ISSN: 2395-0536

INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND NOVEL SCIENCES

IJPRNS

FORMULATION AND EVALUATION OF SALBUTAMOL SULPHATE SUSTAINED RELEASE TABLETS

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ABSTRACT

Salbutamol sulphate (SS), a directly acting sympathomimetic drug, is a good candidate for sustained release formulations due to its short half-life but it is challenging because of its high water solubility. The aim of this work is to design oral sustained release tablets of using hydrophilic polymers, and thus increasing patient compliance by reducing its frequency of administration. Tablets were prepared by wet granulation technique using hydroxypropyl methylcellulose (HPMCK-15), ethylcellulose (EC), carbopol (C940), cellulose acetate phthalate, cetosteryl alcohol (CSA). The compatibility of the drug with the various used excipients was studied using FTIR. The effects of polymer concentration, polymer viscosity and binary mixtures of some polymers on the in vitro drug release were studied. Results of FT-IR confirmed drug-excipients compatibility. The different prepared tablet formulae exhibited content uniformity within the acceptable limit and showed good mechanical properties. It was found that the in-vitro dissolution profile of salbutamol from tablets containing E.C(5%),C.S.A(10%),HPMC K-15(10%),C.940(5%) formula no. **F-12** is almost similar with that of marketed product (salowin-SR).The stability studies showed that the drug content for the best formulation remained same even after storing for three month at different temperatures with a very minute standard deviation.

Key words: Salbutamol sulphate, wet granulation technique, the in-vitro dissolution.

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INTRODUCTION

Patients suffering from chronic diseases like asthma, diabetes and epilepsy may have to take drugs everyday for the rest of their life. 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 .

Different dosage of Salbutamol are available these include transdermal patches, Matrix tablets and Osmotic pump tablets. 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 . Salbutamol sulphate is official in IP 1996.

Salbutamol, *RS*-[4-[2-(*tert*-butylamino)-1-hydroxyethyl]-2-(hydroxymethyl)phenol] is a shortactingβ2-adrenergic receptor agonist used for the relief of Broncho-spasm in conditions such as asthma and chronic obstructive pulmonary disease. Salbutamol is still commonly delivered as a racemic mixture (+,-). Salbutamol, even though S-Salbutamol is known to have a detrimental effect on asthma sufferers (in fact the exact opposite effect of the R Isomer. Selective β2-adrenoceptor stimulant that causes the relaxation of the smooth muscles through the increase of the intracellular cyclic adenosine monophosphate (cAMP) due to this, bronchial and uterine muscles get relaxed, the peripheral vessels are dilated and heart rate increases. Activation of the β-2 adreno-receptors opens ATP ase channels and drives potassium from the extra cellular to the intracellular space. This both decreases extracellular Hyperkalaemia and increases intracellular potassium, so decreasing the chance of arrhythmias. Salbutamol also has certain anti-inflammatory properties whose clinical significance is not determined (1).

Discovery, testing and marketing of new chemical entities, the so – called medicinal agents, is what differentiates the pharmaceutical industry from many other enterprises. The primary objective is to determine the impact of various factors that have forced the drug industry to direct efforts towards development of modified – release or so – called specialized drug delivery systems.

In developing a formulation, product of process, pharmaceutical of otherwise, is rarely known right from the start. Out own past experience, scientific theory, and the contents of the scientific and technical literature may all be of help, but we will still need to do experiments, whether to answer our questions or to conform what we already believe to be the case. And before starting the experimentation, we will need to decide what the experiment is actually going to be. We require an experimental strategy.

The sustained-release products are often designed with an initial dose intended to establish rapidly therapeutic drug blood levels and additional drug intended to maintain those levels for prolonged periods. Those products providing only the slow-release Component and lacking the immediate-release component have sometimes been termed prolonged release (2-4).

The aim of the present study is to prepare sustained release tablets of Salbutamol sulphate which is a Salbutamol (INN) or albuterol (USAN), a moderately selective beta(2)-receptor agonist similar in structure to terbutaline, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases.

MATERIALS AND METHODS

MATERIALS

Salbutamol sulphate from DR.REDDY'S laboratories, Hydroxy propyl methyl cellulose (15cps), Ethyl cellulose, C,940, C.M 1000, C.A.P, C.S.A, Lactose, Magnesium Stearate, Talc, Potassium dihydrogen phosphate, Acetic acid, Perchloric acid, Disodium hydrogen phosphate from SD Fine Chemicals, Mumbai.

METHODS

Preformulation Studies

Drug polymer compatibility studies

The drug and polymer compatibility studies were carried out using FT-IR studies .

Analytical method for estimation of drug by UV method (5, 6)

a) Preparation of 6.8 pH phosphate buffer

Dissolve 28.8 g of disodium hydrogen phosphate and
of potassium dihydrogen phosphate in sufficient water
to 11.45 gm produce 1000 ml.

b) Standard plot of Salbutamol sulphate with 6.8 pH Phosphate buffer

To prepare a standard plot for Salbutamol sulphate using 6.8 pH Phosphate buffer, 100 mg of the drug (Salbutamol sulphate) was dissolved in 6.8 pH Phosphate buffer and made up to 100 ml with the same to give a concentration of 1000 µg/ml. From the primary stock solution, 10 ml was taken and diluted to 100 ml with the same buffer to give the concentration of 100 µg/ml. From this secondary stock solution, aliquots of 1,2,3,4,5 and 6 ml of the solution was transferred to 50 ml volumetric flasks and made up to the volume with phosphate buffer to give the concentrations of 10-100 µg/ml. Then the absorbance was measured at 276 nm against a blank using UV Spectrophotometer. A standard graph was plotted by taking concentration (µg/ml) on X-axis and absorbance (276 nm) on Y-axis.

Formulation of Sustained Release Tablets

Preparation of salbutamol sulphate tablets by we t granulation method, by using the compositions as mentioned in the table-1 given below.

Table-1 Composition of drug and polymers (in mg)

Ing	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Drug	6	6	6	6	6	6	6	6	6	6	6	6	6	6
E.C	15	%10	%10	%5	----	----	%5	----	%10	----	%10	%5	%5	----
C.S.A	----	----	%5	----	%10	----	%5	%10	-----	%15	----	%10	%5	%5
C.M 1000	---	10%	%5	----	%10	----	%10	----	%10	%5	%10	----	%10	%10
C.940	15	10%	%10	%5		%15	%5	---	---	----	%10	%5	---	----
HPMC k15	----	----	----	%15	%10	%15	----	%10	%5	%5	----	%10	---	%10
CAP	----	-----	----	%5			%5	%10	%5	%5	----	----	%10	%5
DCP granule	59.18	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18%	59.18 %	59.18 %
Lactose	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%	5%
Talc	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%
Mg.Ste	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%	2%

***In-Vitro* Drug Release Studies (7)**

These tests serve 2 important functions. First, data from such tests are required as a guide for formulation during the development stage, prior to clinical testing; second, in-vitro testing is necessary to ensure batch-to-batch uniformity in the production of a proven dosage form.

350 mg of drug placed in the USP Dissolution test apparatus paddle-II type stirring element. 900 ml of phosphate buffer solution (pH 6.8) at 37 °C was used as dissolution medium. The basket was rotated at a speed of 100 rpm. A 5 ml of medium was withdrawn at various time intervals of 0 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr,12 hr and so on., with the help of 5 ml pipette and replaced by 5 ml of phosphate buffer solution (pH 6.8).The drug content was estimated by UV Spectro-photometer at 276 nm and thereby the cumulative percentage drug release was obtained from the following formulae.

The drug release follows zero-order drug release and case II transport if the n value is 1. For the values of n higher than 1, the mechanism of drug release is regarded as super case II transport. The model is used to analyze the release of pharmaceutical polymeric dosage forms when the release mechanism is not known or more than one type of release phenomenon was involved. The n value could be obtained from slop of the plot of log cumulative % of drug released Vs log time.

RESULTS AND DISCUSSION

The IR spectra of all the tested samples showed the prominent characterizing peaks of pure drug salbutamol sulphate, individual polymers, HPMC K-15, C.A.S, C.A.P, E.C, C.M-1000 and carbopol 934 and the admixture of drug and polymers and was confirmed that no chemical modification of the drug has been taken place and thus they were proved to be compatible with each other and hence suitable for preparation of sustained release tablets.

The ultraviolet spectrophotometric method was used to analyze salbutamol at a wavelength of 276 nm. The standard plot of salbutamol was performed in phosphate buffer pH 6.8. Salbutamol showed linearity in all diluted solutions at a concentration range of 10 – 100 µg/ml (Fig-1).

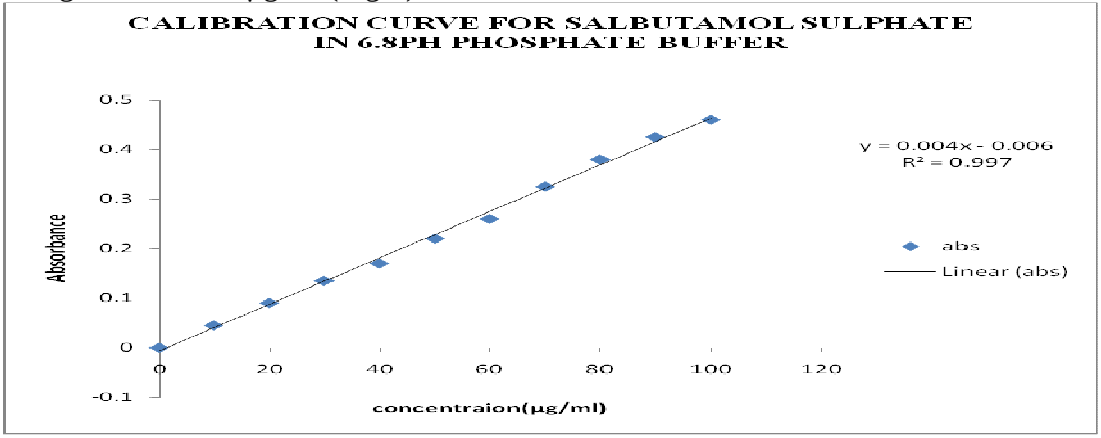

Fig-1 STANDARD PLOT FOR SALBUTAMOL SULPHATE

Evaluation of the Granules

The Flow properties of the granules were evaluated for angle of repose (Flow properties) and derived properties (Bulk density, Tapped density, Carr's index and Hausner's ratio) and the results were tabulated in table-2

Table -2 Results for micromeritic properties

S.NO	Angle of Repose	Bulk density	Tapped density	Carr's Index	Hausner's Ratio
F1	23.33 ± 0.17	0.455 ± 0.11	0.588 ± 0.02	22.61 ± 0.01	1.29 ± 0.11
F2	22.20 ± 0.12	0.445 ± 0.15	0.571 ± 0.11	14.36 ± 0.01	1.16 ± 0.02
F3	25.45 ± 0.11	0.435 ± 0.02	0.565 ± 0.2	16.21 ± 0.15	1.22 ± 0.2
F4	23.63 ± 0.2	0.475 ± 0.01	0.568 ± 0.3	14.61 ± 0..11	1.25 ± 0.3
F5	21.16 ± 0.5	0.445 ± 0.15	0.545 ± 0.15	15.22 ± 0.01	1.22 ± 0.02
F6	23.82 ± 0.15	0.455 ± 0.2	0.538 ± 0.19	19.12 ± 0.05	1.23 ± 0.11
F7	22.69 ± 0.26	0.435 ± 0.23	0.526 ± 0.03	20.12 ± 0.03	1.21 ± 0.07
F8	25.36 ± 0.15	0.475 ± 0.3	0.588 ± 0.2	22.61 ± 0.2	1.29 ± 0.3
F9	21.85 ± 0.26	0.456 ± 0.02	0.578 ± 0.5	22.61 ± 0.02	1.27 ± 0.001
F10	21.63 ± 0.3	0.426 ± 0.23	0.565 ± 0.12	20.61 ± 0.02	1.24 ± 0.02
F11	24.56 ± 0.5	0.465 ± 0.3	0.536 ± 0.25	22.30 ± 0.03	1.25 ± 0.12
F12	26.33 ± 0.2	0.492 ± 0.01	0.595 ± 0.01	23.61 ± 0.11	1.31 ± 0.01
F13	23.22 ± 0.01	0.455 ± 0.2	0.523 ± 0.11	20.61 ± 0.01	1.25 ± 0.12
F14	24.75 ± 0.26	0.485 ± 0.2	0.588 ± 0.02	21.61 ± 0.02	1.23 ± 0.02

The flow properties and other derived properties evaluated for all the 14 formulations were proved to be within limits showing good flow properties while formulation code F-12 showed very good flow properties than all the

other formulations. The tablets were evaluated for Appearance, Weight variation, Thickness, Diameter, Hardness, and Friability to meet the Pharmacopoeial standards (Table-3).

Table-3 Results for Evaluation of the Formulations

S.NO	**Weight Variation**	**Thickness**	**Diameter**	**Hardness**	**Friability**	**Drug content**
F1	348 ± 1.01	4.3 ± 0.08	9.2	6.0 ± 0.71	0.173 ± 0.05	99.50
F2	346±1.11	4.2 ± 0.13	9.2	6.6 ± 0.55	0.188 ± 0.06	92.89
F3	348 ± 1.01	4.5 ± 0.04	9.4	6.2 ± 0.84	0.277 ± 0.12	100.02
F4	346 ±1.11	4.6 ± 0.12	9.3	6.5 ± 0.75	0.094 ± 0.15	99.59
F5	348 ± 1.01	4.4 ± 0.08	9.0	6.4 ± 0.50	0.088 ± 0.05	99.38
F6	346 ± 1.11	4.5 ± 0.14	9.4	6.6 ± 0.85	0.197 ± 0.13	97.05
F7	347 ± 1.15	4.3 ± 0.06	9.0	6.0 ± 0.75	0.096 ± 0.02	99.60
F8	345 ± 1.02	4.6 ± 0.05	9.4	6.6 ± 0.85	0.121 ± 0.05	91.69
F9	348 ± 1.01	4.5 ± 0.03	9.3	6.4± 0.50	0.186 ± 0.02	95.62
F10	344 ± 1.05	4.7 ± 0.09	9.2	6.6 ± 0.85	0.124 ± 0.15	99.56
F11	346 ± 1.11	4.5 ± 0.06	9.0	6.0 ± 075	0.156 ± 0.05	96.25
F12	349 ± 1.00	4.4 ± 0.06	9.0	6.0 ± 0.71	0.094 ± 0.15	100.02
F13	345 ± 1.05	4.6 ± 0.03	9.3	6.5 ± 0.75	0.332 ± 0.06	99.26
F14	347 ± 1.20	4.5 ± 0.08	9.4	6.3 ± 0.80	0.154 ± 0.05	99.66

In Vitro **Drug Release Studies**

The *in-vitro* drug release studies were conducted using pH 6.8 phosphate buffer solution as dissolution medium and the results were tabulated and also represented graphically by taking Time (hrs) on X-axis and Cumulative percentage drug release on Y-axis.

The *in- vitro* drug release studies showed better sustained and prolonged release with all the particles for about 12 hrs while F-12 formulation showed better release from all (Table-4 and 5). From the above observation it was concluded that the morphological characters, other evaluated parameters and *in- vitro* drug release profile for F-12 formulation showed the best results.

Table- 4 ***In-Vitro*** **drug release data for F - 12**

IN-VITRO DRUG RELEASE		**ZERO ORDER DATA**		**FIRST ORDER DATA**	
Time (hrs)	**Cumulative % drug release**	**Time (hrs)**	**Mean % Release**	**Time (hrs)**	**Mean% log un release**
0	0	0	0	0	0
2	32.70	2	32.70	2	1.828
4	45.76	4	45.76	4	1.734
6	57.85	6	57.85	6	1.624
8	69.17	8	69.17	8	1.488
10	83.25	10	83.25	10	1.224
12	96.75	12	96.75	12	0.511

Table-5 *In-Vitro* drug release data for F- 12

HIGUCHI'S DATA		PEPPA'S DATA	
Square root time	**Cumulative % drug release**	**Log time**	**Log cumulative % drug release**
0	0	0	0
1.414	32.70	0.30103	1.514
2	45.76	0.60206	1.654
2.44949	57.85	0.778151	1.762
2.828427	69.17	0.90309	1.839
3.162278	83.25	1	1.920
3.46402	96.75	1.079181	1.985

The drug release in case of Salbutamol marketed product was found to be only up to 12 hrs**:** It was found that the in-vitro dissolution profile of salbutamol from tablets containing E.C (5 %),C.S.A (10 %),HPMC K-15 (10 %),C.940 (5 %) formula No. **F-12** is almost similar with that of marketed product (salowin-SR).

The date for stability studies carried out for F-12 formulation at 40 ^{o}C with 75% RH for 180 days revealed no considerable differences in drug content and dissolution rate.

CONCLUSION

Thus form all the above parameters and results, it was concluded that Salbutamol sulphate with HPMC K-15,C.S.A, C.940,E.C combination of polymers in equal proportions may be a promising form of drug delivery by which the total dose and frequency of drug administration may be considerably reduced thereby improving efficacy and reducing the unwanted effects of salbutamol.

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