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Research Article

Formulation and evaluation of Ebastine mouth dissolving tablets by molecular dispersion technique

Raja Sridhar Rao P.*[1], Chandrasekara Rao G.[2]

[1]Department of Pharmaceutics, S.R. College of Pharmacy, Warangal-506371, Andhra Pradesh, India
[2]Department of Pharmaceutics, Yalamarty College of Pharmacy, Anandapuram, Visakhapatnam-531163, Andhra Pradesh, India

ABSTRACT

Ebastine is a second generation antihistamine mainly used for allergic rhinitis and urticaria. Ebastine is available in India as a conventional immediate release tablet; there is a need of formulating Ebastine in mouth dissolving tablet form to allow the administration of the dosage form without water, where particularly important for geriatrics, pediatrics and mentally retarded patients. Since, Ebastine is insoluble in water, different formulation techniques and excipients were tried for formulation of mouth dissolving tablets, molecular dispersion granulation technique was employed to optimize the formulation. Results were observed that, formulated mouth dissolving tablets are ready to disperse on tongue within a minute and the dissolution is very quick compared to the conventional immediate release tablets. Main physical parameters like weight variation, hardness, friability, fineness of dispersion and disintegration time and chemical quality parameters like assay and dissolution were evaluated during manufacturing and found satisfactory with meeting the pharamacopoeial limits. Finalized formulation F13 was packed in to blisters and charged for stability at 40°C/75%RH. Main physical and chemical quality parameters were evaluated during stability and found satisfactory. Dissolution profile was also generated during stability showed satisfactory results compared to initial dissolution profile.

Keywords: Ebastine; Molecular dispersion; Mouth dissolving tablets; Stability: Tutti frutti

INTRODUCTION

Oral route is the most preferred route for administration of therapeutic agents because of ease of administration, accurate dose, self medication and patient compliance. In this concern tablets and capsules are most preferred dosage forms for oral route. But these dosage forms are difficult to administer pediatrics and geriatrics. So the present authors focused on mouth dissolving tablets due to increasingly aged and development of appropriate dosage form for the elderly is most desirable. Because of change in the physiological functions in the elderly persons is difficult to swallow the normal conventional tablets. So MDTs are most preferable for its ease of administration and improve in therapeutic efficacy of dosage form (Takao Mizumoto et al., 2005; Srikonda Venkateswara Sastry et al., 2000; Gohel MC, 2005).

Mouth dissolving tablets (MDT's) are disintegrates and dissolves in the mouth (in saliva) within few seconds without need of any liquid. Mouth dissolving tablets are also called as fast dissolving, oro dispersible, orally disintegrating and fast melting tablets. MDT's combines the advantage of both conventional and liquid formulations (Bi Y et al., 1996; Fu Y et al., 2004).

Ebastine is second generation antihistamine used to treat allergic rhinitis and urticaria. In India Ebastine is available as conventional immediate release tablet, so there is need to develop the mouth dissolving tablets to allow the administration of dosage form without need of water where particularly important for pediatrics, geriatrics and who is having less access of water. The present authors developed Ebastine mouth dissolving tablets by molecular dispersion granulation technique using gelatin as a dispersing agent.

MATERIALS AND METHODS

Materials

Ebastine is obtained as gift sample from Dr. Reddy's laboratories, Hyderabad and other excipients used in this work was obtained as gift samples from BASF, India.

Methods

Preparation of Mouth dissolving tablets

Initially the authors developed Ebastine mouth dissolving tablets using molecular dispersion granulation

* Corresponding Author
Email: p.rajasridhar@gmail.com
Contact: +91-9849079102
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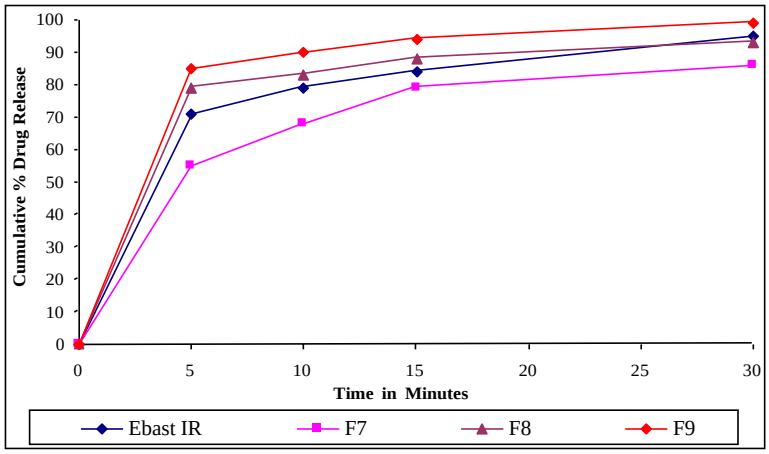

Figure 1: Comparative dissolution graph of F7-F9

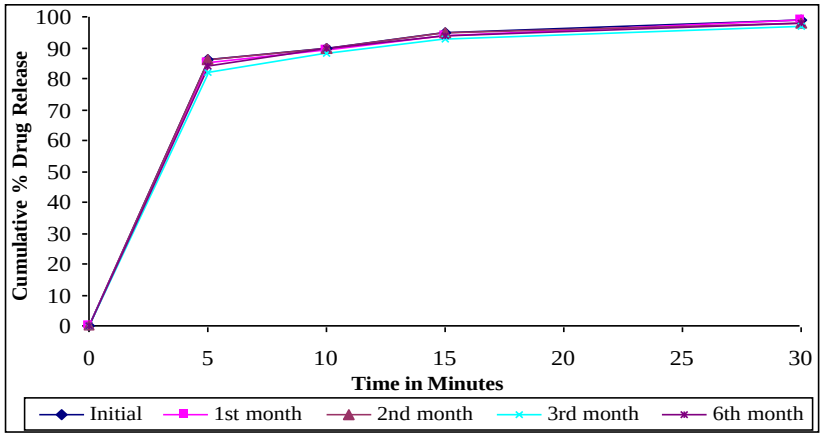

Figure 2: Comparative dissolution graph of Initial Vs Stability

technique with micronized active due to insoluble nature of the active in water. The process is same for all batches except concentration change.

The materials like Ebastine, sodium lauryl sulfate, microcrystalline cellulose PH 101, croscarmellose sodium and crospovidone were sifted through #40 mesh and Neotame, lemon flavor, tutti frutti flavor, colloidal silicon dioxide and magnesium stearate was sifted through #60 mesh and collected separately in polyethylene bag.

According to formula, gelatin and sifted sodium lauryl sulfate was taken in china dish and melted at 70°C, then active was transferred into china dish under continuous stirring. Once it formed homogeneous mixture, it was stored in refrigerator for 5-8 hours. Then mass was cooled, milled and mixed with previously sifted microcrystalline cellulose PH 101, crospovidone and/or croscarmellose sodium and blended for 10 minutes and finally added sifted colloidal silicon dioxide and magnesium stearate to the blender and lubricated for 5 minutes. Then lubricated blend was compressed into tablets by using rotary compression machine. The composition details were given in table 1

Further three more batches i.e. F7-F9 was formulated with combination of two super disintegrants in different concentrations and remaining process are same as previous batches. The composition details were given in table 2.

Same like F9 four more batches were formulated with addition of organoleptic additives like flavoring agents and taste masking agents. The composition details were given in table 3.

Blend parameters

The blend parameters like bulk density, tapped density and compressibility index was performed for all batches of blend (E.C. Abdullah, 1999).

Physical parameters of tablets

The physical parameters like resistant to crushing, friability, weight variation and disintegration time was performed for all batches of the tablets (European pharmacopoeia, 2011; Sateesh K. VEMULA, 2011). Next dispersion time and water absorption ratio was performed for optimized formulation (F13) to study the dispersion time and water absorption capacity of MDT (Hisakadzu Sunada, 2002; Abdelbary, A.H et al., 2009).

***In vitro* drug release studies**

The study was conducted with six tablets for each formulation using USP type II dissolution apparatus using 900 ml of pH 4.5 acetate buffer as dissolution medium at a paddle speed of 50 RPM. As per time points, 10 ml of aliquots were withdrawn through auto sampler and

Table 1: Composition details of F1-F6 with two super disintegrants alone

Composition	Unit formula (mg/tablet)					
	F1	F2	F3	F4	F5	F6
Ebastine	20	20	20	20	20	20
Gelatin	1.5	1.5	1.5	1.5	1.5	1.5
SLS	1.5	1.5	1.5	1.5	1.5	1.5
MCC PH 101	119.5	119.5	116.5	116.5	113.5	113.5
Crospovidone	4.5	---	6.0	---	7.5	---
Croscarmellose sodium	---	4.5	---	6.0	---	7.5
Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5
Magnesium stearate	1.5	1.5	3.0	3.0	4.5	4.5
Total tablet weight	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

Table 2: Composition details of F7-F9 with combination of two super disintegrants

Composition	Unit formula (mg/tablet)		
	F7	F8	F9
Ebastine	20	20	20
Gelatin	1.5	1.5	1.5
SLS	1.5	1.5	1.5
MCC PH 101	115	112	109
Crospovidone	3.0	4.5	6.0
Croscarmellose sodium	3.0	4.5	6.0
Colloidal silicon dioxide	1.5	1.5	1.5
Magnesium stearate	4.5	4.5	4.5
Total tablet weight	**150.0**	**150.0**	**150.0**

Table 3: Composition details of F10-F13 with organoleptic additives

Composition	Unit formula (mg/tablet)			
	F10	F11	F12	F13
Ebastine	20	20	20	20
Gelatin	1.5	1.5	1.5	1.5
SLS	1.5	1.5	1.5	1.5
MCC PH 101	107.35	107.35	106.45	106.45
Crospovidone	6.0	6.0	6.0	6.0
Croscarmellose sodium	6.0	6.0	6.0	6.0
Neotame	0.15	0.15	0.3	0.3
Lemon flavor	1.5	---	2.25	---
Tutti frutti	---	1.5	---	2.25
Colloidal silicon dioxide	1.5	1.5	1.5	1.5
Magnesium stearate	4.5	4.5	4.5	4.5
Total tablet weight	**150.0**	**150.0**	**150.0**	**150.0**

Table 4: *In vitro* drug release data of F7-F9 Vs Reference product

Time in minutes	Reference product (IR)	% Cumulative Drug Release (%RSD)		
		F7	F8	F9
05	71 ± 2.51	55 ± 1.38	79 ± 1.18	85 ± 1.28
10	79 ± 1.66	68 ± 1.15	83 ± 1.36	90 ± 1.04
15	84 ± 1.24	79 ± 1.08	88 ± 1.27	94 ± 1.15
30	95 ± 1.12	86 ± 0.84	93 ± 1.09	99 ± 1.18

filtered through 0.45µ filters and the same amount of dissolution medium was replaced into dissolution apparatus for maintaining the sink condition. The response of aliquots was measured at 262 nm using HPLC. Comparative *in-vitro* dissolution study was conducted for optimized test formulation with reference product (EBAST IR 20mg manufactured by Micro labs).

Flavor and Sweetener optimization

The batches F10-F13 was formulated with tutti frutti and lemon as flavors and neotame as taste masking

Table 5: Comparative stability data with initial at accelerated condition

Name of the parameter	Initial	1st month	2nd month	3rd month	6th month
Appearance*	Complies	Complies	Complies	Complies	Complies
Dissolution					
05 minutes	86	85	86	82	84
10 minutes	90	89	90	88	90
15 minutes	95	94	95	93	94
30 minutes	99	99	98	97	98
Assay	99.7	99.7	99.8	99.4	99.2
Friability	0.15 ± 0.08	0.14 ± 0.04	0.15 ± 0.05	0.16 ± 0.07	0.12 ± 0.09
Disintegration	19 ± 0.98	19 ± 0.68	19 ± 0.62	22 ± 048	20 ± 0.62
Dispersion time	15 ± 0.62	14.5 ± 0.51	14.8 ± 0.35	15 ± 0.42	15.4 ± 0.26

*White to off white coloured round, biconvex uncoated tablets plain on both sides.

agents in different concentrations. All four formulations were given to five human healthy volunteers and evaluated the taste and flavor of the formulations (Jianchen Xu et al., 2008).

Assay by HPLC method

The drug content was measured for optimized formulation (F13) by HPLC method at 262 nm using 250x4.6mm, 5 μ packing RP-C18 column with a injection volume of 20μl at flow rate of 1.5 ml/minute and the run time was about 15 minutes.

Stability studies

As per ICH guidelines, the accelerated stability studies were conducted for optimized formulation (F13) for a period of six months. The samples were withdrawn from stability chamber at intervals of 1st, 2nd, 3rd, 6th months and analyzed for assay, dissolution, friability, disintegration time and dispersion time (ICH Q1E, 2004).

RESULTS AND DISCUSSION

Blend evaluation

All batches of blend was evaluated for blend parameters and confirmed that lubricated blend was very much useful for compression and the results were found satisfactory.

Physical parameters of tablets

All batches of tablets were evaluated for physical parameters like resistant to crushing, friability, weight variation and disintegration time. The results of all parameters were found within the acceptable limit. The optimized formulation showed satisfactory result for dispersion time and water absorption ratio.

***In-vitro* dissolution studies**

The batches F1- F6 was prepared with maximum concentration of super disintegrant alone and results were not meeting with reference product drug release at all time points. So further batches i.e. F7-F9 were planned with combination of superdisintegrants and among three batches F9 batch shows improved rate of drug release than reference product at all time points. The results of the same were given in table 4 and graph of the same was shown in Fig. 1.

Flavor and sweetener optimization

Among all four batches F13 batch was showed very good taste and flavor and confirmed that optimized formulation in concern of physical parameters, chemical parameters as well as organoleptics.

Assay

The results of assay were found within the Pharmacopoeial limits.

Stability studies

From the stability data it was observed that all parameters were found within the limit and the drug was stable for a period of 6 months at accelerated condition without any noticeable change and confirmed that F13 batch is optimized formulation. The results of the same were given in table 5 and the comparative dissolution graph of initial and after stability was showed in Fig. 2.

CONCLUSION

From the above results it revealed that F13 batch is best suitable for preparation of mouth dissolving tablets and the tablets were ready to disperse on tongue within one minute and dissolution is very quick than conventional immediate release reference product. All physical and chemical parameters of tablets were found satisfactory and meeting the Pharmacopoeial standards. The optimized formulation F13 also passes accelerated stability for a period of 6 months without any noticeable change.

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