From Eudragit NE 30 D-coated pellets, 2.43% drug was released at first hour [Figure 4], which might be reasoned by the low permeability properties as well as the presence of carboxylic groups in the film of Eudragit NE 30 D.[10,20] Swelling of pellets was exerted in the dissolution media (at pH 1.2 and pH 6.8) by Eudragit NE 30 D, which also accentuated its release retarding effect.

When dissolution was performed in the buffer media, the cumulative percent of drug release against time shows different release profiles for each individual polymer [Figure 5a]. In case of Eudragit RL 30 D-coated pellets (Formulation F1), it was observed that about 53.71% drug was released at 1 h, indicating the burst release of the drug [Figure 6], which might be due to the higher water permeability property of the polymer.[20,21] It was also found that about 62% of the drug was released at 3 h whereas only 63.78% of the drug was released at 10 h [Figure 5a], which indicated that there was no significant increase in drug release observed over the 7-h dissolution time, which might be due to the initial faster drug release behavior of Eudragit RL 30 D.[21]

Dissolution study of Eudragit RS 30 D-coated pellets (Formulation F2) revealed that at 1 and 3 h, only 7.28 and 31.43% of the drug was released [Figure 5a], which might be due to the low water permeability property of the polymer.[20,21] The dissolution data expressed that 48.68% of the drug was released at 5 h and about 77% of the drug was released at 10 h, indicating that terminal release of the drug was increased faster. Thus, from Eudragit RL 30 D- and Eudragit RS 30 D-coated pellets, it was found that at 3 h about 62% of drug was released when coated with Eudragit RL 30 D but in case of Eudragit RS 30 D, the same percentage of drug was released at 7 h. Again, at 10 h, about 64 and 77% of the

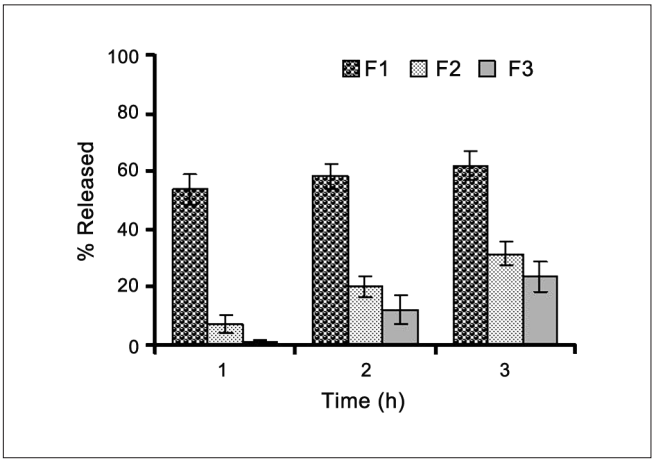

Figure 6: Burst phase release of drug from coated pellets at first 3h in buffer media. (F1: Eudragit RL 30 D, F2: Eudragit RS 30 D, F3: Eudragit NE 30 D)

drug was released from Eudragit RL 30 D- and Eudragit RS 30 D-coated pellets, respectively, [Figure 5a] indicating that, terminally, Eudragit RS 30 D enhanced drug release faster than Eudragit RL 30 D. Thus, after a certain period, the release of drug from these two polymers become closer (62% drug release at 7 h). This phenomenon can be attributed to the presence of hydrophilic groups (amino or hydroxyl groups) within the structure, which control the water absorption, the degree of swelling and the permeability of the films.[20] Both these polymers are water-insoluble over the entire pH range but swell in the digestive fluids independently of pH. In the swollen state, they are then permeable to water and dissolve actives. Thus, greater water permeability and more drug diffusive properties of Eudragit RL 30 D lead the drug to release faster than Eudragit RS 30 D.[20]

In case of Eudragit NE 30 D-coated pellets [Formulation F3], a minimum amount of drug was released initially. Only

Table 4: Kinetic parameters of ambroxol hydrochloride sustained-release pellets

Formulation code	% (w/w) polymer (on dry basis)	Zero order		Higuchi		Korsmeyer		T_{50} (h)
		k_0 (mg/h)	r^2	k_H (mg/h$^{1/2}$)	r^2	*n*	r^2	
F1	10	0.8209	0.6192	3.8469	0.7445	0.067	0.856	-
F2	10	7.5553	0.9715	32.742	0.9992	0.983	0.97	5.14
F3	10	8.6116	0.9900	36.922	0.9966	1.663	0.908	5.86

k_0 = Zero order rate constant; k_H = Higuchi rate constant; *n* = Diffusion coefficient; r^2 = Regression coefficient; F1: Eudragit RL 30 D; F2: Eudragit RS 30 D; F3: Eudragit NE 30 D coated pellets

1.14, 12.53 and 32.64% drug was released at 1, 2 and 4 h, respectively [Figure 5a]. But, from pellets coated with Eudragit RS 30 D and Eudragit RL 30 D, about 7.28 and 53.71% drug was released at the first hour. Such initial least amount of drug release from Eudragit NE 30 D can be attributed to the presence of carboxylic groups in the film of Eudragit NE 30 D, which are normally highly water-resistant and less permeable to water vapor than hydrophilic polymers with amino or hydroxyl groups as well as matrix forming properties of Eudragit NE 30 D.[20,22] Again, at 7 h, about 60% of the drug was released but from 8 h, the release was increased slightly and exceeded the terminal release of drug from Eudragit RL 30 D- and Eudragit RS 30 D-coated pellets [Figure 5a]. About 5.14 and 5.86 h were required for 50% drug release from Eudragit RS 30 D- and Eudragit NE 30 D-coated pellets, respectively [Table 4]. Therefore, Eudragit NE 30 D has shown the best drug release retarding effect among all the polymers. From the overall dissolution study, it was observed that Eudragit RS 30 D and Eudragit NE 30 D released drug in a similar fashion [Figure 5a] and much more consistently. It can thus be said that the physico-chemical nature of the polymers was responsible for showing different drug release patterns.

For both Eudragit RS 30 D and Eudragit NE 30 D polymers, a linear relationship was revealed between the percent of drug release and time throughout the whole dissolution process. The zero order and Higuchi's release rate as well as mean dissolution time (T50) values of different formulations are presented in Table 4. From correlation coefficient (r^2) data, it was expressed that drug release kinetics appeared to follow Higuchi's release fashion for pellets coated with Eudragit RS 30 D and Eudragit NE 30D [Figure 5b] where $r^2 > 0.997$ [Table 4]. As shown in Table 4, the *n*-value indicated the mechanism of release of drug from the coated pellets. From Eudragit RL 30 D-coated pellets (Formulation F1), drug release followed the Fickian (case I) diffusion mechanism ($n < 0.43$ for spheres). But, in case of Eudragit RS 30 D- (Formulation F2) and Eudragit NE 30 D (Formulation F3)-coated pellets, $n \geq 1$, which indicates that the mechanism of drug release from these two polymers is non-Fickian Super Case II transport system.

CONCLUSION

An *in vitro* dissolution study of drug release from the pellets was performed in different dissolution media. Eudragit RL 30 D did not show any release-retarding effect. Eudragit NE 30 D showed maximum a release sustaining effect of drug among all the polymers. The release kinetics of the prepared pellets seemed to be the function of physicochemical properties of the polymers.

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