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COMMUNICATION

MATRIX TABLETS OF SALBUTAMOL SULPHATE

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ABSTRACT

Controlled release tablet of Salbutamol has been shown to be clinically superior to the standard 4 mg Salbutamol tablets given 3-4 times daily. Salbutamol-Sulphate sustained release tablets based on two marketed polymers, Eudragit and Methocel, is presented here. Effect of water insoluble diluents on in vitro drug release was evaluated.

INTRODUCTION

Salbutamol, a potent B_2 adrenoceptor stimulant is used as a bronchiodilator to treat chronic obstructive airways disease. It provides the benefit of bronchodilation without myocardial stimulation (1).

In the present study, Eudragit RS-100, a relatively less permeable polymer and Methocel K 100 M, a fast hydrating polymer were used as matrix formers. Several water insoluble diluents were used to study their effect on in vitro drug release.

EXPERIMENTAL

Materials

Salbutamol Sulphate I.P. obtained as a gift sample from Themis Labs and FDC (Pvt.) Ltd., Methocel K-100M (COLORCON U.K.) Eudragit RS-100 PM and S-100 (ROHM PHARMA, GERMANY). Microcrystalline cellulose (MCC) Calcium Sulphate di-

hydrate ($CaSO_4$), dibasic Calcium phosphate (DCP) heavy magnesium oxide (MgO), Calcium hydroxide, talc, magnesium stearate were of pharmacopoeial grade and used as supplied.

Methods

Salbutamol Sulphate (10.6 mg/tablet) polymer (Eudragit/Methocel) and diluent were blended in dry form and granulated using U.S.P. ethanol/ethanol:water (1:1). A 20/40 fraction was lubricated using 2% w/w talc and 1% w/w magnesium stearate compression was done using 5/15 inch flat faced bevelled punches on a Cadmach Single stroke tabletting machine at a constant pressure. Tablets thus prepared were subjected to quality control tests; viz. assay, content uniformity, hardness, friability, weight variation, dimensions and in vitro dissolution (U.S.P. XIX).

In vitro dissolution : U.S.P. XIX tablet dissolution apparatus was used. Dissolution media used were 250 ml distilled water (D.W.) and buffers (2) (pH 1.2 for 2 hours and pH 7.2 for next 6 hours) maintained at 37°±0.5°C. Speed of rotation of basket was 50 r.p.m. Aliquots were withdrawn at regular time intervals and assayed on a Beckmann DB spectrophotometer at λ = 227 nm.

Stability studies : Tablets were placed in amber coloured bottles and stored at 30°C±2°C, 45°C±2°C, 60°C±2°C and 85% R.H. (30°C). These were suubjected to quality control tests enlisted previously after every 2 weeks.

RESULTS AND DISCUSSION

All the compressed tablets complied with the quality control tests : Assay ±2% w/w, content uniformity ±2% w/w, weight variation ±7.5% w/w, Friability 1% w/w, Hardness 5-7 kg/cm, Diameter 8.4±0.33 mm, Thickness 2.31±0.19 mm.

Kinetics of drug release : Dissolution data obtained was analysed using the equation (3) :

$$\frac{M_t}{M} = kt^n$$

Water insoluble diluents, MCC, DCP, $CaSO_4$, MgO and $Ca(OH)_2$ in concentrations of 85, 75 and 65% w/w each were incorporated in matrices containing Eudragit RS-100. The acrylic polymer concentration was varied from 10% to 30% w/w.

TABLE - 1

Dissolution medium : D.W.

EUD.RS : MgO (% w/w)	K_1^* $(hr)^{-1}$	t_{50} Hours	t_{90} Hours	n
10 : 85	0.0957	3.256	20.098	0.3823
20 : 75	0.0873	5.206	23.773	0.3792
30 : 65	0.0649	5.986	30.773	0.4719

* K_1 - First order release rate constant.

TABLE - 2

Dissolution medium : D.W.

EUD.RS : $Ca(OH)_2$ (% w/w)	K_1 $(hr)^{-1}$	t_{50} Hours	t_{90} Hours	n
10 : 85	0.1155	2.654	16.634	0.3873
20 : 75	0.1011	3.654	19.576	0.4310
30 : 65	0.0433	5.021	21.163	0.5245

MCC, DCP and Calcium Sulphate in all concentrations proved to be unsuitable as diluents in sustaining drug release. Total release (100%) was obtained in 2 hours. Only MgO and Calcium hydroxide significantly retarded drug diffusion. This could be attributed to the formation of insoluble complexes with the acrylic polymer. Retardation in drug release was observed when Eudragit concentration was increased from 10% to 30% w/w. Drug release in distilled water, after 3 hours was very poor. Degradation of the drug was observed at alkaline pH (11-12) contributed by the diluent. Similar effect was observed with Calcium Hydroxide. (Tables 1 and 2). Burst effect in all the formulations was 20-30% w/w.

The overall drug release rate in buffers from Eudragit-MgO based matrices further decreased as compared to in distilled water. (Table 3). The burst effect

TABLE - 3

Dissolution medium : Buffers

EUD.RS : MgO (% w/w)	K_1 $(hr)^{-1}$	t_{50} Hours	t_{90} Hours	n
10 : 85	0.0525	2.922	24.576	0.2340
20 : 75	0.0477	9.507	45.675	0.2948
30 : 65	0.0398	9.645	50.145	0.3429

TABLE - 4

Dissolution medium : Buffers

EUD.RS : $Ca(OH)_2$ (% w/w)	K_1 $(hr)^{-1}$	t_{50} Hours	t_{90} Hours	n
10 : 85	0.2137	1.517	7.990	0.3273
20 : 75	0.1603	1.659	10.662	0.3374
30 : 65	0.1390	2.615	14.207	0.4741

TABLE - 5

Dissolution medium : Buffers

EUD.RS : S-100 : MgO (% w/w)	K_1 $(hr)^{-1}$	t_{50} Hours	t_{90} Hours	n
20 : 10 : 65	0.4237	2.149	5.970	0.5773
25 : 5 : 65	0.1803	2.079	11.006	0.4173
EUD.RS : S-100 : $Ca(OH)_2$				
20 : 10 : 65	0.0883	5.470	23.72	0.475
15 : 10 : 70	0.1403	3.381	14.821	0.474

TABLE - 6

Dissolution medium

Methocel K-100 M : MCC (% w/w)	K_1 $(hr)^{-1}$	t_{50} Hours	t_{50} Hours	n
20 : 75	0.2895	1.864	7.424	0.420
40 : 55	0.1932	2.614	10.945	0.471
60: 35	0.1568	3.200	13.464	0.486
Methocel K-100 M : DCP				
20 : 75	0.2752	1.173	7.022	0.3964
40 : 55	0.2003	2.132	10.176	0.4457
60: 35	0.1577	3.204	13.408	0.5007

was slightly increased due to the formation of the highly soluble salt, Magnesium Chloride in gastric milieu which diffused out rapidly from the porous matrix, increasing rate of release. In intestinal fluid, drug release was retarded due to formation of gel like precipitate of Magnesium hydroxide which increased the tortuoisity of the matrix.

Drug diffusion rate from Eudragit - Calcium hydroxide based matrices in buffers increased as compared to in distilled water (Table 4). The burst effect was increased to 40% w/w owing to the formation of soluble salt, Calcium chloride Drug release was not appreciably affected in alkaline pH from these matrices.

To enhance the release from Eudragit-MgO matrices in intestinal fluids, Eudragit S-100 was incorporated in the matrix (Table 5). Also, incorporation of S-100 in Eud-Calcium hydroxide matrices decreased the total permeability of the matrix in gastric fluids, thereby decreased the burst effect considerably (Table 5).

Drug release from Eudragit matrices followed Fickian diffusion ($n \leq 0.5$) and first-order release kinetics. Polymer relaxation was negligible due to the highly inert nature of the acrylic polymer.

TABLE - 7

Formulation : Methocel K 100 M : DCP (40:55) % w/w

Parameters	30°C±2°C	45°C±2°C	60°C±2°C	85% R.H.
Friability (%)	0.2	0.2	0.2	-
Hardness (kg/cm^2)	6	6	5	-
t_{50} (hr)	2.132	2.118	2.145	1.967
t_{90} (hr)	10.176	7.113	7.204	6.639
K_1 $(hr)^{-1}$	0.2003	0.3067	0.3336	0.3446
n	0.4457	0.4709	0.4775	0.4392

Two insoluble diluents, MCC and DCP, in varying concentrations of 75, 55 and 35% w/w each were incorporated in matrices containing Methocel K100M. Polymer concentration was 20, 40 and 60% w/w respectively. As the Methocel percentage in matrix was increased significant retardation was observed This was attributed to increase in gel strength and diffusion barrier which in turn increased tortoisity of matrix. (Table 6). Similar retardation was observed with Methocel-DCP matrices. No significant differences were observed in release profile between the two diluents.

Drug release from Methocel matrices also followed Fickian diffusion ($n \leq 0.5$) and first-order release kinetics. Methocel hydrated rapidly in contact with aqueous medium and hence polymer relaxation was not the rate determining step.

Stability studies : No changes were observed in the appearance, hardness, friability, average drug content of the matrix tablets. However, there was increase in the release rate. (Table 7). Shelf life of the formulation calculated using Arrhenius equation was 16.263 months.

SUMMARY AND CONCLUSIONS

Magnesium oxide and calcium hydroxide can be successfully used as retardants in formulating sustained release matrix tablets containing Eudragits. Exposure of these tablets to high temperature and humidity should be avoided.

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