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Formulation and Evaluation of Mouth Dissolving Film of Betahistine Dihydrochloride

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ABSTRACT:

Betahistine is anti vertigo drug; mainly used in vertigo associated with M`enie`re's disease. It is vestibular disorder. Main symptoms associated with this disease are spontaneous violent vertigo, fluctuating hear loss, ear fullness, tinnitus, nausea, and vomiting. All above mentioned symptoms requires quick relief so, for this MDF is most suitable which give quick action. Main objective of the study was to formulate film having least disintegration time so give quick drug release which leads to faster onset of action and Formulate film having better mechanical strength. Here HPMC E15 and PVA film forming polymers were used in combination. They are used in different amounts.PG was used as plasticizer. Mouth dissolving films were formulated by solvent casting method and evaluated for its Appearance, folding endurance, tensile strength, disintegration time, in vitro drug release, taste evaluation, %drug content. Formulation F4 (15mg HPMC + 3mg PVA) was optimized on the basis of tensile strength, disintegration time and in vitro drug release.

KEY WORDS: Betahistine dihydrochloride, Mouth dissolving film, Mechanical properties and Disintegration time.

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INTRODUCTION:

Mouth dissolving film is a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dissolving or oral fast-dispersing dosage form.[1]It is prepared by the use of hydrophilic polymers that quickly dissolve/disintegrate in the mouth within few seconds of administration without water and also eliminates the fear of chocking as an substitute to fast dissolving tablets.[2]

Betahistine is anti vertigo drug; mainly used in vertigo associated with M`enie`re's disease. M`enie`re's disease is vestibular disorder. Main symptoms associated with this disease are spontaneous violent vertigo, fluctuating hear loss, ear fullness, tinnitus, nausea, and vomiting. It gives relief of symptoms within 3 hours after dosing. Also it has an advantage of no sedative effect compared to other anti vertigo drugs. All above mentioned symptoms requires quick relief. So, the dosage form with faster onset of action is needed so, the objective of this research was to formulate film having low disintegration time and better mechanical strength that

eventually gives faster onset of action. Thus, MDF was most suitable dosage form for Betahistine.[3,4,5]

MATERIALS AND METHOD:

Betahistine Dihydrochloride (API), Gift sample from Intas pharma; HPMCE15(film forming polymer), Balaji Drugs; PVA(Film forming Polymer),Propylene Glycol (plasticizer) ,Mannitol(sweetening agent) ,ACS chemicals; Citric acid(saliva stimulating agent); Tween 80(surfactant) ,Astron Chemicals India.

METHOD OF PREPARATION:

Mouth dissolving films were prepared by using solvent casting method. The required quantity of film forming polymer was allowed to hydrate in a minimum quantity of distilled water for 1-2 hours. Then it uniformly dispersed to get clear viscous solution of film forming polymer. Then after the required quantity of plasticizer was added to polymer solution (Solution 1).

All other ingredients including drug were dissolved in separate beaker in minimum quantity of water (Solution 2).

Solution 2 is added into solution 1with constant stirring to form clear viscous aqueous solution containing homogeneously dispersed drug (Solution 3).

The above formed solution was set aside in undisturbed condition until entrapped air bubbles were removed. the aqueous solution was casted in petridish made up of glass.[6]

FORMULATION DESIGN:

Table 1: Formulations of factorial batches

INGREDIENTS(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Betahistine Dihydrochloride	8	8	8	8	8	8	8	8	8
HPMC E15	15	17	19	15	17	19	15	17	19
PVA	1	1	1	3	3	3	5	5	5
Propylene Glycol*	20	20	20	20	20	20	20	20	20
Mannitol	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Citric acid	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
Tween 80	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Above table include the material weighed for 4 cm^2 film area * %W/W of dry polymer weight

EVALUATION PARAMETERS:

1. Film Separability:

The ease of film separation from the mould and disintegration time were considered as key parameters for the selection of best film from various batches prepared.

Table 2: Criteria for film separability:

Term	Code
Poor	-
Moderate	+
Good	++

2. Measurements of Mechanical Properties: [7, 2]

A suitable film should have a relatively moderate tensile strength, high % elongation at break The mechanical properties of the film gives idea about to what extent the film can withstand the force or stress during processing, packaging, transport and handling.

but a low elastic modulus.

Film strip with dimension 2x2 cm^2 and free from air bubbles or physical imperfections was held between two clamps positioned at certain distance. The force (gm) was applied by pulling one clamp. The values of mechanical properties were recorded when the film broke. Measurements were run in triplicate for each film.

- Tensile strength:
  It is measured by Tensilometer. Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip.
  T.S= load applied (gm)/ Cross-sectional area of film (cm^2)
- % Elongation:

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases.

It is calculated as =Increase in length /Original length * 100

3. Folding endurance: [1, 10]

Folding endurance was determined by repeatedly folding the film at the same place till visible crack was observed. The numbers of times the film can be folded at the same place without breaking give the value of folding endurance.

4. Thickness of film: [1,2]

The thickness of each sample was measured using a micrometer at five locations (center and four corners), and the mean thickness calculated.

5. Content uniformity: [1, 8, 9]

The film unit (n=3) of the dimensions 2 cm× 2 cm was placed in 100 ml of simulated saliva fluid pH 6.8.After complete solubilization, the solution was diluted appropriately, filtered and analyzed at 252nm using UV-Visible Spectrophotometer (Shimadzu 1800). The average of three films was taken as the content of drug in one film unit.

6. Surface pH: [10]

The film to be tested was placed in a Petri dish and was moistened with 0.5 ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min.

7. Disintegration time: [1, 11, 13]

The film was kept in petri-dish containing 10 ml of simulated saliva fluid pH 6.8 with gentle shaking and time at which it starts to break or disintegrate was taken as disintegration time.

8. In vitro dissolution studies: [10, 12]

The simulated salivary fluid was taken as the dissolution medium to determine the drug release. The dissolution profile was carried out in a beaker containing 30 ml of the simulated salivary fluid (pH 6.8) as a dissolution medium, maintained at 37 ± 0.5°C and then medium was stirred at 100 rpm. Aliquots of the dissolution medium were withdrawn at determined time interval and the same amount was replaced with the fresh medium. Then Samples were assayed spectrophotometrically. The percentage of the drug dissolved at various time intervals was calculated and plotted against time.

9. Evaluation of Taste Masking: [14, 15, 16]

In the present work, the taste acceptability was measured by a taste panel method. Each formulation was given to taste panel experts and it was allowed to hold in the mouth for 10-15 seconds, then spat out and the bitterness level was recorded as bitter index level. Volunteers were asked to gargle with distilled water between the film sample administrations. The scale mentioned in Table was used further in the study for the taste evaluation of the film formulation.

Table 3: Bitter Index Level

Numerical value	Scale
4	Strong bitter
3	Moderately bitter
2	Slightly bitter
1	Acceptable
0	Tasteless or taste masked

RESULT AND DISCUSSION:

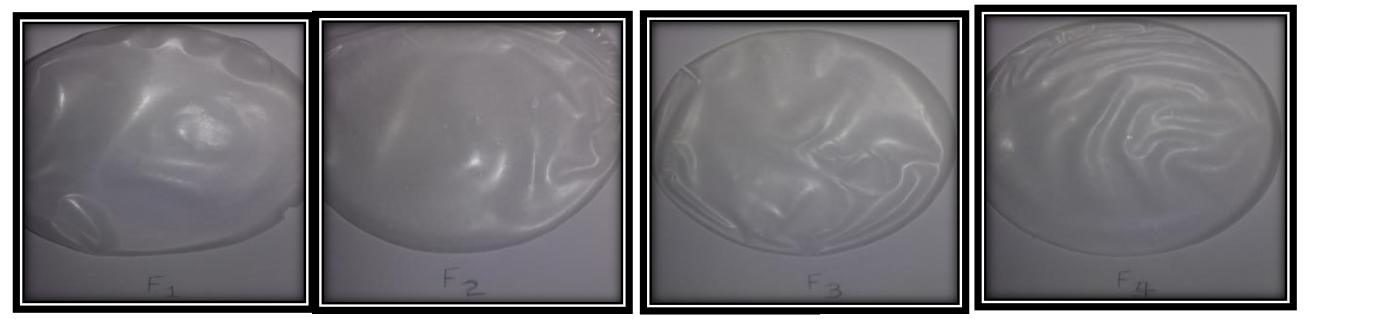

Fig 7: Batch F7

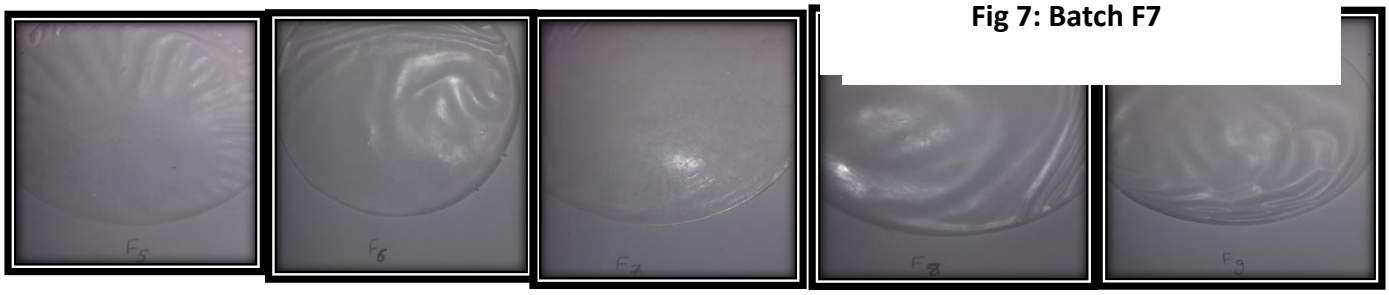

Table 4: Evaluation Parameters for F1 to F5

EVALUATION PARAMETERS	Factorial Batch				
	F1	F2	F3	F4	F5
Appearance	Good	Moderate	Good	Good	Moderate
Separability	+	+	++	++	+
Folding Endurance	>150	>200	>200	>300	>275
Mechanical Properties					
Tensile Strength (gm/cm^2)	22.23± 0.43	25.44± 0.62	29.08± 0.5	43.72± 0.21	56.12± 0.54
% Elongation	9.52	12.13	10.66	27.55	24.34
Thickness (mm)	0.09± 0.013	0.10± 0.011	0.10± 0.012	0.10± 0.008	0.1± 0.01
Surface pH	6.52	6.23	5.92	6.48	5.77
Disintegration Time (sec)	11	19	31	14	23
Assay (%)	92.31	84.49	98.59	96.83	93.84
Bitter Index	2	2	1	1	1

In Vitro drug release:

Table 5: In Vitro drug release for F1 to F5

Time (min)	%CDR				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
1	41.28±0.19	39.48±0.09	47.36±0.11	50.39±0.03	49.09±0.06
2	49.04±0.06	46.39±0.26	52.27±0.28	69.43±0.15	65.59±0.08
3	56.98±0.02	61.45±0.35	73.09±0.23	79.47±0.06	70.63±0.36
4	68.89±0.02	67.08±0.24	82.87±0.03	84.13±0.17	79.86±0.19
5	86.97±0.09	83.98±0.05	85.24±0.02	91.25±0.02	84.29±0.08

Fig 10: % CDR for batches F1 to F5

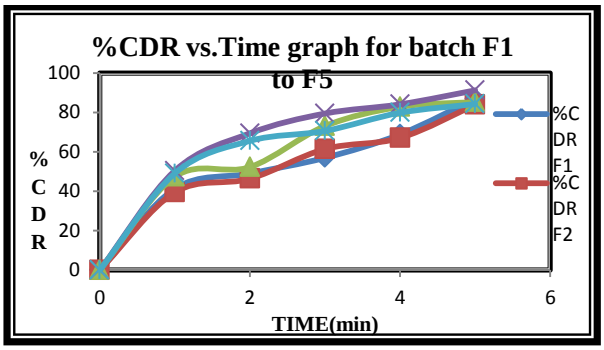

Table 6: Evaluation Parameters for F6 to F9

EVALUATION PARAMETERS	Factorial Batch			
	F6	**F7**	**F8**	**F9**
Appearance	Moderate	Good	Good	Good
Separability	++	+	++	++
Folding Endurance	>300	>300	>250	>250
Mechanical Properties				
Tensile Strength (gm/cm^2)	61.87±0.24	50.37±0.29	65.46±0.63	78.09±0.19
% Elongation	22.27	26.32	31.56	28..47
Thickness (mm)	0.11± 0.01	0.09± 0.01	0.11± 0.013	0.12± 0.008
Surface pH	6.98	6.63	5.97	6.19
Disintegration Time (sec)	34	19	28	39
Assay (%)	98.69	86.79	79.16	91.82
Bitter Index	1	2	1	1

In Vitro drug release:

Table 7: In Vitro drug release for F6 to F9

Time (min)	%CDR			
	F6	**F7**	**F8**	**F9**
0	0	0	0	0
1	46.39±0.03	43.79±0.07	56.28±0.36	55.49±0.18
2	68.73±0.17	65.17±0.29	67.78±0.02	72.89±0.43
3	81.43±0.03	75.35±0.03	72.39±0.21	78.86±0.06
4	85.20±0.09	84.68±0.08	81.02±0.48	82.07±0.07
5	88.37±0.13	89.16±0.19	82.67±0.05	87.43±0.06

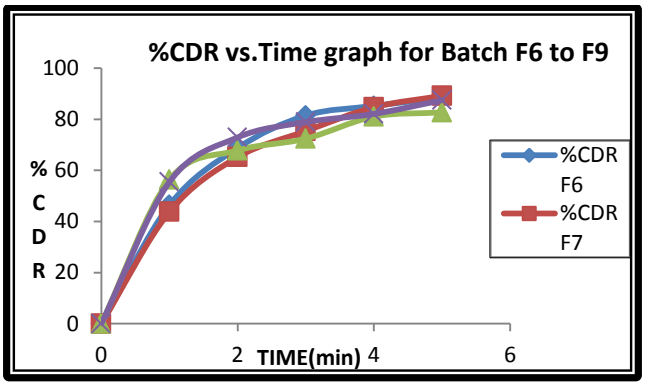

Fig 11: % CDR for batches F6 to F9

Discussion:

- Prelimnary trial batches formulated by use of different single(HPMC E15, PVA, Guar Gum, Xanthan Gum, PVP K30) and combination of polymer(HPMC E15+ PVA, HPMC E15+ PVPK30, HPMC E15+ Xanthan Gum, HPMC E15+ Guar gum) .It can be concluded that no individual polymer was able to produce film of desirable properties. And combination of HPMC and PVA gives good results as compared to all other batches. And type and amount of plasticizer was also optimized by preliminary trial batches formulated by using different plasticisers (PG, Glycerine, Polyethylene glycol 400) and concluded that PG 20%w/w of polymer was optimized from preliminary trial batches on the basis of good folding endurance.
- To the optimized preliminary trial batch polymer combination factorial design was formulated and evaluated.
- Factorial batch F1 produced films having good appearance but they were having moderate separability and tensile strength value was less as compared to other and drug release profile was not desirable. F2 batch produced film with moderate appearance.
- Factorial batch F3 produced film having moderate appearance; here disintegration time measured was also somewhat high.
- Factorial batches F5, F6, F7 produced films having somewhat higher disintegration time as compared to F4 batch. F6 curled on edges. And F5, F6, F7 they have higher tensile strength.
- Factorial Batch F9 produced films having very high tensile strength which was not desirable and F8 produce film with moderate tensile strength but disintegration time was somewhat higher as compared to F4. Batch F9 was gave desirable drug release profile due to higher PVA content but it having higher disintegration time as compared to all other batches because of higher polymer content.
- Factorial batch F4 has given less disintegration time. Also it having desirable mechanical properties that are comparatively moderate tensile strength and higher %elongation that means soft and tough film formulated. Thus F4 considered as an optimized batch. Also it releases the drug in a desirable manner.

CONCLUSION:

From preliminary trial batches optimized combination of polymer was found to be HPMC E15 and PVA. And plasticizer PG in a 20%W/W of polymer was optimized.

Factorial batch F4 had contained HPMC E15 and PVA in 15mg and 3mg quantity respectively in a combination was optimized on the basis of its less disintegration time, moderate tensile strength, and good drug release profile as compared to all other batches, due to less disintegration time it releases drug within less time which is required for getting quick relief of symptoms associated with M`enie`re's disease.

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