Effects of Plastic and Acrylate Polymers on the Release Profile of Ambroxol Hydrochloride Controlled Release Pellets

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ABSTRACT: The effects of Ammonio Methacrylate copolymer dispersion (Eudragit® NE 30 D) and Polyvinyl Acetate dispersion (Kollicoat® SR 30 D) are compared on the *in vitro* release of Ambroxol Hydrochloride from coated pellets in the current study. The nuclei pellets were manufactured by Extrusion-Spheronization with the drug, microcrystalline cellulose, lactose, maize starch, and hydroxypropyl methylcellulose followed by fluid bed coating. Dissolution study of coated pellets was performed with USP Type-II apparatus in acidic (0.1N HCl for 1 h) and buffer (phosphate buffer, pH 6.8 for 11 h) media to simulate gastrointestinal environment. The release profile of drug from two types of polymers were distinct and drug release was sustained longer by Polyvinyl Acetate film than Acrylate polymer.

Key words: Aqueous coating, Eudragit® NE 30D, Kollicoat® SR 30D, release kinetics, pellets, extrusion-spheronization

INTRODUCTION

Now a days aqueous coatings are being used preferentially due to their less toxicity and environment friendliness over organic solvent systems. Insoluble polymers like polyvinyl acetate (PVA, Kollicoat®); Ethylcellulose (Aquacoat®, Surelease®) and methacrylic acid co-polymers (Eudragit® RL 30D, Eudragit® RS 30D and others) are now available as aqueous dispersions. These polymers are used for controlling drug primarily from pellet dosage forms.[1-2] Pellets have several biopharmaceutical advantages over tablet dosage forms like less possibility of dose dumping and their drug release is not affected by gastric emptying.[3]

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Pellets are manufactured by different techniques, commonly used are extrusion- spheronization, solution suspension layering and powder layering.[4] In the current experiment, drug containing cores were prepared by extrusion-spheronization and it was coated with two different polymers which were Kollicoat® SR 30D and Eudragit® NE 30D. Extrusion-spheronization is a multi-step compaction process comprising dry mixing of the ingredients with excipients, wet granulation of the mass, extrusion of the wetted mass, charging the extrudates into spheronizer to produce a spherical shape, drying the wet pellets in a dryer and, finally, screening to achieve the required size distribution.[5]

The drug ambroxol hydrochloride is a mucolytic agent indicated for bronchitis[6] and 30 mg drug should be taken 2 or 3 times daily for the proper action.

Ambroxol has half-life of 4 h[7] which requires multiple dosing. To improve patient compliance different controlled release preparation of ambroxol was prepared by several workers[8-10] and among them once daily extended release pellet formulation is available in the international market (Ambrolan® by Lannacher, Austria) containing 75 mg ambroxol hydrochloride.

The objective of the current study was to coat ambroxol pellets with plastic (PVA) and acrylic polymer and to evaluate the effect of these polymers with respect to polymer type and concentration.

MATERIALS AND METHODS

Ambroxol hydrochloride (Alchymars ICM SM Pvt. Ltd., India), Lactose (The Lactose Co. of New Zealand Ltd.), Microcrystalline cellulose (MCC, Ming Tai Chemical Co. Ltd., Taiwan), Maize starch (Cerestar, Netherlands), HPMC 5 cps (Shin Etsu Chemical Company Ltd., Japan), Eudragit® NE 30 D (Rohm GmbH, Germany), Kollicoat® SR 30D (BASF chemical company, Germany), Purified talc (Asian Mineral Resources Co. Ltd., Thailand), triethyl citrate (Morflex Inc., USA) and other materials used were of reagent grade.

Preparation of nuclei. At first ambroxol was dry mixed with diluents in a laboratory scale planetary mixer (Umang Pharmatech Pvt. Ltd., India) and binder solution of HPMC was added for granulation purpose (Table 1). Rod shaped extrudes were prepared with that wet mass by an extruder (Caleva, UK) having 1 mm screen. The extruded were cut and rounded by a spheronizer (Caleva, UK) operated at 600 rpm for one minute. The prepared nuclei were dried in a tray dryer (Indo-German PVT Ltd., India) and screened using ASTM 20 mesh followed by ASTM 24 mesh to get 710-850 μm size distribution.

Coating with Kollicoat® SR 30D. The coating suspension was prepared with Kollicoat® SR 30D, triethyl citrate as plasticizer and talc as antiadherent and final volume was reached with purified water (Table 1). 400 g nuclei were coated using fluid bed coater (Labcoater; Umang Pharmatech, India) with Kollicoat® SR 30 D containing coating suspension to different thickness equivalent to theoretical polymer load 4%, 8%, 12%, 16% and 20% w/w. The process parameters are shown in Table 2. Samples were drawn for analysis after each level of polymer load.

Table 1. Composition of Ambroxol pellets (Core and Coat formula)

Materials	Pellets coated with Kollicoat® SR 30D	Pellets coated with Eudragit® NE 30D
Core Formula (g)		
Ambroxol hydrochloride	140	140
Lactose	60	60
Maize starch	20	20
MCC	160	160
HPMC 5 cps	20	20
Purified water*	200	200
Coating Formula (g)**		
Kollicoat SR 30D	213.44	-
Eudragit NE 30D	-	177.87
Purified Talc	19.21	26.68
Triethyl Citrate	6.40	-
Purified water*	161.15	195.65

* Less than 0.2% will be present in final preparation.
** Formula of coating material is given for about 20% (w/w) load over nuclei.

Table 2. Machine parameters set up during coating.

Machine	Fluid bed coater (Wurster, Umang Pharmatech Ltd.)
Batch Size	400 g
Inlet air temperature	50-55 ^{0}C
Outlet air temperature	29-32 ^{0}C
Product temperature	35-40 ^{0}C
Chamber Humidity	55%
Air flow	90 m^3/h
Spraying pressure	1.20 bar
Spraying rate	3.0 g/min
Secondary drying	40^{0}C/15 min

Coating with Eudragit® NE 30D. To prepare the spray suspension, talc was suspended in water and the suspension was poured into Eudragit® NE 30 D with continuous gentle stirring. 400 g nuclei were coated using fluid bed coater (Labcoater; Umang Pharmatech, India) to different thickness equivalent to theoretical polymer load 4, 8, 12, 16 and 20% w/w and samples were drawn for analysis simultaneously

after each level of polymer load. The process parameters are shown in Table 2.

Physical Evaluation of coated pellets. Friability of nuclei was tested with friabilator (Erweka, Ensenstam, Germany) at 25 rpm for 10 minutes along with glass spheres of 5µm diameter. The moisture content of coated pellets was determined by loss on drying of the pellet under vacuum at 60ºC for 4 h.

***In Vitro* Dissolution Study.** The dissolution of ambroxol hydrochloride sustained release pellets was studied by USP-28 dissolution tester (Erweka, Germany) using USP apparatus II (Paddle method). The dissolution was carried out in 900 ml of 0.1 N HCl medium at 37 ± 0.5ºC with a rotation of 50 rpm for 1 h. At the end of 1 h the media was replaced by 900 ml of phosphate buffer (Na_3PO_4) of pH 6.8 rotated at 50 rpm at 37 ± 0.5ºC for 11 h. 10 ml sample was drawn every 1 h and replaced by fresh medium to maintain the volume constant and drug content was determined by uv-visible spectrophotometer at 244 nm .

Release kinetics stud. The dissolution data was fitted to the Korsmeyer equation $M_t/M_\alpha = Kt^n$,[17] which is often used to describe the drug release behavior from polymeric systems. M_t is the amount of drug release at time t; M_α is the amount of drug release after infinite time; k is a release rate constant incorporating structural and geometric characteristics of the dosage form; n is the diffusional exponent indicative of the mechanism of drug release.[11]

The log value of percent drug dissolved is plotted against log time for each formulation according to the above equation. In a sphere the value of $n \leq 0.43$ indicates Fickian (case I) release; > 0.45 but < 0.85 for non-Fickian (anomalous) release; and > 0.85 indicates super case II type of release. Case II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.[12]

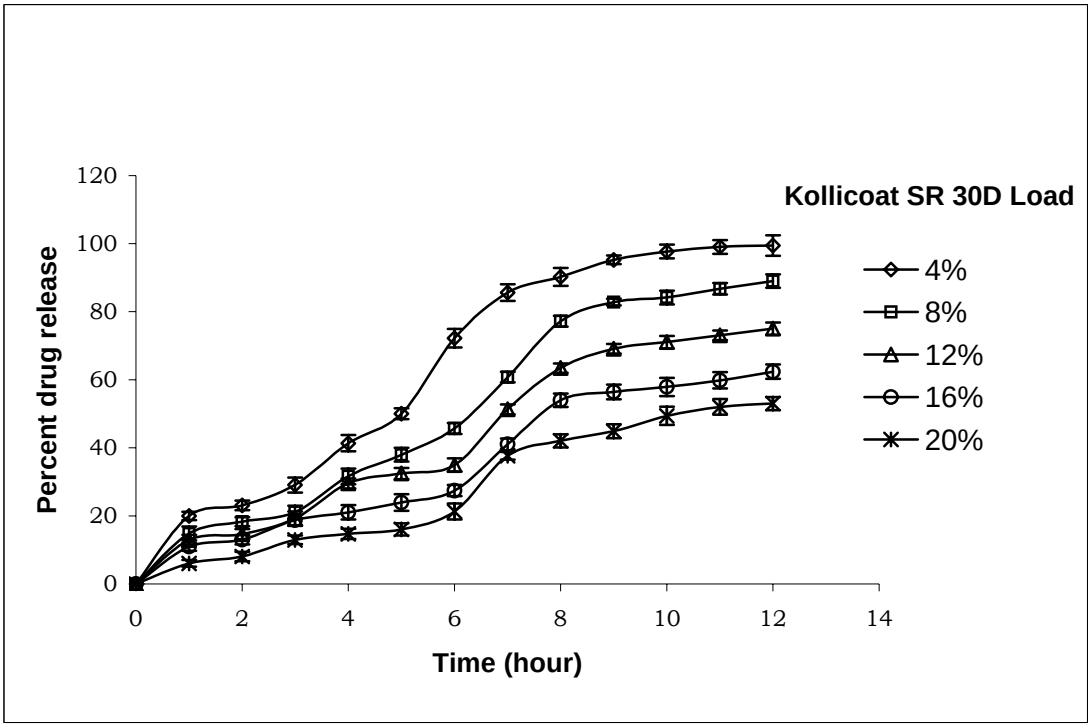
The f_2 value is the measurement of similarity of two different dissolution curves. When two curves are similar, the f_2 value is greater than 50. The value is determined by the following equation 1 where n is the number of dissolution sample times, and R_t and T_t are the individual percentages dissolved at each time point t for the reference and test dissolution profiles respectively.[13]

$$f_2 = 50.\log\left[\{1+(1/n)\sum(R_t-T_t)^2\}^{-0.5}.100\right] \quad \textbf{(Equ. 1)}$$

RESULTS AND DISCUSSION

The color of the drug-loaded pellets was found almost white or colorless and round shaped. The LOD (Loss on Drying) was found 0.18%, which indicated that the layering process as well as the raw materials are suitable for manufacture of stable pellets. The friability of nuclei was 0.26% which is very well within the requirement (below 1%). The pellets coated by Kollicoat® SR 30D showed some degree of surface roughness but pellets coated by Eudragit® NE 30D produced smooth surface. It implies that there is scope for choosing optimum level of plasticizer to obtain a flexible film with Kollicoat® SR 30D. On the other hand, the embedded surfactant of Eudragit® NE 30D can give flexible smooth film which precludes the possibilities of use of additional plasticizer.

The nature of two polymers markedly affected drug release (Figure 1). Almost equal amount of Kollicoat® SR 30D sustained the drug release for longer period of time than Eudragit® NE 30D. The 'n' value (release exponent) from Korsmeyer-Peppas equation for Kollicoat® SR 30D coated pellets were 0.78 - 0.85 for up to 16% coating load which indicated non-Fickian transport mechanism. It can be explained as the soluble povidone in PVA film creates a porous membrane during dissolution, that it helps the drug to leach out from the core. On the other hand, the 'n' value for Eudragit® NE 30D coated pellets were greater than 0.85 from 12% to 20% coating load which indicated Case II or Zero order transport mechanism. The assumption was also confirmed by zero order release kinetics as the correlation coefficients (r^2) were closer to 1.0 in that range. The release mechanism from slightly permeable, slightly swellable Eudragit® NE 30D



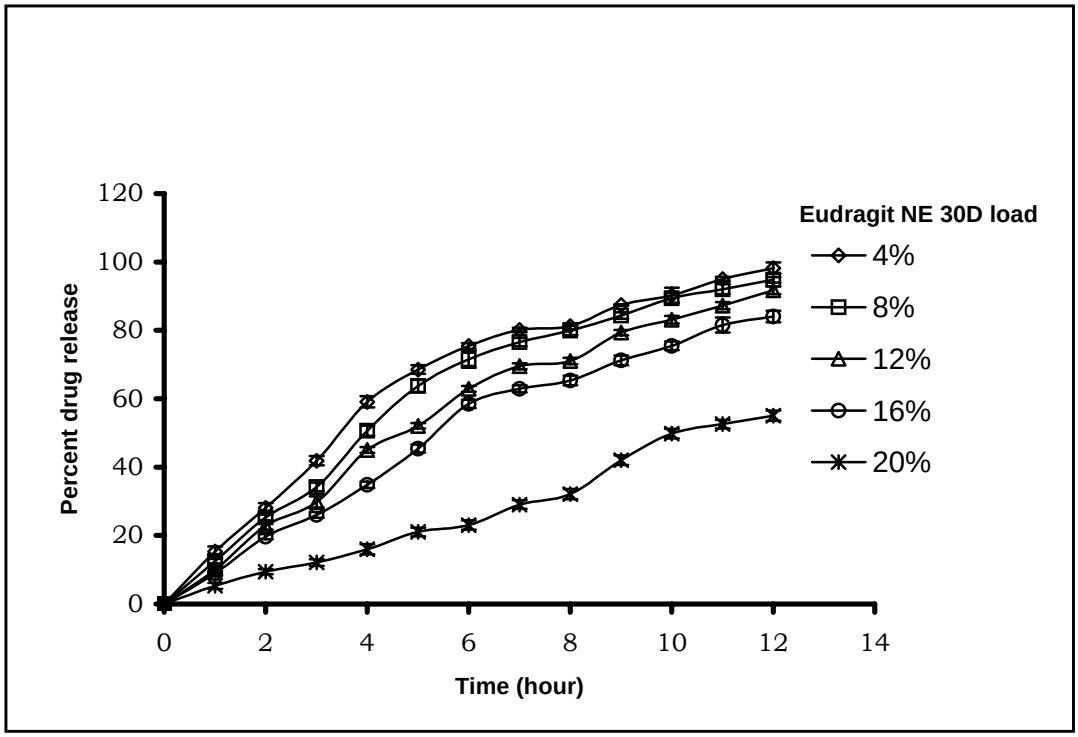


Figure 1. Zero order release of pellets coated with Kollicoat® SR 30D (top) and Eudragit® NE 30D (bottom) (mean ± S.D, n=3)

Table 3. Release kinetics of Ambroxol pellets

	Coating load of Kollicoat® 30D coated pellets					Coating load of Eudragit® NE 30 D coated pellets				
	4%	8%	12%	16%	20%	4%	8%	12%	16%	20%
Zero order										
r^2	0.94	0.97	0.97	0.96	0.96	0.91	0.93	0.96	0.97	0.98
K_0	8.91	8.00	6.66	5.46	4.87	7.85	7.94	7.67	7.17	4.71
First order										
r^2	0.92	0.94	0.95	0.95	0.95	0.93	0.99	0.98	0.99	0.95
K_1	0.19	0.09	0.06	0.04	0.03	0.13	0.11	0.09	0.07	0.03
Higuchi										
r^2	0.93	0.90	0.90	0.89	0.86	0.97	0.97	0.97	0.96	0.87
K_H	32.21	29.87	24.88	20.32	17.82	31.36	31.24	29.68	27.50	17.17
Korsmeyer										
r^2	0.94	0.94	0.93	0.93	0.94	0.96	0.97	0.98	0.99	0.98
n	0.78	0.85	0.85	0.80	0.99	0.74	0.82	0.87	0.90	0.97
K	0.16	0.11	0.09	0.08	0.04	0.18	0.14	0.12	0.10	0.05
MDT	4.66	6.14	7.56	9.88	11.40	4.39	4.81	5.41	6.12	11.62
$t_{25\%}$	1.77	2.63	3.33	4.14	6.37	1.56	2.03	2.32	2.76	5.25
$t_{50\%}$	4.31	5.94	7.52	9.83	12.82	3.98	4.72	5.16	5.94	10.74
$t_{75\%}$	7.25	9.57	12.11	16.29	19.31	6.88	7.74	8.22	9.31	16.31
$t_{90\%}$	9.15	11.86	15.01	20.45	23.22	8.8	9.67	10.1	11.39	19.68

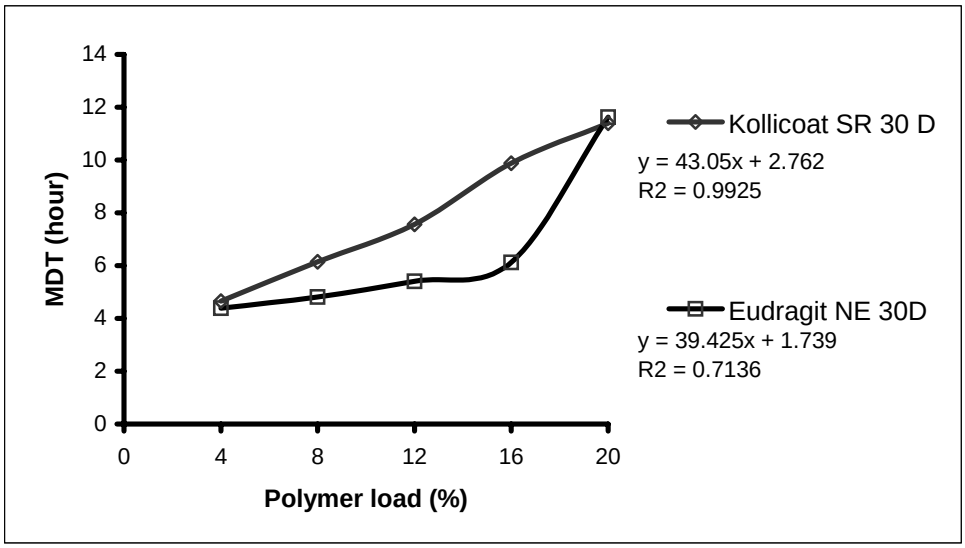


Figure 2. Effect of polymer on mean dissolution time (MDT) of Ambroxol hydrochloride sustained release pellets.

coating can be explained as the water penetrates the polymer, it dissolve the drug and consequently the high concentration of drug at coating surface initiates drug diffusion.[14]

The release of ambroxol from coated pellets not only depended on the nature of polymer but also on the amount of coating thickness. Increasing Kollicoat level changed the shape of release profile from asymptotic to sigmoidal as reported by Shao et al.[215] but that of Eudragit® NE remained the same. The gradual increase of polymer level decreases the drug release for both cases as expected due to decreased porosity of the films. Mean dissolution time (MDT) values were determined to characterize the drug release rate from the coated pellets and the retaining efficiency of the polymer (Table 3). A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa. The Mean Dissolution Time (MDT) of PVA based coating increased linearly (r^2 = 0.99) by increasing polymer load

(Figure 2) but the acrylate coating acted differently. The pellets coated with Kollicoat® SR 30D at 16% coating load have $t_{90\%}$ about 20 h. It implies this polymer is suitable for the preparation of once daily dosage form of ambroxol. But similar amount of Eudragit® NE 30D coating releases 90% of the drug within 11 h (Table 3).

The f_2 value of almost equal amount of Kollicoat and Eudragit at all polymer loads were found below 50. Therefore the curves from two polymers were totally distinct.

CONCLUSION

Both PVA and acrylic polymers are useful for the preparation of ambroxol hydrochloride pellets. Due to the different chemical and physical nature of the two polymers the release profiles were not similar. The pellets coated with Kollicoat® SR 30D retarded drug release more than the Eudragit® NE 30D dispersion. It is possible to modify the release profile of ambroxol pellets by choosing suitable polymers at a suitable level to meet the desired drug concentration.

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