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Formulation and *in vitro-in vivo* evaluation of Salbutamol Sulphate sustained release tablets

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Abstract

The objective of this study was to formulate and evaluate a matrix system for sustained and simultaneous delivery of anti-asthmatic drug Salbutamol sulphate .which is often indicated for the management of asthma, their frequent dosing may reduce compliance, thus making prolonged release formulation necessary. The matrix tablets were prepared by wet granulation method using Ion exchange resins. The granules showed satisfactory flow properties and compressibility. All the five tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specifications for tested parameters. They are evaluated for angle of repose, friability, hardness, disintegration and dissolution.

Keywords: Antiasthmatic, Ion exchange resin, Salbutamol sulphate, Sustained release Formulation .

Introduction

Patients suffering from chronic diseases like asthma, diabetes and epilepsy may have to take drugs everyday for the rest of their life [1]. WHO estimates the number of asthmatic patients to be around 100 to 150 millions around the world and India contribute 10 % of the total and its incidence is escalating every decade at an alarming rate. In management of chronic diseases like asthma, compliance to the dosage regimen is the key to a successful therapy. Patient may be treated with more than one drug and compliance is found to be low in such cases. The short half life (4 to 6 hours) with extensive first pass metabolism of salbutamol is well-known. Although salbutamol is often indicated for the management of asthma, its frequent dosing may reduce

compliance, thus making a prolonged release formulation necessary [2]. Different dosage of Salbutamol are available these include transdermal patches [3], Matrix tablets [4] and Osmotic pump tablets. [5] Salbutamol is readily and well absorbed along the gastrointestinal tract. Even when salbutamol is given as an inhalation, it has been suggested that majority of the dose is swallowed and absorbed from the gut [6]. Salbutamol sulphate is official in IP 1996 [7].

The objective of the present study includes:(a) formulation of a sustained release matrix tablets system containing salbutamol sulphate using Ion exchange resins i.e. INDION® 244, INDION® 254, INDION® 404, TULSION® 344.

Materials and Methods

Materials

Salbutamol sulphate was obtained as a gift sample from Medicore Laboratories, Paithan, and Ion exchange resin were obtained from Ion Exchange India Ltd, Mumbai, Avicel PH 102, Signet Chemical Corporation, Mumbai, and Loba Chem., Mumbai Remaining all the materials were obtained commercially and used as such.

Preparation of Tablets [8]

Different tablet formulations were prepared by wet granulation technique (Table 1). All the powders were passed through 80 mesh. Required quantities of drug and polymer were mixed thoroughly, and a sufficient volume of granulating agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 22/44 mesh. The granules were dried at 40°C for 12 hours and thereafter kept in a desiccator for 12 hours at room temperature. Once dry, the granules retained on 44 mesh were mixed with 15% of fines (granules that passed through 44 mesh). Talc and magnesium stearate were finally added as glidant and lubricant. The practical weight of tablets was calculated based on the drug content of the granulations, and the tablets were compressed using a single-punch tablet compression machine (Cadmach, Ahmedabad, India). Each tablet contained 50 mg of Salbutamol sulphate and other pharmaceutical ingredients as listed in Table 1. Prior to the compression, the granules were evaluated for several tests.Invitro Drug Release Profile of Resinate was shown in Figure 1; % Drug Release of formulated tablet was shown in Figure 2 and Cumulative % Drug Release from Marketed Tablet and Formulated batch (B3) was shown in figure 3.

Table 1: Formulation of Tablet

Ingredient %W/W	Batches				
	B1	**B2**	**B3**	**B4**	**B5**
Salbutamol sulphate	50mg	50mg	50mg	50mg	50mg
INDION® 244 Resinate	21.6	21.6	21.6	21.6	21.6
Avicel 102	75.9	75.9	76.9	76.4	76.4
Talc	0.5	1.5	0.5	1	0.5
Magnesium Sterate	2	1	1	1	1.5

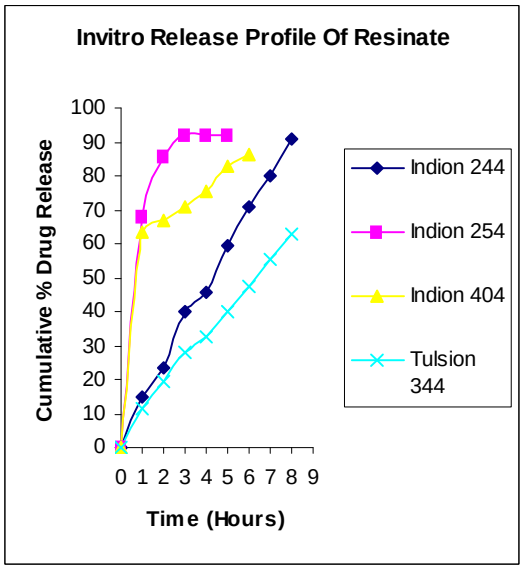

Fig.1: Invitro Drug Release Profile of Resinate

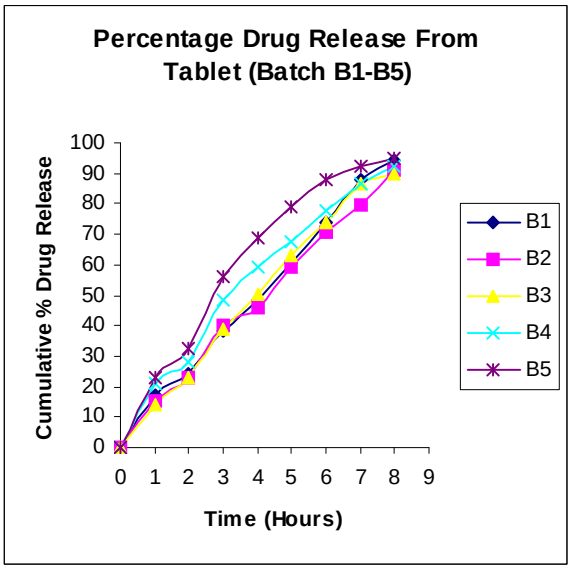

Fig. 2: % Drug Release of formulated tablet

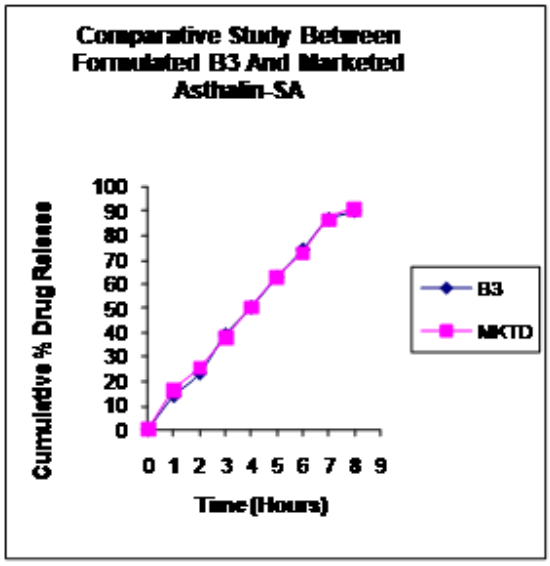

Fig 3: Cumulative % Drug Release from Marketed

Evaluation of Granules

Granules are evaluated for Flow Property (Angle of Repose), Bulk Density, Tap density, Packing Ability /Compressibility Index and its results are shown in table no.2

Table 2: Evaluation of Granules

Character	Indion® 244 resins	*Resinate*	Indion® 254 resins	*Resinate*	Indion® 404 resins	*Resinate*	Tulsion® 344 resins	*Resinate*
Shape	Spherical	Irregular	Irregular	Irregular	Irregular	Irregular	Irregular	Irregular
Angle of Repose	30.42	31.14	28.56	29.12	29.78	30.76	29.34	29.76
Bulk Density	0.666	0.670	0.667	0.685	0.640	0.612	0.607	0.620
Tap Density	0.755	0.766	0.758	0.785	0.712	0.693	0.680	0.695
Carr, s Index	11.78	12.53	12.00	12.73	10.11	11.68	10.73	10.79
Hausner Ratio	1.13	1.14	1.13	1.14	1.11	1.13	1.12	1.12

a) Flow Property (Angle of Repose) [9]
The frictional force in powder can be measured by the angle of repose. It is the maximum angle possible between the surface of pile of powder and the horizontal plane. The blend that has angle of repose between 20^0 to30^0 is best for compression as it has good flow property. Angle of repose is calculated by fixed funnel method. In this method funnel was fixed to a stand so that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on the flat surface. The blend was allowed to fall freely on the graph paper through the Funnel, till the tip of heap formed just touches the funnel. The radius of heap was noted and from this angle of repose was determined.

The angle of repose was determined using following equation.

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

Where,
h = Height of pile in cm.
r = Radius of pile in cm.

b) Bulk Density [10]
Bulk density is defined as the mass of powder divided by bulk volume.
It is calculated using the following equation

Bulk density = Weight of sample taken / Volume noted

A sample of about 20 gm was poured into 10ml-graduated cylinder. The cylinder was dropped at 2-second intervals onto a hard wooden surface three times, from a height of one inch. The volume was recorded and the bulk density was calculated.

c) Tap density

A sample of 25gm was poured gentally into a 100ml graduated cylinder, the surface was carefully smoothed and the volume was measured. Tap density was calculated by measuring final volume after 50 taps on wooden surface from 6 inch height and was expressed in g/cm^3.

d) Packing Ability /Compressibility Index [11]

The packing ability of resins and resinate were evaluated from the change in volume which is due to rearrangement and packing occurring during tapping .It was expressed as Carr's index (cc%) was calculated as follows.

$$CC = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

And as the Hausner ratio was calculated as follows.

$$HR = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Evaluation of Tablet

Tablets were evaluated for following quality control test and results are shown in table no.3

Table 3: Evaluation of Tablet:

Test Parameter	*Batch*				
	Batch B1	**Batch B2**	**Batch B3**	**Batch B4**	**Batch B5**
Hardness (Kg/cm^2)	4.30	5.20	5.10	4.70	5.25
% Friability	0.442	0.376	0.389	0.417	0.367
Thickness	2.0	2.3	2.1	2.3	2.4
Wt variation ±10.00	Passes	Passes	Passes	Passes	Passes
Content uniformity (%)	97.50	97.35	98.37	97.82	96.99

Tablet and Formulated batch (B3)

Hardness

Although hardness test is not an official, tablet should have sufficient handling during packing and transportation. Hardness of tablet was measured with Pfizer hardness tester .It is the pressure required to fracture diametrically placed tablets by applying the force with two plungers. The hardness of 5 tablets, from each batch was determined and mean hardness was taken into account, which was expressed in kg/cm^2.

b) Weight Variation Test

Weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average does USP weight variation test.

c) Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 Revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\text{Friability (f)} = 100\ (1\text{-}W_o/W)$$

Where,

W_o weight of sample taken

W weight of sample after test

d) Thickness

The thickness of the tablet were measured using vernier caliper. Thickness of five tablets from each batch was measured, and mean was calculated.

e) Content Uniformity

For this at least 30 tablets were randomly selected. Out of 30 tablets 10 tablets were crushed into fine powder and assayed individually, the tablet should be within 98% to 101% of the labeled claim.

Results and Discussion

The granules of different formulations were evaluated for angle of repose, compressibility index, total porosity, and drug content (Table 2). The results of angle of repose and compressibility index (%) ranged from 28.56 ± 0.01 to 31.14 ± 0.03 and 10.11 ± 0.02 to 12.73 ± 0.04 respectively. The drug content in a weighed amount of granules of all formulations ranged from 96.53 ± 0.03 to 98.55 ± 0.03%. The average percentage deviation of 20 tablets of each formula was less than ±10%. Drug content was found to be uniform among different batches of the tablets and ranged from 96.99 ± 0.03 to 98.37 ± 0.01. The hardness and percentage friability of the tablets of all batches ranged from 4.3 ± 0.13 to 5.25 ± 0.33 kg/cm ^{2} and 0.367 ± 0.06 to 0.442 ± 0.09%, respectively. The results of dissolution studies of all the formulations were shown in Figure 1. The Formulated tablet (B1-B5) were then tested for *in vitro* drug release. The result shows that batch B3 of tablet formulated with 21.6% Resinate, 76.9% Avicel, 0.5% Talc &1% Magnesium sterate gives zero order drug release with correlation coefficient values of 0. 9912 and follows USP specification, with more than 85% of drug was release in 8 hours.

Conclusion

In-vitro dissolution of the batch B3 was compaired with marketed Asthalin-SA tablet and f_2 value was found to be 99.70, which shows that formulated tablet has similar release profile as

that of marketed tablet. From the above, conclusion was drawn that the ion exchange resins INDION ® 244,coupled with tablet can serve as useful tool to sustained release of water soluble drug Salbutamol sulphate.Thus INDION® 244 Salbutamol sulphate when formulated as tablet using Avicel, Magnesium Sterate & Talc provided sustained release, which satisfied the criteria for sustained release, Zero order release and good stability is observed. Thus, formulated tablet provide pH independent sustained release of Salbutamol sulphate and good stability.

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