Orally Disintegrating Tablets in Fixed Dose Combination containing Ambroxol Hydrochloride and Salbutamol Sulphate prepared by Direct Compression Technique: Formulation Design, Development and *In-Vitro* Evaluation

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Short Title: Orally Disintegrating Tablets in Fixed Dose Combination containing Ambroxol Hydrochloride and Salbutamol Sulphate

ABSTRACT

Aim: The aim of the study deals with the formulation design, development and *in-vitro* evaluation of orally disintegrating tablets of ambroxol hydrochloride and salbutamol sulphate in combination for the treatment of respiratory disorders by using superdisintegrants in combination with suitable binder & excipients. Direct compression method was used to prepare tablets.

Material and Methods: In the present research work, the different concentrations of sodium starch glycolate (SSG) as superdisintegrant were used to optimize the concentration of SSG in the formulation of orally disintegrating tablets. Different concentrations of microcrystalline cellulose and PVP K-30 were also studied along with optimized SSG concentration. The tablets were evaluated for hardness, friability, weight variation, wetting time, *in vitro* disintegration time and % drug content uniformity. Optimized formulation was further evaluated by *in-vitro* release study, drug-excipient compatibility and accelerated stability study.

Result and Discussion: The optimized concentration of sodium starch glycolate was found to be 4% on the basis of lowest disintegration time. The 1% concentration of MCC was selected as optimum binder concentration on the basis of lowest disintegration time. Orally disintegrating tablets passed all the quality control tests viz., weight variation, hardness, friability, *in-vitro* disintegration time, drug content (%) and wetting time. The formulation satisfied the requirements of FDA for rapid dissolving tablets and allowed more than 85% drug to be released within 30 min. The FTIR study reveals that there was no interaction between drug and excipients. The accelerated stability study shows that formulation is quite stable at normal temperature and humidity conditions as well as at extreme temperature conditions.

Conclusion: It was concluded that by adopting a systematic formulation approach, ODT of ambroxol hydrochloride and salbutamol sulphate in fixed dose combination could be formulated using superdisintegrants in combination with appropriate binder & excipients which was found to be economical and industrially feasible.

Keywords: Orally disintegrating tablets, Sodium starch glycolate, *In Vitro* Disintegration time, Ambroxol Hydrochloride, Salbutamol Sulphate, Optimization study.

INTRODUCTION

In the late 80s orally disintegrating tablets (ODT) or orodispersible tablets were developed and they were introduced to the market in early 90s. From that time, orally disintegrating tablet dosage forms are well known solution to geriatric or pediatric populations who have facing difficulties in swallowing solid oral dosage forms [1]. Orally

disintegrating tablet disintegrates within a few seconds in the mouth of patient and they are ideal for the patients suffering from dysphasia. As the saliva passes through the stomach, some of drugs are absorbed from the mouth, pharynx, and esophagus, which ultimately lead to an increase in bioavailability of drug [2]. According to the definition by the Royal Spanish Pharmacopoeia, these tablets should disintegrate in less than 3 min. when tested at temperatures ranging between 35 and 39º C, simulating the temperature of the oral cavity. The others requirements which these dosage forms must comply is mechanical resistance which is important for from the point of view for handling as well as for packaging and storage. ODT must have ideal organoleptic characteristics [3]. Orodispersible tablets are not only applicable for people who have difficulties in swallowing, but also for active people when water is not available, in the case of motion sickness, sudden episodes of coughing during the common cold, allergic conditions, and bronchitis. Due to this, these dosage forms are increasingly being recognized in both industry and academics. Orodispersible tablets are also called mouth-dissolving tablets, melt-in mouth tablets, fast dissolving tablets, rapid melts, porous tablets, quick dissolving, and so forth [4]. Several newer disntegrants have been developed in more recent years, which are often called "super disintegrants." These can be used at lower levels than conventionally used disintegrants. Swelling, Porosity, capillary action, and deformation are the three major mechanisms and factors that affecting the disintegration of tablets [5]. Examples of superdisintegrants are croscarmelose, crospovidone, and sodium starch glycolate (SSG), which symbolize the example of crosslinked cellulose, crosslinked polymer, and a crosslinked starch, respectively. These are the commonly used synthetic origin superdisintegrants [2]. There are various technological processes such as direct compression, freeze-drying and molding by which the orodispersible tablets can be manufactured. The best way to manufacture the orally disintegrating tablets is direct compression method as it is the right compromise among economical, manufacturing and technological needs. To produce the ODT with satisfactory organoleptic, biopharmaceutical and technological characteristics, it is important to select the appropriate excipients which are able to produce the product with desired characteristics, efficacy and pleasant mouth-feel [6]. In the selection of excipients, the excipients having rapid dissolution in water, low viscosity, sweet flavor and high

compressibility are considered. Due to the pleasant taste and ability to masking of other flavors, sugars are most commonly used that dissolves quickly in saliva being very soluble in water [3].

Ambroxol (AMB) is a metabolite of bromhexine with similar actions and uses. It is chemically described as Trans-4-[(2-amino-3,5-dibromobenzyl)amino]-cyclohexanol. Ambroxol hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as, bronchial asthma, chronic bronchitis characterized by the production of excess or thick mucus. Ambroxol hydrochloride has also been reported to have a cough suppressing effect and anti-inflammatory action. It has been successfully used for decades in the form of its hydrochloride as a secretion releasing expectorant in a variety of respiratory disorders [7]. Salbutamol Sulphate is a β-2 adrenergic agent with more bronchodilator effect and is useful in the treatment of asthma. Salbutamol Sulphate must be dosed three to four times a daily to maintain its bronchodilation effect due to the short half is 4-6 hrs [8].

Formulations of the drugs chosen in fixed dose combination for the treatment of sudden allergic attacks and coughing are available in the market in conventional tablet and liquid dosage forms. Due to sore throat conditions, the pediatrics patient experiences difficulty in swallowing a tablet type of dosage form. Liquid dosage forms are having their own limitation from stability and dose measurement perspectives. Hence they do not comply with the prescription that results in high incidence of ineffective therapy and noncompliance. Hence, in the present study it was proposed to formulate fixed dose combination of ambroxol hydrochloride and salbutamol sulphate orally disintegrating tablets by using direct compression technique with an aim of improving/enhancing patient convenience and compliance, reducing the lag time, and providing faster onset of action to relieve the respiratory disorders immediately.

MATERIALS AND METHODS

Materials

Ambroxol hydrochloride and salbutamol sulphate used as model drugs were obtained from Trojan Pharma, Baddi, India as gift samples. Microcrystalline cellulose as binder/disintegrant (Avicel PH-102) was received from NB Entrepreneurs, Nagpur, India

as a gift sample. Sodium Saccharin as sweetening agent was obtained from Loba Chemie, Mumbai and talc as glidant from Nice Chemicals Private Limited, Hyderabad, India. Sodium Strearyl Fumarate as a lubricant was purchased from Himedia. PVP K-30 as binder was obtained from Himedia. Sodium Starch Glycolate as superdisintegrant (Primogel) and directly compressible Mannitol (D-Mannitol) as a diluent were obtained from Qualikems Fine Chem Pvt. Ltd. All the chemicals and reagents used in research work were of analytical grade.

Selection and Optimization of Excipients (Methodology)

The most important parameter that requires to be optimized in the development of orally disintegrating tablets is disintegration time. ODTs were prepared by direct compression technique using different excipients such as binders and superdisintegrants. Various evaluation parameters like friability, hardness and disintegration time were performed to select the best combination for formulation of ODTs. The combination with lowest disintegration time, optimum friability and hardness was selected for further study.

Optimization of Sodium Starch Glycolate (SSG)

The various concentrations (1%, 2%, 4%, 6%, 8% and 10%) of SSG were used in the preparation of ODT to study the effect of concentration of superdisintegrants on evaluation parameters of tablets. Total six formulations (F1-F6) were manufactured by the direct compression technique as given in Table 1. For each specified formulation, required quantity of each ingredient was taken. All the ingredients were passed through mesh no.60. co-grind in a pestle motor. Finally talc and sodium stearyl fumarate were added and mixed for 5 minutes. The mixed blend of excipients was compressed into tablets using 8mm punch in multi punch tablet compression machine (Dhiman Industries, India).

Optimization of PVP K-30 or MCC (Avicel PH-102) with Optimized Concentration of SSG

In this method, the different concentrations of binder along with the optimized concentration of SSG were used to produce the tablets. Total 14 formulations (B1-B14) were manufactured to study the effect of type of binder with optimized concentration of

SSG as given in Table 2. For each specified formulation, required quantity of each ingredient was taken. All the ingredients were passed through mesh no.60. co-grind in a pestle motor. Finally talc and sodium stearyl fumarate were added and mixed for 5 minutes. The mixed blend of excipients was compressed into tablets using 8mm punch in multi punch tablet compression machine (Dhiman Industries, India).

Formulation of Ambroxol hydrochloride, Salbutamol Sulphate ODTs

ODTs of ambroxol hydrochloride and salbutamol sulphate in fixed dose combined form were manufactured by direct compression technique. Required quantity of each ingredient was taken for formulation shown in Table 3. Accurately weighed quantities of ambroxol hydrochloride and salbutamol sulphate taken with optimized concentration of SSG and binder with excipients were co-grind in geometric progression in a dry and clean mortar. All the ingredients were passed through mesh no.60. Finally sodium stearyl fumarate and talc were added and mixed for 5 minutes. The mixed blend of excipients was compressed into tablets using 8mm punch in multi punch tablet compression machine (Dhiman Industries, India).

Evaluation Parameters

Weight Variation Test

Twenty FDT tablets were selected at random from each formulation and weighed individually on digital weighting balance (Ohaus, USA). The individual weights were compared with the average weight for determination of weight variation. For passing the weight variation test, the tablets within the range of 80mg-250mg weight should not deviate more than or less than (±7.5) % from its average weight according to IP limits [9].

Hardness

To perform this test tablets were placed between two anvils, force to the anvils and the crushing strength that just causes the tablets to break was recorded. Monsanto hardness tester was used to measure the hardness of tablets. Three tablets from each formulation batch were tested randomly and the average reading noted results were expressed in kg/cm^2 [10].

Thickness

Thickness of tablets was determined using vernier caliper (Indian Caliper Industries, Ambala, India). Three tablets from each batch were used, and an average value was calculated [11].

Friability

Twenty tablets, from each formulation, were accurately weighed and placed in the drum of Roche friabilator (Camp -bell Electronics, Mumbai). The tablets were rotated at 25 rpm for a period of 4 min. and then removed, dedusted and accurately re-weighed (Ohaus, USA). The friability has been expressed in terms of weight loss and has been calculated in percentage of the initial weight; according to Indian Pharmacopeia specifications, friability under 1% has been considered acceptable [12].

$$\text{Percentage friability} = \frac{\text{Initial weight } (W_0) - \text{Final weight } (W)}{\text{Initial weight } (W_0)} \times 100$$

In vitro Disintegration Test

The disintegration time of the tablet was measured in 900 ml of distilled water (37±2°C) using Digital Tablet Disintegration Tester (Veego, India). The time in seconds taken for the complete disintegration of the tablet with no palpable mass in the apparatus was measured in seconds. Six tablets from each batch (formulation) were tested for the disintegration time calculations [13].

Wetting Time

A piece of tissue paper folded twice was placed in a small petridish (ID6.5cm) containing 6ml of distilled water was taken. A tablet containing a small quantity of amaranth color was placed on this was put on the paper and the time for the upper surface of the tablet to become complete red was measured. Three trials for each batch were performed [14].

Drug Content (%)

For the estimation of drug content (%), ten tablets were selected randomly and the average weight was calculated. The tablets were crushed in a mortar and an

accurate weight equivalent 7.5 mg of ambroxol hydrochloride and 2 mg of salbutamol sulphate was weighed and dissolved in suitable quantity of 6.8 pH phosphate buffer.. The solution was sonicated, filtered and suitably diluted and the drug content (%) was determined form simultaneous equation method by using Double Beam UV Spectrophotometer (UV-1800 Shimadzu) at 244 nm and 276 nm wave-lengths corresponds to ambroxol hydrochloride and salbutamol sulphate respectively. Each sample was analyzed in triplicate. The tablets should complies as per IP specifications i.e. 85%-110% [15].

In vitro Drug Release Studies

In vitro drug release studies of all the formulations were carried out using USP eight stage dissolution testing apparatus- 2 (paddle method) (Lab, India) at 50rpm. Phosphate buffer pH 6.8 (500 ml) was used as the dissolution media with temperature maintained at 37 ± 0.5°C. 5mL Samples were withdrawn at different intervals, diluted suitably and analyzed at 244 nm and 276 nm. An equal volume of fresh dissolution medium was replaced to maintain the original volume. The *in-vitro* release studies were carried out in triplicate. Absorbance of these solutions was measured at their respective λ_{max} [16]. Cumulative percentage (%) drug release was calculated from simultaneous equation method which is given as

At 244 nm $A_1 = 0.025\ c_A + 0.0017\ c_S$

At 276 nm $A_2 = 0.0030\ c_A + 0.0066\ c_S$

Whereas C_A- concentration of ambroxol hydrochloride, C_S- concentration of salbutamol sulphate. By putting the values of Absorbances A_1 and A_2 at their respective λ_{max}, the concentrations of ambroxol hydrochloride and salbutamol sulphate were obtained in sample solutions [17].

Drug-Excipient Compatibility Studies

This study generally includes FTIR spectroscopy and these are generally performed to confirm the drug- excipients compatibility. In order to find compatibility between pure drugs with the excipients used in formulation, FTIR spectra of physical mixture of pure drugs and optimized ODT formulation were recorded on FTIR Spectrophotometer

(Bruker, USA) in scanning range of 4000 to 600 cm^{-1} and the resolution was $1cm^{-1}$. FTIR scans were then evaluated for shifting and masking and appearance of new peaks due to drug-excipient incompatibility [18].

Accelerated Stability Studies

Accelerated stability studies were performed out on formulated ODTs (Formulated in three primary batches) which were wrapped in aluminium foil and then stored in air-tight containers that is impermeable to solid, liquid and gases, for a period of one month as prescribed by ICH guidelines at temperature of 40 ± 2°C and at ambient humidity as well as at room temperature (25± 2°C). For achieving these types of storage conditions ,we kept the sample in two stability chambers (Thermolab) for attaining above said conditions. The tablets were withdrawn on 15th, 30th day and analyzed for drug content (%), friability, hardness and *in-vitro* disintegration time [19].

RESULTS AND DISCUSSION

Optimization of Superdisintegrant Sodium Starch Glycolate

The results for optimization of superdisintegrant concentration in ODTs are shown in Table 4. From the evaluation parameters, it was observed that sodium starch glycolate in 4% concentration was the optimum concentration for rapid tablet disintegration on the basis of lowest disintegration time observed with F3 formulation. The superdisintegrant action of SSG is exhibited by swelling and capillary action which causes rapid disintegration of tablets. Due to its hydrophilic nature, it rapidly absorbs water and swells up to 200-300% of their own weight. It is used in concentration range of 4-8%. Disintegration time increases above 4% due to gelling effect of the SSG [20].

Optimization of PVP K-30 or MCC (Avicel PH-102) along with Optimized Concentration of SSG

The results for optimization of different binders in ODTs are given in Table 5. It was observed from the evaluation parameters, the disintegration time of the formulation B8 was further decreased and friability and hardness of tablet comply with the Indian Pharmacopoeia (IP) limits. The lowest disintegration time was observed in B8

formulation i.e. 1% MCC as compared to B2 formulation i.e. 2% PVP K-30. The probable reason was that MCC has strong binding property alongside its good disintegration attributed to swelling or capillary action and high dilution potential. The strong binding property of MCC is a result of its plastic deformation under pressure. Generally, plastic deformation occurs if the crystal structure or shape is changed under compression against the intermolecular forces which restore the crystal features to its original form [21].On the other hand, water soluble materials such as PVP K-30 dissolves faster rather disintegrate. Therefore as optimum binder concentration, 1% MCC was selected for final formulation of ambroxol hydrochloride & salbutamol sulphate ODT. The study concluded that optimization of binder:superdisintegrant concentration is essential in reducing the disintegration time of the tablets.

Evaluation parameters for ambroxol hydrochloride & salbutamol sulphate ODT

ODTs were prepared by direct compression method evaluated for hardness, weight variation, friability, Thickness, percentage drug content uniformity, *in-vitro* disintegration time, the results of which are shown in Table 6. Weight variation of formulated batches was shown to be within the acceptable IP limits. The drug content (%) was found to be AMB: 106.5 ± 1.53%, SAL: 93.33 ± 2.25%. The drug content (%) was found in the range of 85-115% of the label claim (IP acceptable limit). Tablets require a certain amount of hardness and resistance to friability to withstand mechanical shock in manufacture, packing and shipping. Hardness was found to be 2.5 ± 0.29 kg/cm^2. Friability of the tablets was found below 1 % indicating a good mechanical resistance of tablets. The *in-vitro* disintegration time (DT) of the tablets was found to be less than 60 second as shown. The wetting time was practically good for formulation. The formulated ODTs showed low DT indicating suitability of formulation for mouth dissolving tablet. From the *in-vitro* release study, it was observed that 93.23 ± 0.25 % of Ambroxol Hydrochloride released in 20 minutes and 89.23 ± 1.03% of salbutamol sulphate released in 12 minutes indicated that the tablet complies as per IP specifications i.e. 85%-110% as given in Figure 1.

Drug-Excipient Compatibility Studies

FTIR Spectra of pure drugs in combination and formulated ODT containing drugs were obtained on FTIR spectrophotometer. The results obtained with FTIR studies as given in Figure 2 and Figure 3, indicated that there were no interaction between the drug and other excipients used in the formulation. FTIR Spectra of Physical Mixture of Ambroxol Hydrochloride & Salbutamol sulphate shown intense band at 696.34 cm^{-1}, 1611.17 cm^{-1} and 1279.00 cm^{-1} corresponding to the presence of functional groups such as aliphatic bromo compound, secondary amine and secondary alcohol in Ambroxol Hydrochloride and at 1389.84 cm^{-1}, 1611.17 cm^{-1} and 1389.84 cm^{-1} corresponding to the presence of functional groups such as trimethyl, secondary amine and phenol in Salbutamol sulphate. The FTIR of Ambroxol Hydrochloride & Salbutamol sulphate ODT formulation also showing intense absorption bands at 651.32 cm^{-1}, 1611.97 cm^{-1} and 1280.03 cm^{-1} for Ambroxol Hydrochloride and at 1389.04 cm^{-1}, 1611.97 cm^{-1} and 1389.04 cm^{-1} for Salbutamol sulphate indicates no changes in the functional groups confirmed undisturbed structure of Ambroxol Hydrochloride, Salbutamol sulphate, which indicates no drug-excipient incompatibility as shown in Figure 2 and 3.

Accelerated Stability Studies

Accelerated stability studies of final optimized ODTs (Prepared in three primary batches), which were wrapped in aluminium foil to simulate the Alu Alu packing of drug products and then stored in air tight containers impermeable to solid, liquid and gases for a period of 1 month as prescribed by ICH guidelines. The product is exposed to normal and extreme condition of temperature and humidity. The stability data of formulation was given in Table 7 and Table 8. The result of the stability study indicated that there were not much differences observed in hardness, disintegration time, drug content uniformity and friability before and after the storage period at room temperature and at ambient humidity but at temperature of 40ºC±2ºC and at ambient humidity. Hardness was found to be increased with time, prolonged the DT of the tablet [22]. The probable reason was loss of moisture from tablets but in all cases, DT is within the specified IP limit (with in 3 min.). This indicates that formulation is fairly stable at both storage conditions. Statistical analysis (ANOVA) was also performed with the Graph Pad

In Stat 3 statistical package for Windows. Stability data shown in tables for three primary batches of formulations were evaluated for drug content (%), friability, hardness and disnintegration time before and after stability testing represented mean of three or six determinations± standard deviation (SD). Statistical significance of the differences between the evaluation parameters of three primary batches was calculated by the Tukey-Kramer multiple comparison test, and probability value of P smaller than 0.05 indicated a statistically significant difference.

CONCLUSION

The objective of the present investigations has been achieved by preparing orally dissolving drug delivery system of ambroxol hydrochloride and salbutamol sulphate in fixed dose combination with faster and quick onset of action by using an optimum amount of superdisintegrant sodium starch glycolate and binder microcrystalline cellulose using direct compression technique. The optimization methods mentioned in the report were proved useful in the development of orally disintegrating tablets. The orally disintegrating tablets developed in this work will hopefully contribute to improve drug administration to patients with swallowing and chewing difficulties. The prepared ODTs passed all the quality control tests viz., weight variation, hardness, friability, *in-vitro* disintegration time, drug content (%), and wetting time. *In-vitro* dissolution results were also studied. The ODT formulation satisfied the requirements of FDA for rapid dissolving tablets and allowed more than 85 % drug to be dissolved within 30 min. The FTIR study reveals that there was no interaction between drug and excipients. The accelerated stability study shows that formulation is quite stable at normal temperature and humidity conditions as well as at extreme temperature and humidity conditions. Thus, it is concluded that by adopting a systematic formulation approach, ODT of ambroxol hydrochloride and salbutamol sulphate in fixed dose combination could be formulated using superdisintegrants in combination with appropriate binder & excipients which was found to be economical and industrially feasible.

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List of Tables

Table 1. Formula for 1 Tablet (200 mg) of different concentration of sodium starch glycolate

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**
Ambroxol Hydrochloride	7.5	7.5	7.5	7.5	7.5	7.5
Salbutamol Sulphate	2	2	2	2	2	2
Sodium Starch Glycolate	2	4	8	12	16	20
Microcrystalline Cellulose	2	2	2	2	2	2
Sodium Stearyl Fumarate	4	4	4	4	4	4
Talc	2	2	2	2	2	2
Sodium Saccharin	3	3	3	3	3	3
Mint flavor	8	8	8	8	8	8
Mannitol	169.5	167.5	163.5	159.5	155.5	151.5

Table 2. Formula for 1 Tablet (200 mg) for the optimization of PVP K-30 or MCC with optimized concentration of SSG

Ingredients / Formulation No.	AMB HCl (mg)	SAL (mg)	SSG (mg)	PVP K-30 (mg)	MCC (mg)	SSF (mg)	Talc (mg)	SS (mg)	Mint Flavour	Mannitol (mg)
B1	7.5	2	8	2	-	4	2	3	8	163.5
B2	7.5	2	8	4	-	4	2	3	8	161.5
B3	7.5	2	8	6	-	4	2	3	8	159.5
B4	7.5	2	8	8	-	4	2	3	8	157.5
B5	7.5	2	8	10	-	4	2	3	8	155.5
B6	7.5	2	8	12	-	4	2	3	8	153.5
B7	7.5	2	8	14	-	4	2	3	8	151.5
B8	7.5	2	8	-	2	4	2	3	8	163.5
B9	7.5	2	8	-	4	4	2	3	8	161.5
B10	7.5	2	8	-	6	4	2	3	8	159.5
B11	7.5	2	8	-	8	4	2	3	8	157.5
B12	7.5	2	8	-	10	4	2	3	8	155.5
B13	7.5	2	8	-	12	4	2	3	8	153.5
B14	7.5	2	8	-	14	4	2	3	8	151.5

MCC: Microcrystalline cellulose, SSG: Sodium starch glycolate, PVP K-30: Polyvinylpyrrolidone K-30, AMB HCl: Ambroxol hydrochloride, SAL: Salbutamol Sulphate, SSF: Sodium stearyl fumarate, SS: Sodium Saccharin

Table 3. Formula of ambroxol hydrochloride and salbutamol sulphate ODT

Ingredients	Formula for 1 Tablet (200 mg)
Ambroxol Hydrochloride	7.5
Salbutamol Sulphate	2
Sodium Starch Glycolate	8
Microcrystalline Cellulose	2
Sodium Stearyl Fumarate	4
Talc	2
Sodium Saccharin	3
Mint Flavor	8
Mannitol	163.5

Table 4. Evaluation parameters for the optimization of sodium starch glycolate

Evaluation Parameters	F1 (1%)	F2 (2%)	F3 (4%)	F4 (6%)	F5 (8%)	F6 (10%)
*Weight variation (mg) ± S.D	198± 2.0	202± 1.0	201± 2.0	198±3.0	197±2.0	201±1.0
Friability (%)± S.D	0.8±0.1	0.8±0.2	0.1±0.1	0.3±0.1	0.1±0.1	0.1±0.1
*Hardness (Kg/cm^2) ± S.D	2.8± 0.57	2.6 ± 0.28	2.5 ± 0.28	2.5 ± 0.32	2.8 ± 0.57	2.8 ± 0.28
**Disintegration time (s) ± S.D	65 ± 1.74	48 ± 1.35	34 ± 1.86	45 ± 2.36	72 ± 1.76	90 ± 2.64

IP stands for Indian Pharmacopoeia , S.D is standard deviation
* represents the average of n=3 determinations
** represents the average of n=6 determinations

Table 5. Evaluation parameters for the optimization of PVP K-30 or MCC (Avicel PH-102) with optimized concentration of SSG

Evaluation Parameters / Formula No.	*Weight variation (mg)± S.D	*Friability (%) ± S.D	*Hardness (Kg/cm^2) ± S.D	**Disintegration time (s) ± S.D
B1	200±2.0	0.1±0.1	2.5± 0.28	56 ± 1.78
B2	201±1.0	0.2±0.1	2.0 ± 0.28	40 ± 1.67
B3	197±2.0	0.5±0.2	2.0 ± 0.00	54 ± 2.89
B4	199±3.0	0.3±0.2	3.0 ± 0.76	71 ± 2.40
B5	204±2.0	0.3±0.1	2.5 ± 0.50	82 ± 5.16
B6	202±2.0	0.8±0.3	2.5 ± 0.50	95 ± 5.77
B7	198±1.0	0.8±0.2	2.0 ± 0.00	105 ± 5.43
B8	201±1.0	0.1±0.1	2.5± 0.50	36 ± 2.13
B9	204±2.0	0.1±0.1	2.5 ± 0.28	43 ± 1.34
B10	197±3.0	0.2±0.2	2.5 ± 0.28	55 ± 1.10
B11	199±2.0	0.1±0.1	2.5 ± 0.28	64 ± 1.32
B12	203±2.0	0.1±0.25	2.5 ± 0.28	78 ± 2.08
B13	201±1.0	0.1±0.25	2.5 ± 0.28	92 ± 1.84
B14	202±1.0	0.1±0.25	2.5 ± 0.28	103 ± 1.73

S.D is standard deviation
* represents the average of n=3 determinations
** represents the average of n=6 determinations

Table 6. Evaluation Parameters for Ambroxol Hydrochloride & Salbutamol sulphate ODT

Evaluation Parameters	Results
*Weight variation (mg) ± S.D	201±2.0
*Thickness (mm) ± S.D	3.63± 0.06
*Hardness (Kg/cm^2) ± S.D	2.5 ± 0.29
*Friability (%)± S.D	0.2± 0.15
**Disintegration Time (s) ± S.D	34 ± 1.14
*Wetting Time (s) ± S.D	26 ± 1.53
*Drug Content Uniformity± S.D	AMB: 106.5 ± 1.53, SAL: 93.33 ± 2.25

S.D is standard deviation
* represents the average of n=3 determinations
** represents the average of n=6 determinations

Table 7. Accelerated stability data of ambroxol hydrochloride & salbutamol sulphate ODT at temperature (40 ºᐩ 2ºc) and at ambient humidity

	Three Primary Batches								
Time Interval	**0 Day**			**15th Day**			**30th Day**		
Evaluation Parameters	**B-1**	**B-2**	**B-3**	**B-1**	**B-2**	**B-3**	**B-1**	**B-2**	**B-3**
***Hardness** (Kg/cm^2) ± S.D	2.7 ± 0.29	2.5 ± 0.00	2.5 ± 0.00	2.9 ± 0.29	2.7 ± 0.29	2.8± 0.29	3.0 ± 0.29	3.2 ± 0.29	3.2 ± 0.29
*Friability (%)± S.D	0.2±0.1	0.3±0.1	0.2±0.1	0.5±0.2	0.4±0.1	0.3±0.1	0.3±0.1	0.2±0.1	0.3±0.1
*Drug Content (%) ± S.D	AMB-90.8 ±3.36, SAL-104.7 ± 1.97	AMB-95.6 ± 2.34, SAL - 95.4 ± 2.86	AMB-93.8 ± 1.24, SAL - 97.7 ± 3.97	AMB-92.5± 2.14, SAL-103 ± 1.76	AMB-93.5 ± 2.67, SAL-98.6 ± 2.07	AMB-94.8± 1.23, SAL-93.4 ± 1.77	AMB-91.3 ± 1.98, SAL-97.8 ± 2.97	AMB-94.4 ± 1.65, SAL-97.7 ± 2.75	AMB-95.7 ± 3.63, SAL-94.2 ± 2.43
****Disintegration Time (s) ± S.D	42 ± 2.14	38± 1.67	43 ± 3.31	46 ± 4.94	43 ± 3.06	48 ± 1.59	48 ± 2.38	47 ± 2.67	50 ± 3.51

S.D is standard deviation
* represents the average of n=3 determinations
** represents the average of n=6 determinations

Table 8. Accelerated stability data of ambroxol hydrochloride & salbutamol sulphate ODT at room temperature and at ambient humidity

	Three Primary Batches								
Time Interval	**0 Day**			**15th Day**			**30th Day**		
Evaluation Parameters	**B-1**	**B-2**	**B-3**	**B-1**	**B-2**	**B-3**	**B-1**	**B-2**	**B-3**
***Hardness (Kg/cm^2) ± S.D	2.7 ± 0.29	2.5 ± 0.00	2.5 ± 0.00	2.7 ± 0.29	2.3 ± 0.29	2.5 ± 0.00	2.5 ± 0.00	2.5 ± 0.29	2.3 ± 0.29
Friability (%) ± S.D	0.2±0.1	0.3±0.1	0.2±0.1	0.3±0.1	0.3±0.1	0.3±0.1	0.3±0.1	0.4±0.2	0.5±0.2
*Drug Content (%) ± S.D	AMB-90.8 ±3.36,	AMB-95.6 ± 2.34,	AMB-93.8 ± 1.24,	AMB-96.8± 4.23,	AMB-94.5 ± 3.78,	AMB-96.8± 2.31,	AMB-95.6 ± 3.21,	AMB-94.4 ± 3.14,	AMB-95.7 ± 4.34,
	SAL-104.7 ± 1.97	SAL-95.4 ± 2.86	SAL-97.7 ± 3.97	SAL-100.3 ± 4.13	SAL-93.6 ± 3.45	SAL-98.4 ± 2.54	SAL-99.3 ± 3.35	SAL-92.7 ± 1.42	SAL-97.3 ± 3.24
**Disintegration Time (s) ± S.D	42 ±2.14	38± 1.67	43 ± 3.31	42 ± 3.97	41 ± 4.52	47 ± 1.66	46 ± 2.83	44 ± 2.52	48 ± 3.75

S.D is standard deviation
* represents the average of n=3 determinations
** represents the average of n=6 determinations

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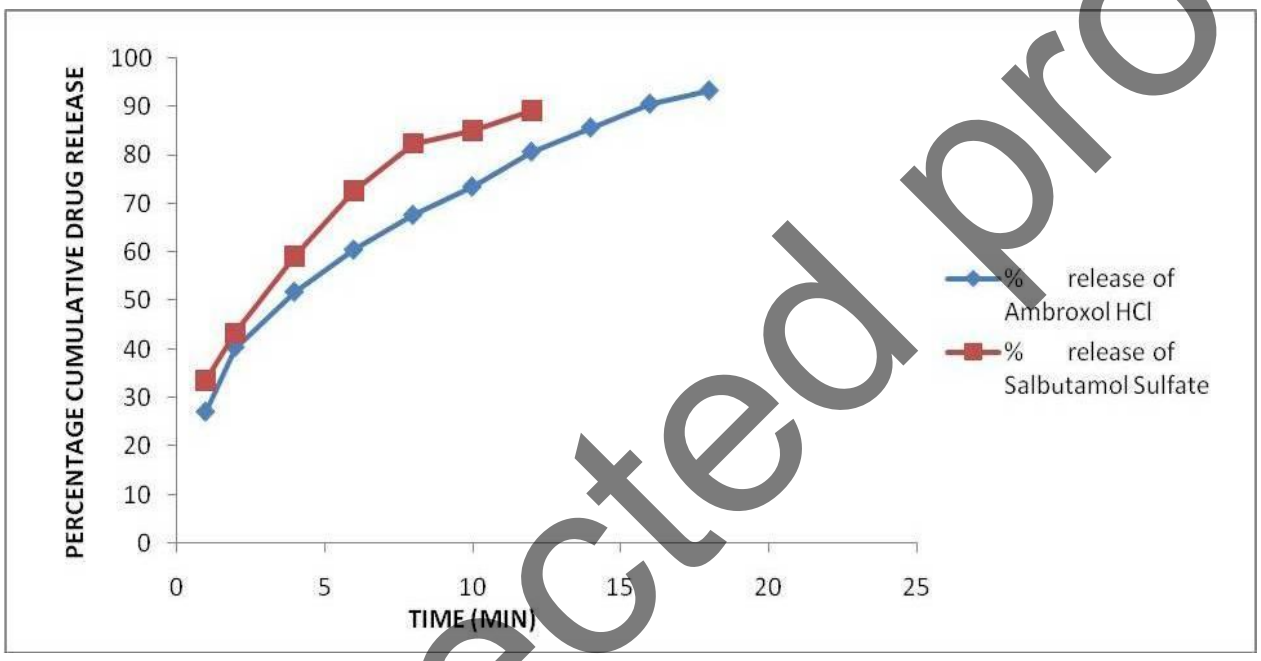

Figure 1. *In-vitro* drug release profile of ambroxol hydrochloride, salbutamol sulphate ODT

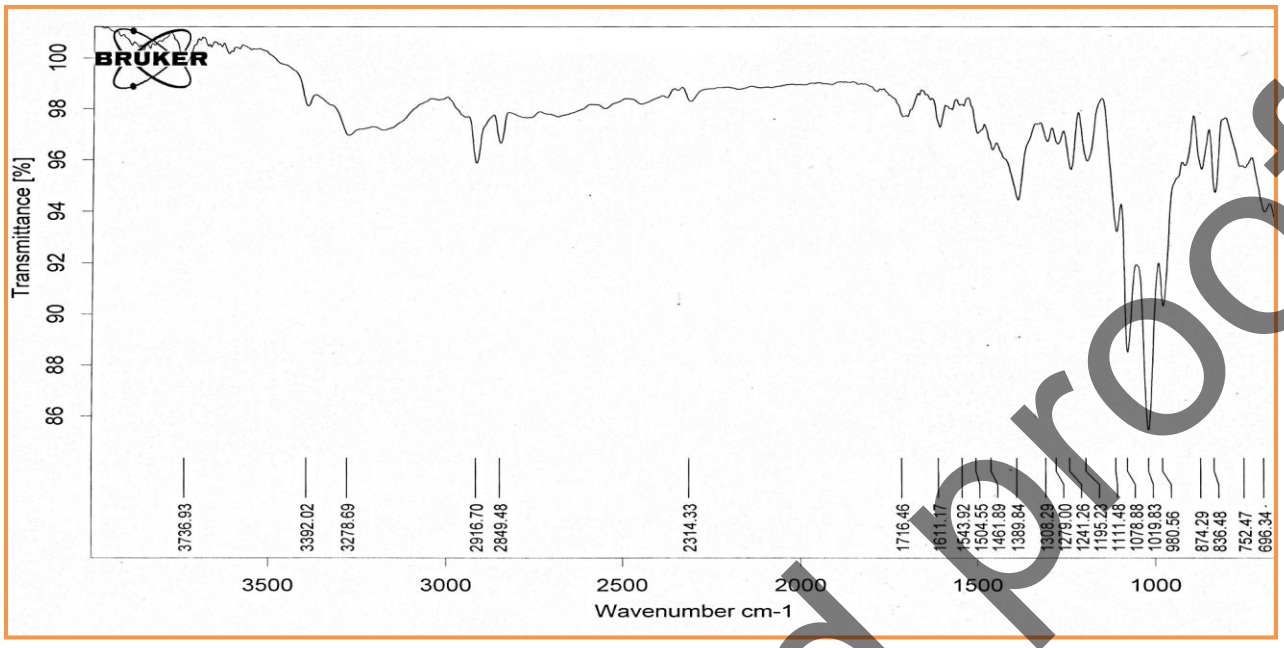

Figure 2. FTIR Spectra of Physical Mixture of ambroxol hydrochloride, salbutamol sulphate and blend

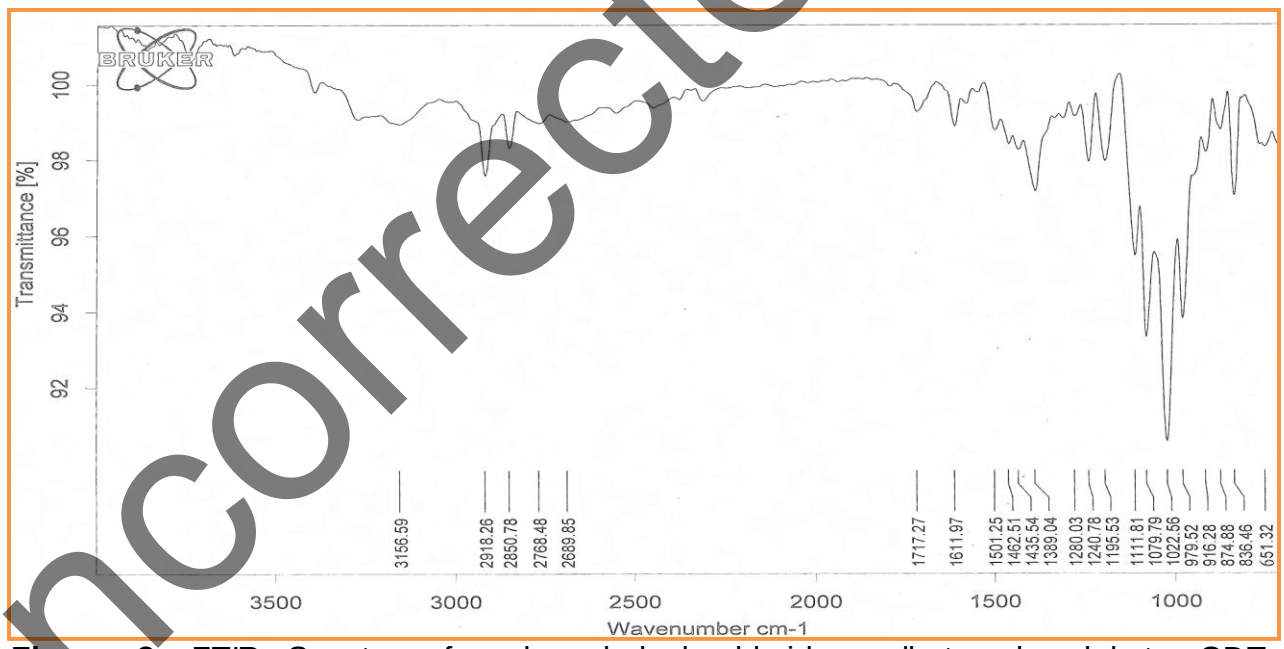

Figure 3: FTIR Spectra of ambroxol hydrochloride, salbutamol sulphate ODT formulation