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Comparative Study of Aqueous Dispersion of Different Types of Polymers on Release Behavior of Salbutamol Sulphate from Coated Pellets

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Abstract:
The present study was designed to investigate the effect of different types of coating polymers such as Eudragit RL 30D, Eudragit RS 30D, Eudragit NE 30D, Surelease, and Kollicoat SR 30D on physical properties and release pattern of salbutamol sulphate (SS) pellets which were prepared by Extrusion-Spheronization technology. All the polymers used in coating solution were in aqueous dispersion form where Surelease was 25% aqueous dispersion and rest of the polymers was 30% dispersion. Surface morphology of the coated pellets was examined by Scanning Electron Microscope (SEM). All the pellets were of white to off-white color and spherical in shape. There was no marked difference in the values of % yield, loss on drying (LOD), % potency, and bulk density of the coated pellets from polymer to polymer. But a significant difference was found in % friability and % drug release. % Friability value was found maximum (0.59%±0.01) for Eudragit NE 30D and was minimum (0.0.12%±0.08) for Eudragit RL 30D. After 10 hours of dissolution in distilled water, almost same amount of drug was released from the pellets coated with the coating polymers. But considering first hour of dissolution, surelease showed more sustaining behavior than all the polymers. After 1 hour dissolution, only 12% of drug was released in case of surelease where as this was 80%, 83%, 63%, and 26% for Eudragit RL 30D, Eudragit RS 30D, Eudragit NE 30D, and Kollicoat SR 30D respectively.
Key words: Pellet, Extrusion-spheronization, Salbutamol sulphate, Aqueous dispersion, Sustained release

Introduction:

The popularity of controlled-release multiple unit dosage forms has increased when compared to single unit dosage forms. Although similar drug release profiles can be obtained with both types of dosage forms, multiparticulates offer several advantages. The coated pellets spread uniformly throughout the gastrointestinal tract and high local drug concentrations can be avoided, along with the risk of a localized toxic reaction due to a restricted tablet in the gastrointestinal tract.

Premature drug release from enterically coated dosage forms in the stomach may result in drug degradation or irritation of the gastric mucosa. These problems can be reduced with coated pellets due to the rapid transit time when compared to enterically coated tablets. The better distribution of multiparticulates throughout the GI-tract has, in several instances, improved the drug bioavailability which potentially could result in a reduction in the side effects and the drug dosage requirements. Inter- and intra-individual variations in bioavailability that may be caused by food effects are often reduced with multiparticulates [1].

Formulation of a drug into pellet form provides many advantages over other sustain release dosage forms. It reduces gastric irritation, because the drug is released slowly over a period of time. Pellet dosage form allows drug to be absorbed gradually, therefore reducing the incidence of side effects by preventing high C_{max}. A major advantage of pellet dosage form is that pellets are less affected by the effect of stomach emptying. Pellets will gradually reach the small intestine each time the stomach empties, whereas a single enteric coated tablet may be delayed in the stomach for a long time due to erratic stomach emptying. Enteric coated pellets are relatively unaffected by the presence of food [2]. So, the better distribution of multiparticulates throughout the GI-tract has, in several instances, improved the drug bioavailability which potentially could result in a reduction in the side effects and the drug dosage requirements. Inter and intra-individual variations in bioavailability that

may be caused by food effects, are often reduced with multiparticulates [1].

Salbutamol sulphate (SS) was chosen as a model drug. It is water soluble, and a well known bronchodilator with a short half life 3-8 h [3] and is an appropriate candidate for controlled release formulations [4]. SS is a potent B-2 adrenoceptor stimulant used for the treatment of bronchial asthma [5]. As it has a short elimination half life of 3-8 hours, frequent dosing is necessary to maintain therapeutic plasma levels. Therefore, there is a need for controlled-release formulation of salbutamol sulphate.

Eudragit RL 30D, Eudragit RS 30D, Eudragit NE 30D, Surelease, Kollicoat SR 30D are used here as sustain release polymer. Eudragit RL 30D, Eudragit RS 30D, and Eudragit NE 30D are most widely used sustain release polymers amongst the other acrylic polymers. All of the three polymers were in 30% dispersion form. These polymers are widely used in sustain release coating for different types of solid dosage forms especially for sustain release pellets. These polymers are used for enteric coating as well [6-12].

Kollicoat SR 30 D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. The dispersion is suitable for the manufacture of pH independent sustain release formulations. Very effective control of drug release is achieved by coating pellets, granules and crystals [13]. Kollicoat SR 30D was also used successfully in several research works before to prepare sustain release pellets or beads [14-17].

Surelease or ethyl cellulose is also a good sustain release polymer. Though surelease is mostly known for its common application in microencapsulation technology, it was used in different studies before to prepare sustain release pellets also [11, 18, 19].

Triethyl citrate (TEC) is a good plasticizer and is the most widely used plasticizer in aqueous and organic film coatings [17, 20, 21]. Triethyl citrate is also the most compatible plastizer for the polymers used in this study especially for Kollicoat SR 30D. TEC reduces the minimum film forming temperature (MFT) of Kollicoat SR 30D more than any other plasticizer [13]. This plasticizer has an official monograph in the current U.S.P./NF [22].

To avoid sticking problems in the coating chamber, high levels of anti-adherent, purified Talc was used to prevent adhesion during the coating process and to avoid similar problems during the curing or heat treatment of the coated pellets [1].

The aim of this study is to compare the release retarding effect of different types of sustained release polymers having various physicochemical properties.

Materials and Methods:

Materials:

Materials that are used throughout the experiment are Salbutamol Sulphate (Index Pharma, India), Maize starch (Cerestar, Netharland), Lactose (The Lactose Co. of Newzealand Ltd. Newzealand), Avicel PH101 (Maple Bioteech Pvt. Ltd. India), HPMC 6cps (Shin-etsu, Japan), Eudragit RL 30 D (Degussa, Germany), Eudragit RS 30 D (Degussa, Germany), Eudragit NE 30 D (Degussa, Germany), Surelease (Colorcon, UK), Kollicoat SR 30 D (BASF, Germany), Talc (Asian Mineral, Thailand), Titanium Dioxide (Warner Jenkinson, Italy), Triethyl Citrate (Morflex Inc. USA). All other chemicals used were of analytical grade and were used as received.

Design of experiments:

In this investigation, the independent variable was polymer content and particle size, drug loading, were the dependent variables. The independent variable (polymer content) and its effect on drug release, particle morphology, drug loading were investigated. The general formula applied for the study is shown in Table 1

Table1: Formulation for Salbutamol Sulphate Pellets

Formula for Nuclei					
Materials	**Amount (gm)**				
Salbutamol Sulphate	200.00				
Avicel PH 101	1600.00				
Maize Starch	360.00				
HPMC 6cps	40.00				
Water up to	300.00				
Formula for Coating					
Materials	**Amount (gm)**				
	L1	**L2**	**L3**	**L4**	**L5**
Nuclei	300	300	300	300	300
Eudragit RL 30 D ¥	100	—	—	—	—
Eudragit RS 30 D ¥	—	100	—	—	—
Eudragit NE 30 D ¥	—	—	100	—	—
Surelease Ψ	—	—	—	120	—
Kollicoat SR 30 D ¥	—	—	—	—	100
Purified Talc	15	15	15	15	15
TiO2	3	3	3	3	3
Triethyl Citrate	6	6	6	6	6
Water up to	200	200	200	200	200

¥= 30% Dispersion; Ψ = 25% Dispersion

Preparation of Salbutamol Sulphate pellets:

The cores of salbutamol sulphate sustain release (SR) pellets were prepared by Extrusion-Spheronization technology. In this process required amount of Salbutamol sulphate, Avicel PH 101 & Maize Starch was sieved through 80 mesh stainless steel screen and mixed properly to prepare a homogenous powder mix. Then the solution of HPMC 6cps in purified water was added drop wise to the powder mix and wet mass was prepared having sufficient binding affinity (Table 1). Then this wet mass was passed through the 0.8 mm stainless steel screen of fully automated Extruder (Caleva, UK) to prepare extrudes. Then these extrudes were loaded onto the specially designed stainless steel plate of Spheronizer (Caleva, UK) which was then rotated at 550 RPM to prepare the spheres of salbutamol core. The core pellets was then dried at 65ºC for 5 hours. Then dried core pellets were sieved through 18/24 mesh screen. In this case the pellets surface was found rough to some extent.

Coating suspension was prepared by using Purified Talc, Titanium Dioxide, Triethyl Citrate, Eudragit RL 30D in purified water (Table 1) with the help of Silverson Stirrer (Silverson, UK) and sieved through 80 mesh stainless steel screen to discard larger size particles.

Then salbutamol pellets core were loaded in the Lab coater (Wuster column) and coating suspension was sprayed using the peristaltic pump. After completion of spraying, the coated pellets were dried at 60 ^{0}C for 4 hours. The coated pellets were then sieved through 18 mesh and 24 mesh respectively to get the desired size (18/24) of the salbutamol SR pellets and the batch is termed as L-1.

Same process was applied in case of other polymers according to table 1 to prepare the other batches termed as L-2, L-3, L-4, L-5.

Surface Morphology Study by Scanning Electron Microscope (SEM):

Scanning Electron Microscope (SEM) was used to study the morphology of the prepared pellets as such without any coating around the pellets during analysis. Scanning electron microscopy was performed using Hitachi (Model: S-3400 N, Japan) scanning electron microscope at 5 KV having different magnifications. The scanning electron micrographs are presented in Figure 2A-2E.

In vitro Dissolution Study of Salbutamol Sulphate Pellets:

For dissolution purpose, USP XXIII paddle type (apparatus 2) apparatus was used. A weighed amount of pellet equivalent to 8 mg was placed in the dissolution basket containing 500 ml distilled water as

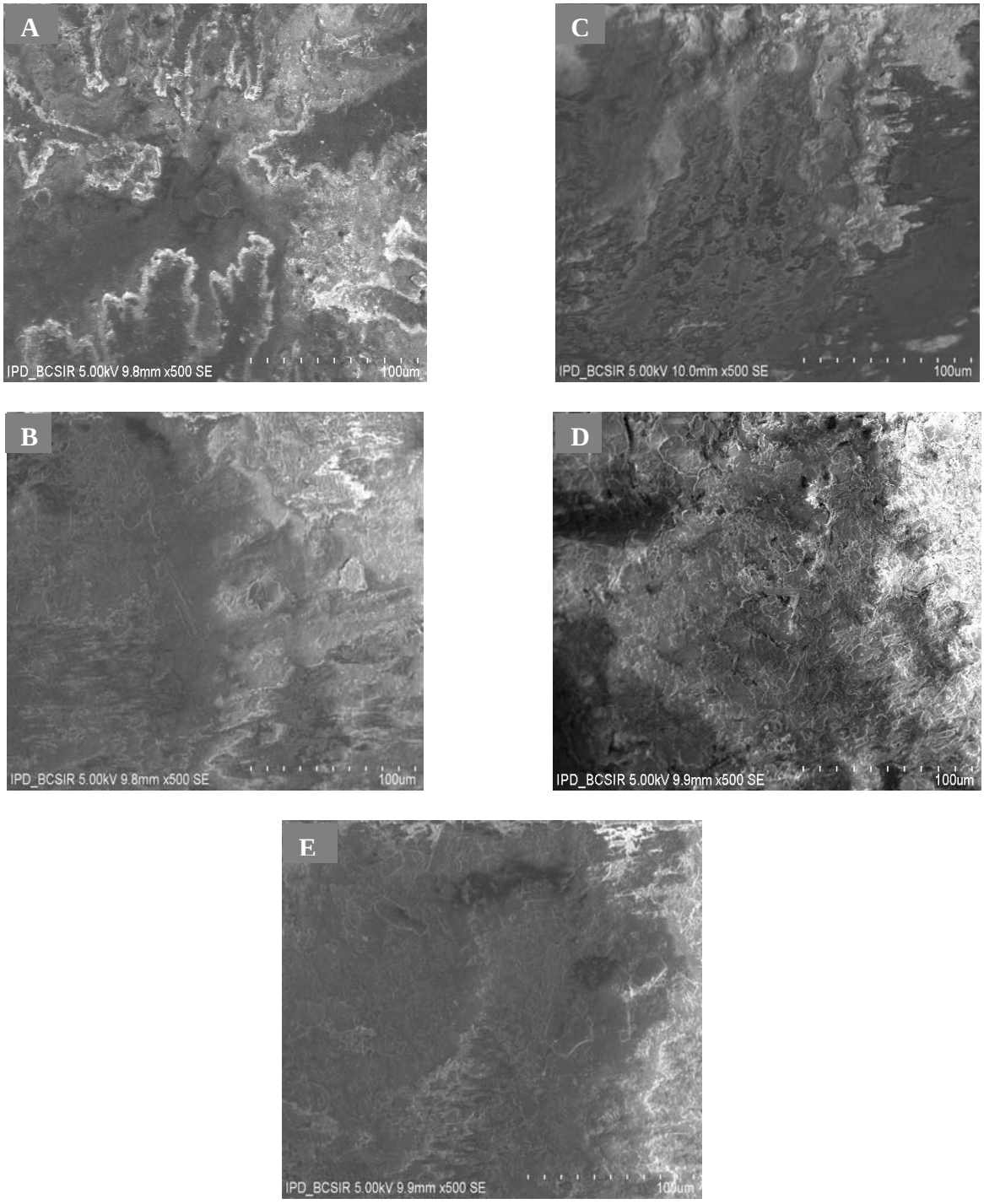
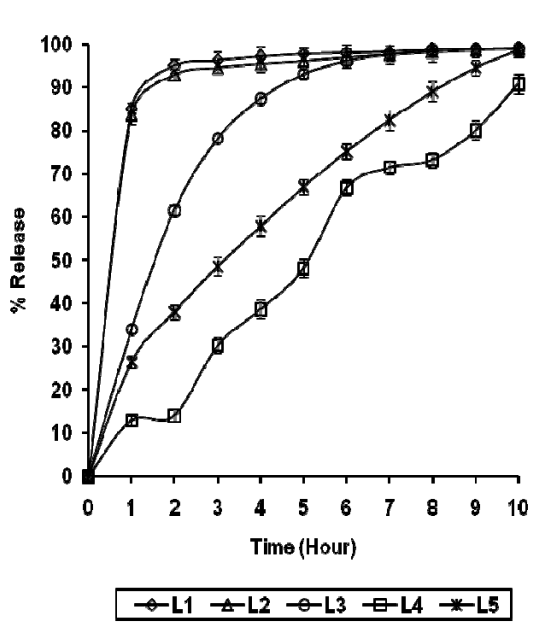
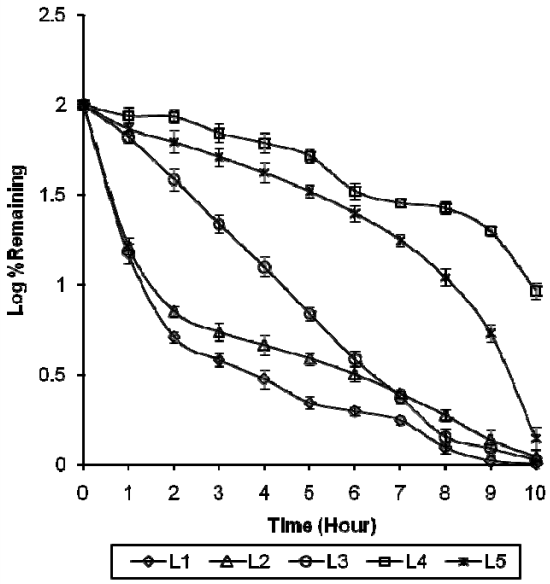


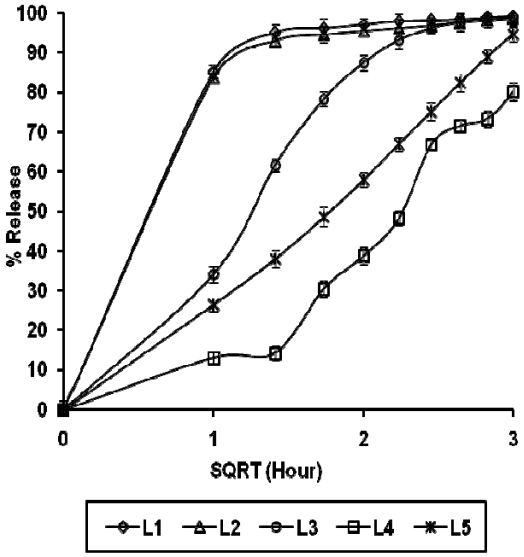
Figure 1: Scanning electron micrographs of Salbutamol sulphate sustained release pellets. (A: Eudragit RL 30D; B: Eudragit RS 30D; C: Eudragit NE 30D; D: Surelease; E: Kollicoat SR 30D)



A



B



C

Figure 2: Mean (±SD) of percent release of Salbutamol Sulphate from coated pellets (n=3) where A= Zero Order, B= 1st Order and C= Higuchi Release. L1 = Eudragit RL 30D; L2 = Eudragit RS 30D; L3 = Eudragit NE 30D; L4 = Surelease; L5 = Kollicoat SR 30D.

dissolution medium. The paddles were set at 100 rpm and the temperature was maintained 37^0 C. Samples were withdrawn at predetermined intervals. The salbutamol sulphate content of each sample was assayed by UV spectroscopy (Shimadzu, Japan) at 275 nm.

Results and Discussions:

Physical Properties of the SS Pellets:

Initially the color of the pellets was white to off-white and no difference in color was found from batch to batch. So formulation variables have no effect on the color of the pellets.

Percent yields of salbutamol sulphate were satisfactory for almost all the batches. Maximum percent yield was 98.36 for Kollicoat SR 30D (L-5) and minimum percent yield was 94.36 for Eudragit NE 30D (L-3) (Table 2).

Loss on Drying (LOD) values of the formulas were 2.76%, 2.36%, 1.92%, 1.84%, 1.87% for Eudragit RL 30D (L-1), Eudragit RS 30D (L-2), Eudragit NE 30D (L-3), Surelease (L-4), and Kollicoat SR 30D (L-5) respectively (Table 2). Though it was tried to keep the LOD value of all the formulas below 2.0%, Eudragit RL 30D and Eudragit RS 30D containing pellets contained more moisture than the others and this partially affected the release behavior of the salbutamol sulphate from the pellets.

The bulk densities of the pellets were found 0.93 g/cc, 0.89 g/cc, 0.92 g/cc, 0.91 g/cc, and 0.98 g/cc for Eudragit RL 30D (L-1), Eudragit RS 30D (L-2), Eudragit NE 30D (L-3), Surelease (L-4), and Kollicoat SR 30D (L-5) respectively (Table 2). Density values were almost equal to unit value and this also signifies the spherical shape of the pellets.

The friability values for the formulation were found within the range of 0.12%-0.59% (Table 2). Friability test reveals that 0.12% weight loss occurred for Eudragit RL 30D (L-1) which might be due to high moisture content of the pellets. Similar friability nature was observed for Eudragit RS 30D also (L-2). Pellets formulated with Eudragit NE 30D (L-3), Surelease (L-4), and Kollicoat SR 30D (L-5) showed comparatively high values of friability and this might be due to comparatively low moisture content and harder nature of the pellets.

Surface Morphology of the SS Pellets:

SS coated pellets were examined under SEM to observe the variation in surface morphology due to the presence of different coating polymers. Figure 1 shows the SEM photograph of the surfaces of the coated pellets. In case of Eudragit RL 30D (Fig. 1A), large cracks were observed on the surface. In contrast, surfaces of the pellets coated with Eudragit RS 30D and Eudragit NE 30D appeared little smoother and containing less cracks which are seen in Fig. 1B and Fig.1C respectively. On the other hand, surface of the pellets coated with Surelease appeared smooth and compact (Fig.1D). However, surface appeared smooth containing small cracks and was similar to those of Eudragit RS 30D and NE 30D while Kollicoat SR 30D was used.

Release Profile of SS from Coated Pellets:

Drug Release from Salbutamol Sulphate pellets formulated with different types of polymers has been shown in Figure 2. Percent release data found were fitted in three different types of release curves: zero order (Figure 2A), first order (Figure 2B), higuchi release (Figure 2C). After 10 hours of dissolution, percent release of salbutamol sulphate from pellets were 98.99%, 98.88%, 98.93%, 90.75%, and 98.59% for Eudragit RL 30D (L-1), Eudragit RS 30D (L-2), Eudragit NE 30D (L-3), Surelease (L-4), and Kollicoat SR 30D (L-5) respectively (Figure 2). Only pellets formulated with surelease showed comparatively less % release of salbutamol sulphate. Almost 100% drug was released from the rest of the formulations.

Table 2: Physical parameters of Salbutamol Sulphate pellets prepared by Extrusion-Spheronization technology (n=3)

Parameters	Formulation code				
	L-1	**L-2**	**L-3**	**L-4**	**L-5**
Appearance	White to off-white spherical pellets	White to off-white spherical pellets	White to off-white spherical pellets	White to off-white spherical pellets	White to off-white spherical pellets
% Yield	98.18	96.71	94.36	98.22	98.36
Loss on drying (%)	2.76 ± 0.45	2.76 ± 0.45	1.92 ± 0.08	1.84 ± 0.15	1.87 ± 0.33
% Potency	6.37 ± 2.04	6.04 ± 2.04	6.68 ± 1.11	6.82 ± 1.07	6.51 ± 1.07
% Friability	0.12%± 0.08	0.23%± 0.08	0.59%± 0.01	0.37%± 0.05	0.43%± 0.01
Bulk density (g/cm^3)	0.93 ± 0.02	0.89 ± 0.02	0.92 ± 0.03	0.91 ± 0.04	0.98 ± 0.02

Table 3: R^2 values of Different Curves of Release Pattern of Salbutamol Sulphate pellets.

Formulation code	Correlation coefficient (R^2)		
	Zero order	**First Order**	**Higuchi**
L1	0.5626	0.7748	0.6117
L2	0.7012	0.8293	0.6315
L3	0.7092	0.9839	0.9122
L4	0.9839	0.9294	0.9215
L5	0.9716	0.8827	0.9939

Pellets formulated with Eudragit RL 30D showed initial burst release. More than 80% drug was released within first hour of dissolution. Marked cracks as well as uniform film formation were observed on the surface of the pellets under SEM photograph (Figure 1A). Most of the drug was then released through this crack within first hour of dissolution (Figure 2, L-1).

Pellets formulated with Eudragit RS 30D also showed a similar pattern of drug release where 83% drug was released within 1 hour (Figure 2, L-2). Unlike Eudragit RL 30D, small cracks were observed on the pellet surface (Figure 1B).

Amongst the acrylic polymers, Eudragit NE 30D showed more satisfactory result. Though almost all the drug was released within 10 hours, it was able to control the initial burst release of the drug. 63% salbutamol sulphate was released from the pellets within first hour (Figure 2, L-3). Few discrete cracks were observed on the surface of the pellet (Figure 1C). These discrete cracks might be the reason to release this amount of drug within first 1 hour.

Almost 90% drug was released at 10 hour from the pellets formulated with Surelease. Surelease also showed a more sustain activity considering initial few hours of

dissolution than the other polymers. Only 12% drug was released from the pellets within first hour of dissolution (Figure 2, L-4). This more controlled nature of drug release is clearly understood from SEM image of the pellet surface. The surface is uniform and more compact in nature. There is no crack on the surface. But the surface is very rough and due to this rough nature of the surface (Figure 1D) a zig-zag pattern of drug release was obtained (Figure 2, L-4)

Though almost all the drug was released from the pellets formulated with Kollicoat SR 30D, this polymer was able to reduce the amount of drug released within first hour. 26% drug was released within 1 hour (Figure 2, L-5). Most importantly the drug release pattern, unlike that of Surelease, was very uniform and a typical sustain release curve was obtained for Kollicoat SR 30D. The reason of this sustain release behavior and a uniform release pattern of salbutamol sulphate from the pellets might be smooth, plain nature of the surface of the pellets (Figure 1E)

Percents amount of drug release of all the formulations were also fitted in 1st Order model (Log of %remaining Vs Time) and Higuchi model (% Drug Release Vs Square Root of Time-SQRT). The values of correlation-coefficient (R^2 values) of all the curves are shown in Table 3. Considering R^2 values, salbutamol sulphate was released from polymers formulated with the polymers following Higuchi mechanism.

Conclusions:

Salbutamol sulphate pellets formulated with Eudragit RL 30D, Eudragit RS 30D, Eudragit NE 30D, Surelease, Kollicoat SR 30D containing a fixed amount of plasticizer, triethyl citrate (TEC) were spherical in nature and also showed a good sustain release activity for up to 10 hours. Drug-polymer ratio was also maintained fixed for all the formulations. Pellet surface nature, release behavior of drug was changed only due to change of polymer. A good comparative study of different types of sustained release polymers has also been done throughout this study.

Eudragit NE 30D, Surelease and Kollicoat SR 30D showed good release retarding property but drug was released more linearly and consistently from Kollicoat SR 30D coated pellets.

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