FORMULATION, DEVELOPMENT AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS CONTAINING SALBUTAMOL SULPHATE

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Summary

The objective of this study was to formulate and evaluate Salbutamol sulphate matrix tablets, sustained release dosage form, for the treatment of Chronic Obstructive Pulmonary Disease (COPD). The matrix tablets were prepared by direct comression method using two polymers such as hydroxyl propyl methyl cellulose (HPMC) and xanthan gum in varying ratios. Tablets blends were evaluated for loose bulk density, tapped bulk density, compressibility index and angle of repose, shows satisfactory results. The compressed tablets were then evaluated for various physical tests like diameter, thickness, uniformity of weight, hardness, friability, and drug content. The results of all these tests were found to be satisfactory. The in vitro dissolution study was carried out for 12 hours using paddle method in phosphate buffer (pH 6.8) as dissolution media. Formulation F1 to F3 failed to sustain release beyond 8 hours. Among all the formulation, F4 shows 99.15% of drug release at the end of 12 hours. This finding reveals that above a particular concentration of HPMC K-100 and xanthan gum are capable of providing sustained drug release.

Key words HPMC K-100, Xanthan gum, Salbutamol sulphate, matrix tablets

Introduction

Oral route of drug administration is oldest and safest mode of drug administration. It posses several advantage. It dose not pose the sterility problem and minimal risk of damage at the site of administration. Increased compliance and expense involved in marketing of new drug entities has focused greater attention on development of sustained release or controlled release drug delivery systems. Matrix systems are the most popular method among innumerable methods used in the development of controlled release formulations. Hydrophilic polymeric matrix systems are widely used in controlled drug delivery, since they make it easier to achieve a desirable drug release profile, are cost effective and have broad FDA acceptance [1,2].

The selected drug, Salbutamol is a sympathomimetics amine which is used as a bronchodilator in the treatment of reversible bronchospasm. It can be specifically prescribed in case of acute asthma and also for symptom relief during maintenance therapy of asthma and other conditions with reversible airways obstruction (including COPD). This drug has a daily dose of 4-8 mg because of shorter biological half-life (1.2 hrs); it needs multiple administrations, which often results in dose related side effects and poor patient compliance[3-7]. So it is selected to prepare a sustained release tablet. The present investigation is concerns to develop a sustained release tablet of salbutamol sulphate which releases the drug in a sustained manner over a period of 12 hours, by using different polymers.

Materials and methods

Materials: Salbutamol sulphate, HPMC K-100 and xanthan gum, were received as gift samples from Alkem Laboratories, Himachal Pradesh. Colloidal silicon dioxide, aerosil, magnesium stearate, was of AR Grade.

Methods

Preparation of matrix tablets: All ingredients was collected and weighed accurately. Sifted salbutamol sulphate and polymers through sieve no. 60# and then rinsed with remaining excipients. Sifted colloidal silicon dioxide (Aerosil-200) and magnesium stearate separately, through sieve no. 60#. Preblending of all ingredients (except lubricant magnesium stearate) in blended for 15 minutes. Blend then again blended for 5-6 min then added magnesium stearate blended 5 min. Lubricated powder was compressed by rotary machine having circular concave shaped and one side break line on upper punch, with pressure of 7-8 tons. Compressed tablets were examined as per official standards and unofficial tests. Prior to the compression the drug and polymers were evaluated for several tests. The composition of different formulation of salbutamol sulphate was given in table 1.

Evaluation of tablet blends

Angle of repose: The angle of repose of tablet blends was determined by the funnel method. The blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\text{Tan } \theta = h/r$$

Where ‘h’ and ‘r’ are the height and radius of the powder cone, respectively.

Bulk density: Apparent bulk density was determined by pouring a weighed quantity of tablet blends into graduated cylinder and measuring the volume and weight.

$$\text{Bulk Density} = \text{Mass of powder} / \text{Bulk Volume of the powder}$$

Tapped bulk density: It was determined by placing a graduated cylinder, containing a known mass of drug-excipient blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10 cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

Tapped density = Weight of powder / Tapped volume of the powder

Carr's index: Carr's compressibility index CI (Carr, 1965) is defined as follows:

$CI = \rho t - \rho a / \rho t = Va - Vt / Vt$

Where ρt and ρa – tapped and poured bulk density; And Vt and Va – tapped and poured bulk volume respectively.

Hausner's ratio: A similar index has been defined by Hausner[8-11].

Hausner's ratio = Tapped density / Poured Density

Evaluation of Tablets

Thickness: The thicknesses of the tablets were determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

Uniformity of weight: Every individual tablet in a batch should be in uniform weight and weight variation in within permissible limits. The weights were determined to within ±1mg by using digital balance. Weight control is based on a sample of 20 tablets

Drug content: For this at least 30 tablets were randomly selected. Out of 30 tablets 10 tablets were crushed into fine powder assayed individually after proper dilution at 277 nm using a UV spectrophotometer.

Hardness and friability: For each formulation, the hardness and friability of 20 tablets each were determined using the Pfizer hardness tester and Electro lab friabilator test apparatus, respectively.

***In vitro* release studies:** The *in vitro* dissolution studies were performed using USP -22 type I dissolution apparatus 37±5°C, at 50 rpm. Placed the 900 ml of pH 6.8 phosphate buffer in the vessel of apparatus and assembled, equilibrate the dissolution medium to 37 ±0.5 °C. Placed 1 tablet in basket and immediately operated the apparatus at 100 rpm. Withdrawn the 5 ml samples at 1 hour, 2 hours, 4 hours, 8 hours and 12 hours, from midway between the surface of dissolution medium and the top of the rotating basket, not less than 1 cm from the vessel wall and replaced with fresh buffer solution. After appropriate dilution the samples were analyzed[12-16].

Results and Discussions

The present investigation was undertaken to design, formulate and evaluate Salbutamol sulphate matrix tablets for sustained release dosage form. The blends of different formulations were evaluated for angle of repose, bulk density, tapped bulk density, compressibility index and hausner's ratio. The results of bulk density, tapped bulk density, compressibility index and hausner's ratio are mentioned in table 2. The bulk density of the tablet blend was in the range of 0.29± 0.03 to 0.39± 0.05 g/ml; the tapped density was in the range of 0.42± 0.02 to 0.49± 0.07 g/ml, which indicates that the powder was not bulky. The blend indicated good flow properties for all the formulation with the angle of repose values 28° 13'±0.47 to 32° 21'±0.16 according to fixed funnel and free standing cone method. The results of compressibility index lies between range from 14.58±1.19 to 18.32±1.18, while hausner's ratio lies between 1.12±0.03 and 1.19±0.02 indicating good to excellent flow properties. The tablets of different batches formulated were evaluated for test such as hardness, friability, thickness, uniformity of weight and drug content. The results obtained from all formulations were within the range. The weight variation test indicates that all the tablets were uniform with low standard deviation values and hence all formulation passed the test for uniformity of weight. The tablets mean thickness values ranged from 4.8±0.25 mm to 4.8±0.67 mm. The hardness of all the tablets was within the range of 7±0.02 to 7±0.08 kg/cm^2. The loss in friability test was in a range of 0.05 to 0.11%. The percentage drug content for different tablet formulations were discrete from 97.27% to 99.12%, were found to be within range (table 3).

In vitro dissolution studies of all the formulations of sustained release tablets of salbutamol sulphate were carried out in pH 6.8 phosphate buffers for 12 hours. Only three (F4 to F6) tablet formulations showed acceptable properties as shown in table 4. The result of the dissolution study indicating that F1 to F3 released almost drug at the end of 8 hrs, from the released pattern of first three formulation the 100% released was found before 12 hrs. Formulation F4, F5 and F6 released 99.15%, 98.51% and 91.23% at the end of 12 hrs. Here we observed that on increasing the quantity of xanthan gum and decreasing the proportion of HPMC K-100, it retards the drug release from matrix. This might be due to slow hydration of matrix and its property to form a thick gel layer, which retard the drug release from the tablet. It is expected that the developed formulation should have the following theoretical drug release profile, i.e., 100% for 12 hrs. Formulations F1 to F3 failed to meet the needed theoretical drug release profile. Formulation F4, F5 and F6 met the needed theoretical drug release profile and has the sustain action i.e., retarding the drug release so the release is for a long time and thus more bioavailability. Formulation F4 release 100% drug at the end of 12 hrs, for these reasons, it was considered the best formulation among all the six formulations of this series.

Table 1: Composition of Salbutamol sulphate SR matrix tablet

S. No.	Ingredient	F1	F2	F3	F4	F5	F6
1.	Salbutamol sulphate	8	8	8	8	8	8
2.	HPMCK-100	100	80	60	40	20	-
3.	Xanthan Gum	-	20	40	60	80	100
4.	Aerosil	4	4	4	4	4	4
5.	Magnesium Stearate	2	2	2	2	2	2
6.	Theoretical Weight	114	114	114	114	114	114

Table 2: Physical characteristics of prepared blend of Salbutamol sulphate

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Angle of repose	31° 54' ± 0.34	29° 16' ± 0.14	30° 27' ± 0.21	32° 21' ±0.61	29° 42' ± 0.38	28° 13' ± 0.47
Bulk density	0.35 ± 0.01	0.32 ± 0.04	0.39 ± 0.05	0.31 ± 0.02	0.36 ± 0.04	0.29 ±0.03
Tapped bulk density	0.45 ± 0.02	0.49 ± 0.07	0.48 ± 0.06	0.42 ± 0.02	0.47 ± 0.01	0.43 ± 0.02
Compresibility Index	16.14	15.32	18.16	16.25	14.58	18.32
Hausner's Ratio	1.12 ± 0.03	1.16 ± 0.02	1.15 ± 0.07	1.13 ± 0.04	1.19 ± 0.02	1.18 ± 0.03

Table 3: Evaluation of Salbutamol sulphate sustained release matrix tablet

Parameters	F-1	F-2	F-3	F-4	F-5	F-6
Uniformity of weight (mg)	114±5	114±4	114±7	114±5	114±4	114±6
Thickness (mm)	4.8±0.31	4.8±0.25	4.8±0.67	4.8±0.55	4.8±0.30	4.8±0.28
Friability (%)	0.05	0.11	0.08	0.09	0.07	0.10
Tablet Hardness (Kp)	7±0.04	7±0.06	7±0.08	7±0.02	7±0.04	7±0.06
Assay (%)	99.01	98.14	98.56	99.12	98.61	97.27

Table 4: *In vitro* drug release data

Time in	Cumulative Percent Drug Release					
Hours	F1	F2	F3	F4	F5	F6
0	0.00	0.00	0.00	0.00	0.00	0.00
1	20.14	22.32	16.53	16.19	15.62	13.85
2	45.36	41.61	35.42	30.72	34.25	29.48
4	73.47	76.43	70.91	65.41	68.13	63.17
8	99.25	98.38	96.49	88.37	85.37	79.56
12	-	-	-	99.15	98.51	91.23

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