DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 17(10), 1373-1380 (1991)

COMMUNICATIONS

SUSTAINED RELEASE FORMULATION OF SALBUTAMOL SULPHATE

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ABSTRACT

Sustained release tablets containing salbutamol sulphate has been prepared by wax matrix granulation method and were evaluated for *in vitro* release profile and *in vivo* availability studies in dogs. Out of the release retarding waxy materials used combinations of carnauba wax and stearyl alcohol in concentration range between 60 to 70% of the weight of the tablet were found to be optimum in fabricating sustained release tablets for twenty-four hours duration of action. The formulations were also compared with marketed products of salbutamol for *in vitro* release profile.

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INTRODUCTION

Salbutamol sulphate is a selective B_2 adreno-receptor stimulant and is used in the treatment of bronchial asthma[1] In acute asthmatic conditions, salbutamol is given four times daily in a dose of 2.4 mg orally to maintain therapeutic blood level. The drug being safe with an average biological half life of 4.5 hrs, it is suitable for construction in an oral sustained release dosage form for twelve to twenty-four hours duration of action. Salbutamol sulphate being fairly soluble in water, construction of sustained release product in a waxy matrix is more convenient[2-5]. The present study includes the preparation and evaluation of sustained release tablets of salbutamol sulphate using waxy granulating agents containing carnauba wax and stearyl alcohol.

MATERIALS AND METHODS

Salbutamol sulphate B.P.(I.D.P.L.), povidone (CDH), sodium carboxy methyl cellulose (H.P.C.), sorbitol 70% solution (Sarabhai M.Chemicals), bees wax (Colmite India, Bombay), carnauba wax (L.R.Richerdson, U.K.), stearic acid (Godrej Soaps and Oils, Bombay), stearyl alcohol (Fluka A.G.,Switzerland). Other materials were of analytical reagent grades.

Preparation of tablets: 9.6 mgs of salbutamol sulphate equivalent to four doses was used to prepare sustained release

tablets of twenty-four hours duration of action as calculated by the Nelson's equation[6]. The initial dose (2.4 mgs) was granulated using Polyvinyl Pyrrolidone (PVP), in the concentration 2-5% by wet granulation method. Lactose and dry starch (5%) were used as diluent and disintegrating agents respectively. Retard granules were prepared using different waxy materials (Bees wax, carnauba wax, stearic acid and stearyl alcohol) in concentration range between 20 to 70% alone or in combinations. The moltan wax was mixed with the drug-diluent (lactose) mixture at temperature just above the melting point of the wax and then granulated by passing through Sieve No.30. Granules were compressed manually on Cadmach machine after lubrication using talc (1%) and magnesium stearate (1%) into 3 types of tablets viz. plain tablets containing one dose of the drug (2.4 mg); retard release tablets containing 3 doses of the drug (7.2 mg) and sustained release tablets using mixture of plain granules and retard release granules containing one dose and three doses of the drug respectively. Tablet hardness was kept constant in the range of 4-5 kg in case of retard and sustained release tablets and 6-7 kg in case of plain tablets on Stoke's hardness tester. The average total weight of all types of tablets were maintained around 200 mg.

In vitro release rate study

Dissolution test apparatus U.S.P. was used and the study was conducted as per U.S.P. method[7] using simulated

gastric fluid U.S.P. maintained at 37±1°C. Samples (5 ml) were withdrawn after 15 min, 30 min and 60 min, filtered and analysed for the drug content. After 60 min, the gastric media was replaced by the simulated intestinal media U.S.P. and dissolution test was continued for twenty-four hours. Samples were filtered and analysed for salbutamol content by spectrophotometric method described by Shingbal and Naik[8].

In vivo availability study

Group of six healthy dogs of either sex weighing between 10 to 11 kg was used for the study. The fasted dogs were administered with the sample orally and blood samples were withdrawn at convenient intervals of time for twenty-four hours. These samples were added with trichloro acetic acid to precipitate protein, centrifuged and the supernatant was taken to analyse for salbutamol content by the method described earlier. Total drug content in the blood was calculated taking the blood volume of the dog to be 8% of its body weight.

RESULTS AND DISCUSSIONS

In vitro dissolution profile of various batches of retard release tablets (MD_1 to MD_9) and sustained release tablets (SR_1 to SR_3) are given in Table-1 and are compared with that of marketed sustained release tablets (MSR) of salbutamatol sulphate. Batches containing stearic acid (MD_3) and bees wax (MD_1) showed high release rate than those con-

TABLE-1

In vitro dissolution rate data of retard tablets and sustained release tablets containing salbutamol sulphate

Batch	Initial dose Binder(%)	Maintenance dose retard material(%)	Dissolution rate		
			t 30% (hrs)	t 50% (hrs)	% dissolution in 6 hours
MD_1	-	B.W.(20)	1.0	3.0	62.4
MD_2	-	C.W.(20)	1.3	6.6	45.2
MD_3	-	S.A.(20)	0.25	0.5	87.0
MD_4	-	S.Al.(20)	1.0	2.5	59.0
MD_5	-	C.W.(35) + S.Al.(35)	10.0	-	23.0
MD_6	-	C.W.(35) + S.Al.(30)	9.0	-	26.0
MD_7	-	C.W.(35) + S.Al.(25)	6.5	-	29.0
MD_8	-	C.W.(15) + S.Al.(30)	1.0	7.5	49.0
MD_9	-	C.W.(10) + S.Al.(30)	0.5	1.0	73.0
SR_1	PVP(2)	C.W.(35) + S.Al.(25)	0.75	4.0	58.0
SR_2	PVP(2)	C.W.(35) + S.Al.(30)	1.0	5.0	53.0
SR_3	PVP(2)	C.W.(35) + S.Al.(35)	1.0	7.0	48.0
MSR_1	-	-	-	2.0	83.0
MSR_2	-	-	-	1.5	71.0

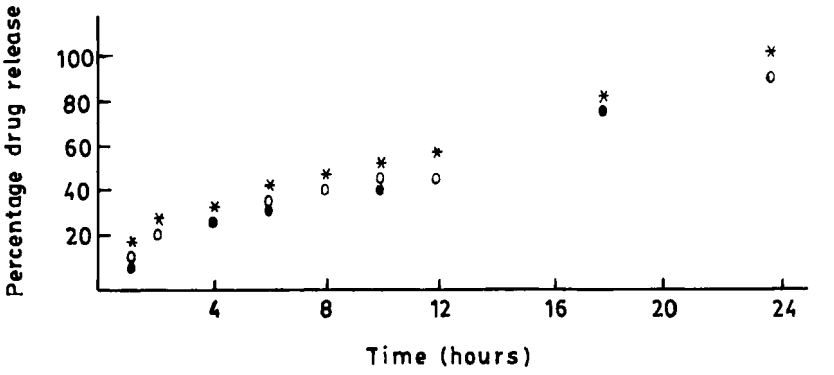

FIGURE-1

In vitro dissolution profile of different batches of sustained release tablets of salbutamol sulphate SR_1 (*); SR_2 (o) and SR_3 (o).

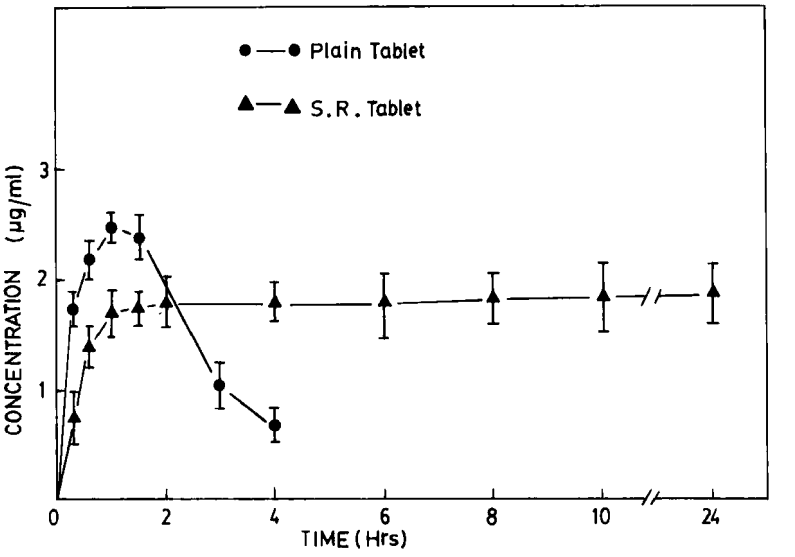

FIGURE-2

In vivo availability study of the sustained release tablets of salbutamol sulphate compared with plain tablets.

taining carnauba wax and stearyl alcohol. No much difference in the release rates were observed between batches containing carnauba wax (MD_2), stearyl alcohol (MD_4) alone and their combination containing low percentage of carnauba wax (MD_8 and MD_9). Batches (MD_5 to MD_7) containing high percentage of carnauba wax (35%) in combination with stearyl alcohol (25 to 25%) showed drug release pattern characteristics of a monolithic inert matrix type delivery system[9].

In vitro dissolution pattern of different batches of sustained release tablets prepared using both plain and retard granules are graphically represented in Fig.1. Among these, tablets (Batch No.SR_1) prepared using plain granules containing 2% PVP and retard granules containing 35% carnauba wax and 25% stearyl alcohol showed satisfactory release pattern for an ideal sustained release tablets as reported by Goodhart et al[10]. In vivo absorption rate studies of this batch of sustained release tablet conducted on dogs showed consistent blood level concentration ranging from 1.83 to 1.87 mcg/ml for 24 hours with the t_p value of 2 hours after administration (Fig.2). This result is very much in confirmation with the results obtained by single dose oral administration of salbutamol plain tablets which gave average C_{max} value 2.5 mcg/ml with the t_p value of 1.5 hours after administration.

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