International Journal for Pharmaceutical Research Scholars (IJPRS)

V-5, I-2, 2016 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Formulation and Evaluation of Orodispersible Films of Bromhexine HCl – A Patient Friendly Approach

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Manuscript No: IJPRS/V5/I2/00061, Received On: 15/04/2016, Accepted On: 22/04/2016

ABSTRACT

The present investigation was carried out with the objective of formulating orodispersible forms of the mucolytic drug, Bromhexine HCl to enhance convenience and compliance to the elderly and paediatric patients for better therapeutic efficacy. Orodispersible films of Bromhexine HCl were prepared by solvent evaporation technique. Formulation studies were carried out using different polymer combinations, the obtained films were evaluated for their appearance, color, elegance, continuity, texture, presence of air bubbles, stickiness to Petri dish, cracks, cuttings, and imperfections. Alginate and HPMC based films recorded the fastest disintegration when used alone and in mixtures with PVP-K25 and maltodextrin. Xanthan gum film had the longest disintegration time. Moreover, adding xanthan gum, Na CMC, and carbopol prolonged the disintegration time of HPMC and alginate films. A good correlation existed between the calculated dissolution rate of each film and its disintegration time. Formulas F1and F7 showed the highest resistance against moisture absorption and recoded tensile strength values of 15.47 and 17.16 kg/mm^2, respectively after storage. Films based on HPMC alone or in combination with other polymers exhibited high resistance against moisture absorption except with Na CMC. Alginate and xanthan gum based films had a higher affinity for moisture absorption. The addition of maltodextrin significantly decreased the percentage moisture absorption after storage at 97% relative humidity. This effect was concentration-dependent. Thus disintegration time of film was 25 s, drug content 92.4 % and drug release was 96.3 %. The developed formulation was found to be stable under the conditions tested.

KEYWORDS

Bromhexine HCl, Orodispersible Film, Oral Drug Delivery, Solvent Casting

INTRODUCTION

Among the various routes of drug administration, oral route is most common and convenient for patient use. Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets/ capsules to orally disintegrating tablets to wafer to the recent development of orodispersible films (ODFs).[1] ODFs are prepared by using hydrophilic polymers that rapidly dissolves on the tongue or in the buccal cavity. Drug is incorporated into these hydrophilic polymers with the help of other suitable excipients.[2]

Being a non-invasive system, ODFs have become an important technology for the administration of drugs that are likely to degrade in the gastrointestinal tract.[3] Using ODFs, drugs can be

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directly absorbed avoiding first-hepatic metabolism and stomach's acidic environment. Consequently, efficacy and safety profile of the drug can be enhanced and bioavailability can be improved.[4] Paediatric, geriatric and psychotic patients experience difficulties in swallowing traditional oral dosage forms. Hence ODFs are a good alternative for them as well as bedridden, patients with persistent nausea; patients suffering from dysphasia, Parkinson's disease and motion sickness.[5-7] Furthermore, ODFs are devoid of friability problems associated with orodispersible tablets.[8]

Bromhexine hydrochloride, *N*-(2-Amino-3, 5-dibromobenzyl)-*N*-methylcyclohexanamine hydrochloride, [9] is a mucolytic expectorant which exhibits its action by increasing the production of serous mucus in the respiratory tract and makes the phlegm thinner and less viscous. It is used in the treatment of bronchopulmonary diseases associated with abnormal mucus secretion and impaired mucus transport. Bromhexine hydrochloride is rapidly absorbed from the gastrointestinal tract but it has a limited oral bioavailability of 20% as it undergoes extensive first-pass metabolism in the liver. The marketed formulations available for the drug are tablets and oral solution. No orodispersible formulation of bromhexine hydrochloride is reported in the literature. Hence the aim of the present work was to formulate orodispersible films of bromhexine hydrochloride which will release the drug rapidly resulting in quick onset of action, relief from congestion due to clearance of mucus in the airways and improved bioavailability.[9,10,11]

MATERIAL AND METHODS

Bromhexine hydrochloride was obtained as a gift sample from Kwality Pharma, Amritsar, India. Citric acid, gaur gum, menthol, sodium carboxymethyl cellulose, propylene glycol, polyvinyl pyrrolidone K-25, sodium alginate and xanthan gum were purchased from S.D. Fine Chemicals, Mumbai, Carbopol 974 P was kindly gifted by Lubrizol, Mumbai, hydroxypropyl methyl cellulose E-5 was purchased from Nikita Chemicals, Nagpur, chitosan was gifted by Indian Sea Foods, Cochin, maltodextrin was gifted by Sigma Alrich, Mumbai, Pearlitol 200 SD was procured from Signet Chemical Pvt. Ltd., Mumbai. All other chemicals and solvents used in the research work were of AR grade. Doubled distilled water used for analysis purpose was generated in house using steam distillation unit.

Preparation of Placebo Films of Bromhexine HCl

The films were prepared by solvent evaporation method. Placebo films were formulated using different polymers like HPMC E-5, maltodextrin, Na. CMC, xanthan gum, carbopol 974 P, PVP-K-25, sodium alginate, gaur gum and chitosan in various combination and concentration. The formulation trials for the blank films are given in Table 1. Based on the preliminary studies combinations suitable for the formulation of orodispersible films of bromhexine hydrochloride were selected.

Table 1: Formulation trials for placebo films

Form^{n} Code	Film Forming Polymer	Plasticizer: water ratio
F1	5 % HPMC: maltodextrin (1:1)	1:19
F2	3.75 % HPMC: Na.CMC (2:1)	1:19
F3	3.125 % HPMC: xanthan gum (4:1)	1:19
F4	3.125 % HPMC: carbopol (4:1)	1:19
F5	3.75 % HPMC: PVP-K-25 (2:1)	1:19
F6	3.125 % HPMC: sodium alginate (4:1)	1:19
F7	5 % HPMC: sodium alginate: maltodextrin (2:1:1)	1:19
F8	3.75 % HPMC: guar gum (2:1)	1:19
F9	3.125 % HPMC: chitosan (4:1)	1:19

Preparation of Orodispersible Films of Bromhexine HCl

Solvent evaporation technique was used for the preparation of orodispersible films.[12] 47.1 mg of drug was dissolved in 5 ml of 95% ethanol and 9 mg of menthol was added to it to get solution A. Likewise, 100 mg of sodium alginate was dissolved in 15 ml of hot water followed by simultaneous addition of 100 mg of maltodextrin, 200 mg of HPMC - E5 and 6 mg of Pearlitol® 200 to get solution B. Both the solutions were mixed together along with the addition of 100 mg of citric acid and 0.3 ml of propylene glycol. The resulting solution was stirred for 30 min using a magnetic stirrer to obtain a homogenous solution. The solution was allowed to stand for 30 min to remove air bubbles. The solution was then cast into a petri plate having an area of 80cm^2 and 1.5 cm wall height. The petri plate was kept in a hot air oven for 8 h at 50ºC. After drying, films were removed with the help of sharp blade and kept in desiccators for 24 h. The films were cut into small pieces having an area of 3cm^2 each. Films with cuts, imperfection or air bubbles were excluded from the study.

Evaluation of Orodispersible Films

Surface Texture and Physical Appearance

The physical appearance and surface texture of the films were checked by visual inspection and feel/touch respectively.[13]

Surface pH

The films were allowed to swell in 10ml of phosphate buffer, pH 6.8 at room temperature for 30 min. The pH of the film was measured by placing the electrode in contact with the surface of the oral film.[14]

Percentage Moisture Absorption

The films were weighed and placed in a desiccator containing 100 ml of saturated solution of aluminium chloride. A relative humidity of 75 ± 5% was maintained. After three days, the films were reweighed and the percentage moisture absorption was calculated using the formula:

%Moisture absorption = [(Final weight-Initial weight)/Initial weight] x 100.[15]

Disintegration Time

Disintegration time is defined as the time at which a film starts to breaks when brought in contact with water or saliva. It provides an indication about the disintegration and dissolution characterization of the film. It is usually recorded in seconds.[16]

Uniformity of Weight

The films were weighed individually using electronic balance and average weight was calculated.[17]

Uniformity of Thickness

The thickness was measured at three different locations of the films using screw gauge with a least count of 0.01mm and the average value was determined.[18]

Uniformity of Drug Content

A film of size 4 cm^2 was cut and dissolved in 50ml of phosphate buffer having pH 6.8. From the resulting solution 1ml was diluted further to 10ml with buffer and the absorbance was measured at 221nm.[19]

Tensile Strength

The tensile strength of the film was measured using a texture analyser. The film was held between two clamps 8 mm apart. The film was pulled by the clamp at a rate of 4 mm / min. Tensile strength was calculated using the formula:

Tensile strength = Force at break/initial cross-sectional area of film in mm^2.[20]

Percentage Elongation

Elongation is defined as the deformation of the film divided by its original dimension. Percentage elongation was calculated using the formula:

Percentage elongation = (Increase in length /original length) x 100.[21]

Folding Endurance

Folding endurance of the film was determined by repeatedly folding one film at the same place till it breaks. The number of times of film could be folded at the same place without breaking was noted.[22]

In vitro Drug Release Studies

In vitro drug release studies were carried out using basket type USP dissolution test apparatus containing 900 ml of phosphate buffer, pH 6.8 as the dissolution medium. The medium was maintained at a temperature of 37±0.5 ºC and stirred at a rate of 50 rpm. Aliquots of 5 ml were withdrawn at time intervals of every 30 s and replaced with equal volumes of fresh dissolution medium. The aliquots were analyzed at 221 nm using UV-vis spectrometer and % cumulative drug release at various time intervals were calculated.[23]

Stability Studies

Three batches of the optimized formulation of films were evaluated for stability at two storage conditions-2-8^{0}C (45% RH) and 25-30^{0}C (75 % RH) for a period of six months. The stability batches were evaluated for physical changes, disintegration time, and drug content and % cumulative drug release.

RESULTS AND DISCUSSION

Formulation of Orodispersible Films

The results for formulation trials of placebo orodispersible films revealed that xanthan gum gave acceptable but less elegant films, whereas guar gum, carbopol 947 P, Na CMC, PEG 4000, PVP K-25, PVA, and maltodextrin failed to form films when used separately at any of the tested concentrations. The above results suggested the use of the polymers in combination for formulating ODFs. Polymer combinations of HPMC/xanthan gum, HPMC/PVP, HPMC/Na CMC, HPMC/maltodextrin, Na alginate/xanthan gum, Na alginate/carbopol 947 P and HPMC/ maltodextrin/Na alginate formed successful films and were considered for further evaluations. Propylene glycol was more efficient as a plasticizer than sorbitol in obtaining acceptable film properties probably due to its more negative heat of solution and less hygroscopicity as compared to sorbitol. Such a negative heat of solution is expected to give more cooling sensation in the mouth hence propylene glycol was used in all films.

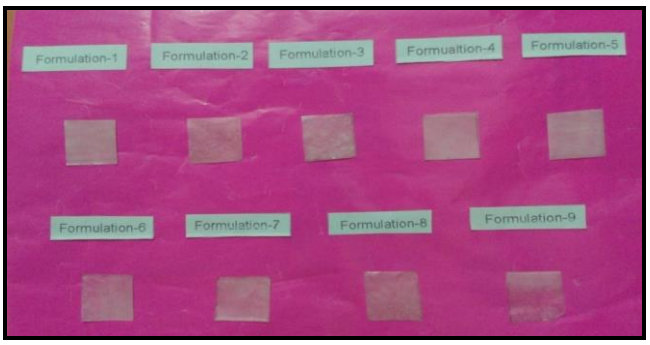

Figure: 1 depicts the images of orodispersible films formulated using different polymer combinations

Evaluation of Orodispersible Films

The results for evaluation of various parameters of the formulated ODFs are summarized in Table: 2, Table: 3, Table: 4 and Table: 5.

The time required for complete film disintegration was related to the polymer type rather than total polymer concentration, tensile strength or plasticizer amount. Alginate and HPMC-based films recorded the fastest disintegration when used alone and in mixtures with PVP-K25 and maltodextrin. Results showed that Formulation F7 forms smooth, thin and transparent film wherein HPMC E5, Na alginate and maltodextrin were used in a ratio of 2:1:1. The films of F7 were free from air bubbles, cuttings, or cracks and could be easily removed from the petri dishes.

Figure: 2 shows the *in vitro* drug release profile of formulations- F1 to F9. As seen from the graphs, all films released more than 60% of the drug in 180 sec (3 min). This prompt release can be attributed to the presence of sodium alginate and maltodextrin which acts as a superdisintegrant. Film formulas could be arranged according to their dissolution efficiency values as F7 > F9 > F6 > F5 > F4 > F8 > F1 > F3 >F2. The drug release was found to be highest for F7.

Table 2: Physical evaluation of Bromhexine HCl ODFs

Formulation Code	Physical Appearance	Surface Texture	Uniformity of Weight* (mg)	Surface pH	Thickness* (mm)
F1	Transparent	Smooth	33.1 ± 0.072	6.57	0.0124 ± 0.003
F2	Transparent	Smooth	46.2 ± 0.057	6.81	0.163 ± 0.004
F3	Transparent	Smooth	57.1 ± 0.173	6.15	0.178 ± 0.004
F4	Transparent	Smooth	62.4 ± 0.11	6.76	0.253 ± 0.003
F5	Transparent	Smooth	37.2 ± 0.028	6.52	0.124 ± 0.003
F6	Transparent	Smooth	49.4 ± 0.112	6.80	0.238 ± 0.004
F7	Transparent	Smooth	60.1 ± 0.129	6.53	0.245 ± 0.005
F8	Transparent	Smooth	67.1 ± 0.086	6.56	0.292 ± 0.001
F9	Transparent	Smooth	55.2 ± 0.072	6.59	0.206 ± 0.001

* Mean ± SD, n = 3

Table 3: Physicochemical evaluation of Bromhexine HCl ODFs

Formulation Code	% moisture loss	% moisture absorption	Disintegration time* (s)	Drug content* (%)
F1	1.12	3.11	51 ± 0.23	82.7 ± 0.027
F2	2.62	2.14	48 ± 0.31	88.72 ± 0.023
F3	1.33	3.54	39 ± 0.22	90.34 ± 0.058
F4	2.11	3.12	29 ± 0.35	89.04 ± 0.031
F5	1.43	4.23	33 ± 0.45	86.45 ± 0.022
F6	1.97	3.28	24 ± 0.52	91.08 ± 0.026
F7	1.21	2.94	25 ± 0.11	92.4 ± 0.07
F8	2.34	4.82	32 ± 0.49	86.12 ± 0.011
F9	2.10	3.11	41 ± 0.34	89.43 ± 0.014

* Mean ± SD, n = 3

Table 4: Mechanical evaluation of Bromhexione HCl ODFs

Formulation Code	Folding Endurance*	Tensile Strength* (Kg/cm^2)	Percentage Elongation*
F1	255 ± 3	15.47 ± 0.034	22.5 ± 6
F2	253 ± 4	10.58 ± 0.018	22.7 ± 4
F3	286 ± 3	6.28 ± 0.073	24.6 ± 7
F4	254 ± 6	8.13 ± 0.054	28.6 ± 3
F5	275 ± 5	4.11 ± 0.067	23.6 ± 5
F6	277 ± 7	11.45 ± 0.098	25.3 ± 7
F7	289 ± 2	17.16 ± 0.034	28.6 ± 6
F8	262 ± 4	12.22 ± 0.0133	35.0 ± 2
F9	297 ± 6	10.78 ± 0.0.065	24.4 ± 9

* Mean ± SD, n = 3

Table 5: *In vitro* drug release studies of Bromhexine HCl ODFs

Time (s)	Cumulative Drug Release Profile								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
30	39.233	43.631	39.774	32.597	51.232	55.259	56.112	42.731	55.713
60	42.512	49.227	46.721	44.125	59.791	64.331	64.781	54.293	60.638
90	53.113	56.291	48.33	55.637	68.773	73.652	76.192	66.555	74.638
120	66.272	59.421	59.296	67.717	76.799	78.223	88.714	74.258	84.694
150	76.513	62.594	67.953	73.757	80.742	80.961	91.334	79.796	89.792
180	82.115	73.277	75.775	89.776	93.252	95.235	96.300	86.545	95.535

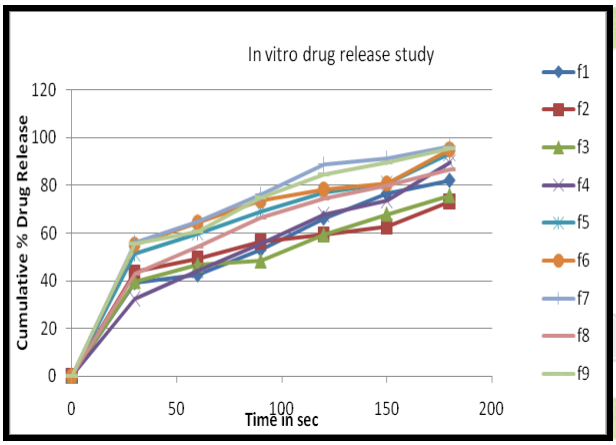

Figure 2: *In vitro* drug release profile of formulations – F1 to F9

Thus, it was found that bromhexine HCl orodispersible film were successfully prepared from HPMC E5, sodium alginate and maltodextrin with less disintegration time and high dissolution rate and drug content. Hence from the results obtained formulation- F7 was selected as the optimized batch and it was evaluated for stability studies.

Results for evaluation of stability studies revealed that all the three batches of formulation-F7 were found to be physically and chemically stable as they showed no significant change in terms of physical characteristics and drug content at lower temperature and at room temperature (Table: 6).

However, when stored at 45-50^{0}C for 45 days, films became brittle. The *in vitro* drug release profile of all the stability batches is shown in Figure: 3.

Table 6: Stability data for three batches of optimized formulation - F7

No. of days	**Disinteg-ration time*(s)**	**Drug content* (%)**	**% drug release***
0	26 ± 2	94.15 ± 1.56	96.84 ± 2.94
10	25 ± 3	93.48 ± 2.04	96.3 ± 2.14
20	25 ± 2	92.69 ± 1.48	96.39 ± 1.69
35	26 ± 4	94.34 ± 1.03	96.29 ± 2.05
45	26 ± 3	93.27 ± 2.29	96.20 ± 2.67

* Mean ± SD, n = 3

As shown in the graph, it was observed that the drug does not show any sign of deterioration during the period of stability. So it was concluded that orodispersible films of optimized formulation – F7 were stable under the conditions tested.

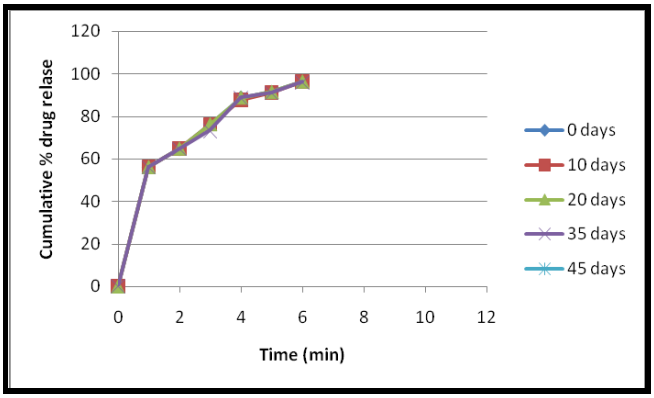

Figure: 3 *In vitro* drug release profile of stability batches

CONCLUSION

The present investigation was carried out with the objective of formulating orodispersible films of the mucolytic drug, Bromhexine HCl (BXH) to enhance convenience and compliance to the elderly and paediatric patients for better therapeutic efficacy. The results obtained revealed that the disintegration time and in vitro drug release from the optimized formulation was within the acceptance criteria. The optimized formulation was found to be stable under the conditions tested. However, further work needs to be done to evaluate the in vitro- in vivo correlation of the formulation with respect to pre-clinical and clinical evaluation.

ACKNOWLEDGEMENT

The authors would like to thank Dr. Paraag Gide, principal, Dr. L. H. Hiranandani College of Pharmacy and the HSNC Board, Mumbai for their constant support and motivation.

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