RESEARCH ARTICLE

Design Development and *In Vitro* Evaluation of Novel Orally Disintegrating Tablets in Fixed-dose Combination Containing Ambroxol Hydrochloride and Cetirizine Hydrochloride Prepared by Direct Compression Technique

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Abstract

Aim: The aim of the study deals with the design development and *in vitro* evaluation of orally disintegrating tablets (ODTs) of ambroxol hydrochloride (AMB HCl) and cetirizine hydrochloride (CTZ HCl) in combination for the treatment of respiratory disorders by using superdisintegrants in combination with suitable binder and excipients. Direct compression method was used to prepare tablets. **Materials 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 ODTs. Different concentrations of microcrystalline cellulose (MCC) and polyvinylpyrrolidone 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 (DT), and % age 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 SSG was found to be 4% on the basis of least DT. MCC in 1% was selected as optimum binder concentration on the basis of least DT. ODTs passed all the quality control tests, namely, weight variation, hardness, friability, *in vitro* DT, % age drug content uniformity, 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 Fourier-transform infrared 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 AMB HCl and CTZ HCl in fixed-dose combination could be formulated using superdisintegrants in combination with appropriate binder and excipients which was found to be economical and industrially feasible.

Key words: Ambroxol hydrochloride, cetirizine hydrochloride, *in vitro* disintegration time, optimization study, orally disintegrating tablets, sodium starch glycolate

INTRODUCTION

In the late 80s, orally disintegrating tablets (ODTs) or orodispersible tablets were developed and they were introduced to the market in early 90s. From that time, ODTs dosage forms are well-known solution to geriatric or pediatric populations who have facing difficulties in swallowing solid oral dosage forms.[1] ODTs disintegrate within a few seconds in the mouth of patient and ideal for the patients suffering from dysphasia. As the saliva passes down the stomach, some of drugs are absorbed from the mouth, pharynx, and esophagus, which ultimately lead

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to an increase in bioavailability of drug.[2] According to the definition by the Royal Spanish Pharmacopoeia, these tablets should disintegrate in <3 min when tested at temperatures ranging between 35 and 39°C simulating the temperature of the oral cavity. The others requirement 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 disintegrants have been developed in more recent years, which are often called "superdisintegrants." 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 croscarmellose, crospovidone, and sodium starch glycolate (SSG), which symbolize the example of cross-linked cellulose, cross-linked polymer, and a cross-linked 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 ODTs 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 mouthfeel.[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 It is chemically described as trans-4-[(2-amino-3,5-dibromobenzyl)amino]-cyclohexanol. AMB hydrochloride (AMB HCl) is an expectorant improver and a mucolytic agent used in the treatment of respiratory disorders such as bronchial asthma and chronic bronchitis characterized by the production of excess or thick mucus. AMB HCl 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 HCl as a secretion releasing expectorant in a variety of respiratory disorders.[7] Cetirizine hydrochloride (CTZ HCl), a piperazine derivative and metabolite of hydroxyzine, is described as long-acting non-sedating antihistamine with some mast cell stabilizing activity. CTZ HCl, a human metabolite of the piperazine H1-receptor antagonist hydroxyzine, is used to treat seasonal allergic rhinitis, chronic idiopathic urticaria, perennial allergic rhinitis, and allergic asthma.[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 non-compliance. Hence, in the present study, it was proposed to formulate fixed-dose combination of AMB HCl and CTZ HCl ODTs using direct compression technique with the 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

AMB HCl and CTZ HCl used as 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 sweetening agent was obtained from Loba Chemie, Mumbai, and talc as glidant from Nice Chemicals Private Limited, Hyderabad, India. Sodium stearyl fumarate as lubricant was purchased from Himedia. Polyvinylpyrrolidone (PVP) K-30 as binder was obtained from Himedia. SSG 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 ODTs is disintegration time (DT). ODTs were prepared by direct compression technique 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 the formulation of ODTs. The combination with least DT, optimum friability, and hardness was selected for further study.

Optimization of 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. Cogrind in a pestle motor. Finally, talc and sodium stearyl fumarate were added and mixed for 5 min. The mixed blend of excipients was compressed into tablets using 8 mm 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 concentration of binder along with the optimized concentration of SSG was used to produce the tablets. Total 14 formulations (F1-F14) 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. Cogrind in a pestle motor. Finally, talc and sodium stearyl fumarate were added and mixed for 5 min. The mixed blend of excipients was compressed into tablets using 8 mm punch in multi-punch tablet compression machine (Dhiman Industries, India).

Formulation of AMB HCl and CTZ HCl ODTs

ODTs of AMB HCl and CTZ HCl 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 AMB HCl and CTZ HCl taken with optimized concentration of SSG and binder with excipients were cogrind 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 min. The mixed blend of excipients was compressed into tablets using 8 mm punch in

Table 1: Formula for 1 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
Cetirizine hydrochloride	5	5	5	5	5	5
Sodium starch glycolate	2	4	8	12	16	20
Polyvinylpyrrolidone K-30	4	4	4	4	4	4
Sodium stearyl fumarate	3	3	3	3	3	3
Talc	3	3	3	3	3	3
Sodium saccharin	5	5	5	5	5	5
Mannitol	170.5	168.5	164.5	160.5	156.5	152.5

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)	CTZ HCl (mg)	SSG (mg)	PVP K-30 (mg)	MCC (mg)	Sodium stearyl fumarate (mg)	Talc (mg)	Sodium saccharin (mg)	Mannitol (mg)
F1	7.5	5	8	2	-	2	2	5	168.5
F2	7.5	5	8	4	-	2	2	5	166.5
F3	7.5	5	8	6	-	2	2	5	164.5
F4	7.5	5	8	8	-	2	2	5	162.5
F5	7.5	5	8	10	-	2	2	5	160.5
F6	7.5	5	8	12	-	2	2	5	158.5
F7	7.5	5	8	14	-	2	2	5	156.5
F8	7.5	5	8	-	2	2	2	5	168.5
F9	7.5	5	8	-	4	2	2	5	166.5
F10	7.5	5	8	-	6	2	2	5	164.5
F11	7.5	5	8	-	8	2	2	5	162.5
F12	7.5	5	8	-	10	2	2	5	160.5
F13	7.5	5	8	-	12	2	2	5	158.5
F14	7.5	5	8	-	14	2	2	5	156.5

MCC: Microcrystalline cellulose, SSG: Sodium starch glycolate, PVP K-30: Polyvinylpyrrolidone K-30, AMB: Ambroxol hydrochloride, CTZ: Cetirizine hydrochloride

Table 3: Formula of ambroxol hydrochloride and cetirizine hydrochloride ODT

Ingredients	Formula for 1 tablet (200 mg)	Formula for 100 tablets (200 mg)
Cetirizine hydrochloride	5	500
Ambroxol hydrochloride	7.5	750
Sodium starch glycolate	8	800
Microcrystalline cellulose	2	200
Sodium stearyl fumarate	4	400
Talc	2	200
Sodium saccharin	8	800
Mint flavor	8	800
Mannitol	155.5	15550

ODT: Orally disintegrating tablet

multi-punch tablet compression machine (Dhiman Industries, India).

Evaluation parameters

Weight variation test

A total of 20 FDT tablets were selected at random from each formulation and weighed individually on digital weighing balance (Ohaus, USA). The individual weights were compared with the average weight for determination of weight variation.[9]

Hardness

Tablets require a certain amount of hardness and resistance to friability to withstand mechanical shock in manufacture, packing, and shipping. To perform these 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

A total of 20 tablets, from each formulation, were accurately weighed and placed in the drum of Roche friabilator (Campbell Electronics, Mumbai). The tablets were rotated at 25 rpm for 4 min and then removed, dedusted, and accurately reweighed (Ohaus, USA). The friability has been expressed in terms of weight loss and has been calculated in percentage of the initial weight; according to pharmacopeia specifications, friability under 1% has been considered acceptable.[12]

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

In vitro disintegration test

The DT of the tablet was measured in 900 ml of distilled water (37°C ± 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 DT calculations.[13]

Wetting time

A piece of tissue paper folded twice was placed in a small Petri dish (ID6.5 cm) containing 6 ml 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 uniformity

For the estimation of drug content, 10 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 HCl and 5 mg of CTZ HCl 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 from simultaneous equation method using double beam UV spectrophotometer (UV-1800 Shimadzu) at 244 nm and 230 nm wavelengths corresponds to AMB HCl and CTZ HCl, respectively. Each sample was analyzed in triplicate.[15]

In vitro 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 50 rpm. Phosphate buffer pH 6.8 (500 mL) was used as the dissolution media with temperature maintained at 37°C ± 0.5°C. 5 mL samples were withdrawn at different intervals, diluted suitably, and analyzed at 244 nm and 230 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 $A_1=0.025\ C_A+0.0063\ C_C$

At 230 nm $A_2=0.019\ C_A+0.0338\ C_C$

Whereas C_A - concentration of AMB HCl, C_C - concentration of CTZ HCl. By putting the values of absorbances A_1 and A_2 at their respective $\lambda_{max,}$ the concentrations of AMB HCl and CTZ HCl were obtained in sample solutions.[17]

Drug-excipient compatibility studies

This study generally includes Fourier-transform infrared (FTIR) spectroscopy and these are generally performed to confirm the drug-excipients compatibility. 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 4000–600/cm and the resolution was 1/cm. 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 aluminum foil and then stored in air-tight containers that are impermeable to solid, liquid, and gases, for 1 month as prescribed by ICH guidelines at temperature of 40°C ± 2°C and at ambient humidity as well as at room temperature. The tablets were withdrawn on 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 optimization of superdisintegrant concentration in 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 least DT 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%. DT increases above 8% 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 binder in ODTs are given in Table 5. It was observed from the evaluation parameters, the DT of the formulation F8 was further decreased and friability and hardness of tablet comply with the Indian Pharmacopoeia (IP) limits. The least DT was observed in F8 formulation, i.e. 1% MCC as compared to F2 formulation, i.e. 2% PVP K-30. The probable reason was that MCC exceptionally 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. In general, 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, 1% MCC was selected as optimum binder concentration selected for final formulation of AMB HCl and CTZ HCl ODT. The study concluded that optimization of binder: Disintegrant concentration is essential in reducing the DT of the tablets.

Evaluation parameters for AMB HCl and CTZ HCl ODT

ODTs were prepared by direct compression method evaluated for hardness, weight variation, friability, thickness, percentage drug content uniformity, and *in vitro* DT, the results of which are shown in Table 6. Weight variation of formulated batches was shown to be within the acceptable limits. The % drug content was found to be AMB: 94.09 ± 2.17%, CTZ: 89.4 ± 2.60%. The % drug content was found in the range of 85–115% of the label claim (acceptable limit). 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* DT of the tablets was found to be <60 s as shown. The wetting time was practically good for formulation. The formulated ODTs shown low DT indicating suitability of formulation for mouth dissolving tablet. From

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 (IP)	Passed	Passed	Passed	Passed	Passed	Passed
Friability (%)	0.8	0.8	0.1	0.3	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	75±1.34	50±2.62	36±2.63	43±3.54	112±2.92	90±3.79

IP: Indian Pharmacopoeia, SD: 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	Weight variation (IP)	Friability (%)	*Hardness (Kg/cm²)±SD	**Disintegration time (s)±SD
Formula No.				
F1	Passed	0.1	2.2±0.28	58±1.78
F2	Passed	0.2	1.8±0.28	42±1.67
F3	Passed	0.5	2.0±0.00	59±2.89
F4	Passed	0.3	3.2±0.76	73±2.40
F5	Passed	0.3	1.6±0.50	86±5.16
F6	Passed	0.8	2.5±0.50	105±5.77
F7	Passed	0.8	2.0±0.00	125±5.43
F8	Passed	0.1	2.5±0.50	38±2.13
F9	Passed	0.1	2.2±0.28	46±1.34
F10	Passed	0.2	2.5±0.28	57±1.10
F11	Passed	0.1	2.8±0.28	68±1.32
F12	Passed	0.1	2.5±0.28	80±2.08
F13	Passed	0.1	2.8±0.28	93±1.84
F14	Passed	0.1	2.6±0.28	103±1.73

IP: Indian Pharmacopoeia, SD: Standard deviation, MCC: Microcrystalline cellulose, PVP: Polyvinylpyrrolidone. *Represents the average of *n*=3 determinations. **Represents the average of *n*=6 determinations

Table 6: Evaluation parameters for ambroxol hydrochloride and cetirizine hydrochloride ODT

Evaluation parameters	Results
Weight variation (IP)	Passed
*Thickness (mm)±SD	3.7±0.00
*Hardness (Kg/cm²)±SD	2.5±0.29
Friability (%)	0.4
**Disintegration time (s)±SD	38±1.14
*Wetting time (s)±SD	26±2.06
*Drug content uniformity (%)±SD	AMB: 94.09±2.17, CTZ: 89.4±2.60

IP: Indian Pharmacopoeia, SD: Standard deviation, ODT: Orally disintegrating tablet, AMB HCl: Ambroxol hydrochloride, CTZ HCl: Cetirizine hydrochloride. *Represents the average of *n*=3 determinations. **Represents the average of *n*=6 determinations

the *in vitro* release study, it was observed that 89.49 ± 0.93% of AMB HCl released in 18 min and 91.16% ± 1.51% of CTZ HCl released in 16 min indicates that the tablet complies as per IP specifications, i.e. 85–110% as shown 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 shown in Figures 2 and 3, that there was no interaction between the drug and other excipients used in the formulation. FTIR spectra of physical mixture of AMB HCl and CTZ HCl are shown intense band at 695.70/cm, 1581.64/cm, and 1277.37/cm corresponding to the presence of functional groups such as aliphatic bromo compound, secondary amine, and secondary alcohol in AMB h HCl and at 756.14/cm, 1313.02/cm, 1077.32/cm, and 1182.93/cm corresponding to the presence of functional groups such as aliphatic chloro compound, carboxylic acid, alkyl substituted ether, and tertiary amine in CTZ HCl. The FTIR of AMB HCl and CTZ HCl ODT formulation is also showing intense absorption bands at 695.71/cm, 1576.69/cm, and 1282.46/cm for AMB HCl and at 752.51/cm, 1316.47/cm, 1060.47/cm, and 1189.63/cm for CTZ HCl indicates no changes in the functional groups confirmed undisturbed structure of AMB HCl and CTZ HCl, which indicates no drug-excipient incompatibility as shown in Figures 2 and 3.

Accelerated stability studies

Accelerated stability studies of final optimized ODTs (Prepared in three primary batches), which were wrapped in aluminum foil to simulate the Alu packing of drug products and then stored in air-tight containers impermeable to solid, liquid, and gases for 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 were given in Tables 7 and 8. The result of the stability study indicated that there were not much differences 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°C ± 2°C and at ambient humidity, hardness was increases with time, prolonged the DT of the tablet.[22] The probable reason was loss of moisture from tablets but in

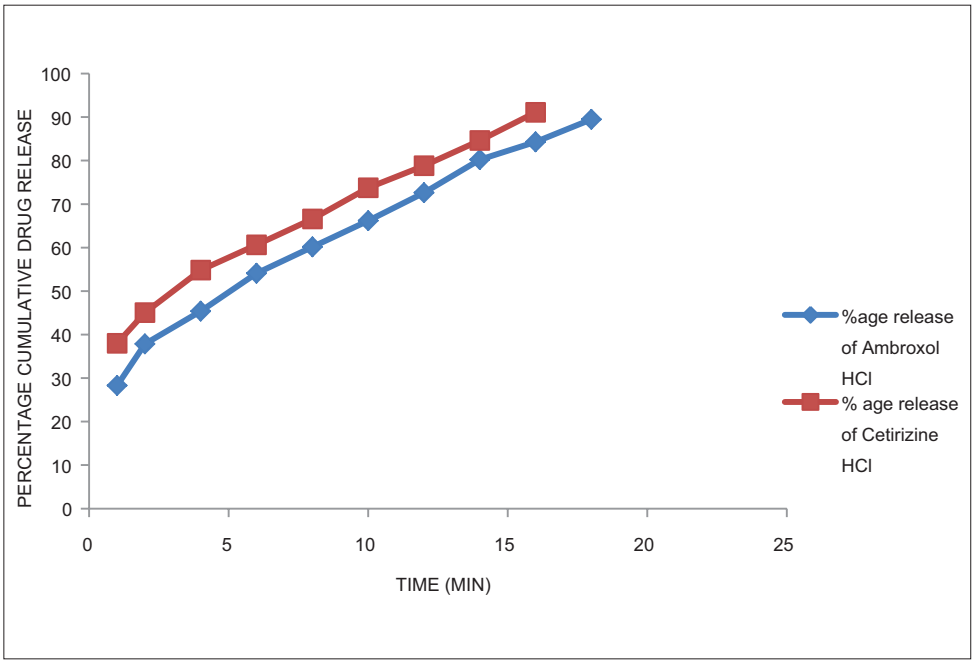

Figure 1: In vitro drug release profile of ambroxol hydrochloride, cetirizine hydrochloride orally disintegrating tablet

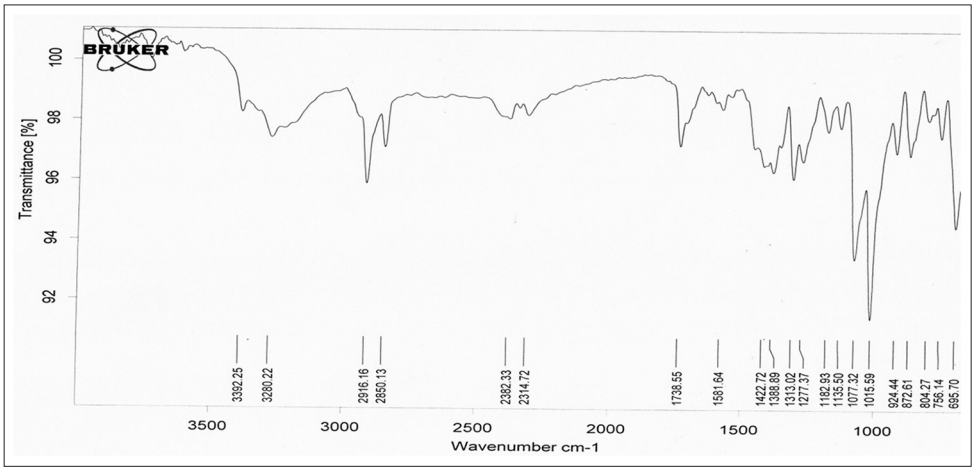

Figure 2: Fourier-transform infrared spectra of physical mixture of ambroxol hydrochloride, cetirizine hydrochloride, and blend

all cases, DT is within the specified IP limit (within 3 min). This indicates that formulation is fairly stable at both storage conditions. Statistical analysis (ANOVA) was also performed with the GraphPad InStat 3 statistical package for Windows. Stability data shown in tables for three primary batches of formulations were evaluated before and after stability testing represented mean of three or six determinations ± standard deviation. Statistical significance of the differences between the evaluation parameters of three primary batches was calculated by the Tukey-Kramer multiple comparison tests, and 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 AMB HCl and CTZ HCl in fixed-dose combination with faster and quick onset of action using an optimum amount of superdisintegrant SSG and binder MCC using direct compression technique. 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 improve drug administration to patients with swallowing and chewing difficulties. The prepared ODTs passed all the quality control tests, namely, weight variation, hardness, friability, *in vitro* DT, % age drug content uniformity, 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

Table 7: Accelerated stability data of ambroxol hydrochloride and cetirizine hydrochloride ODT at temperature (40°C±2°C) and at ambient humidity

Time interval	Three primary batches								
	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/cm²)±SD	2.7±0.29	2.5±0.00	2.5±0.00	2.7±0.29	2.7±0.29	2.8±0.29	2.8±0.29	2.8±0.29	3±0.00
Friability (%)	0.2	0.3	0.2	0.5	0.4	0.3	0.3	0.2	0.3
*Drug content uniformity (%)±SD	AMB - 90.8±3.36, CTZ - 104.7±1.97	AMB - 95.6±2.34, CTZ - 95.4±2.86	AMB - 93.8±1.24, CTZ - 97.7±3.97	AMB - 92.5±2.14, CTZ - 103±1.76	AMB - 93.5±2.67, CTZ - 98.6±2.07	AMB - 94.8±1.23, CTZ - 93.4±1.77	AMB - 91.3±1.98, CTZ - 97.8±2.97	AMB - 94.4±1.65, CTZ - 97.7±2.75	AMB - 95.7±3.63, CTZ - 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, AMB HCl: Ambroxol hydrochloride, CTZ HCl: Cetirizine hydrochloride. *Represents the average of *n*=3 determinations. **Represents the average of *n*=6 determinations

Table 8: Accelerated stability data of AMB and CTZ ODT at room temperature and at ambient humidity

Time interval	Three primary batches								
	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/cm²)±SD	1.7±0.29	1.5±0.00	1.5±0.00	1.7±0.29	1.3±0.29	1.5±0.00	1.5±0.00	1.5±0.29	1.3±0.29
Friability (%)	0.2	0.3	0.2	0.3	0.3	0.3	0.3	0.4	0.5
*Drug content uniformity (%)±SD	AMB - 90.8±3.36, CTZ - 104.7±1.97	AMB - 95.6±2.34, CTZ - 95.4±2.86	AMB - 93.8±1.24, CTZ - 97.7±3.97	AMB - 96.8±4.23, CTZ - 100.3±4.13	AMB - 94.5±3.78, CTZ - 93.6±3.45	AMB - 96.8±2.31, CTZ - 98.4±2.54	AMB - 95.6±3.21, CTZ - 99.3±3.35	AMB - 94.4±3.14, CTZ - 92.7±1.42	AMB - 95.7±4.34, CTZ - 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, AMB HCl: Ambroxol hydrochloride, CTZ HCl: Cetirizine hydrochloride. *Represents the average of *n*=3 determinations. **Represents the average of *n*=6 determinations

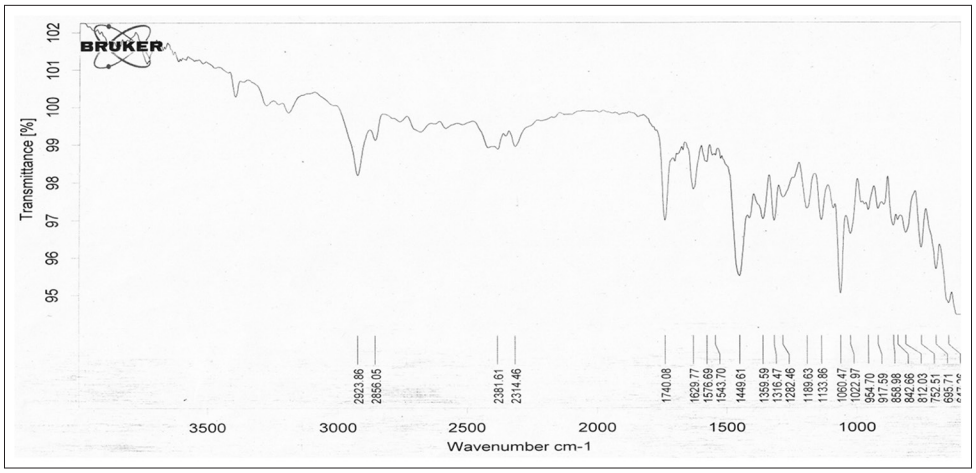

Figure 3: Fourier-transform infrared spectra of ambroxol hydrochloride, cetirizine hydrochloride orally disintegrating tablet formulation

as at extreme temperature and humidity conditions. Thus, it is concluded that by adopting a systematic formulation approach, ODT of AMB HCl and CTZ HCl in fixed-dose combination could be formulated using superdisintegrants in combination with appropriate binder and excipients which was found to be economical and industrially feasible.

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