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RESEARCH ARTICLE

Formulation & Development of Amlexanox Loaded Oral Dispersible Tablets For Management of Aphthous Ulcers

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ABSTRACT:

Amlexanox is the active ingredient in a common topical treatment for recurrent aphthous ulcers of the mouth (canker sores), reducing both healing time and pain. The aim of the present research is to develop oral dispersible tablet dosage form of a drug meant for management of aphthous ulcers of the mouth (canker sores) to allow the administration of the dosage form without water. For formulation of oral dispersible tablets, molecular dispersion granulation technique was employed to optimize the formulation. Formulations are characterize for various parameters like weight variation, hardness, friability, fineness of dispersion, disintegration time and dissolution were evaluated during manufacturing and found satisfactory with meeting the pharamacopoeial limits. Finalized formulation was packed in to blisters and studied for stability at 400C/75%RH. Main physical and chemical quality parameters were evaluated during stability and found satisfactory and within the limits.

KEYWORDS: Amlexanox; aphthous ulcers; Molecular dispersion; oral dispersible tablets; Stability studies.

INTRODUCTION:

Drug delivery has major challenge to the pharmaceutical industry is to control the delivery rate of active pharmaceutical ingredient to a presumed site in human body. So researcher focused on designing different controlled release drug delivery systems to improve efficacy and patient compliance.[1-3] Controlled release of drugs assures that the drug remains primarily localized or get enter into the systemic circulation in significant amounts so as to offer desired result.[4-6]

Because of change in the physiological functions in the elderly persons is difficult to swallow the normal conventional tablets. So Oral dispersible dosage forms ODTs are most preferable for its ease of administration and improve in therapeutic efficacy of dosage form.[7-9]

ODTs are disintegrates and dissolves in the mouth (in saliva) within few seconds without need of any liquid. These tablets are also called as fast dissolving, mouth dissolving, orally disintegrating and fast melting tablets. ODTs combines the advantage of both conventional and liquid formulations[10-12]

Amlexanox is an antiallergic drug, clinically effective for atopic diseases, especially allergic asthma and rhinitis. Amlexanox as a topical paste is a well tolerated treatment of recurrent aphthous ulcers. Recurrent aphthous ulcer (RAU) is the most prevalent oral mucosal disease in humans, estimated to affect between 5% and 50% of the general population. [13-15] Amlexanox is the active ingredient in a common topical treatment for recurrent aphthous ulcers of the mouth (canker sores), reducing both healing time and pain.[12-13]

Its mechanism of action is not well-determined, but it might inhibit inflammation by inhibiting the release of histamine and leukotrienes. It has been shown to selectively inhibit TBK1[disambiguation needed] and IKK-ε, producing reversible weight loss and improved insulin sensitivity, reduced inflammation and attenuated hepatic steatosis without affecting food intake in obese mice.[17-19] As a benzopyrano-bipyridine carboxylic acid derivative, amlexanox has anti-inflammatory and antiallergic properties. It inhibits chemical mediatory release of the slow-reacting substance of anaphylaxis (SRS-A) and may have antagonistic effects on interleukin-3. When cells are under stress, they release an inactive form of human fibroblast growth factor 1 (FGF-1), a potent mitogen (entity that causes mitosis). Amlexanox binds to FGF1, increasing its conformational stability, sterically blocking Cu(2+) induced oxidation which normally leads to activation of FGF-1.[4-6]

Amlexanox applied to an aphthous ulcer is largely absorbed through the gastrointestinal tract; an insignificant amount enters the bloodstream through the ulcer itself. After a single 100 mg dose, mean maximum serum concentration occurs 2.4 +/- 0.9 hours after application, with a half-life of elimination (through urine) of 3.5 +/- 1.1 hours. With multiple daily applications (four doses per day), steady state serum levels occur after one week, with no accumulation occurring after four weeks.[19-20]

METERIAL AND METHOD:

Amlexanox is obtained as gift sample from Torrent Pharmaceutical private limited, Ahmedabad. and other excipients used in this work was obtained as gift samples from BASF, Loba Chemical Private Limited Mumbai, India.

Method:

Preparation of oral dispersible tablets:

Amlexanox oral dispersible tablets were prepared using molecular dispersion granulation 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 Amlexanox, 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.[21-23]

According to formula, gelatin and sifted sodium lauryl sulfate was taken in china dish and melted at 70^0C, 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.[24-25] The composition details were given in table 1.

Table 1: Composition details of oral dispersible tablets

Composition	Unit formula (mg/tablet)												
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
Amlexanox	20	20	20	20	20	20	20	20	20	20	20	20	20
Gelatin	1.5	1.5	1.5	1.5	1.5	1.5	1.5	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	1.5	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	115	112	109	107.35	107.35	106.45	106.45
Crospovidone	4.5	---	6.0	---	7.5	---	3.0	4.5	6.0	6.0	6.0	6.0	6.0
Croscarmellose sodium	---	4.5	---	6.0	---	7.5	3.0	4.5	6.0	6.0	6.0	6.0	6.0
Colloidal silicon dioxide	1.5	1.5	1.5	1.5	1.5	1.5	1.5	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	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Total weight	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

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. Same like F9 four more batches were formulated with addition of organoleptic additives like flavoring agents and taste masking agents.

Blend parameters

The blend parameters like bulk density, tapped density and compressibility index was performed for all batches of blend.

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. Then dispersion time and water absorption ratio was performed for optimized formulation (F13) to study the dispersion time and water absorption capacity of ODT.[26]

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 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 λmax of drug using UV spectroscopy.

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.

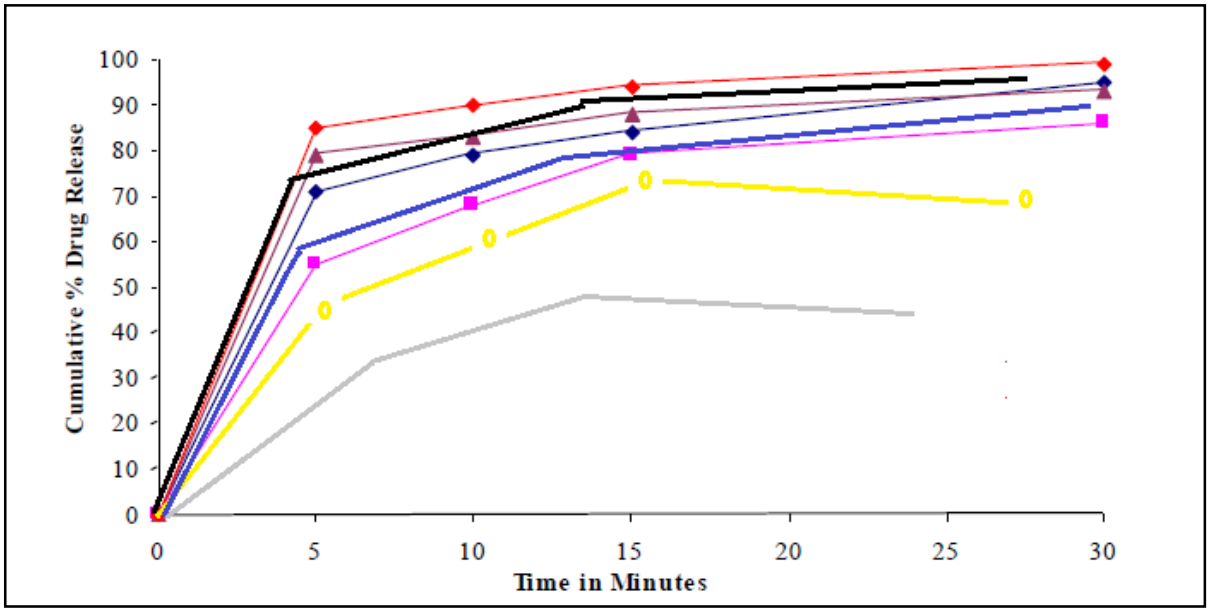

Figure 1: Comparative dissolution profile for the formulations

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.

Table: 2. Stability profile of optimized formulation

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

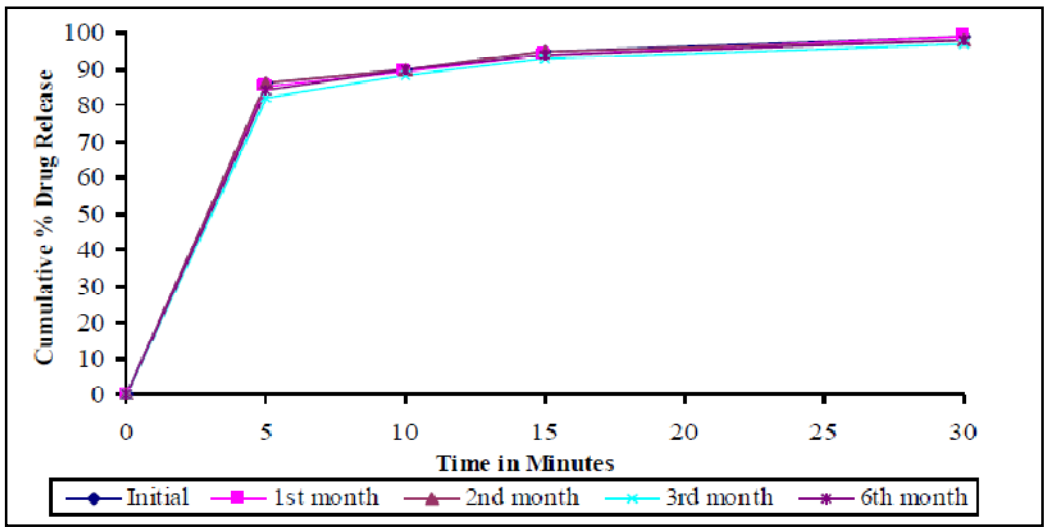

Figure 2: Comparative dissolution graph of Initial Vs Stability

CONCLUSION

From the above results it revealed that F13 batch is best suitable for preparation of oral dispersible 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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