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Formulation and Optimization of Orally Disintegrating Film of Betahistine Dihydrochloride

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ABSTRACT

Oral route of drug administration, many substitutes have consistently been introduced by involving ongoing novel advancements for pediatrics, geriatrics, queasy, and rebelliousness patients. Bioadhesive mucosal measurement structures including cement tablets, gels, and fixes are results of a mechanical turn of events. Orally disintegrating films (ODF) have recently become one of the most popular forms of drug administration due to their excellent patient convenience and compliance. It can be placed on the tongue without the need for water. Compared to conventional oral dosage forms, ODFs usually result in enhanced bioavailability with a faster onset of action. Oral strip technology provides an alternate route for drugs with first-pass metabolism. This review gives details of materials used in ODF, manufacturing aspects, technologies, evaluation tests.

INTRODUCTION:

The oral route of drug administration has been one of the utmost expedients and acknowledged routes of drug delivery and amongst it, the intraoral route is the most ideal due to its ease and rapid onset of action. [1] The majority of the intraoral dose structures are expected to disintegrate, dissolve or release the drug in the oral cavity where it has an open door to be privately assimilated, to a limited extent or entire and then again might be swallowed and subsequently absorbed along the gastrointestinal tract (GIT).[2]

Rapidly dissolving films mostly dissolve within seconds to release the active agents but can be adapted to release the drug more slowly depending upon film thickness and an assortment of the polymer matrix. A film or strip can be distinct as a dosage form that employs water dissolving polymer which permits the dosage form to quickly hydrate, adhere and dissolve when placed on the tongue or in the oral cavity to offer rapid local or systemic drug delivery.[3-6]

Betahistine is an antivertigo drug (BCS Class I) frequently used in balance disorders or to alleviate vertigo symptoms associated with Meniere disease. Betahistine is a highly hygroscopic molecule and acidic. The purpose is to formulate stable mouth dissolving films of Betahistine. Hence an attempt shall be made to formulate and evaluate the fast-releasing oral thin films of Betahistine for dissolution and absorption of the drug, which may produce the rapid onset of action in the treatment of vertigo. [7]

In the present scenario mouth dissolving strips have been introduced towards effective management of immediately attacked diseases. This research involves the formulation optimization of stabilized Betahistine mouth dissolving strips that shall be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism.

MATERIALS AND METHODS:

Betahistine dihydrochloride was a gift sample from Intas pharma. Hypromellose (HPMC 15 cps) was purchased from Balaji drugs and Polyvinyl Alcohol was purchased from Nippon Gohsei. All other excipients were in the house.

Table-1: Composition of ODF Betahistine dihydrochloride

INGREDIENTS	FUNCTION	F1	F2	F3	F4
Betahistine dihydrochloride	Anti- vertigo	10	10	10	10
HPMC 15CPS	Film forming agent	14	14	15	15
Polyethylene Glycol	Plasticizer	20	20	20	20
Glycerine	Plasticizer	4	4	4	4
Polyvinyl Alcohol	Film forming agent	3	3	2	2
Sodium Benzoate	Preservative	0.1	0.1	0.1	0.1
Citric Acid	pH adjusting agent	6	6	6	6
Sucralose	Sweetener	1	1	1	1
Aspartame	Sweetener	1	1	1	1
Beta cyclodextrin	Complexing agent	0.1	0.1	0.1	0.1
Croscarmellose Sodium	Super disintegrant	0.8	0.8	0.8	0.8
Purified water	Vehicle	Q. S	Q. S	Q. S	Q. S

METHODS:

Formulation ingredients with their extents were as specified in table-1. Oral disintegrating films of Betahistine dihydrochloride were prepared by solvent casting method. Take purified water and added preservatives Sodium benzoate in it. Then added HPMC 15 cps and the homogenous polymeric solution was prepared by continuous stirring. Then added Beta cyclodextrin to it. Added sweetener Sucralose, Aspartame in it and mix well. Betahistine dihydrochloride was dissolved in a small amount of solution. Both the solution was combined by using the high shear method. In a separate container took polyethylene glycol, Polyvinyl alcohol, and Glycerine was mixed well and added in the above step. The solution formed was then cast as a film and poured. The solution in a glass mold and allow the solution to dry in the oven at 45 – 50˚C. Then cut into pieces of the desired size.

EVALUATION: [8,9]

1. Uniformity of Weight:

Each film was individually weighed on electronic balance (Effem (OHAUS)) and an average weight of 3 films was found. A large difference in weight denotes the non-uniform distribution of the drug in the film. (n=3)

2. The thickness of Film:

The thickness of the different films was measured using a calibrated dial gauge (Baker Precision Measuring Instruments) with an accuracy of 0.001 mm.

3. Surface pH

Surface pH of the film, the film was placed in a Petri dish and was moistened with 0.5 mL of distilled water and kept for 30 sec. The surface pH was measured utilizing a pH digital meter (Lab India) placed on the surface of the swollen films. An average of 3 determinations for each formulation was found. (n=3)

4. Folding Endurance

Folding endurance was measured manually for the prepared films. A 7.07 cm^2 ODF was repeatedly folded at 180°C angles of the plane at the same place until it breaks. The number of times the film could be folded at the same place without breaking was noted for 3 films of the same batch.[10]

5. HPLC Analysis

An HPLC method was used in the determination of drug content of films and analysis of samples in drug release studies using HPLC. The mobile phase was a mixture of two in the proportion 60: 40: the first one was the buffer of pH 2.5 prepared with 0.1% Dibasic sodium phosphate, 0.1% ammonium acetate, and 0.1% sodium pentanesulfonate filtered through a 0.45-micron filter and the second one was acetonitrile and methanol mixed in the proportion of 20 : 20, sonicated, and degassed for 10 minutes by using a sonicator. [11,12]

6. Drug Content and Uniformity of Dosage Units

A film was taken in a 100 mL volumetric flask and sonicated with 70 mL of methanol for 5 minutes after which the volume was made up to 100 mL with methanol. Then 1.0 mL of this solution was diluted to 100 mL with 0.1 N hydrochloric acid which was filtered through a 0.45-micron filter and diluted as required and the drug content was found out by HPLC analysis.

7. *In Vivo* Disintegration Time

In vivo disintegration time indicate that ODF disintegrated within 30 seconds and correlated well with in vitro dispersion time and disintegration time.

8. *In Vitro* Drug Dissolution Study

The dissolution studies were performed in 900 mL of simulated salivary fluid as well as 0.1 N hydrochloric acid using Lab India DS8000 dissolution (paddle) apparatus (Lab India Instruments Pvt. Ltd., India) with autosampler at °C with paddle rotation speed at 50 rpm. The samples were collected through a built-in 10 µ filter which was diluted previously to HPLC analysis.[13]

RESULTS AND DISCUSSION:

1. Appearance, Weight, and Thickness

The ODFs were homogenous, smooth, and rough surfaces. The weight variation was found to be minimum as indicated by a small standard deviation of ±1.66 mg. The thickness shows a narrow range of 124.26 to 129.63 µm further substantiating the above inference.

2. Surface pH

The ODFs were pH having 7.03 to 7.08.

Table- 2 Evaluation of ODFs

Formulation	Appearance	Weight	Thickness	pH
F1	Transparent	92.4 ± 1.36	124.26 ± 3.32	7.03±0.2
F2	Transparent	93.2 ± 1.62	129.26 ± 3.12	6.98±1.1
F3	Transparent	92.2 ± 0.96	127.26 ± 3.08	7.01±0.1
F5	Transparent	92.6 ± 1.16	125.26 ± 2.18	7.12±0.2

3. Folding Endurance [Table – 3]

Formulation	Folding Endurance
F1	5±1
F2	5±1
F3	5±1
F5	5±1

4. *In-vitro* Dispersion & Disintegration Time – As per the FDA recommendation the dispersion time of mouth dissolving films is less than 30s or less based on ODT's Disintegration test. The disintegration time of Betahistine dihydrochloride is 12sec.

5. *In-Vitro* Drug Release Study – In-vitro release study of oral dissolving films carried out in simulated saliva fluid & 0.1N HCL for 30 minutes. Betahistine Dihydrochloride oral dissolving films show rapid release in both media, which correlated the disintegration time & in-vitro dispersion.

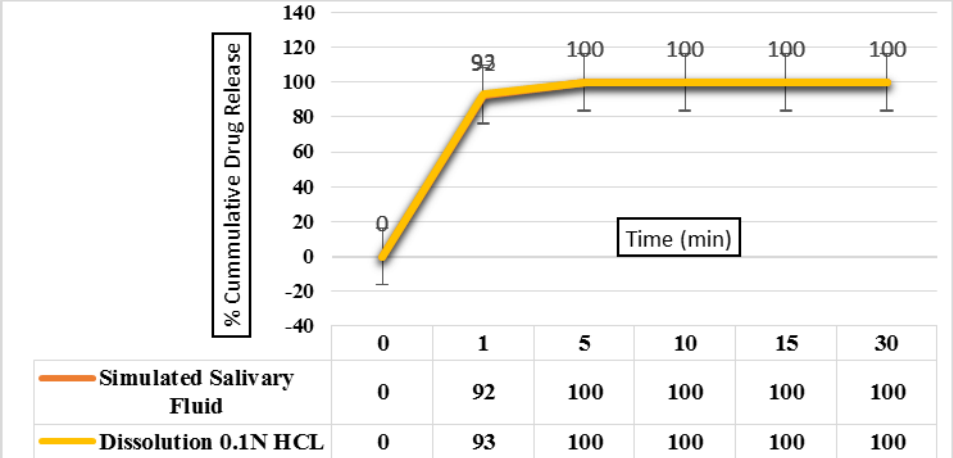

Fig – 1 *In-vitro* release study

6. Taste Evaluation –

Table -4 Results of Disintegration & Palatability

In-Vivo Disintegration Time (sec)	**Average rating by 10 Human Volunteers**			
	Initial Observation			
8.2 ± 0.5 sec	Sweetness	Mouth Feel	Bitterness	Flavor
	4.7	4.2	3.8	4.9
	After 5 minutes			
	4	4.5	4.1	4.6

CONCLUSION:

ODFs have a few positive viewpoints contrasted and the other oral dose structures. They offer minimal expense treatment with further developed bioavailability, adequacy, and patient consistence. To achieve this, the developed Betahistine DihydrochlorideODF with both enhanced dissolution and acceptable taste-masking was achieved by forming inclusion with HPMC 15CPS film-forming agent, Beta Cyclodextrin, sucralose, and aspartame. Formulation F3 and F4 achieved a better result than F1 and F2. The preparation possessed transparent in color and almost neutral in pH, having folding endurance near about 5±1 and disintegrating within 8.2 ± 0.5 sec. This formulation also provided a desirable taste and hence could be considered as a promising ODF formulation.

Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES:

1. Arya, A. Chandra, V. Sharma, K. Pathak Fast dissolving oral films: an innovative drug delivery system and dosage form Int. J. Chem. Tech. Res., 2 (2010), pp. 576-583.
2. I. Chauhan, M. Yasir, P. Nagar Insights into polymers: film formers in mouth dissolving films Drug Invent. Today, 3 (2012), pp. 56-73.
3. S.Gaisford, A. Verma, M. Saunders, and P. G. Royall, "Monitoring crystallization of drugs from fast-dissolving oral films with isothermal calorimetry," International Journal of Pharmaceutics, vol. 380, no. 1-2, pp. 105–111, 2009.
4. J. C. Souza, H. A. Tajiri, C. S. Morsch, et al., "Tribocorrosion behavior of Ti6Al4V coated with a bioabsorbable polymer for biomedical applications," Journal of Bio-and Tribo-Corrosion, vol. 1, no. 4, pp. 1–6, 2015.
5. M. Preis, "Orally disintegrating films and mini-tablets—innovative dosage forms of choice for pediatric use," AAPS PharmSciTech, vol. 16, no. 2, pp. 234–241, 2015.
6. S. S. Ölmez and İ. Vural, "Advantages and quality control of orally disintegrating tablets," FABAD Journal of Pharmaceutical Sciences, vol. 34, no. 3, pp. 167–172, 2009.
7. Martinez DM. The effect of Serc (betahistine hydrochloride) on the circulation of the inner ear in experimental animals. Acta Otolaryngol Suppl. 1972;305:29–47.
8. S. K. Yellanki, S. Jagtap, and R. Masareddy, "Dissofilm: a novel approach for delivery of phenobarbital; design and characterization," Journal of Young Pharmacists, vol. 3, no. 3, pp. 181–188, 2011.
9. P. Joshi, H. Patel, V. Patel, and R. Panchal, "Formulation development and evaluation of mouth dissolving film of domperidone," Journal of Pharmacy and Bioallied Sciences, vol. 4, no. 5, pp. S108–S109, 2012.
10. N. A. Nafee, N. A. Boraie, F. A. Ismail, and L. M. Mortada, "Design and characterization of mucoadhesive buccal patches containing cetylpyridinium chloride," Acta Pharmaceutica, vol. 53, no. 3, pp. 199–212, 2003.
11. M. Haque, S. Nasrin, M. M. Monir, M. M. Rahman, and S. Chowdhury, "Method development and validation of RP-HPLC method of etoricoxib in bulk and its tablet dosage forms," American Journal of PharmTech Research, vol. 2, no. 6, pp. 275–283, 2012.
12. S. Topalli, T. G. Chandrasekhar, and M. M. Annapurna, "Validated RP-HPLC method for the assay of etoricoxib (a nonsteroidal anti-inflammatory drug) in pharmaceutical dosage forms," E-Journal of Chemistry, vol. 9, no. 2, pp. 832–838, 2012.
13. U. S. Department of Health and Human Services, Food, and Drug Administration, Guidance for Industry, Orally Disintegrating Tablets, U. S. Department of Health and Human Services, FDA, 2008.

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