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Preparation and characterization of Oro-dispersible tablets of Bromhexine hydrochloride

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Abstract:

Background: The oral route is a widely accepted route for drug administration but having a common difficulty in swallowing tablets and capsules, could limit its application. Therefore, new dosage forms were developed such as oro-dispersible tablets. The dispersible systems could be defined as systems that dissolve or disintegrate within seconds to a few minutes following their placement in the mouth. Methods: In the present work, oro-dispersible tablets of bromhexine hydrochloride were prepared by direct compression method. Two different super disintegrants were used: croscarmellose sodium and banana powder. Results: Four formulations with different super disintegrants concentrations were prepared. The prepared oro-dispersible tablets were evaluated for weight variation, hardness, wetting time, disintegration time and *in vitro* dissolution time. Conclusion: It could be concluded that formulations containing croscarmellose (Formula 1 and 2) had the lowest wetting and disintegration times and the highest percentage of drug release. On the other hand, banana containing formulations (Formula 3 and 4) required longer times to wet and disintegrate and had the lowest percentage of bromhexine release.

Keywords: Oro-dispersible tablet, bromhexine HCl, Dosage form, Drug administration.

INTRODUCTION

The most important method for drug administration for systemic effects is the oral route as it is probable that at least 90% of all drugs used to produce systemic effects are administered by oral route [(1)].Tablets are the most widely used dosage form due to their convenience in terms of self-administration, ease in manufacturing and low cost [(2)]. Tablets have many advantages like that they have the least content variability, light weight, yet most compact, easy and cheape to package, product identification is potentially the simplest, not need for additional processing steps, can be made in special release profile products such as enteric coated or sustained –release products and have the best combined properties of chemical, mechanical and microbiological stability of all oral dosage forms [(1).]

Oro-dispersible tablets are solid unit dosage forms as conventional tablets, but they contain super disintegrants, which allow them to dissolve the tablets within a minute in the mouth in the presence of saliva without any difficulty of swallowing. It has many advantages with respect to its stability, administration without water, accurate dosing, easy manufacturing, small packaging size and handling [(2)].

On the other hand, bromhexine hydrochloride is an oral mucolytic agent useful for treatment of respiratory disorders that are associated with viscous or excessive mucus production (Ref). It is very slightly soluble in water and exhibits slow dissolution properties. The rate of absorption and bioavailability for such an insoluble hydrophobic drug are controlled by the rate of dissolution in gastrointestinal fluids. Therefore, it is important to enhance its solubility and dissolution to improve its bioavailability [(3)].

The objective of this study was to formulate an orally disintegrating tablet of bromhexine hydrochloride that dissolves in the mouth within seconds without water with the employment of a natural super disintegrating agent.

MATERIALS AND METHODS

Bromhexine (BHX) was supplied by Samara Drug Industry, Croscarmellose sodium (CCS) was purchased from Hangzhou Hyper Chemical Limited, China. All other chemicals and solvents were of analytical reagent grade. Also, deionized water was used in this study.

1. Formulation of Bromhexine HCl Oro-dispersible Tablets (ODTs)

Four formulas of BHX ODTs were prepared with different super disintegrant quantities. All formulas were prepared using direct compression technique. Each formula was formulated by mixing all the ingredients (except the lubricant **Magnesium stearate**) for 15 min after which the lubricant was added and blended for another 3 min. The final mixture was compressed using a single punch machine. Table 1 presents the quantities of materials used in preparing the four BHX formulas.

Table 1: Composition of bromhexine HCl oro-dispersible formulas.

Material (mg)	Formulas			
	F1	**F2**	**F3**	**F4**
Bromhexine HCl	8	8	8	8
Croscarmellose sodium	5(2.5%)	10(5%)	-	-
Banana powder	-	-	10(5%)	20**(10%)**
Saccharin sodium	4(2%)	4(2%)	4(2%)	4(2%)
Magnesium stearate	2(1%)	2(1%)	2(1%)	2(1%)
Mannitol	181	176	176	166
Total weight (mg)	200	200	200	200

2. Characterization of Bromhexine HCl

2.1. Determination of Melting Point of Bromhexine HCl

The melting point of BHX was measured using DSC apparatus. Differential scanning calorimetry was performed using Shimadzu DSC-60 machine. A five-mg sample was weighed and placed in a standard aluminum pan and sealed using a manual crimper. The sample was held isothermally for 2 min at 50 ºC, heated from 50 ºC to 300 ºC at 20 ºC/min and held isothermally for 2 min at 300 ºC. Then the sample was cooled from 300 ºC to 50 ºC at 20 ºC/min cooling rate.

2.2. Determination of λ_{max} of Bromhexine HCl

A solution of 15 mg/100 mL of BHX in methanolic (3%) 0.1N HCl (pH = 1.2) was papered and scanned by a UV spectrophotometer from (200-400) nm and the λ_{max} was determined[(4)].

2.3. Determination of Calibration Curve of Bromhexine HCl solutions:

Calibration curve of BHX in methanolic (3%) 0.1N HCl (pH= 1.2) was constructed by preparing serial dilutions of the drug (20, 40, 80, 120, 160 and 200) µg/mL from a stock solution of 15 mg/100 mL. Samples were analyzed spectrophotometrically at the detected λ_{max} of BHX. The determined absorbance was recorded and plotted versus concentration (µg/mL) [(4)].

2.4. Compatibility Study

Before formulation of BHX as ODT, chemical stability of the proposed formulations was characterized. Hence, Shimadzu FTIR spectrometer was utilized to study the possibility of any chemical interaction between BHX and the excipients. The materials alone and the formulations were mixed with dry powdered potassium bromide. A diffuse reflectance sampler was used to take the

mixtures and the spectra were recorded by scanning in the wavelength region (400-4000 cm^{-1}).
The IR spectrum of the drug was compared with that of the mixture of drug and excipients to investigate for any drug-excipients interaction.

3. Evaluation of the Prepared Bromhexine HCl Oro-dispersible Tablets

3.1. Weight Variation

Weight variation was determined for the prepared ODTs of BHX according to the British Pharmacopoeia (BP). Twenty tablets were weighed individually and the mean (±SD) weight was calculated [4].

3.2. Hardness

Three oro-dispersible tablets were selected randomly from each formulation and their hardness (kg) was tested using Erweka hardness tester. Results are expressed as a mean (±S.D) [5].

3.3. Wetting Time

A conventional method was used to measure wetting time of all the prepared oro-dispersible formulations of BHX. Each tablet was placed in a Petri dish (5.5 cm in diameter) containing six ml of distilled water at room temperature and the time in sec for complete wetting was recorded. The measurements were repeated three times and the mean (±SD) value was calculated [6].

3.4. Disintegration Test

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test was carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 cm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 mL of 0.1N HCl which is maintained at 37±2 ºC. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30 seconds.In this study the disintegration test was determined by using acidic media (pH= 1.2) [4].

3.5. Dissolution Test

The paddle apparatus was used to determine the release profile of the drug from the prepared bromhexine oro-dispersible tablets. The test was carried out in 900 ml of 0.1N HCl (pH= 1.2) at 37 ± 0.5°C with constant stirring speed of 50 r.p.m for 30 min. A 5-ml samples were withdrawn at (1, 2, 5, 10, 15, 20, 25 and 30) min using a syringe with a microfilter (0.45 µm pore size). The withdrawn amount was replaced by 5 ml of fresh dissolution media. Samples were analyzed spectrophotometrically at the λmax of bromhexine. Dissolution percentages of the prepared formulations and the profiles of drug release of all the formulas within time (min) are reported [7].

Statistical Analysis

Statistical analysis was performed to determine the correlation between wetting and disintegration times of the prepared formulas. Additionally, the correlation between proportion of drug release from the prepared bromhexine HCl oro-dispersible tablet formulas and time (min), was determined**.** Both analyses were determined at 95% confidence interval using Graph Pad Prism 7 Demo program.

RESULTS

1. Characterization of Bromhexine HCl

1.1. Determination of Melting Point of Bromhexine HCl

The melting point of BHX powder was 233.57 ºC (Figure 2) which is within the reported range of 232-235) ºC [3].

1.2. Determination of λ_{max} of Bromhexine HCl

The UV scan of BHX in 0.1N methanolic HCl (pH= 1.2) showed a peak at 245 nm which was regarded as the λ_{max} (Figure 3).

1.3. Determination of Calibration Curve of Bromhexine HCl solutions

A straight line with a high regression coefficient (R^2 = 0.997) was obtained by plotting the absorbance (nm) versus the concentration (µg\mL) (Figure 4).

1.4. Compatibility Study

Table 2 documents the reported peaks of BHX from published literature [27]. Figures 5, 6 and 7 show the identified peaks of BHX and prepared BHX formulas of current study.

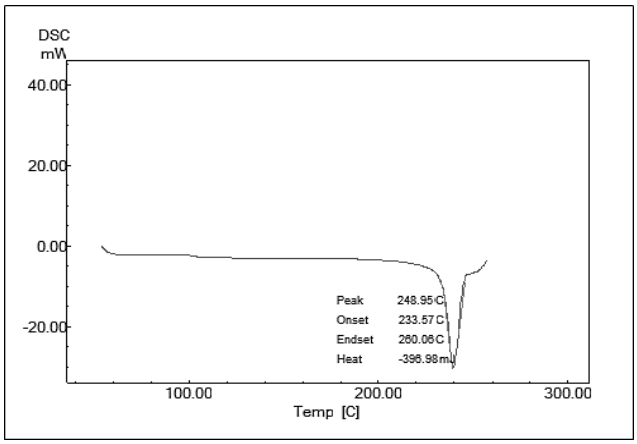

Figure 2: Melting point of bromhexine HCl measured by DCS apparatus

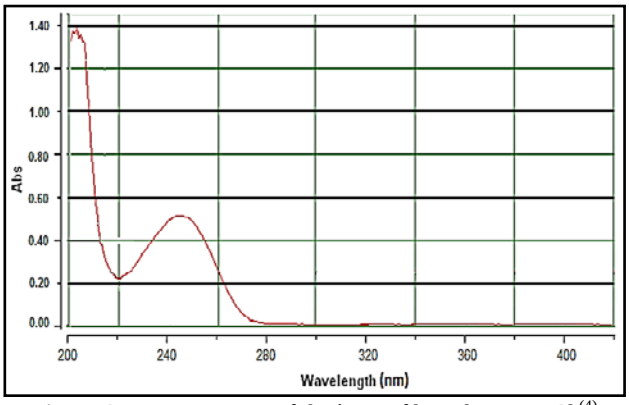

Figure 3: Determination of the λ_{max} of bromhexine HCl [4]

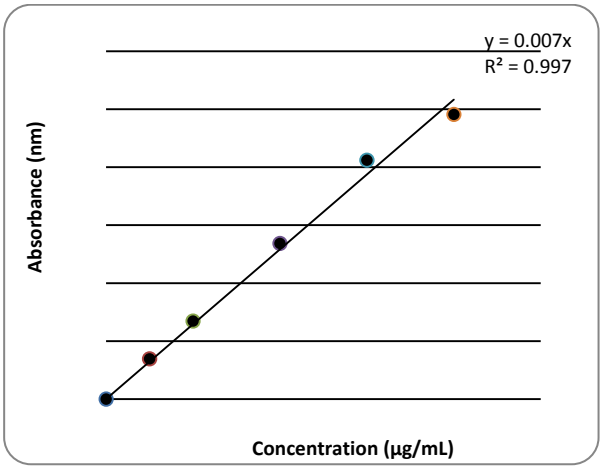

Figure 4: Calibration curve of bromhexine HCl in methanolic HCl (pH= 1.2) at 245 nm

.

Table 2: FTIR measurements of pure BHX and prepared BHX formulas [27]

Reported Peaks (cm^{-1})	Functional Group Assignment
3441.51	N−H stretching of primary amine
3201.78, 3232.20 and 3301.55	aromatic stretching of C−H
2933.24	alkyl stretching of $-CH_3$
1634.36	N−H bending vibration of primary amine
1453.03	C−C scissoring
1350–1250	aromatic C−N stretching
690.29	C−Br stretching

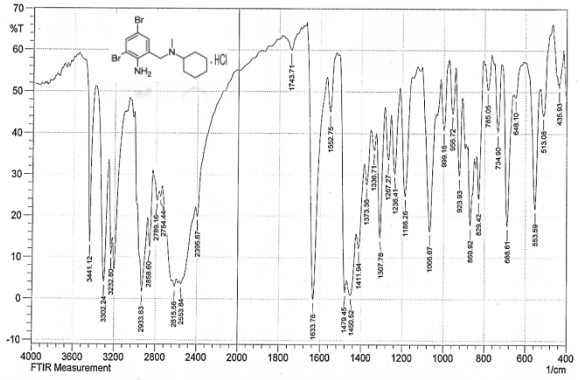

Figure 5: FTIR measurement of pure bromhexine HCl powder

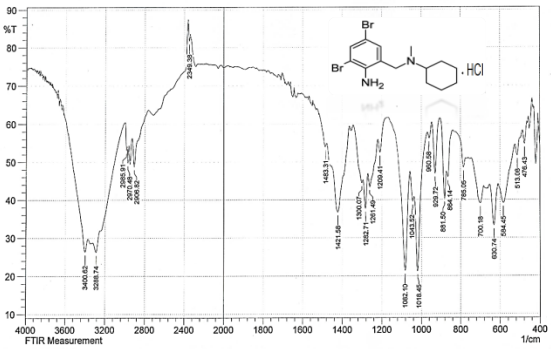

Figure 6: FTIR scan of Formula1 within wavelength region (400-4000 cm^{-1})

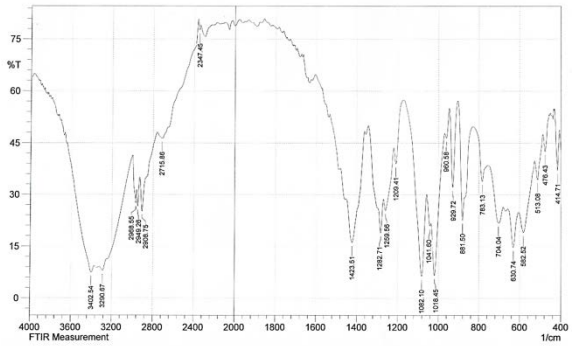

Figure 7: FTIR scan of Formula 3 within wavelength region (400-4000 cm^{-1})

2. Evaluation of the prepared bromhexine HCl oro-dispersible tablets

2.1. Weight variation

Table 3 shows the average weight (±SD) of the BHX ODTs. The measured weights complied with the BP criteria.

2.2. Hardness

The hardness of the prepared ODTs was kept near 3.5 kg (Table 3).

2.3. Wetting Time

Wetting times in seconds (mean±SD) of the prepared BHX ODT formulations are presented in Table 3. Figure 8 shows a completely wetted tablet.

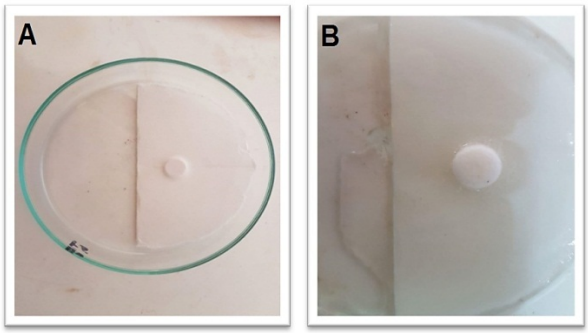

Figure 8: Wetting test of bromhexine HCl ODT. **(A)** Resembles an ODT of BHX from F1 (a tablet was placed in a Petri dish contained a folded filter paper and filled with 6 mL distilled water). **(B)** Resembles a completely wetted ODT of BHX from F1 (a complete wetting was achieved after 52 seconds).

3. *In vitro* Disintegration Test

The reported disintegration times (sec) of bromhexine hydrochloride ODTs are showen in Table 3.

Table 3: The results for weight variation, hardness, wetting and disintegration times of oro-dispersible tablets of bromhexine HCl.

Formula	Weight Variation (mg)*	Hardness (kg)**	Wetting Time (sec)**	Disintegration Time (sec)***
F1	197±2.2	3.8±0.5	52±0.3	20±3.2
F2	197±3.4	3.5±0.2	51±0.2	20±2.5
F3	196±2.8	3.6±0.2	123±1.2	250±4.6
F4	198±3.5	3.9±0.1	155±2.3	290±5.1

Values represent mean±SD.
* (n=20), ** (n=3), *** (n=6), where n is number of samples.

4. Correlation between Wetting and Disintegration Times

There was strong positive correlation between the two variables (r= 0.990) as shown in Figure 9.

5. *In Vitro* Dissolution Test

The results of the dissolution test for 30 minutes of BHX formulations which was assigned as percentage of drug release within unit time (min) are presented in Table 4. In addition, the release profile of the prepared formulas are shown in Figure 10.

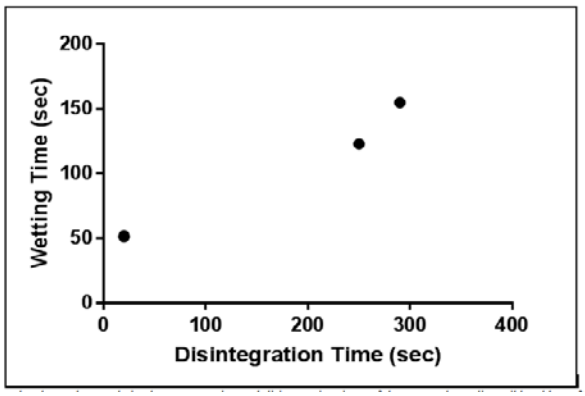

Figure 9: A scatter plot shows the correlation between wetting and disintegration times of the prepared oro-dispersible tablets of bromhexine HCl.

Table 4: Dissolution study of bromhexine HCl ODT formulations in 0.1N HCl expressed as percentage of drug release for 30 min

Time (min)	% drug release			
	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
1	44.8	40.50	24.54	30.64
2	45.9	42.10	24.98	31.77
5	46.4	43.75	26.79	32.86
10	47.3	48.39	36.96	43.57
15	47.5	48.75	38.71	44.29
20	48.75	48.75	38.96	44.46
25	49.6	48.93	47.50	45.00
30	49.62	49.28	47.89	45.89

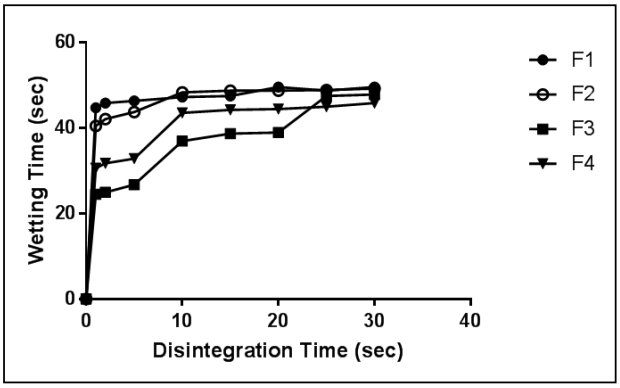

Figure 10: Dissolution test (% drug release within time) for F1, F2, F3 and F4 of bromhexine hydrochloride ODTs.

DISCUSSION:

In present study, bromhexine HCl which is an example of Class II drugs was selected to be formulated as an oro-dispersible tablet [8]. ODTs could be prepared for insoluble drugs if their dose is lower than 400 mg. Hence, materials were selected of analytical grade to be of high purity for analytical study and reduce the effect of impurities on BHX solubility. CCS and banana powder were the selected disintegrating agents. The low effect of Magnesium stearate (Mg St) on tablet hardness and disintegration had made it the optimal lubricant to be used [9]. Saccharin was added as a sweetener. Mannitol was selected as a diluent due to its cooling effect on the mouth and its free flow ability. Unlike other dosage forms, the excipients for oro-dispersible tablets should be selected carefully. The solubility of the tablet matrix can significantly affect the effectiveness of super disintegrants in promoting tablet disintegration. Using water-soluble excipients decreases the efficiency of super disintegrants. Tablets composed primarily of water-soluble components often tend to dissolve rather than disintegrate resulting in a much longer disintegration time. As the soluble materials dissolve on the surface of the tablet, the rate of water penetration into the tablet core decreases because of the formation of concentrated viscous layer. On the other hand, water-soluble excipients are essential for the formulation of oro-dispersible tablets. Salts, sweeteners and water penetration enhancers are examples of such materials. Therefore, it is important to keep a balance between these opposite requirements [10].

The purity of BHX was confirmed by its measured melting point which was 233.57 C. Since BHX exhibits polymorphism character, melting point determination using the capillary tube method was challenging [11]. Therefore, DSC was employed to measure the melting point of bromhexine. In addition to melting point, the λ_{max} of BHX was referred to characterize the powder. Figure 3 showed the UV scan of BHX in 0.1N methanolic (3%) HCl (pH= 1.2). Beer-Lambert's law was obeyed since a straight line was obtained by plotting absorbance versus concentration during determination of the calibration curve of BHX (Figure 4). Four formulas were proposed and their chemical stability was confirmed by FTIR study where the appearance of new peaks or shifting of BHX peaks was absent as shown in Figures 5-7. Oro-dispersible tablets of bromhexine were prepared by direct compression method as it is regarded the simplest and most economic technique for tablets production [12]. Tablets are compressed individually using constant compression force. Hence, post-compression physical parameters had fulfilled the stated values for an accepted oro-dispersible tablet.

It could be demonstrated from Table 6 that F2 (which contains 5% CCS) had the shortest wetting and disintegration times while F4 (which contains 10% of banana powder) had the longest times. However, there was a strong positive correlation between wetting and disintegration times (r= 0.9901; Figure 9). It was also noted that there was direct relationship between the increment in percentage of banana powder in the formulas and their wetting and disintegration times. This finding could be attributed to the fact that banana could work as a binder and a disintegrating agent since it has a starch nature [1]. When comparing the dissolution profiles of BHX ODT formulations in Table 4, it could be noticed that after 1 min of the dissolution test, F3 and F4 (which contained banana powder as a super disintegrating agent) had the lowest percentage of drug release. Additionally, the lowest values for percentage release were produced at the end of the proposed study period. It was determined that the type and amount of super disintegrant had significant effect on wetting and disintegration times. Nevertheless, the percentage of drug release from F3 and F4 could be comparable with those of F1 and F2 (Figure 10).

CONCLUSION:

In current study, bromhexine oro-dispersible tablets were prepared by incorporating croscarmellose sodium as a super disintegrating agent. Also, it could be concluded that formulations containing croscarmellose (F1 and F2) had the lowest wetting and disintegration times and the highest percentages of drug release profiles. On the other hand, banana containing formulations (F3 and F4) required longer times to wet and disintegrate and had the lowest percentages of bromhexine release.

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