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RESEARCH ARTICLE

DEVELOPMENT AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF SALBUTAMOL SULPHATE USING HYDROPHILIC AND HYDROPHOBIC POLYMERS

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In the present study, an attempt has been made to evaluate the effect of hydrophilic and hydrophobic polymers on the release profile of drug from matrix system. Salbutamol sulphate, an anti-asthmatic agent, was used as a model drug to evaluate its release characteristics from different matrices. Matrix tablets of salbutamol sulphate were prepared by direct compression process using hydrophobic polymer ethyl cellulose (F1-F4) and hydrophilic polymer HPMC (F4-F8). Release kinetics of salbutamol sulphate from these sustained release matrices in distilled water using USP paddle method with sinker for 12 h were studied. Statistically significant differences were found among the drug release profile from different formulations. The release mechanism was explored and explained with zero order, first order, Higuchi and Korsmeyer equations. The results generated in this study showed that the profile and kinetics of drug release were functions of polymer type, polymer level and physico-chemical properties of the drug. The present study concluded that the hydrophilic matrix tablets of formulation F8 prepared using HPMC showed drug release of 91.32% and can be employed as twice-a-day oral sustained release drug delivery system whereas hydrophobic matrix tablets of formulation F4 prepared using ethyl cellulose showed drug release of 64.2% and can be employed as once a day oral sustained release drug delivery system. Therefore, ethyl cellulose is suggested as an ideal polymer for production of directly compressed matrix sustained release salbutamol tablets.

Key words: Salbutamol sulphate, Matrix tablets, HPMC, Ethyl cellulose, Sustained release.

INTRODUCTION

Asthma is a common chronic inflammatory disease characterized by variable and recurring symptoms, airflow obstruction, and bronchospasm with wheezing, coughing, chest tightness, and shortness of breath. These acute episodes may be triggered by such things as exposure to an environmental stimulant (or allergen), cold air, exercise or exertion, or emotional stress. In children, the most common triggers are viral illnesses such as those that cause the common cold. During asthma attacks, the smooth muscle cells in the bronchi constrict, the airways become inflamed and swollen, and breathing becomes difficult. This is often referred to as a tight chest and is a sign to immediately take medication (Nayak *et al* 2010). Salbutamol sulphate is a white or almost white odorless powder. It is soluble in four parts of water; slightly soluble in 95% alcohol, chloroform and ether. It is chemically described as 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(tert-butyl amino) ethanol sulphate. The elimination half life of inhaled or oral salbutamol is between 2.7 and 5 h. Its short elimination half life calls for frequent daily dosing (2 to 3 times)

and therapeutic use in chronic respiratory diseases necessitates its formulation into sustained release dosage form. Therefore, development of sustained release dosage form of salbutamol is of therapeutic relevance and can be used to provide a consistent dosage through sustaining an appropriate level of drug over time (Rahman *et al* 2011). Sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of the drug for extended period of time with minimized local or systemic adverse effects. Sustained release dosage forms would be most applicable for drugs having short elimination half lives (Gonjari *et al* 2009). Matrix systems appear to be a very attractive approach from the economic as well as from the process development and scale-up points of view in controlled release systems (Pasa *et al* 2012). Hydrophilic polymer matrix systems are widely used for designing oral controlled drug delivery dosage forms because of their flexibility to provide a desirable drug release profile, cost effectiveness and broad regulatory acceptance. For the present research work, hydroxylpropyl methylcellulose (HPMC) and ethyl cellulose (EC) were used as matrix formers. Past literature is enriched with variety of sustained and controlled delivery of pharmaceuticals (Dahiya and Gupta, 2011; Kumar and Dureja, 2011; Tripathi *et al* 2011; Mohabe *et al* 2011; Talegaonkar *et al* 2011). Keeping in mind the scope of these systems, the present study was undertaken to develop sustained release matrix formulations of salbutamol sulphate and to examine the effects of both hydrophilic and hydrophobic polymers on *in vitro* drug release. In present study, salbutamol sulphate matrix formulations were prepared using hydrophilic polymer, HPMC and hydrophobic polymer, EC alone to study release kinetics and find out effects of both polymers.

MATERIALS AND METHODS

Materials

Salbutamol sulphate, HPMC and ethyl cellulose were procured from Glukem Chemicals, Hyderabad, India. Lactose and magnesium stearate were procured from Finar Chemicals, Ahmedabad, India. Other materials and solvents used were of analytical grade.

Methods

Preparation of tablets

Salbutamol sulphate matrix tablets were prepared using HPMC and ethyl cellulose. The active ingredients and excipients were sieved through sieve no. 60 mesh individually. The ingredients were weighed individually and mixed well. The mixed powder ingredients were granulated using isopropyl alcohol. The damp coherent mass obtained was sieved through sieve no. 10 mesh and dried in hot air oven for few minutes. The granules were again sieved in sieve no. 20 mesh and lubricated with magnesium Stearate. The granules were compressed to fixed average weight, using single punch machine.

Quality control tests for matrix tablets

The tablets of the proposed formulations (F1-F8) were evaluated for hardness, weight variation, friability and drug content. Hardness of 10 matrix tablets from each formulation was measured using Monsanto Hardness tester. Friability of the tablets was determined in a Roche Friabilator. Weight variation test was performed according to the official method. Drug content for salbutamol sulphate was carried out by measuring the absorbance of the sample at 277 nm using Elico UV spectrophotometer and comparing the content from a calibration curve prepared with standard salbutamol sulphate in the same medium.

In vitro dissolution study of tablets

Dissolution test was performed on six tablets from the formulations. The USP apparatus 2 (Veego Dissolution Tester) at a speed of 50 rpm, with 900 ml distilled water as the dissolution medium was used, and samples were taken after 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300, 330, 360, 390, 420, 450, 480, 510, 540, 570, 600, 630, 660, 690 and 720 min. The temperature was maintained at 37±1 °C. The amounts of dissolved Salbutamol were then determined by spectrophotometer at 277 nm, using filtered portions of the samples. The release in any time was obtained by calculating the mean cumulative percent release of the 6 tablets tested. The percent drug release was then plotted against time and the release profiles were studied. Three different kinetic models *i.e.* Zero order, Higuchi and Korsmeyer models were studied (Dash *et al* 2010) using non-linear regression analysis and the best equations were suggested.

Kinetic analysis of release data

Different kinetic models (Zero-order, Higuchi's and Korsmeyer's) were applied to interpret the

release profile from matrix system. The best fit with higher correlation ($R^2 > 0.995$) was found with Korsmeyer's equation for tablet formulated with EC whereas the best fit with higher correlation ($R^2 > 0.999$) was found with the zero order equation for tablet formulated with HPMC.

RESULTS AND DISCUSSION

Physical evaluation of salbutamol sulphate matrix tablets

The tablets of the proposed formulations (F1-F8) were evaluated for hardness, weight variation, friability and drug content. The hardness and percentage friability of the tablets of all batches ranged from 6.17-6.98 kg/cm^2 and 0.67 to 0.76 % respectively. The average weight percentage deviation of the 20 tablets of each formula was less than ± 5%. Drug content among different batches of tablets ranged from 7.652 mg to 7.689 mg. Thus, all the physical parameters of the matrices were practically within limits (**Table 1**).

Table 1. Physical evaluation of salbutamol sulphate matrix tablets

Formulation	Hardness (kg/cm^2)	Weight variation (%)	Friability (%)	Drug content (mg)
F1	6.17	3.124	0.69	7.653
F2	6.21	2.438	0.71	7.681
F3	6.87	1.489	0.68	7.652
F4	6.54	2.234	0.67	7.673
F5	6.98	2.631	0.75	7.684
F6	6.43	3.209	0.73	7.657
F7	6.23	2.103	0.69	7.689
F8	6.81	3.123	0.76	7.668

Effect of ethyl cellulose and HPMC on release pattern of salbutamol sulphate

Different matrix tablets containing salbutamol sulphate as active ingredient having ethyl cellulose polymer 20%, 30%, 40% and 50% respectively of total tablet weight with the formulation code F1, F2, F3 and F4 were prepared to evaluate the effect of this polymer. After preparation their dissolution studies were carried out using paddle apparatus at 50 rpm in distilled water medium at 37 °C (±1 °C). Six tablets from each formulation were used in dissolution study. The release profile of salbutamol sulphate was monitored up to 12 h. A release profile of salbutamol sulphate containing ethyl cellulose matrix tablet of four formulations was obtained from the graphs. The total percentage of salbutamol release from the formulations F1, F2, F3 and F4 were 70.1%, 68.9%, 65.3% and 64.2% respectively. It was observed that the release rate was extended with the increase of polymer percentage. The highest percent of drug release (70.1%) within 12 h was obtained from F1 where polymer content was 20% of total tablet weight (**Table 2**). However, in F4, the polymer content was 50% of total tablet weight and the release of drug was with 64.2 % within 12 h. The standard graph of salbutamol sulphate is shown in the **Figure 1**. The rate of drug release was found to be inversely related to the amount of ethyl cellulose present in the matrix structure *i.e.* the drug release increased with decrease in the polymer content of the matrix tablet (**Figure 2**). Different matrix tablets containing salbutamol sulphate as active ingredient having HPMC polymer 20%, 30%, 40% and 50% respectively of total tablet weight with the formulation code F5, F6, F7 and F8 were prepared to evaluate the effect of this polymer. After preparation according to the formulation, their dissolution studies were carried out in paddle method at 50 rpm in distilled water medium at 37 °C (±1 °C). Six tablets from each formulation were used in dissolution study. The release profile of salbutamol sulphate was monitored up to 12 h. To determine the effects of polymers on the drug release, different kinetic models such as Zero order, Korsmeyer, Higuchi were investigated (**Table 3**). A release profile of salbutamol sulphate containing ethyl cellulose matrix tablet of four formulations was obtained from the graphs. The total percentage of Salbutamol release from the formulations F5, F6, F7 and F8 were 71.5%, 77.8%, 84.3% and 91.32% respectively. It was observed that the % drug release was enhanced with the increase in polymer percentage. The highest percent of drug

Table 2. Percent drug release of the formulations (F1-F8)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
30	2.1	1.8	1.6	1.2	2.6	3.4	3.9	5.3
60	4.3	3.9	3.4	2.9	5.8	6.9	8	9.1
90	6.2	5.7	4.8	3.9	8.8	9.9	11	13.1
120	8.9	7.5	6.2	5.4	10.7	12.9	14.1	16.2
150	10.4	9.6	7.5	6.9	13.9	15.1	17.2	19.4
180	12.8	11.4	9.8	8.2	15.8	18.2	20.3	22.5
210	15.7	13.9	11.2	9.7	18.6	21.9	24	26.1
240	17.9	16.5	13.4	11.4	20.6	25.7	29.1	30
270	20.1	19.2	16.7	14.2	24.9	28.2	32.4	34.6
300	23.4	22.3	19.9	16.9	29.5	33	36.4	38.6
330	26.1	24.9	22.1	19.8	33.4	37.9	39.1	42.3
360	29.2	28	26.2	23.1	37.6	41.8	43.1	46.3
390	33.1	31.8	29.4	25.9	41.5	44.8	47	49.2
420	36.4	33.2	33.3	30.1	45	48.2	50.5	52.9
450	40.3	36.8	35.9	32.9	48.5	50.8	54.1	56.3
480	45.4	40.1	39.1	36.7	51.2	53.2	58.5	60.8
510	49.3	43.9	42.3	39.4	54.4	57.8	63.1	64.3
540	54.2	49.1	45.4	42.2	57.6	59.7	66	68.2
570	57.9	51.7	49.6	46.4	59.9	62.8	70.2	72.4
600	60.2	53.3	52.8	49.8	63.2	65.8	74.1	76.3
630	62.1	57.6	55.3	52.1	65.8	67.2	78.2	80.3
660	63.9	61.9	59.8	54.4	67.3	69.9	80.3	84.5
690	67.8	64.2	62.1	59.9	69.2	73.1	82.1	88
720	70.1	68.9	65.3	64.2	71.5	77.8	84.3	91.3

Table 3. Release kinetics (r^2) of formulations (F1-F8)

Formulation	Zero order model	Higuchi model	Korsmeyer model
F1	0.989	0.993	0.994
F2	0.990	0.930	0.995
F3	0.987	0.922	0.988
F4	0.980	0.906	0.988
F5	0.993	0.965	0.996
F6	0.996	0.974	0.997
F7	0.998	0.967	0.998
F8	0.999	0.964	0.996

release (91.32%) within 12 h was obtained from F8 where polymer content was 50% of total tablet weight However, in F5, the polymer content was 20% of total tablet weight and the release of drug was with 71.5 % within 12 h. The rate of drug release was found to be directly related to the amount of HPMC present in the matrix structure *i.e.* the drug release increased with increase in the polymer content of the matrix tablet (**Figure 3**).

The comparison of percent drug release of the formulations (F1-F8) using Zero order, Higuchi and Korsmeyer model was done (**Figure 4-6**).

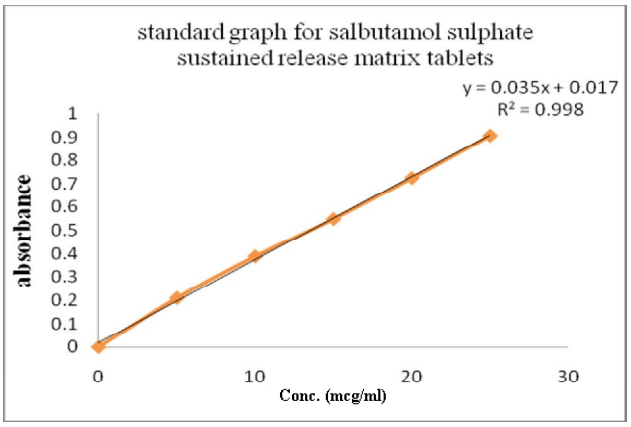

Fig. 1. Standard graph of salbutamol sustained release matrix tablets

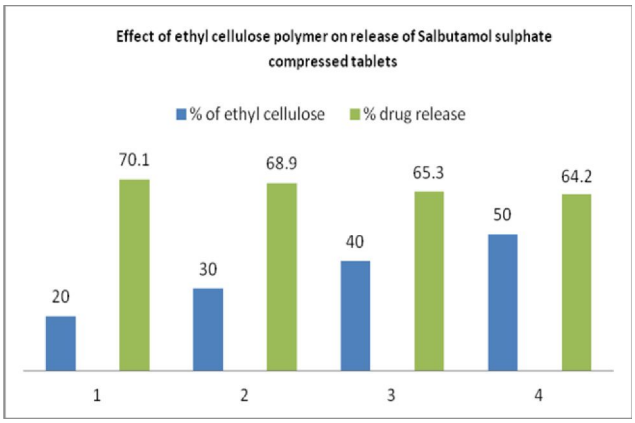

Fig. 2. Effect of ethyl cellulose on release of salbutamol sulphate matrix tablets

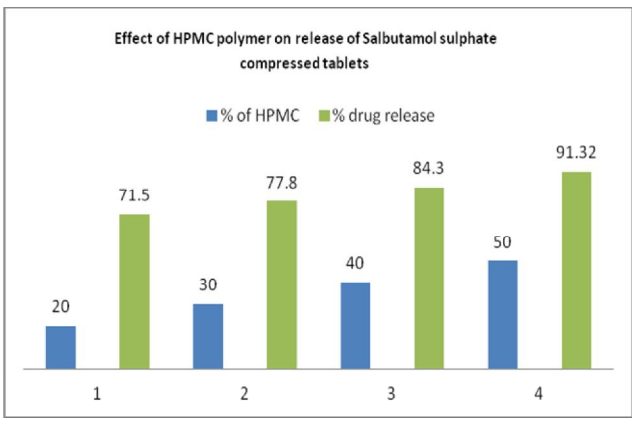

Fig. 3. Effect of HPMC on release of salbutamol sulphate matrix tablets

Fig. 4. Zero order plot for release kinetics of salbutamol sulphate matrix tablets

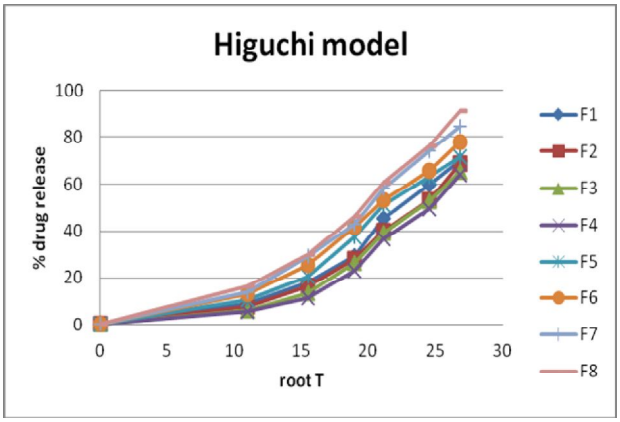

Fig. 5. Higuchi plot for release kinetics of salbutamol sulphate matrix tablets

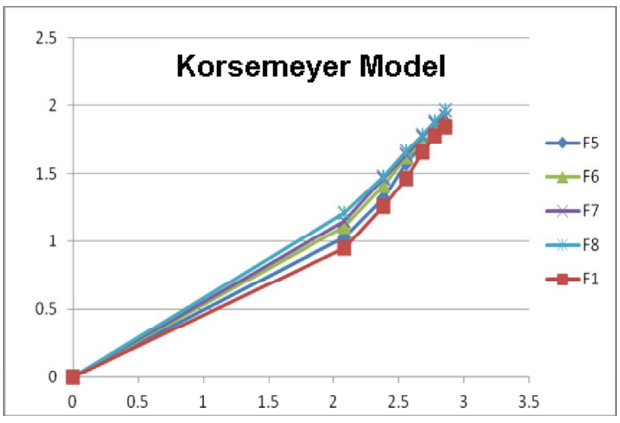

Fig. 6. Korsmeyer plot for release kinetics of salbutamol sulphate matrix tablets

CONCLUSION

It may be concluded from the present study that the hydrophilic matrix tablets of formulation F8 prepared using HPMC showed drug release of 91.32% and can be employed as twice-a-day oral sustained release drug delivery system. However, the hydrophobic matrix tablets of formulation F4 prepared using ethyl cellulose showed drug release of 64.2% and can be employed as once a day oral sustained release drug delivery system. Therefore, ethyl cellulose is suggested as an ideal polymer for production of directly compressed matrix sustained release salbutamol tablets.

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