Turk J Pharm Sci 2018;15(1):29-37
DOI: 10.4274/tjps.24633

ORIGINAL ARTICLE

Orally-disintegrating Tablets in Fixed-dose Combination Containing Ambroxol Hydrochloride and Salbutamol Sulphate Prepared by Direct Compression: Formulation Design, Development and *In Vitro* Evaluation

Doğrudan Basım ile Hazırlanan Ambroksol Hidroklorür ve Salbutamol Sülfat İçeren Sabit Doz Kombinasyonu Oral-dağılan Tabletler: Formülasyon Tasarımı, Geliştirilmesi ve *İn Vitro* Değerlendirilmesi

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ABSTRACT

Objectives: To design a formulation and develop ODTs of AMB hydrochloride and salbutamol sulphate in combination for the treatment of respiratory disorders and perform an *in vitro* evaluation using superdisintegrants in combination with a suitable binder and excipients. Direct compression was used to prepare the tablets.

Materials and Methods: In the present research work, different concentrations of SSG as a superdisintegrant were used to optimize the concentration of SSG in the formulation of ODTs. Different concentrations of MCC and PVP K-30 were also studied along with the optimized SSG concentration. The tablets were evaluated for hardness, friability, weight variation, wetting time, *in vitro* DT, and percentage drug content uniformity. The optimized formulation was further evaluated in an *in vitro* release study, and drug-excipient compatibility and accelerated stability study.

Results: The optimized concentration of SSG was found as 4% on the basis of the lowest DT. The 1% concentration of MCC was selected as the optimum binder concentration on the basis of the lowest DT. ODTs passed all the quality control tests viz., weight variation, hardness, friability, *in vitro* DT, drug content (%) and wetting time. The formulation satisfied the requirements of the FDA for rapid-dissolving tablets and allowed more than 85% drug to be released within 30 min. The fourier transform infrared spectroscopy study revealed that there was no interaction between the 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: By adopting a systematic formulation approach, ODTs of AMB hydrochloride and salbutamol sulphate in fixed-dose combination can be formulated using superdisintegrants in combination with appropriate binder and excipients; this was found to be economical and industrially feasible.

Key words: Orally-disintegrating tablets, sodium starch glycolate, *in vitro* disintegration time, ambroxol hydrochloride, salbutamol sulphate, optimization study

ÖZ

Amaç: Solunum bozukluklarının tedavisi için oral-dağılan AMB hidroklorür ve salbutamol sülfat kombinasyon tabletlerinin (ODT) geliştirilmesi ve kombine süper dağıtıcıların uygun bağlayıcı ve eksipiyanlar ile kombine kullanımı ile *in vitro* değerlendirmenin yapılmasıdır. Tabletleri hazırlamak için doğrudan basım kullanıldı.

Gereç ve Yöntemler: Bu araştırmada, oral dağılan tabletlerin formülasyonunda SNG konsantrasyonunu optimize etmek için farklı SNG konsantrasyonları süper dağıtıcı olarak kullanıldı. Farklı konsantrasyonlarda MCC ve PVP K-30 da optimize SNG konsantrasyonu ile birlikte çalışıldı. Tabletler, sertlik,

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Received: 12.03.2017, Accepted: 13.04.2017

kırılganlık, ağırlık değişimi, ıslanma süresi, *in vitro* dağılma süresi ve yüzde etken madde içerik tekdüzeliği açısından değerlendirildi. Optimize edilmiş formülasyon ayrıca *in vitro* salım çalışması ve etken madde-eksipiyan geçimliliği ve hızlandırılmış stabilite çalışmasıyla değerlendirildi.

Bulgular: En düşük dağılma süresine dayanarak SNG'nin optimum konsantrasyonu, %4 olarak bulundu. MCC'nin %1 konsantrasyonu, en düşük dağılma süresine dayanarak optimum bağlayıcı konsantrasyonu olarak seçildi. Oral dağılan tabletler, ağırlık değişimi, sertlik, kırılganlık, *in vitro* dağılma süresi, etken madde içeriği (%) ve ıslanma süresi gibi tüm kalite kontrol testlerini geçti. Formülasyon, hızlı çözünen tabletler için FDA şartlarını yerine getirdi ve %85'den fazla etken maddenin 30 dakika içinde salımını sağladı. Fourier dönüşümü kızıl ötesi spektroskopi çalışması, etken madde ve eksipiyanlar arasında herhangi bir etkileşimin olmadığını ortaya koymuştur. Hızlandırılmış stabilite çalışması, normal sıcaklık ve nem koşullarında ve aşırı sıcaklık koşullarında formülasyonun oldukça kararlı olduğunu göstermektedir.

Sonuç: Sistematik bir formülasyon yaklaşımı benimseyerek, sabit doz kombinasyonundaki AMB hidroklorür ve salbutamol sülfat ODT'leri, süper dağıtıcıların uygun bağlayıcı ve eksipiyanlar ile kombinasyonu kullanılarak formüle edilebilir; bunun ekonomik ve endüstriyel olarak uygulanabilir olduğu bulunmuştur.

Anahtar kelimeler: Oral dağılan tabletler, sodyum nişasta glikolat, *in vitro* dağılma süresi, ambroksol hidroklorür, salbutamol sülfat, optimizasyon çalışması

INTRODUCTION

In the late 80's, orally-disintegrating tablets (ODTs) or orodispersible tablets were developed and they were introduced to the market in early 90's. From that time, ODT dosage forms have become a well-known solution for geriatric or pediatric populations, which face difficulties in swallowing solid oral dosage forms.[1] ODTs disintegrate within a few seconds in the mouth of the patient and they are ideal for patients with dysphasia. As the saliva passes through the stomach, some 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 39˚C, simulating the temperature of the oral cavity. The others requirements with which these dose forms must comply is mechanical resistance, which is important from the handling point of view as well as for packaging and storage. ODTs must have ideal organoleptic characteristics.[3] Orodispersible tablets are applicable for people who have difficulties in swallowing and 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 dose forms are increasingly being recognized in both industry and among 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 affect 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 super disintegrants.[2] There are various technological processes such as direct compression, freeze-drying, and molding, by which orodispersible tablets can be manufactured. The best way to manufacture ODTs is direct compression because it is the right compromise among economical, manufacturing, and technological needs. To produce ODTs with satisfactory organoleptic, biopharmaceutic, and technological characteristics, it is important to select appropriate excipients that are able to produce the product with desired characteristics, efficacy, and pleasant mouth-feel.[6] In the selection of excipients, those with rapid dissolution in water, low viscosity, sweet flavor, and high compressibility are considered. Due to the pleasant taste and ability to mask other flavors, sugars are most commonly used, which dissolve quickly in saliva because they are 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. AMB hydrochloride is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as bronchial asthma and chronic bronchitis, which are characterized by the production of excess or thick mucus. AMB 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 a greater bronchodilator effect and is useful in the treatment of asthma. Salbutamol sulphate must be given three to four times daily to maintain its bronchodilation effect due to the short half-life of 4-6 hrs.[8]

Formulations of the drugs chosen in fixed-dose combinations for the treatment of sudden allergic attacks and coughing are available in the market in conventional tablet and liquid dose forms. Due to sore throat conditions, pediatric patients experience difficulty in swallowing tablet-type dose forms. Liquid dose forms have their own limitations vis-a-vis stability and dose measurement perspectives. Hence, they do not comply with the prescription, which results in a high incidence of ineffective therapy and noncompliance. Therefore, in the present study, it was proposed to formulate a fixed-dose combination of AMB hydrochloride and salbutamol sulphate ODT by using direct compression with the aim of improving/enhancing patient convenience and compliance, reducing the lag time, and providing faster onset of action to immediately relieve respiratory disorders.

MATERIALS AND METHODS

Materials

AMB hydrochloride and salbutamol sulphate, which were used as the model drugs, were obtained from Trojan Pharma, Baddi, India as gift samples. Microcrystalline cellulose (MCC) as binder/disintegrant (Avicel PH-102) was received from NB Entrepreneurs, Nagpur, India, as a gift sample. Sodium saccharin, as a sweetening agent, was obtained from Loba Chemie, Mumbai, and talc as a glidant from Nice Chemicals Private Limited, Hyderabad, India. Sodium stearyl fumarate, as a lubricant, was purchased from Himedia. Polyvinylpyrrolidone (PVP) K-30, as a binder, was obtained from Himedia. SSG, as a superdisintegrant, (Primogel) and directly compressible mannitol (D-mannitol), as a diluent, were obtained from Qualikems Fine Chem Pvt. Ltd. All chemicals and reagents used in this research were of analytical grade.

Selection and optimization of excipients (Methodology)

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

Optimization of SSG

Various concentrations (1%, 2%, 4%, 6%, 8%, and 10%) of SSG were used in the preparation of ODTs to study the effect of concentration of superdisintegrants in the evaluation of the parameters of the tablets. A total of six formulations (F1-F6) were manufactured using direct compression as given in Table 1. For each specified formulation, the required quantity of each ingredient was taken. All the ingredients were passed through a no.60 mesh and co-ground in a pestle and mortar. Finally, talc and sodium stearyl fumarate were added and mixed for 5 min. The mixed blend of excipients was compressed into tablets using an 8-mm punch in a 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. A total of 14 formulations (B1-B14) were manufactured to study the effect of the type of binder with the optimized concentration of SSG as given in Table 2. For each specified formulation, the required quantity of each ingredient was taken. All the ingredients were passed through a no.60 mesh and co-ground in a pestle and mortar. Finally, talc and sodium stearyl fumarate were added and mixed for 5 min. The mixed blend of excipients was compressed into tablets using an 8-mm punch in a multi-punch tablet compression machine (Dhiman Industries, India).

Formulation of AMB hydrochloride, salbutamol sulphate ODTs

ODTs of AMB hydrochloride and salbutamol sulphate in fixed-dose combined-form were manufactured through direct compression. The required quantity of each ingredient was taken for formulation as shown in Table 3. Accurately-weighed quantities of AMB hydrochloride and salbutamol sulphate were taken and the optimized concentration of SSG and binder with excipients were co-ground in geometric progression in a dry and clean mortar. All ingredients were passed through a no.60 mesh. Finally, sodium stearyl fumarate and talc were added and mixed for 5 min. The mixed blend of excipients was compressed into tablets using an 8-mm punch in a 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 a digital balance (Ohaus, USA). The individual weights were compared with the average weight for the determination of weight variation. To pass the weight variation test, tablets within the range of 80-250 mg should not deviate more than or less than (±7.5%) from its average weight according to Indian Pharmacopeia (IP) limits.[9]

Table 1. Formula for one tablet (200 mg) of different concentrations 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 one 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 Flavor	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: Ambroxol, HCl: Hydrochloride, SAL: Salbutamol sulphate, SSF: Sodium stearyl fumarate, SS: Sodium saccharin

Table 3. Formula of ambroxol hydrochloride and salbutamol sulphate ODT

Ingredients	Formula for one tablet (200 mg)
Ambroxol hydrochloride	7.5
Salbutamol sulphate sodium	2
Starch glycolate	8
Microcrystalline cellulose	2
Sodium stearyl fumarate	4
Talc	2
Sodium saccharin	3
Mint flavor	8
Mannitol	163.5

ODT: Orally-disintegrating tablet

Hardness

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

Thickness

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

Friability

Twenty tablets from each formulation were accurately weighed and placed in the drum of a Roche friabilator (Campbell 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). Friability is expressed in terms of weight loss and was calculated as the percentage of the initial weight according to the IP specifications; friability under 1% was considered acceptable.[12]

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

In vitro disintegration test

The DT of the tablet was measured in 900 mL of distilled water (37±2˚C) using a 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 DT calculations.[13]

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish (ID 6.5 cm) containing 6 mL of distilled water. A tablet containing a small quantity of amaranth color was placed on the paper and the time for the upper surface of the tablet to become

completely 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 AMB hydrochloride and 2 mg of salbutamol sulphate was weighed and dissolved in a suitable quantity of 6.8 pH phosphate buffers. The solution was sonicated, filtered, and suitably diluted and the drug content (%) was determined using the simultaneous equation method with a double-beam UV spectrophotometer (UV-1800 Shimadzu) at 244 nm and 276 nm wave-lengths, which correspond to AMB hydrochloride and salbutamol sulphate, respectively. Each sample was analyzed in triplicate. The tablets should comply with the IP specifications i.e. 85%-110%.[15]

In vitro drug release studies

In vitro drug release studies of all the formulations were performed using USP eight-stage dissolution testing apparatus-2 (paddle method) (Lab, India) at 50 rpm. Phosphate buffer pH 6.8 (500 mL) was used as the dissolution media with the temperature maintained at 37±0.5˚C. Five milliliter 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 perfomed in triplicate. Absorbance of these solutions was measured at their respective λ_{max}.[16] Cumulative percentage (%) drug release was calculated using the simultaneous equation method, which is given as:

At 244 nm $A_1 = 0.025_A + 0.0017_S$

At 276 nm $A_2 = 0.0030_A + 0.0066_S$

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

Drug-excipient compatibility studies

This study generally includes fourier transform infrared spectroscopy (FTIR) and these are generally performed to confirm the drug- excipients compatibility. In order to determine the compatibility between pure drugs with the excipients used in formulation, the FTIR spectra of the physical mixture of the pure drugs and optimized ODT formulation were recorded on an FTIR spectrophotometer (Bruker, USA) in the scanning range of 4000 to 600 cm^{-1} and the resolution was 1 cm^{-1}. FTIR scans were then evaluated for shifting and masking and the appearance of new peaks due to drug-excipient incompatibility.[18]

Accelerated stability studies

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

RESULTS AND DISCUSSION

Optimization of superdisintegrant SSG

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

Optimization of PVP K-30 or MCC (Avicel PH-102) along with the optimized concentration of SSG

The results for optimization of different binders in the ODTs are given in Table 5. It was observed from the evaluation parameters that the DT of formulation B8 was further decreased and friability and hardness of the tablet complied with the IP limits. The lowest DT was observed in formulation B8 i.e. 1% MCC as compared with the B2 formulation i.e. 2% PVP K-30. The probable reason was that MCC has strong binding properties alongside its good disintegration, which is 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

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) ± SD	198±2.0	202±1.0	201±2.0	198±3.0	197±2.0	201±1.0
Friability (%) ± SD	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) ± SD	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) ± SD	65±1.74	48±1.35	34±1.86	45±2.36	72±1.76	90±2.64

IP: Indian Pharmacopoeia, SD: Standard deviation, *represents the average of 3 determinations, **represents the average of 6 determinations

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

Evaluation parameters	*Weight variation (mg) ± SD	*Friability (%) ± SD	*Hardness (kg/cm^2) ± SD	**Disintegration time (s) ± SD
Formula no.				
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

SD: Standard deviation, PVP K-30: Polyvinylpyrrolidone K-30, MCC: Microcrystalline cellulose, SSG: Sodium starch glycolate, *represents the average of 3 determinations, **represents the average of 6 determinations

the intermolecular forces that restore crystal features to its original form.[21] On the other hand, water-soluble materials such as PVP K-30 dissolve faster rather disintegrate. Therefore, as the optimum binder concentration, 1% MCC was selected for the final formulation of the AMB hydrochloride and salbutamol sulphate ODT. The study concluded that optimization of the binder: superdisintegrant concentration was essential for reducing the DT of the tablets.

Evaluation parameters for AMB hydrochloride&salbutamol sulphate ODT

ODTs were prepared through direct compression and evaluated for hardness, weight variation, friability, thickness, percentage drug content uniformity, and *in vitro* DT; the results of which are shown in Table 6. The weight variation of the 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. The friability of the tablets was found below 1%, indicating a good mechanical resistance of the tablets. The *in vitro* DT of the tablets was found to be less than 60 seconds as shown. The wetting time was good in practical terms for formulation. The formulated ODTs showed low DT, indicating the suitability of the formulation for being a mouth-dissolving tablet. From the in vitro release study, it was observed that 93.23±0.25% of AMB hydrochloride released in 20 min and 89.23±1.03% of salbutamol sulphate released in 12 min, indicating that the tablet complied with IP specifications i.e. 85%-110%, as given in Figure 1.

Table 6. Evaluation parameters for ambroxol hydrochloride and salbutamol sulphate ODT

Evaluation parameters	Results
*Weight variation (mg) ± SD	201±2.0
*Thickness (mm) ± SD	3.63±0.06
*Hardness (kg/cm^2) ± SD	2.5±0.29
*Friability (%) ± SD	0.2±0.15
**Disintegration time (s) ± SD	34±1.14
*Wetting time (s) ± SD	26±1.53
*Drug content uniformity ± SD	AMB: 106.5±1.53 SAL: 93.33±2.25

SD: Standard deviation, ODT: Orally-disintegrating tablet, AMB: Ambroxol, SAL: Salbutamol sulphate, *represents the average of 3 determinations, **represents the average of 6 determinations

Drug-excipient compatibility studies

The FTIR spectra of pure drugs in combination and formulated ODT-containing drugs were obtained on an FTIR spectrophotometer. The FTIR results, as given in Figure 2 and Figure 3, indicated that there were no interaction between the drug and other excipients used in the formulation. The FTIR spectra of the physical mixture of AMB hydrochloride and salbutamol sulphate showed an 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 AMB 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 AMB hydrochloride and salbutamol sulphate ODT formulation also showed intense absorption bands at 651.32 cm^{-1}, 1611.97 cm^{-1}, and 1280.03 cm^{-1} for AMB hydrochloride and at 1389.04 cm^{-1}, 1611.97 cm^{-1}, and 1389.04 cm^{-1} for salbutamol sulphate, indicating no changes in the functional groups and confirmed the undisturbed structures of AMB hydrochloride and salbutamol sulphate, which indicated no drug-excipient incompatibility, as shown in Figures 2 and 3.

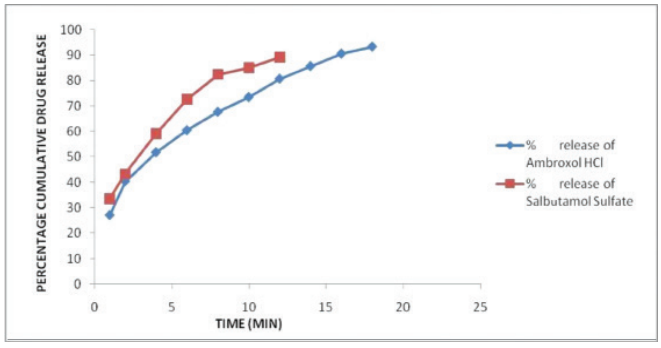

Figure 1. *In vitro* drug release profile of the ambroxol hydrochloride and salbutamol sulphate orally-disintegrating tablet

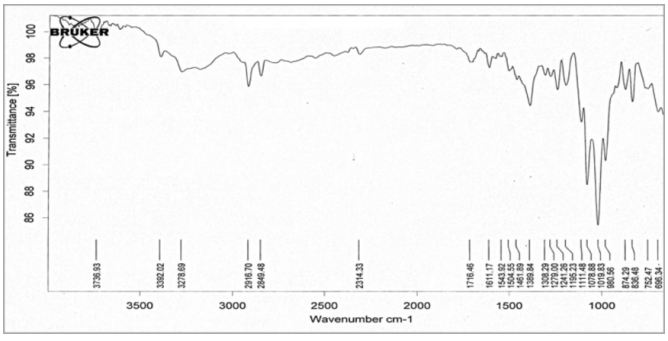

Figure 2. Fourier transform infrared spectroscopy spectra of the physical mixture of ambroxol hydrochloride, salbutamol sulphate, and blend

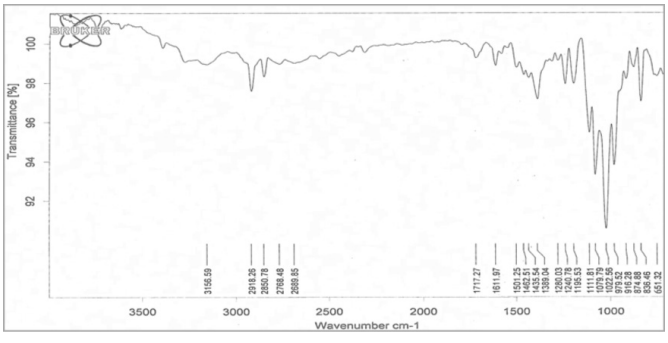

Figure 3. Fourier transform infrared spectroscopy spectra of ambroxol hydrochloride and salbutamol sulphate orally-disintegrating tablet formulation

Accelerated stability studies

Accelerated stability studies of the final optimized ODTs (prepared in three primary batches), which were wrapped in aluminium foil to simulate the Alu packing of drug products and then stored in air-tight containers impermeable to solids, liquids, and gases for a period of 1 month as prescribed by the ICH guidelines. The product was exposed to normal and extreme conditions of temperature and humidity. The stability data of the formulation are given in Table 7 and Table 8. The results of the stability study indicated that there was little difference observed in hardness, DT, drug content uniformity and friability before and after the storage period at room temperature and at ambient humidity, but at temperature of $40^0C \pm 2^0C$ and at ambient humidity. Hardness was found to be increased with time and prolonged the DT of the tablet.[22] The probable reason was loss of moisture from tablets but in all cases, DT was within the specified IP limit (within 3 min.). This indicates that the formulation was fairly stable in both storage conditions. Statistical analysis (ANOVA) was also performed using the Graph Pad in Stat 3 statistical package for Windows. The stability data shown in the tables for the three primary batches of formulations were evaluated for drug content (%), friability, hardness, and disnintegration time before and after stability testing, represented by the mean of three or six determinations ± standard deviation. The statistical significance of the differences between the evaluation parameters of three primary batches was calculated using the Tukey-Kramer multiple comparison test, and the probability value of p smaller than 0.05 indicated a statistically significant difference.

CONCLUSION

The objective of the present investigations was achieved by preparing an orally-dissolving drug delivery system of AMB hydrochloride and salbutamol sulphate in fixed-dose combination with a faster onset of action by using an optimum amount of superdisintegrant SSG and binder MCC using direct compression. The optimization methods mentioned in the report were proved useful in the development of ODTs. The ODTs developed in this work will hopefully contribute to improving 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* DT, drug content (%), and wetting time. *In vitro* dissolution results were also studied. The ODT formulation satisfied the requirements of the Food and Drug Administration for rapid-dissolving tablets and allowed more than 85% of drug to be dissolved within 30 min. The FTIR study revealed that there was no interaction between drug and excipients. The accelerated stability study showed that the formulation was 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, ODTs of AMB hydrochloride and salbutamol sulphate in fixed-dose combination can be formulated using superdisintegrants in combination with appropriate binder and excipients, which was found to be economical and industrially feasible.

Table 7. Accelerated stability data of the ambroxol hydrochloride and salbutamol sulphate ODT at temperature (40±2˚C) 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) ± SD	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 (%) ± SD	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 (%) ± SD	AMB-90.8±3.36	AMB-95.6±2.34	AMB-93.8±1.24	AMB-92.5±2.14	AMB-93.5±2.67	AMB-94.8±1.23	AMB-91.3±1.98	AMB-94.4±1.65	AMB-95.7±3.63
	SAL-104.7±1.97	SAL-95.4±2.86	SAL-97.7±3.97	SAL-103±1.76	SAL-98.6±2.07	SAL-93.4±1.77	SAL-97.8±2.97	SAL-97.7±2.75	SAL-94.2±2.43
**Disintegration time (s) ± SD	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

SD: Standard deviation, ODT: Orally-disintegrating tablet, AMB: Ambroxol, SAL: Salbutamol sulphate, *represents the average of n=3 determinations, **represents the average of n=6 determinations

Table 8. Accelerated stability data of the ambroxol hydrochloride and 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) ± SD	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 (%) ± SD	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 (%) ± SD	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) ± SD	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

SD: Standard deviation, ODT: Orally-disintegrating tablet, AMB: Ambroxol, SAL: Salbutamol sulphate, *represents the average of 3 determinations, **represents the average of 6 determinations

ACKNOWLEDGEMENTS

The authors highly acknowledge NB Entrepreneurs, Nagpur and Trojan Pharma, Baddi, India for providing gift samples of AVICEL PH-102 and drugs, and Rayat Bahra Institute of Pharmacy, Hoshiarpur Jalandhar for their efforts to facilitate the use of the necessary instruments and materials required during the entire course of this research work.

Conflict of Interest: No conflict of interest was declared by the authors.

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