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Original Article

Formulation and Evaluation of Oro-dispersible Bromhexine Hydrochloride Granules Using Sachelac-80

Anita P Ayre*, Shilpa A Gajbhiye

Department of Quality Assurance, Vivekanand Education Society's College of Pharmacy, Mumbai, Maharashtra, INDIA.

ABSTRACT

Background: Patients with sudden episodes of allergic or epileptic attacks and those who are mentally ill are less non-compliant and there is a lack of effective therapy. The need for delivering therapy at a very fast pace is the primary objective. Though oral medications exist for such patients these have their own disadvantages. **Methods:** Wet granulation method was used for preparation of Orodispersible (ORD) granules using Pearlitol 200 SD and Sachelac 80. Water soluble Bromhexine HCl granules were prepared by incorporating suitable surfactants, binder, to some extent co-surfactant and oils as well, so as to increase its bioavailability. The prepared granules were characterized by standard methods. **Results:** FTIR studies show drug- excipient compatibility. Formulation F1 shows superior results than other batches. Drug content of 97.5 %, with excellent flow properties and drug release of 102.3 % was observed for F1. A temperature of 40 ± 2°C and relative humidity of 75 ± 5% RH, was found to be most stable for F1 formulation as it indicated there were no significant changes in any of the parameters mainly in drug content. Similarly, FTIR study suggests compatibility as there are no interaction between any of the excipients as well active ingredient. **Conclusion:** This study showed that the method used for preparation resulted in pharmaceutical preparation that had fast onset of action, enhanced bioavailability, compliance in patients, enhanced stability and was cost effective.

Keywords: Granules, Bromhexine Hydrochloride, Sachelac 80, Surfactant, Solubility and Bioavailability.

Correspondence
Dr. Anita P Ayre
Department of Quality Assurance, Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai 400 074, Maharashtra, INDIA.
Email id: anita.ayre@ves.ac.in

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INTRODUCTION

The success in designing novel drug delivery systems like orodispersible granules remains to be influential for the rapidly growing Pharma sector due to its easy handling and ready use for consumption. Orodispersible granules due to their uniform dosage distribution and painless delivery are one of the most preferred dosage forms.[1] Understanding how these novel formulations are being used for administration to pediatrics, geriatric, bedridden patients, physically disabled, mentally sick patients has been an important area of research.[2] Patients who suffer from motion-sickness and sudden episodes of allergic or epileptic attacks are on rise. In such patients due to non-compliance and lack of effective therapy the need for medication that could be delivered easily has been a top priority.[3] In order to help such patients and to ensure a smooth and fast delivery of drug a solid dosage form that has the tendency to disintegrate fast or quickly dissolve in mouth when taken orally without water was developed.[4] However, these developed solid dosage forms had disadvantages such as slow absorption followed by slow onset of action. The issue could be counteracted by development of oral dispersible form that would provide instant effect.[5] The orodispersible dosage form such as granules are somewhat novel dosage techniques that entail rapid disintegration absorption and quick onset of action when placed in mouth due to saliva.[6] These granules are subjected to fast disintegration on oral administration within 30 to 50 sec of being in contact with salivary secretions in mouth.[7] As these granules are absorbed from the mouth, they enter in the pharynx and reach the esophagus due to salivary movement and finally enter in the stomach.[8] To achieve the desired effect the active ingredient is absorbed through epithelial cells of the gastrointestinal tract.[9] Due to the rapid dissolution of the ingredient in mouth followed by fast movement into the gastrointestinal tract there is significantly higher bioavailability of the active ingredient. Orodispersible granules offer superior properties over conventional oral drugs with respect to uniform particle size of granules, pleasant taste, excellent flow property, good wetting, high drug content and more stability than powders.[10] Bromhexine hydrochloride (BHX) is routinely uses as expectorant. Bromhexine is used to treat chronic bronchitis. Oral administration of Bromhexine has shown that the peak serum concentration is attained in almost 1 hr. The drug is metabolized by the liver and is excreted in urine as

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Table 1: Composition of orodispersible Bromhexine HCl Granules.

Ingredients	F1	F2	F3	F4
Bromhexine HCl	4 mg	4 mg	4 mg	4 mg
PVP K-30	2 mg	2.5 mg	3 mg	3.5 mg
Pearlitol 200 SD	25 mg	30 mg	35 mg	30 mg
Citric acid	12 mg	10 mg	13 mg	14 mg
Menthol	5 mg	7 mg	5 mg	7 mg
Tween 80	0.15%w/v	0.15%w/v	0.15%w/v	0.15%w/v
Propylene glycol	2.5%	2.0%	2.5%	2.0%
Iso-propyl alcohol	1.5 ml	2 ml	1 ml	1.5 ml

a primary metabolite. Bromhexine has a half-life of 6.5 hrs. post which it is eliminated from the body. It is used to treat mild-to-moderate type of kerato-conjunctivitis sicca generally associated with Sjogren's syndrome.[11]

Bromhexine HCl has poor solubility in aqueous systems and displays no amphiphilic character.[12] The poor aqueous solubility limits its absorbance and thus bio-availability. Thus, solubility is the rate limiting step in bioavailability of Bromhexine. Moreover, conventional tablets, capsules and suspensions are available in market as mucolytic or expectorant but its main advantage is easy consumption with smaller oral dose. In suspension, Bromhexine particles undergo rapid degradation as they are sensitive to light.[13] The present study is aimed at synthesizing orodispersable granules of Bromhexine hydrochloride which could be easily disintegrate in mouth and have excellent drug release *in vitro.*

MATERIALS AND METHODS

Bromhexine HCl was a kind gift from Kwality Pharma, Amritsar. Sachelac 80 was procured from Anshul Life Sciences, Mumbai, and Pearlitol 200 SD was received from Signet Chemical Corporation Pvt. Ltd, Mumbai. Mannitol was purchased from commercial sources. PVP K-30 used as a binder was procured from commercial sources. Citric Acid, Menthol, Tween 80, Propylene glycol used for the experiment were lab grade whereas Isopropyl alcohol used was analytical grade.[7]

Preparation of granules

Wet granulation method

The method involved mixing Bromhexine HCl powder with liquid solution in presence or absence of binder to form a wet mass. The adhesive forces help in formation of granules rather than compaction. Agglomerates are further formed during the drying process due to strong permanent bonds established between the molecules.[14,15] The granule preparation involved distinct steps such as dispensing, sifting, mixing, granulation and drying. In step 1 the required quantity of Bromhexine HCl, Citric Acid, Sachelac 80, Pearlitol 200 SD, Menthol, Propylene Glycol, Tween 80, PVP K-30 and Iso-Propyl alcohol were weighed accurately for the granulation process. Weighted quantities of Bromhexine HCl, Pearlitol, PVP K-30, Sachelac 80, Menthol were passed through sieve # 40 or sieve # 60 to ensure proper mixing of the powder in the sifting step. Dry mixing process was followed for proper mixing of the samples. Once the mixing is completed the granulation fluid is added to the powder mixture in a rapid mixer granulator (RMG). Granulation was achieved by adding PVK-30 dissolved in IPA. The solution was stirred constantly so as to ensure proper mixing. The speed of the impeller was optimized between 70-150 rpm for 10 to 15 min for dry mixing, then binder addition and kneading. The mass was unloaded in oscillating granulator with sieve of #16. Following granulation, the granules were dried at ambient temperature of 40°C for 24 hrs and were passed through sieve# 16 or sieve# 20.

Once the granules were synthesized the moisture content of granules was estimated. Loss on drying method was used to check moisture content. It must be in the range of 3-5 % w/w. Dry screening was performed by passing through sieve 12# and then again through sieve 20#. Oversize granules were collected and packed in a well tight and light resistant sachets which are well labeled.

Four different formulations of Orodispersible Bromhexine HCl granules were prepared.

A summary of composition of granules of four different formulations is presented in Table 1.

Evaluation of the orodispersible granules:

Flow properties of the Bromhexine HCl granule.

Bulk density (BD) and Tapped density (TD)

Evaluation of flow properties of granules was done by estimating the bulk and tapped density. Adequate amount of granules were weighed and the bulk density (BD) as well as tapped density (TD) were measured using 100ml measuring cylinder. Volume obtained initially was considered as the initial volume of the granules. The cylinder was tapped from a height of 2.5 cm and again tapping is repeated after a few intervals till no change in volume was seen in the measuring cylinder. Accordingly, the tapped density and the bulk density were calculated.[16]

$$\text{Bulk density (BD)} = \frac{\text{Weight of Granules}}{\text{Bulk Volume}}$$

$$\text{Tapped density (TD)} = \frac{\text{Weight of Granules}}{\text{Tapped volume}}$$

Carr's index (CI)

Carr's index of orodispersible granules was calculated by using the bulk density and tapped density. The sample granules Carr's index values were compared with that of reference sample.[17]

$$\text{Carr's index (CI)} = \frac{(TD - BD)}{TD} \times 100$$

Hausner's ratio (H)

Hausner's ratio (H) is used to determine the flowability of a powder or granules. The flow property of orodispersible Bromhexine HCl granules was determined with the help of below mentioned equation. Hausner's ratio with > 1.25 value signifies good powder flow.[1] Hausner's ratios between values 1.25 to 1.6 signifies moderate powder flow whereas value < and 1.6 are mostly cohesive powders.[18]

$$\text{Hausner' ratio (H)} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose (ɵ)

Angle of repose (ɵ) was determined with the help of funnel method. Granules were poured from a particular height into the funnel placed on a tripod stand arranged horizontally.[11] The granules flow and form a cone-like shape. The mean diameter was calculated to get angle of repose using equation.[19]

$$\text{Tan}(\theta) = \frac{H}{0.5 * D}$$

Particle size analysis (PSD)

The particle-size distribution (PSD)[15] of granular material can be determined by using ASTM sieve shaker. The average size of the particle was estimated by this method.[20]

Drug content

10 mg equivalent of Bromhexine HCl Granules were weighted and dissolved in 10 ml of methanol.[18] The solution was filtered using Whatman filter paper to filter sample solutions. The solution was further diluted using methanol and the dilute samples were estimated spectrophotometrically at 211 nm using suitable blank.[21]

Drug release

The drug release of Bromhexine granules was estimated using USP paddle apparatus. The release was measured by stirring granules in 900 ml of 6.8 pH buffer solution at 37±0.5°C and at a speed of 75 rpm. 5 ml of aliquot was withdrawn at regular intervals, filtered, suitably diluted and absorbance of this solution was noted. The concentration of drug and hence the amount released at each time point was determined using linear regression analysis.[8]

Stability studies[2]

Accelerated stability test was done using the ICH guidelines.

RESULTS

Excipient Compatibility Studies

FTIR spectroscopy was used to perform drug-excipient compatibility studies. Characteristic IR bands of the drug were observed both in physical blend as well as formulation. Thus, the stability of the drug in the formulation was demonstrated. The IR spectra of pure compound and the granules is shown in Figure 1 and 2.

Flow parameters of synthesized granules

In the present work, novel orodispersible Bromhexine HCl granules were formulated and evaluated. The formulation utilized

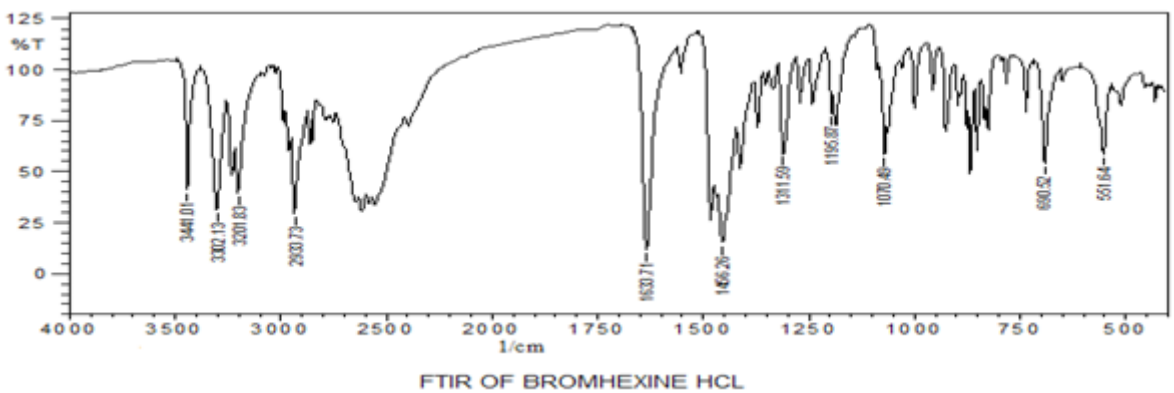

Figure 1 FTIR of Bromhexine HCl.

Table 2: Flow parameters of orodispersible Bromhexine HCl Granules.

Formulations	Formulation 1	Formulation 2	Formulation 3	Formulation 4
Bulk Density (g/cm^3)	0.422	0.479	0.440	0.444
Tapped Density(g/cm^3)	0.534	0.587	0.559	0.556
Angle Of Repose	23.11	29.67	25.19	26.30
Carr's Index	10	15	12	20
Haussner's Ratio	1.01	1.12	1.22	1.35

Table 3: Physical parameters optimization.

Formulation	Taste	Water Solubility	Flow of Granules
F1	Good	Clear	Excellent
F2	Good	Turbid	Good
F3	Good	Turbid	Poor
F4	Good	Clear	Good

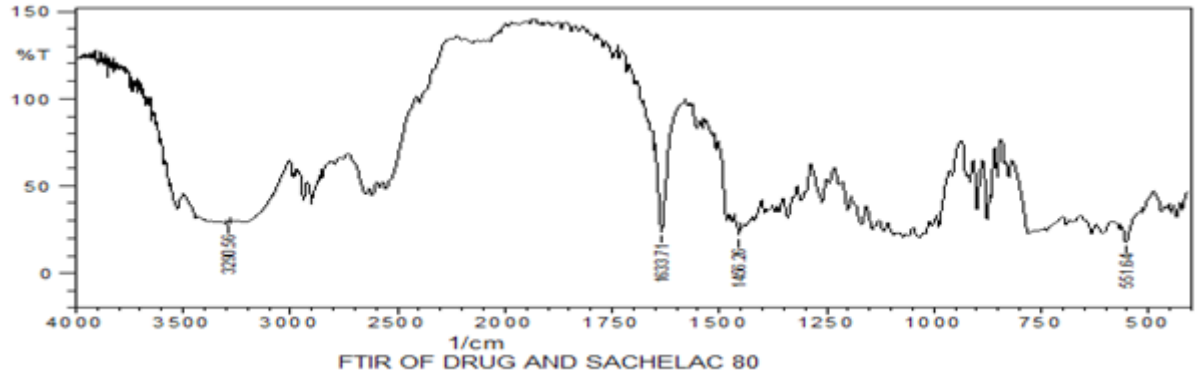

Figure 2: FTIR of Bromhexine HCl and Sachelac 80.

Figure 3: Orodispersible Bromhexine HCl granules.

natural binders such as PVP K-30 for granular formation. Sachelac 80 was used to enhance the flow property of the granules. Different formulations were tried which resulted in improved drug release characteristics and excellent flow of granules. The prime objective of the study was to enhance drug release rate and stability, thereby imparting a good taste to the granules by masking the bitter taste of Bromhexine HCl with mannitol. Different formulations exhibited different flow properties. The summary of various properties of the different formulations is presented in Table 2. The results reveals that of the various formulations F1 to F4, formulation F1 shows excellent flow property, excellent angle of repose, car's index and Hausner's ratio.

Physical parameters

A summary of the various parameters is presented in Table 3. Based on various physical parameters it was concluded that formulation 1 was found to best as per observation and

Table 4: Stability study was physically determined for an optimized batch.

Formulation	Time	2-8°C	40°C/75 RH	25°C	RT
F1	Initial	✓	✓	✓	✓
	15 Days	✓	✓	✓	✓
	1 Month	✓	✓	✓	✓

Stable - ✓ Unstable - X

Table 5: Particle Size analysis of granules.

Formulation	Time	2-8°C (d.nm)	40°C/75%RH (d.nm)	25°C/60%RH (d.nm)	R.T (d.nm)
F1	0 (initial)	268.9	248.4	243.4	257.4
	1 Month	271.2	248.7	246.9	267.6
F2	0 (initial)	323.1	302.8	312.5	310.4
	1 Month	331.2	303.7	315.3	310.9
F3	0 (initial)	295.4	285.6	286.3	2.74.6
	1 Month	305.2	395.8	292.5	272.5
F4	0 (initial)	254.9	264.3	224.6	254.3
	1 Month	266.4	268.4	226.1	294.5

Table 6: *In vitro* evaluation tests – drug content and drug release.

Formulation	Drug content (% w/w)	Drug release (%)
F1	97.5±0.11	102.3%
F2	87.3±0.11	100.7%
F3	79.1±0.11	86.54%
F4	90.5±0.11	83.11%

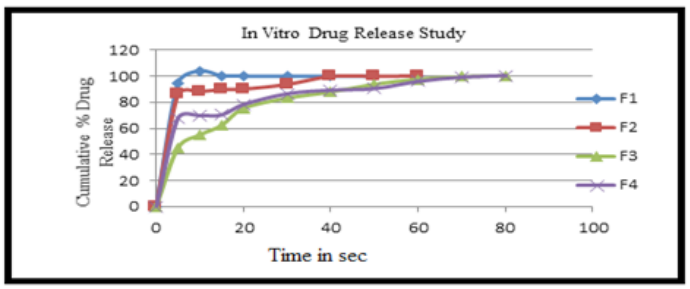

Figure 4: Drug release of orodispersible Bromhexine granules.

compliance. The Formulation F1 shows good solubility in water with a cool pleasant taste of menthol and good flow properties. The appearance of the formulations is shown in Figure 3.

Stability study

The stability study of the formulations was done at different temperatures and relative humidity for over a month. The study observed all the formulations are stable at variable temperatures and relative humidity. A summary of observations is presented in Table 4.

Particle size analysis

Particle size analysis of granules was done at different temperatures and relative humidity. The various formulations were tested for accelerated stability by incubating them at 25°C/60%RH for 1 month. The summary of the size analysis of various formulations is shown in Table 5. The results of the study show that all the four formulations had good stability even after 1 month of storage. The size of granules is smaller at 25°C/60%RH and 40°C/75%RH when compared to 2-8°C

Drug content and drug release studies

Drug release and drug content of various formulations was estimated. A summary of the same is presented in Table 6 and Figure 4. Of the four formulations tested drug content of the optimized batch that is formulation F1 was found to be 97.5 % (w/w) and drug release of the formulation F1 was 102.3%.

DISCUSSION

The oral route is one of the most important routes for drug administration. In most of the cases oral drugs are manufactured as tablets. Tablets are easy to make, have a low cost of manufacture and are self-administered. Most of the oral dosage forms have limitations associated with their disintegration time which affects their bio availability. Enteric coated or sustained release forms have been developed which resist chemical, mechanical and microbiological degradation resulting in exceptionally stable oral dosage forms. In order to overcome the problems associated with traditional oral dosage forms orodispersible tablets have been developed.[22]

Oral fast disintegrating tablets or films are one of the novel developments in the field of pharmaceutical industry. They have improved acceptance and patient compliance which makes them suitable to be used by any age group patients. Oral disintegrating films are available for hypertension, acidity, allergy and pain. Oral disintegrating formulations typically contain the active ingredient, hydrophilic polymer, plasticizer and color, filler, flavor. There are several classes of drugs such as antihistamines, anti-asthmatics, vasodilators and antidiarrheals whose orodispersible formulations are made.[23] Orodispersible tablets are synthesized to help patients for rapid delivery of drugs. Oral drugs which have fast disintegration help in delivery of active ingredients even in absence of water. Fast disintegrating tablets are solid unit dosage forms that dissolve in seconds. They have been designed to help pediatric and geriartic populations. Drugs belonging to Class II as per Biopharmaceutical classification system serve as perfect molecules for fast disintegration synthesis. These molecules which include Bromhexine hydrochloride have extremely low solubility and high permeability. These tablets are synthesized using super disintegrants which help in rapid dissolution. The super disintegrants include classes of PEG's, Tween and PVP.[24]

Bromhexine hydrochloride is an oral mucolytic agent. Due to its low solubility in water increasing its solubility would help in enhancing the bioavailability of the drug. Orodispersible tablets of Bromhexine hydrochloride have been prepared and shown to have excellent dissolution in saliva in seconds. Croscarmellose sodium and banana powder were used as superdisintegrants while formulating the tablet. Comparison of Croscarmellose sodium and banana powder showed that Croscarmellose sodium helped in wetting of tablets in minimal time and maximum drug release was observed. Thus, Croscarmellose sodium is a novel agent for preparation of orodispersible tablets.[25] In the present study orodispersible Bromhexine hydrochloride was prepared using PVP-30, Pearlitol 230 SD AND Sachelac 80. The present study showed excellent synthesis of Bromhexine hydrochloride orodispersible sachet granules which had superior properties and thus serves as a pharmaceutical agent for further evaluation in humans.

CONCLUSION

In the present study four different orodispersible formulations of Bromhexine hydrochloride were prepared by Wet granulation methods. Formulation 1 was found to have superior properties in terms of drug release, stability and physical parameters. Thus, the present study was successful in synthesizing sachet granules of the active ingredient. The dissolution property of BXH has been improved by preparing granules of it with sachelac-80 resulting in granules with excellent flow property. There are several salient features of synthesized sachet granules in the present study. The features include accurate dosing, fast onset of action, enhanced bioavailability, compliance in patients, relative ease of administration, enhanced stability, improved palatability, cost effective and simple packaging. The technology used was versatile and easy to use for synthesis of sachet granules. The method developed could further be utilized for large scale synthesis of the granules of the active ingredient. The sachet granules of the active ingredient are extremely useful and could be validated further for its application as a novel pharmaceutical agent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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