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Research Article

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DESIGN AND OPTIMIZATION OF IMMEDIATE RELEASE TABLET OF SALBUTAMOL SULPHATE BY DIRECT COMPRESSION TECHNIQUE

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ABSTRACT

This study is about a tablet, which disintegrates or dissolves quickly when placed in the oral cavity. Studies on formulation development of Salbutamol Sulphate Immediate Release Tablet, suitable for manufacturing by direct compression have been carried out. Trial formulations using various excipients were developed and evaluated for various qualities like hardness, friability, disintegration time, content uniformity and dissolution. Study concluded that Immediate Release Tablet of Salbutamol Sulphate can be prepared successfully with added patient benefit and increased consumer satisfaction.

INTRODUCTION

The oral route of administration is preferred to be the most convenient route due to its manifold advantages including self administration, compactness, easy manufacturing, ease of ingestion, avoidance of pain, adaptability and most importantly patient compliance [1]. Maximum therapeutically active substances are present in the form of tablet, capsule, and pill or powder for oral administration. These dosage forms are to be swallowed so that the pharmaceutically active substance can be absorbed via the gastrointestinal tract. Among all other oral solid dosage forms tablet hold the premier position due to its above mentioned convenience. Some times the administration of tablet and capsules with a glass of water become inconvenient or impractical for some patients, particularly pediatric and geriatric patients find difficulty in swallowing or chewing solid dosage forms [1, 2]. Many patients are unwilling to take these solid preparations due to fear of choking [3]. The administration problem is also allied with number of medical conditions including stroke, Parkinsonism and other neurological disorders [1]. Immediate Release Drug Delivery System (IRDDS) has acquired an important position in the market by overcoming previously encountered administration problems. IRDDS has the unique property of rapidly disintegrating or dispersing and releasing the drugs as soon as they come in contact with the saliva, thus obviating the requirement of water during administration [4].

The drug of interest in the present research venture is Salbutamol Sulphate, a freely water-soluble Beta-receptor agonist widely used as bronchodilator to relieve acute as well as chronic attacks of asthma and the reversible element of

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airways obstruction commonly found in Chronic Obstructive Pulmonary Disease (COPD) [5, 6]. Among the β_2-adrenoceptor agonists Salbutamol Sulphate is the most preferred drug.

Drug substances are classified according to Biopharmaceutics Classification System in four distinct categories, depending on the basis of permeability and solubility of the drug molecule, which are as follows-

Class I - High Permeability, High Solubility
Class II - High Permeability, Low Solubility
Class III - Low Permeability, High Solubility
Class IV - Low Permeability, Low Solubility [7, 8]

Salbutamol Sulphate, the therapeutic moiety of this study comes under Class III, suggesting that it is highly soluble but less permeable. The oral bioavailability depends upon the drugs' permeability, and the oral bioavailability of Salbutamol Sulphate is 71 ± 9%, which indicates that it is less permeable. Because, according to BCS, a drug substance will be considered as highly permeable when the extent of absorption in humans is determined to be more than 90% of an oral dose [7]. Beside this 1 gm of Salbutamol Sulphate effortlessly dissolves in less than 10 ml of water, thus it can be considered as freely soluble and enlisted in BCS Class III scheduled drugs.

The objective of the present study was to formulate and investigate the influence of different diluents, disintegrants and its different concentrations on the release of Salbutamol Sulphate and other physicochemical parameters of the formulated tablets.

MATERIALS & METHODS

Salbutamol Sulphate IP, (98.04% w/v) was obtained as a gift sample from Inga Laboratories (Mumbai). Sodium Starch Glycolate (Extra pure) was procured from Loba Chemie Pvt. Ltd. (Mumbai), micro crystalline cellulose, talc, magnesium stearate, mannitol were AR grade, obtained from S.D. Fine-Chem. Limited (Mumbai) and used as such.

Preparation of tablets

All the ingredients were screened through a sieve (#60). Required amount of Salbutamol Sulphate equivalent to 4 mg of Salbutamol was then mixed thoroughly with diluents (mannitol, lactose) for 5 minutes in the formulations as designed in Table-1 and Table-2. There are several batches without drug. To the above mixture superdisintegrant (sodium starch glycolate, micro crystalline cellulose) was added and again mixed for 5 minutes. Then lubricants (magnesium Stearate and talc) were passed through the sieve and added to the above blend and again mixed for another 2 minutes. The mixed blend was compressed using 10 station rotary tablet punching machine (Rimek Minipress I, Ahmedabad) producing biconcave tablets of 6 mm diameter and weighing around 110 mg. a total of 20 batches of tablets were made containing 100 tablets in each batch and hardness was kept around 4 kg/cm^2.

Evaluation of IRTs

All the batches of prepared IRT were evaluated for weight variation, friability, drug content uniformity and disintegration time. *In vitro* dissolution studies were also performed for the selected batches.

Determination of Thickness and Diameter of the tablets

Thickness and diameter of five randomly selected tablets from each batch were measured with a Slide Calipers. Then the average diameter, thickness and standard deviation were calculated.

Weight Variation Test

A random sample of 20 tablets was taken and total as well as individual weights were recorded. Average weight was calculated and deviation of individual tablet weight from average weight was calculated. Theoretically the weight of the tablets should be within ±7.5% of the tablet weight [10].

Wetting time

Wetting time of dosage form is related with the contact angle. Wetting time of the IRT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablets; a lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured using a simple procedure. Five circular tissue papers of 6 cm diameter are placed in a petridish with a 6 cm diameter. 10 ml of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time [2].

Friability

A sample of 20 tablets were taken and dedusted carefully prior to testing. The tablets were placed in the drum of friability tester and rotated for 100 times at the speed of 25 rpm (Roche friabilator). Then the tablets were removed, dedusted and accurately weighed. The friability is expressed as the loss of mass and it is calculated as a percentage of the initial mass [10].

Disintegration time

One tablet was placed in each of the six tubes of the basket and apparatus was operated using water maintained at 37°± 1° C as immersion fluid. The time of disintegration of all tablets with no palpable mass remaining in the tube was noted [10].

Fourier Transformed Infrared Study

Fourier Transformed Infrared **(**FT-IR) spectrum (FTIR-8400S, Shimadju, Japan) of Salbutamol Sulphate and the formulations (F3 and F8), which were grinded separately and mixed with dried and ground potassium bromide (FT-IR grade) at 1:100 ratio, pelletized at 10-ton pressure by using potassium bromide press. Then the prepared pellets were scanned and the spectrum was recorded between 4000–400 cm^{-1} using a high-energy helium neon laser source and DLATGS (L-alanine-doped deuterated triglycine sulphate) detector. Finally the spectrum was analyzed by using the IR Solution software (version 1.30 by Shimadju Corporation, Japan).

Dissolution test *[10, 11]*

In-vitro dissolution studies of the formulations F1-F10 were carried out using USP Dissolution Apparatus II (Veego, VDA-8DR USP Standard), 900 ml of phosphate buffer solution pH 6.8 was used as dissolution medium at 37°± 0.5° C at 50 rpm for 30 minutes. 5 ml of aliquots was withdrawn at predetermined intervals by maintaining sink condition. Finally the solution was filtered and analyzed by U.V. Visible spectrophotometer (Shimadzu, UV-1700 Pharmaspec) at 276 nm.

Table-1: *Composition of different formulations*

Ingredients (%)	DM1	DM2	DM3	DM4	DM5	DL1	DL2	DL3	DL4	DL5
Salbutamol Sulphate	-	-	-	4.46	4.46	-	-	-	4.46	4.46
Starch	3	3	3	3	3	3	3	3	3	3
Sodium Starch Glycolate	-	5	-	5	-	-	5	-	5	-
Micro Crystalline Cellulose	-	-	5	-	5	-	-	5	-	5
Talc	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Lactose	-	-	-	-	-	qs	qs	qs	qs	qs
Mannitol	qs	qs	qs	qs	qs	-	-	-	-	-

Table-2: *Composition of different formulations of different type and concentration of superdisintegrant*

INGREDIENTS (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Salbutamol Sulphate	4.46	4.46	4.46	4.46	4.46	4.46	4.46	4.46	4.46	4.46
Starch	3	3	3	3	3	3	3	3	3	3
Sodium Starch Glycolate	2.5	5	10	15	20	-	-	-	-	-
Micro Crystalline Cellulose	-	-	-	-	-	2.5	5	10	15	20
Talc	1	1	1	1	1	1	1	1	1	1
Magnesium Stearate	1	1	1	1	1	1	1	1	1	1
Mannitol	qs	qs	qs	qs	qs	qs	qs	qs	qs	qs

Kinetic Treatment

To elucidate kinetics of drug release from the prepared IRTs, cumulative percentage of drug release and cumulative percentage of drug remained was plotted as the function of time (t) different release model. Peppas and Korsmeyer equation was used to determine the mechanism of rate of release of drug. The 'n' value in Peppas and Korsmeyer equation represents diffusional exponent, if it is less than 0.5, diffusion is the major driving force, and is normally said to follow Fickian diffusion and when 'n' is more than 0.5, the drug release is mainly controlled by degradation and follows non-Fickian or anomalous release [12].

RESULTS& DISCUSSIONS

The compositions of various formulations were prepared by direct compression were shown in and Table-1 and Table-2

respectively and evaluated for different physicochemical parameters. Weight variation, friability, wetting time of the prepared batches of the tablets were complied with official limits and shown in Table-3. Other physical parameters such as diameter and thickness of the tablets were also presented in the same table.

Choice of diluents and superdisintegrants in the formulation development of an effective IRDDS is largely depending upon the governing factors such as wetting time and disintegration time. Mannitol, lactose as diluents and sodium starch glycolate, micro crystalline cellulose as superdisintegrants were experimented in these protocols (DM1-DM5 and DL1-DL5). Among different combinations tried, the combination of mannitol with sodium starch glycolate (DM4) as well as mannitol with micro crystalline cellulose (DM5) showed better result, because of low disintegration time (54.66 ±5.46 s, 65.66 ±5.46 s) and wetting time (27.33 ±2.73 s, 33.16 ±2.85 s) respectively. Mannitol is a good diluent for direct compression in the formulation of IRT because it is a directly compressible sugar with a sweet taste that aids in taste masking also and it gives a cooling sensation in the mouth due to its negative heat of solution.

Table-3*: Different physical parameters evaluated of the prepared batches.*

Batch	Mean ± SD					
	Diameter [a] (mm)	Thickness [a] (mm)	Weight [b] (mg)	% Friability	Wetting time (sec) [c]	Disintegration time (sec) [c]
DM1	6.22±0.04	3.74±0.05	110.05±2.41	0.347	62.33±4.36	123.66±8.61
DM2	6.24±0.05	3.82±0.04	109.45±2.92	0.359	30.83±3.31	62.16±6.794
DM3	6.22±0.08	3.72±0.04	108.9±1.94	0.402	30.66±2.33	61.83±4.83
DM4	6.20±0.07	3.82±0.08	111.5±2.50	0.405	27.33±2.73	54.66±5.46
DM5	6.22±0.08	3.86±0.05	110.7±1.83	0.364	33.16±2.85	65.66±5.46
DL1	6.24±0.09	3.78±0.08	111.2±2.16	0.268	64.16±4.44	127.33±7.44
DL2	6.28±0.04	3.82±0.04	110.8±2.31	0.393	32.83±3.92	64.33±5.95
DL3	6.16±0.05	3.86±0.05	108.9±2.62	0.591	33.83±2.92	66.16±7.33
DL4	6.24±0.05	3.78±0.04	110.9±2.63	0.357	31.66±3.44	65.33±9.13
DL5	6.22±0.04	3.8±0.07	110.95±2.76	0.352	35.83±3.54	71.83±7.08

a: n =10 b: n = 20 c: n = 6

Fourier Transformed Infrared Study

FT-IR studies at 150 scan and at resolution of 1cm^{-1} were recorded and presented in Fig No-1, for over laid spectra of Salbutamol Sulphate and formulation F3 and in Fig No-2, for overlaid spectra of the drug and formulation F8.In FT-IR studies the characteristic C—N stretching at around 1258 cm^{-1} and C—H aromatic bending at around 839 cm^{-1} were clearly distinguishable in Salbutamol Sulphate loaded Immediate Release Tablet [13]. Additionally O—H bending of Salbutamol Sulphate at around 1080 cm^{-1} as well as C—H aromatic bending at around 881 cm^{-1} in both the formulations as well as in the drug powder suggesting no drug-excipients chemical interactions as such. The FT-IR studies thus indicated that the model drug Salbutamol Sulphate was entrapped in unbound amorphous form. In the next step, different formulations (F1-F10) were further prepared and evaluated to select and optimize the concentration of super disintegrant between sodium starch glycolate and micro crystalline cellulose (Table-2), keeping all other parameters constant. Micro crystalline cellulose is mainly used as filler in the preparation of tablets, but it is also used as a disintegrant at low concentration. Thus batches were prepared with the microcrystalline cellulose in different concentration as like sodium starch glycolate. All the prepared batches showed almost similar diameter (6.18-6.28 mm) and thickness (3.78-3.84 mm). Friability of all the formulations was found within the official limit. Formulation F4 represents the lowest wetting time and disintegration time (17.66 ±1.36 and19.83 s ±1.83 s respectively) which indicates a better result among the prepared batches, on the basis of these two governing parameters. These two time parameters helps to point out that, with further increase in the disintegrant concentration, the disintegration time may not reduce or this is

the optimum concentration of the specific disintegrant beyond which the disintegration time may not reduce significantly because these two physical parameters are the sensitive tools for pharmaceutical development of IRDDS.

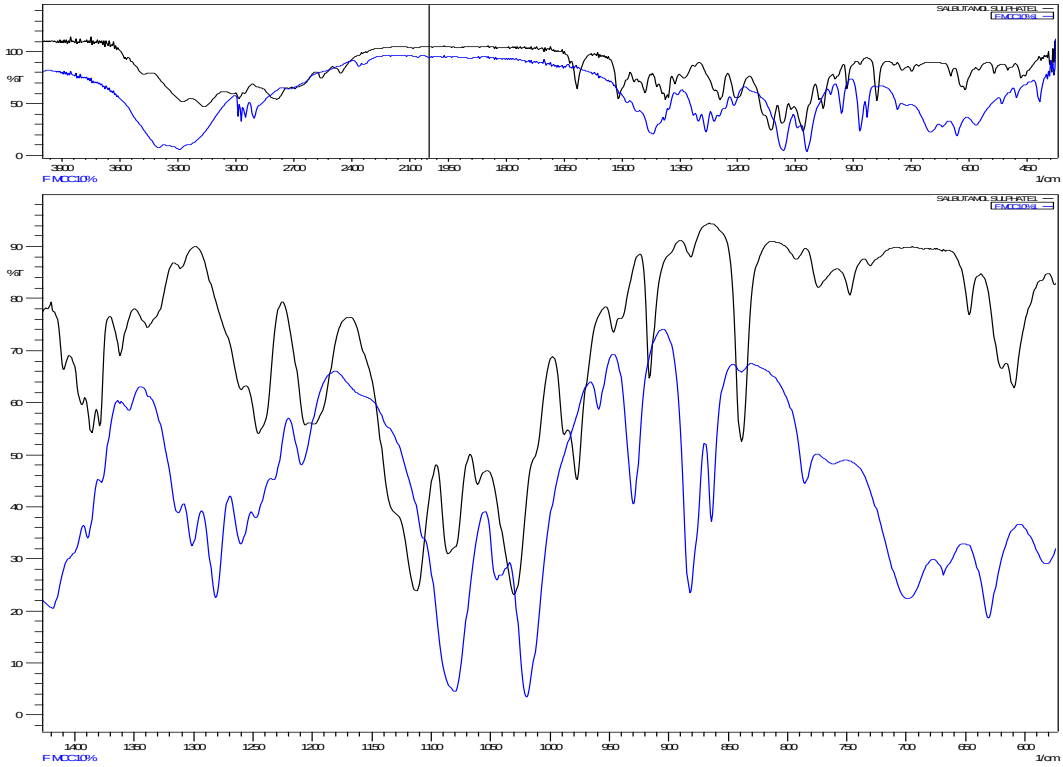

Fig-1. *FT-IR overlaid spectra of Salbutamol Sulphate (——) and Salbutamol Sulphate loaded formulation (F3) (——).*

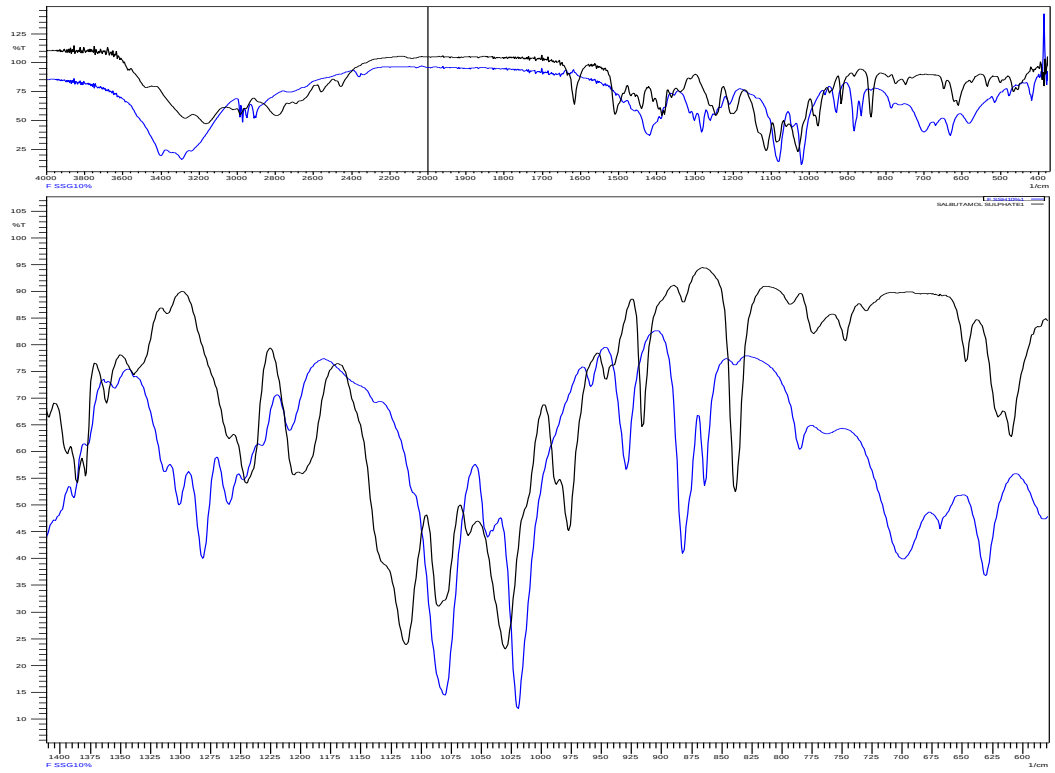

Fig-2. *FT-IR overlaid spectra of Salbutamol Sulphate (——) and Salbutamol Sulphate loaded formulation (F8) (——).*

Table-4: *Different evaluation parameters of the prepared batches.*

Batch	Mean ± SD						Cumulative % release after 15 minutes
	Diameter [a] (mm)	Thickness [a] (mm)	Weight [b] (mg)	% Friability	Wetting time (sec) [c]	Disintegration time (sec) [c]	
F1	6.24±0.08	3.82±0.08	110.5±2.64	0.316	25.33±2.16	80.33±5.12	86.36
F2	6.22±0.08	3.84±0.05	109.7±2.31	0.364	23.16±2.13	53.66±2.25	89.11
F3	6.26±0.05	3.84±0.05	109.25±2.48	0.405	21.16±1.16	36.66±2.06	89.37
F4	6.28±0.04	3.82±0.11	110.65±2.25	0.362	17.66±1.36	19.83±1.83	93.29
F5	6.18±0.08	3.82±0.08	110.2±2.52	0.363	19.16±1.94	21.16±2.04	93.99
F6	6.18±0.08	3.78±0.08	110.1±2.55	0.451	37.33±2.42	88.66±3.14	78.65
F7	6.24±0.05	3.84±0.09	110.5±2.25	0.637	34.5±2.16	55.83±2.48	80.54
F8	6.26±0.11	3.78±0.08	109.75±2.22	0.405	25.33±1.96	50.16±2.63	85.71
F9	6.22±0.11	3.78±0.08	110.75±2.76	0.407	25.16±2.13	25.83±1.94	93.04
F10	6.18±0.04	3.82±0.08	109.95±2.43	0.541	28.66±2.80	25.33±3.07	91.75

a: n =10 b: n = 20 c: n = 6

More than 78% of drug released within 15 minutes. F4, F5, F9 and F10 these formulations releases more than 91% of drug within 15 minutes. Though F4, F5 and F9 releases almost similar amount of drug but based on the wetting time and *in-vitro* disintegration time F4 was taken as the best formulation among all the formulations.

When treated with the first order and zero order kinetics it was observed that all the formulations followed first order kinetics except F3 and F7, which followed zero order kinetics, as evident from regression coefficient values. The finally selected formulation F4 was evidently following swelling controlled, first order-Fickian diffusion release kinetic [14, 15].

Overall results suggest that IRT of Salbutamol Sulphate can be prepared successfully and 15% disintegrant concentration is suitable for the preparation of Salbutamol Sulphate IRT as well as tablets containing sodium starch glycolate is the best.

CONCLUSION

This article demonstrate recent advances in formulation development and processing technologies need the effort to achieve more sophisticated drug delivery system.

The present study was carried out to meet the forgoing dialogue regarding the idea that Class III (high-solubility, low-permeability) compounds should also be eligible for a biowaiver as well as to improve patient compliance. The present invention is a rapid orally disintegrating pharmaceutical solid dosage form for water soluble but less permeable pharmaceutically active ingredient, combined with conventional pharmaceutical excipients and compressed into a tablet by using conventional pharmaceutical tabletting techniques. The use of organoleptically pleasing ingredients such as mannitol (mannitol has a negative heat of solution which further adds to the organoleptically pleasing nature of the formation); one obtains a dosage form which rapidly disintegrates and forms a watery slurry which is much more organoleptically pleasing and very easy to swallow.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest

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