RESEARCH ARTICLE

Formulation of taste masked oro-dispersible tablets of ambroxol hydrochloride

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Ambroxol hydrochloride (HCL) is a potent mucolytic capable of inducing bronchial secretion. It is used in the treatment of asthma, bronchitis, and cough. But it is a very bitter drug and slightly soluble in water. Thus, in the work under taken, an attempt was made to mask the taste and to formulate into a oro-dispersible tablet by complexation with ion exchange resins, which also acts as super disintegrating agents. Since, these tablets can be swallowed in the form of dispersion, it is suitable dosage form for pediatric and geriatric patients. Cation exchange resins like Indion-204 and Indion-234 were utilized for the sorption of drug. Drug-resinates were prepared in drug to resin ratio of 1:5 and 1:6. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, wetting time, *in vitro* and *in vivo* disintegration time, and *in vitro* dissolution studies. Tablets with both the resins have shown quick disintegrating features, i.e., within 20 s, which is very characteristic of oro-dispersible tablets. Also, the dispersion not showing any bitter taste, indicate the capability of ion exchange resins used, both as taste masking and super disintegrating agents. Almost more than 90 percent of drug was released from both the formulations within 1 h. Further formulations were subjected to stability testing for 3 months at temperatures 25±5ºC/60±5%RH and 40±5ºC/75±5%RH. Both tablets have shown no appreciable changes with respect to taste, disintegration, and dissolution profiles.

Key words: *Ambroxol HCl, oro-dispersible tablets, resinate*

INTRODUCTION

More than 50 percent of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem encountered with such oral products.[1] Taste of a pharmaceutical product is an important parameter for governing compliance. Thus, taste masking of oral pharmaceuticals has become an important tool to improve patient compliance and the quality of treatment especially in pediatrics. Therefore, formulation of taste masked products is a challenge to the pharmacists.[2][13]

Ambroxol hydrochloride (HCL) is a potent mucolytic, used in the treatment of asthma. It is a very bitter drug and slightly soluble in water.[3] The main objective of the present work is to formulate taste masked dispersible or oro-dispersible tablets of ambroxol hydrochloride. Such taste-masked formulations have been found to improve the quality of treatment in pediatric patients. The oro-dispersible tablets can be swallowed without water in the form of dispersion. They increase the patient compliance as well as provide quicker onset of action.

Ion exchange resins have been increasingly used as taste masking agents.[4] They are also known to be useful as disintegrating agents superior to other conventional agents. Thus, the study undertaken was aimed at using ion exchange resins for both the purposes, thus formulating taste-masked oro-dispersible tablets of ambroxol hydrochloride. Such a tablet may be swallowed in the form of a dispersion, as it is expected to disintegrate quickly when in contact with saliva.[4][13] The bitter taste may not be felt, because the ion exchange resin complex does not release the drug at the salivary pH. When it comes in contact with acidic environment of the stomach, the complex will be broken down quickly and releasing the drug which may then be absorbed in usual way.[5] The plan of work was complexing the drug with the resins (Indion-204, Indion-234) to form drug-resinate, evaluation of drug-resinate complexes and compressing drug-resinate complexes into tablets.

MATERIALS AND METHODS

Preparation of non bitter drug-resinate complex

Ion exchange resins like Indion 204 and Indion 234 were

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pretreated with 1N HCl and 1N NaOH in order to remove impurities. Drug and resins were mixed in various ratios 1:1 to 1:6 on weight basis and stirred at magnetic stirrer for a period of 4 to 8 h using deionized water. The resinate obtained was separated by filtration and dried. Non bitter complex was yielded at 1:5 and 1:6 drug to resin ratio using deionized water of pH 7 and also maximum percentage drug loading (96.5 and 98.8 percent) was determined at the same ratio.[6]

Evaluation of amount of non-complexed drug

The mixtures to be evaluated were kept aside to allow the particles to sediment and then filtered. From this filtrate, 1 ml was transferred in to 100 ml volumetric flask and the volume was made up to 100 ml and absorbance were noted, from which amount of non-complexed drug was calculated.[5]

Production of tablets

Granules of drug resinate earlier obtained were mixed with mannitol, flavoring agents (mint flavor) and talc (2 percent). Before compression, hardness was adjusted. Drug-resinates equivalent to 30 mg of ambroxol HCl were compressed on cadmach single punch tablet press machine equipped with 10 mm flat faced beveled edge punches and same hardness was used for the required number of tablets.

Prepared tablets were evaluated for post compression parameters like thickness, hardness, weight variation, friability test, drug content uniformity, taste evaluation, wetting time, *in vivo* dispersion, *in vivo* disintegration time, and stability studies.

General appearance, thickness, hardness test

Five tablets from both batches were randomly selected and organoleptic properties such as color, odor, taste, shape, were evaluated. The thickness of five tablets was measured using vernier calipers. The diameter was also determined by using vernier calipers. Hardness of the tablets was tested by using 'Monsanto' hardness tester. [7]

Drug content uniformity

Five tablets were taken randomly and individual tablet were crushed, the 50 ml of 0.1M methanolic HCl was added. Shaken for 30 min and added sufficient 0.1 M methanolic HCl to produce 100 ml and filtered. In this 1 ml was taken in 100 ml volumetric flask, again made up the volume up to the mark with same acid solution. The absorbance was measured spectrophotometrically at 208.6 nm. The tablets complied with the test if not more than one of the individual values thus obtained is outside the limit 85 to 115% of the average value.[8,12]

Weight variation test and friability test

Weighed 20 tablets were selected randomly and the average weight was calculated. Then percentage deviation from the average was calculated and then friability of prepared tablets was determined using Roche friabilator.

Table 1: Formulation of tablets formulated with Indion 204 resin (F_1) and Indion 234 resin (F_2)

Ingredients	Formula for 100 tablets (F_1)	Formula for 100 tablets (F_2)
Drug resinates equivalent to 30 mg of ambroxol HCl	18 g	21 g
Mannitol	3.6 g	4.2 g
Talc (2%)	0.36 g	0.42 g
Mint flavor	Quantity sufficient	Quantity sufficient

In vitro **disintegration test**

This test was performed to ensure disintegration of tablets in water, if it is to be used as a dispersible tablet. To be complied with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min when examined by the disintegration test for tablets.

In vitro **dispersion test**

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a oro-dispersible tablet. *In vitro* dispersion time was measured by dropping a tablet in a measuring cylinder containing 6 ml of simulated salivary fluid of pH 6.8. Five tablets from each formulation were randomly selected and *in vitro* dispersion time was performed. (Preparation of simulated salivary fluid: Phospate buffer pH 6.8 mimics the salivary fluid. Dissolve 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate in sufficient water to produce 1000 ml.)

In vivo **disintegration time**

Six healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. After the test, mouth was washed with distilled water. Three trials were performed with 2 days interval, between trials.[9]

Wetting time[

This method will duplicate the *in vivo* disintegration, as the tablet is motionless on the tongue. Wetting time was measured by placing a tablet on a piece of tissue paper folded twice, and was placed in a small petri dish containing 6 ml of simulated saliva pH 6.8, and the time for complete wetting was measured. Five tablets from each batch were used and results were compared with commercial product.[10]

Uniformity of dispersion

This test was applicable only to dispersible tablets. In the method, two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion must be obtained which passes through a sieve screen with a nominal mesh aperture of 710 µm (sieve no. 22).[8]

Table 2: Results of post compression parameters

Batches	Diameter* (mm) ±SD	Thickness* (mm) ±SD	Hardness* Kg/sq.cm^2 ±SD	Friability (%)	Weight variation (mg) Mean ± SD n=20	Drug content uniformity (%)
F_1	10 ± 0.020	2.9 ± 0.050	4.1 ± 0.1	0.59	228.2 ± 1.45	92.5
F_2	10 ± 0.050	2.9 ± 0.020	3.0 ± 0.2	0.71	274.4 ± 2.89	95.7

Table 3: Taste evaluation of F_1 and F_2 formulations

Volunteers	Bitterness level after								Mouth feel	
	10 s		30 s		1 min		2 min			
	F1	F2	F1	F2	F1	F2	F1	F2	F1	F2
1	O	O	O	O	O	O	X	O	X	O
2	O	O	O	O	O	O	O	1	O	O
3	O	O	O	O	O	O	O	O	x	O
4	O	O	O	O	O	O	O	x	O	O
5	O	O	O	O	O	O	O	O	O	O

O-tasteless; 2-moderate bitter; 1-slight bitter; 3 -strong bitter; x-threshold bitter

Taste evaluation

Taste evaluation was done by a panel of six volunteers using time intensity method. One tablet was held in mouth for 10 s bitterness levels were recorded instantly and then at the end of 10 s, 30 s, 1 min, and 2 min, bitterness levels are again noted and recorded and compared with commercial product.[5,11]

Mouth feel

The same human volunteers participated in taste evaluation test, were asked to give their opinion about the feeling of smoothness or grittiness of the dispersion soon after the tablet got disintegrated.[11]

In vitro dissolution studies

The dissolution rate of ambroxol hydrochloride from the tablets was studied in 0.1 N hydrochloric acid using USP XXIII dissolution test apparatus employing paddle stirrer and assayed spectrophotometrically at 208.6 nm. Similar test was carried out for a commercial product for comparison.

Stability studies

Stability studies were carried out at 25 ± 5˚C/60 ± 5%RH and 40 ± 5˚C/75 ± 5%RH for a period of 3 months for both F_1 and F_2 formulations as per ICH guidelines.

RESULTS AND DISCUSSION

Both formulations were prepared by direct compression technique [Table 1]. The data obtained for post-compression parameters such as uniformity of thickness, hardness, weight variation, friability test, drug content uniformity, taste evaluation, wetting time, *in vivo* dispersion, and *in vivo* disintegration time are shown in the Table 2. The tablets diameters were almost uniform in F_1 and F_2 formulations and thickness range was very well within ±5% of the standard value in both batches.

The measured average hardness of the tablets was 4.3 and 3.0 Kg/cm^2, respectively for the two formulations, this ensures good handling characteristics of both formulations. The percentage drug content of all tablets in both formulations was found to be between 92 and 99% which complied with the limits established in the pharmacopoeia (Indian pharmacopoeia). The percentage friability was less than 1% in both F_1 and F_2 formulations, ensuring that the tablets were mechanically stable.

All the tablets passed weight variation test, as % weight variation was within the pharmacopoeial limits i.e., ±7.5%. To be compliance with the pharmacopoeial standards, dispersible tablets must disintegrate within 3 min. But, formulated products have exhibited very low disintegrating time (i.e., 14 and 21 seconds), indicating that both formulations were suitable for oro-dispersible tablets. In the *in- vivo* disintegration time, wetting time was observed to be very fast in F_1 formulation when compared to F_2 and marketed product [Figure 1].

Panel of healthy human volunteers for taste masking evaluation using time intensity method, which shows satisfactory masking of taste as shown in the Table 3. Both

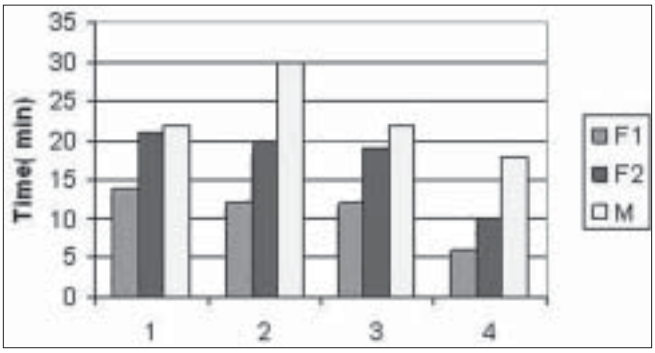

Figure 1: Comparison of disintegration properties

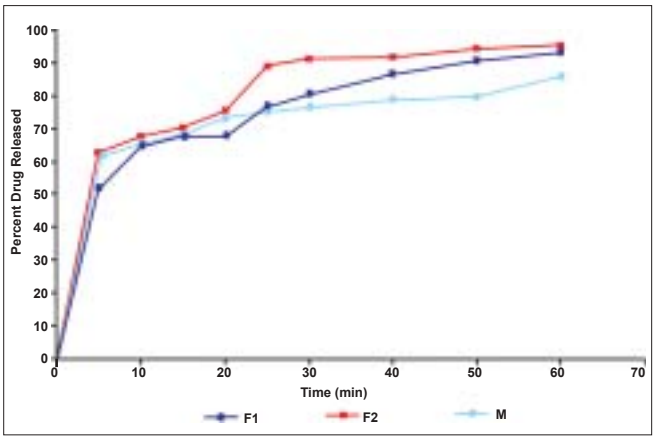

Figure 2: Drug release profiles

F_1 and F_2 formulations did not show any bitter taste when tablets are held in the mouth by using time intensity method, which shows excellent taste masking effect of the resins. In case of marketed formulation, bitterness was felt by all the volunteers.

Both formulations show smooth and pleasant mouth feeling, thus fulfill the requirements of oro-dispersible tablets [Figure 1]. The complex was subjected to dissolution studies in 0.1N HCl using USP (XXIII) paddle apparatus at 100 rpm and 37°C temperature which shows that drug release was more than 90% within an hour [Figure 2]. Stability study was conducted. There was no significant taste, color, and odor change at any temperature. There was no significant variation in the *in vitro* dispersion time, *in vivo* disintegration time, wetting time, and *in vitro* dissolution profiles after three months of stability studies for both the formulations at different temperatures.

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