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CONTROLLED RELEASE SALBUTAMOL SULPHATE MOLDED TABLETS USING EUDRAGIT RETARD

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ABSTRACT

Permeable acrylic resins were used as efficient retarding materials to prepare controlled release salbutamol sulphate molded tablets. The formulation is simple, efficient, economic and is easily shaped into molded tablets. The effects of two types of acrylic resins, namely: Eudragit RL100 and Eudragit RS100 in concentrations 1,2 and 5% w/w on the physical characteristics as well as on the in vitro release patterns of salbutamol sulphate from molded tablets prepared with either polyethylene glycol (PEG) 4000 or 6000 were studied. It was revealed that, as the molecular weight of the PEG increased, the hardness of the tablets increased. Considerable retardation in the drug release was observed by using Eudragit RS100 as compared to Eudragit RL100. The formulation prepared with PEG 6000 and 5% Eudragit RS100 produced much more release time prolongation than the other tested formulations. On the other hand, tablets prepared by the direct compression technique produced a faster release of salbutamol sulphate than those prepared by molding.

INTRODUCTION

The use of molded tablets technique for the production of controlled release tablets has not been reported in the literatures. Thus, it was worthy to formulate potent drugs in a prolonged release form using this technique.

Salbutamol sulphate was chosen for that study due to its effectiveness as bronchodilator in small doses ranging from 2-4 mg as well as its high stability and ease of assay.

Eudragit retard is a permeable acrylic resin which has been reported to be a potential sustained release coating for oral pharmaceuticals[1]. The permeability of this resin is independent on the pH in the different sections of the gastrointestinal tract. Two types of Eudragit are available, Eudragit RL100 which has a high permeability characteristics and causes only little delay of drug release, while Eudragit RS100 forms films of low permeability characteristics. Christenson and Dale[2] described the application of hydrophilic polymers as additives for sustained action. Eudragit retard was utilized by Lehmann and Dreher[3] for controlling the release of trifluoperazine hydrochloride from its pellets. The release mechanism in this type of resin was attributed to the presence of pores in the membrane allowing the diffusion of the incorporated drug[4]. The objective of this study was to obtain controlled release salbutamol sulphate tablets by changing the dissolution behaviour of the medicament through molded tablet formulations. In the meantime directly compressed salbutamol sulphate tablets were prepared and compared with the proposed formulations.

EXPERIMENTAL

Materials and Methods:

Salbutamol sulphate (Allen & Hanburys, UK), polyethylene glycol 4000 and 6000 (Prolabo-France), Eudragit RL100 and RS100 (Rohm Pharma G.HBH, Darmstadt, W. Germany).

TABLE 1

Table 1 : In vitro data for salbutamol sulphate molded tablets*.

Eudragit %	PEG mol.wt	Hardness Kg	Thickness mm	Dissolution time** t_{90}, min
0	4000	0.5±0.14	3.61±0.6	<5
	6000	1.0±0.27	3.35±0.6	<5
RL100				
1	4000	1.0±0.42	3.67±0.7	<5
	6000	1.5±0.21	3.42±0.6	5
2	4000	1.0±0.23	3.70±0.5	5
	6000	1.5±0.13	3.42±0.6	8
5	4000	1.7±0.32	3.72±0.8	10
	6000	2.3±0.49	3.43±0.5	43
RS100				
1	4000	1.6±0.39	3.57±0.8	5
	6000	2.0±0.51	3.42±0.5	10
2	4000	1.6±0.28	3.60±0.6	10
	6000	2.0±0.13	3.42±0.4	15
5	4000	2.5±0.21	3.55±0.7	52
	6000	3.0±0.25	3.40±0.6	90

* Mean of five determinations ± S.D., Tablets weighing approximately 50±2 mg.

** Dissolution time for 90% of medicament release from five tablets, mean of three determinations.

Preparation of tablets by molding:

The drug and Eudragit retard were physically dispersed into the melted mass of PEG. Then, the melted mass was molded just before congealing to assure a uniform distribution. The tablets were ejected from the mold with mild pressure. It was difficult to incorporate more than 5% Eudragit retard in molten PEG. The formulations are listed

in table 1. The tablets were physically evaluated regarding weight variation, hardness, thickness and friability. Also, all formulations were tested for drug content.

Determination of the drug content:

Five tablets from each batch were crushed in a mortar and shaken for 15 min with 100 ml of 0.1M HCl. The clear filtrate was assayed spectrophotometrically at 278 nm (Spectrophotometer, Model 550 S, PERKIN ELMER, D-Uberlingen). The mean of three determinations was calculated.

Weight variation:

Twenty tablets from each batch were weighed, and the average weight and percent deviation from each tablet was calculated.

Hardness Test:

The hardness of five tablets from each batch was determined using an ERWEKA hardness tester (Model TBT, ERWEKA, D-Heusenstamm).

Friability Test:

Friability was determined by means of a Roche-type friabilator (100 revolutions within 4 min).

Preparation of tablets by direct compression:

Two formulations were chosen for direct compression based on the results obtained from molded tablets. The molten mass containing the drug and either Eudragit RL100 or Eudragit RS100 in concentration of 5% w/w was passed through a nest of standard sieves. The fraction which has the particle size of 250-315 μm was directly compressed at

9.0 Ibs gauge pressure (Erweka press, Type EKO No 11144, W. Germany). Tablets of approximately 50 mg which contain 2.5 mg salbutamol sulphate were obtained.

Dissolution rate determination:

The dissolution rates of either molded or compressed tablets were measured using Levy's beaker method (5). Five tablets were placed in a beaker containing 200 ml of 0.1M HCl (pH 1.12). The dissolution medium was maintained at 37±0.5°C, and agitated at 100 rpm by means of a three blade glass stirrer. Samples of 1 ml were taken at 5,10 15, 30, 45, 60 and 90 min, and immediately replaced with an equivalent volume of dissolution medium. The withdrawn samples were assayed spectrophotometrically for salbutamol sulphate content by diluting each sample to 5 ml with 0.1M HCl, and measuring the absorbance at 278 nm against a blank. The presence of the acrylic resin did not interfere with the drug assay. All dissolution tests were repeated three times and the average was taken.

RESULTS AND DISCUSSION

The actual amounts of salbutamol sulphate present in either molded or compressed tablets ranged from 95.2 to 102.6% w/w. Weight variation for all formulations was within ±5%, while friability fell within a range of 0.01-0.08%.

Table 1 shows the hardness as well as thickness values of all prepared formulations. In general, the hardness observed by using PEG 6000 was higher than that showed by PEG 4000. The higher the molecular weight of PEG, the

greater was the hardness of the obtained tablets. These results are in agreement with those previously reported by Lachman[6]. Increased Eudragit concentration from 1 to 2% w/w was found to have no effect on the hardness. However, a marked increase in hardness was observed in formulations containing 5% of both types of Eudragit. It was also shown that tablet thickness was changed very slightly with increasing hardness.

The results of the dissolution tests of the molded tablets are presented in table 1 and Figs. 1 and 2. The table and Figs. demonstrated, the effects of both PEG and either Eudragit retard on the release of the drug. Tablets without Eudragit and those prepared with 1% Eudragit RL100 in presence of PEG 4000 or 6000 were found to dissolve in less than 5 min.

Tablet formulations containing Eudragit RL100 and PEG 6000 showed an increase in the time for 90% drug release from less than 5 min for the control to 8 min and 43 min for 2% and 5% Eudragit content respectively. In formulations containing Eudragit RS100 and PEG 6000, this effect was still more pronounced as the respective times for 90% drug release were 10 min., 15 min. and 90 min for 1%, 2% and 5% of Eudragit content respectively. A similar relationship was found for tablet formulations of PEG 4000 with both Eudragit RL100 and RS100. However, in this study the corresponding formulations yielded much lower values for drug release times. In general, tablets of either Eudragit retard prepared with PEG 6000 released drug at lower rates than those prepared with PEG 4000. This behaviour was more

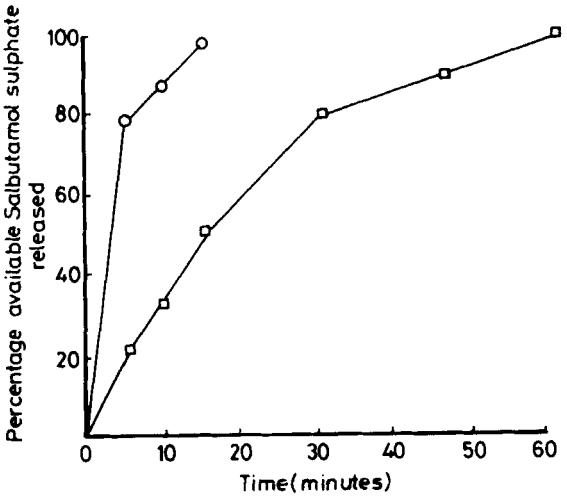

FIGURE 1.

Dissolution Profile of Salbutamol sulphate from Molded Tablets Containing 5% w/w Eudragit RL 100

Key: o Tablets containing PEG 4000
□ Tablets containing PEG 6000

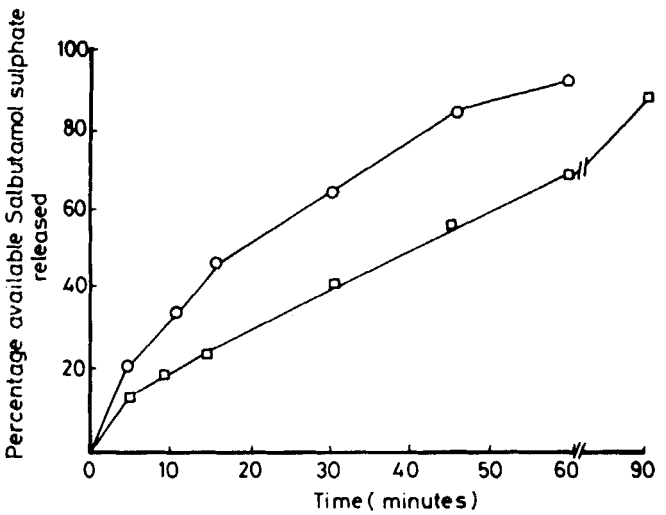

FIGURE 2.

Dissolution Profile of Salbutamol sulphate from Molded Tablets Containing 5% w/w Eudragit RS100.

Key: o Tablets containing PEG 4000
□ Tablets containing PEG 6000

TABLE 2

Table 2: In vitro data for Salbutamol sulphate compressed tablets*.

Eudragit %	PEG mol.wt	Hardness Kg	Thickness mm	Dissolution time** t_{90}, min
0	4000	3.20±0.25	1.85±0.6	5
	6000	3.50±0.39	1.90±0.7	5
RL100				
5	4000	4.00±0.59	1.85±0.5	5
	6000	4.25±0.13	1.90±0.6	5
RS100				
5	4000	4.00±0.13	1.95±0.8	30
	6000	4.25±0.49	2.0±0.6	45

* Mean of five determinations ± S.D.

**Dissolution time for 90% of medicament release from five tablets, mean of three determinations.

pronounced in using 5% of either Eudragit retard (Figs. 1 and 2). This could be due to the hardness which significantly affected the dissolution rate of the tablets. Wiseman and Federici[7] found that drug release from prolonged release tablets was controlled by the hardness to which the tablets were compressed and the ratio of the retarding agent to the drug.

The difference observed in drug release from tablets of either Eudragit retard in presence of PEG 4000 or 6000 may be related to the difference in permeability of Eudragit used. A case which was in accordance with that reported before[1,3].

Table 2 revealed that, direct compression technique gave tablets with the higher hardness and a faster dissolution of salbutamol sulphate than those prepared by molding technique (Table 1). This result indicates that, the technique of the manufacture of tablets greatly affected the hardness and drug dissolution from tablets. Similarly, as noticed in the molding technique, directly compressed tablets containing Eudragit RS produced the lower drug dissolution as compared with the tablets containing Eudragit RL100 (Table 2). In conclusion, the study revealed that, molded tablets technique was superior to direct compression method in formulation of controlled release salbutamol sulphate tablets. Both Eudragit RL100 and RS100 retarded the release of the drug in presence of PEG 4000 or 6000, yet the maximum retardation was achieved only in tablet formulation containing 5% of Eudragit RS100 and PEG 6000.

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