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Design and evaluation of taste masked chewable dispersible tablet of lamotrigine by melt granulation

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Abstract

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Lamotrigine is also used in the treatment of depression and bipolar disorder. But it is a 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 chewable dispersible tablet by complexation with Precirol ATO-05, which also acts as taste masking agent. Since, these tablets can be swallowed in the form of dispersion; it is suitable dosage form for paediatric and geriatric patients. Drug-Precirol ATO-05 was prepared in drug to Precirol ATO-05 ratio of 1:2, 1:1.5, 1:1, 1:0.5. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, in *vitro* disintegration time, and *in vitro* dissolution studies. Tablets with Precirol ATO-05 have shown good disintegrating features, also, the dispersion not showing any bitter taste, indicate the capability of Precirol ATO-05 used, both as taste masking agents. Almost more than 90 percent of drug was released from the formulation within 1 h. Further formulations were subjected to stability testing for 3 months at temperatures 25±5ºC/60±5%RH; 30±5ºC/65±5%RH and 40±5ºC/75±5%RH. Tablets have shown no appreciable changes with respect to taste, disintegration, and dissolution profiles.

Keywords: Lamotrigine; Melt granulation; Precirol; Taste masking; Chewable dispersible tablets.

Introduction

The bitter taste of the drugs which are orally administered often contributes to patient non-compliance in taking medicines, especially for children and elderly [1]. Unfortunately, majority of the drugs have a natural bitter taste that can create a burning feeling in the throat or in the mouth. In particular, a bitter taste can decrease the patient compliance and thus reducing an effective pharmacotherapy. In order to achieve an acceptable palatability, the addition of flavors or sweeteners is limited and may not be efficient enough to mask the taste buds of drugs and requires the use of technological processes [2]. A number of taste masking approaches like the use of ion exchange resins [3], the use of inclusion complexes with cyclodextrins [4], viscosity modifications [5] and melt granulation [6] have been described. More than 50 percent of pharmaceutical products are orally administered for several reasons and undesirable taste is one of the important formulation problem

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encountered with such oral products [7]. The 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 [8, 9].

In recent decades, a variety of research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication [10]. Among the dosage forms developed to facilitate ease of medication, the chewable dispersible tablet (CDT) is one of the most widely employed commercial products. The CDT has remarkable disintegration properties; it can disintegrate without water in the mouth. CDTs are useful in patients such as pediatric, geriatric, bedridden, or developmentally disabled who may face difficulty in swallowing conventional tablets or capsules leading to ineffective therapy, persistent nausea, sudden episodes of allergic attacks, or coughing. CDTs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores, or teething and to deliver sustained release multiparticulate system to those who cannot swallow intact sustained action tablets/capsules. Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. Chewable tablets are prepared by compression, usually utilizing, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste. Chewable dispersible tablets have the advantages like better bioavailability through bypassing disintegration (and perhaps enhancing dissolution), patient convenience through the elimination of the need for water for swallowing, possible use as a substitute for liquid dosage forms where rapid onset of action is needed, improved patient acceptance through pleasant taste, and product distinctiveness from marketing perspective. Chewable dispersible tablets represent the largest market segment of chewable dosage forms.

Melt granulation is a process by which pharmaceutical powders are efficiently agglomerated by the use of a binder which can be a molten liquid or a solid that melts during the process. [11]. Melt granulation has been successfully applied to develop sustained release formulations, taste masked formulations with lipophillic melting binders, such as glycerol monostearate, a combination of a hydrophobic materials, a starch derivative and Stearic acid among others [12-15].

Lamotrigine, an antiepileptic drug (AED) of the phenyltriazine class, is chemically unrelated to existing antiepileptic drugs. Lamotrigine is also used in the treatment of depression and bipolar disorder. Lamotrigine is thought to exert its anticonvulsant effect by stabilizing presynaptic neuronal membranes. Lamotrigine inhibits sodium currents by selectively binding to the inactivated state of the sodium channel and subsequently suppresses the release of the excilatory amino acid, glutamate.

Lamotrigine is very slightly soluble in water (0.17 mg/mL at 25°C) and slightly soluble in 0.1 M HCl (4.1 mg/mL at 25°C),having plasma half life of 24 to 35 hours [16]. In the present study it was proposed to formulate an oral delivery device in the form of chewable dispersible tablets of Lamotrigine using melt granulation technology using disintegrant Crosspovidone and taste masking agent Precirol ATO-05 with the aim of high drug serum concentration in a short period of time. The effect of different concentrations of disintegrant on disintegration time and effect of Precirol ATO-05 on taste masking and drug release was studied.

Materials and methods

Materials

Lamotrigine was obtained from Watson Pharma Pvt. Ltd. Ambernath, Thane. Crosspovidone and sodium starch glycol ate was kindly donated by Cromovideo, Italy and Scientific and Surgical Corporation, Mumbai respectively. Precirol ATO-05, Pearlitol SD 200, aspartame, sodium chloride, mint flavour, peppermint flavour were kindly donated by Watson Pharma Pvt. Ltd. Ambernath, Thane. Stearic acid, Tween 80, magnesium stearate, talc and colloidal silicone dioxide were obtained from Beijing Jingqiu Chemical Industry Co. Ltd. Beijing, China.

Compatibility study

The compatibility study was carried out to study the interaction between the drug Lamotrigine and excipients. Lamotrigine was mixed separately with the excipients at an appropriate ratio. Each mixture was stored in an open glass bottle at 40°C/75% relative humidity (RH) for 1 week. Lamotrigine was also stored alone as a reference. The interaction between the drug and excipients was then assayed using FT-IR.

Table 1. Formulation design of Lamotrigine chewable dispersible tablet.

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Hydrochlorothiazide	25	25	25	25	25	25
Crosspovidone	-	-	-	-	10.5	125
Precirol ATO-05	50	37.5	-	-	50	50
Tween-80	0.4	0.75	-	-	1.25	1.50
Pearlitol SD-200	96	65.25	142.5	102.5	49.2	47.8
Cherry flavor	3	2.25	2.25	3	2.25	2.25
Mint flavor	0.75	0.56	0.25	0.75	0.56	0.56
Sodium chloride	0.75	0.56	-	0.75	0.56	0.56
Aspartame	4	3	4	4	3	3
Aerosil	5	3.75	5	5	3.75	3.75
Magnesium stearate	5	3.75	5	5	3.75	3.75
Sodium starch glycol ate	10	7.5	10	10	-	-
Eudragit EPO	-	-	1	2.5	-	-
Stearic acid	-	-	2	1.5	-	-

Preparation of chewable dispersible tablets

The formulation design for different batches of chewable dispersible tablets of Lamotrigine is given in Table 1. The required quantity of Precirol ATO-05 was weighed. It was melted in porcelain dish at 75 ^{0}C - 80 ^{0}C for 5 min and Tween 80 was added in it. The molten mixture was added to a mixture of Lamotrigine (25mg) and Crosspovidone. The molten mixture was allowed to cool and solidify at room temperature. The solidified mass was crushed in mortar and passed through a 16 mesh sieve and thus granules were prepared.

The granules, Pearlitol SD200, aspartame, Crosspovidone (superdisintegrant), colloidal silicon dioxide and mixed fruit flavors were admixed for about 15 min to make a uniform blend. Magnesium Stearate was passed through sieve 100 and mixed with the above blend for approximately 5-7 min.

Characterization of powder blend of active pharmaceutical ingredient and excipients

The powder blend of formulation as shown in Table 1 was evaluated for following flow properties.

Angle of repose

Angle of repose was determined using funnel method [17]. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (q) was calculated using the following formula:

$$q = \tan^{-1}\frac{h}{r}$$

Bulk density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density (ρ_b) was calculated using following formula [17],

$$\rho_b = \frac{V_b}{M}$$

Table 2. Characterization of formulation blends of Lamotrigine and excipients

Parameter	F1	F2	F3	F4	F5	F6
Angle of Repose	24.15±0.1	27.40±0.1	26.17±0.03	27.17±0.01	28.45±0.05	27.38 ±0.0
Bulk Density(g/cm3)	0.492±0.0	0.464±0.01	0.477 ±0.00	0.486±0.2	0.526±0.02	0.544±0.03
Tapped Density(g/cm3)	0.538±0.01	0.559±0.01	0.589±0.1	0.593±0.0	0.662±0.1	0.660±0.0
Compressibility Index (%)	10.42±1.21	10.52±1.21	12.74±0.09	12.07±1.14	14.64±1.04	13.85±0.40
Hausner's Ratio	1.12±0.014	1.12±0.015	1.148±0.01	1.137±0.01	1.181 ±0.01	1.158±0.00
Flowability	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent

Tapped density

The measuring cylinder containing a known mass of blend (M) was tapped for a fixed time (100 tapping). The minimum volume (V_t) occupied in the cylinder and weight of the blend was measured. The tapped density (ρ_t) was calculated using following formula [17],

$$\rho_t = \frac{V_t}{M}$$

Compressibility index

The simplest method of measurement of free flow of powder is compressibility. An indication of the ease with which material can be induced to flow is given by compressibility index (I) which is calculated as follows [17],

$$I = \frac{\rho_t - \rho_b}{\rho_t} \times 100$$

Where ρ_t indicates the tapped density; ρ_b indicates the bulk density.

Hausner's ratio (H)

This is an indirect index of ease of powder flow. It is calculated by the following formula [17],

$$H = \frac{\rho_t}{\rho_b}$$

Where ρ_t indicates the tapped density; ρ_b indicates the bulk density.

Compression of powder blend

The resulting powder blends were directly compressed using 8 mm, round flat faced tooling to make the tablets of said compression specifications; using 8 station RIMEK compression machine. The tablet press setting was kept constant for all batches of formulations.

Table 3. Evaluation of prepared Lamotrigine taste masked chewable dispersible tablets.

Evaluation parameters	F1	F2	F3	F4	F5	F6
Average Weight (mg)	150	150	150	150	150	150
Thickness (mm)	3.20-3.4	3.2-3.5	3.24-3.30	3.23-3.35	3.28-3.30	3.24-3.30
Hardness (Kg/cm^2)	3.2-3.3	3.2-3.8	3.3-3.7	3.2-3.7	3.2-3.30	5.3-5.6
Friability (%)	0.512	0.528	0.312	0.298	0.265	0.219
Disintegration time (sec)	540	458	203	130	152	148
Drug Content (%)	102.36	100.23	98.45	98.43	99.69	99.24%
Cumulative drug release (%)	73.26	82.02	47.34	62.19	83.20	99.15%

Evaluation of chewable dispersible tablets

The various standards or quality control tests carried out on compressed tablets as follows:

General appearance, thickness and hardness test

Five tablets from all batches were randomly selected and organoleptic properties such as color, odor and shape were evaluated. The thickness and diameter of five tablets was measured using Vernier caliper. Hardness of the tablets was tested by using Monsanto hardness tester [18].

Table 4. Comparative dissolution profile of chewable dispersible tablets in 0.1N HCl.

Time	Cumulative % Drug Release					
(min)	F1	F2	F3	F4	F5	F6
5	16.646	46.18	7.54	22..63	29.29	40.64
10	39.189	54.36	10.43	29.02	40.315	59.55
20	58.58	62.30	24.22	38.28	51.63	74.06
30	64.27	64.87	37.24	50.98	61.32	80.72
40	64.75	70.34	40.42	53.995	68.65	83.55
50	69.17	75.31	46.65	56.15	76.58	87.07
60	73.26	82.02	47.34	62.19	83.20	99.15

Drug content uniformity

Twenty tablets were weighed and powdered. The blend equivalent to 25 mg was weighed and dissolved in sufficient quantity of 0.1M HCl. The solution was filtered through Whatmann filter paper (no.41), suitably diluted with 0.1M HCl and assayed at 267.0nm using a UV-Visible double beam spectrophotometer [19].

Weight variation and friability test

Weight variation test was performed by weighing 20 tablets individually; calculating the average weight and comparing the individual tablet weight to the average. Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for this purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Preweighed sample of tablets

was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not loose more than 1% of their weigh [20].

Table 5. Result of taste experiments.

	Score of taste test											
	F1		F2		F3		F4		F5		F6	
	No. of peoples	score	No. of peoples	score	No. of peoples	score	No. of peoples	score	No. of peoples	score	No. of peoples	score
No bitter taste	0	0	0	0	0	0	0	0	1	0	6	0
Slight bitter taste	0	0	4	0	0	0	4	4	0	0	1	5
Strong bitter taste	6	18	5	15	6	18	2	6	5	15	0	0
Mean score overall evaluation	-	03	-	1..66	-	03	-	1.66	-	03	-	0.71

***In vitro* disintegration test**

For a drug to be absorbed from a solid dosage form after oral administration it must first be in solution and the first important step toward this condition is usually the break-up of the tablet, a process known as disintegration. The disintegration time of tablet was measured in water (37^0C) according to USP Disintegration test apparatus. Three trials for each batch were performed [20].

***In Vitro* dispersion test**

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 determined [20].

***In vitro* dissolution studies**

The release rate of HCT from chewable dispersible tablet was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of 0.1 N HCL, at 37±0.5 ^{0}C and at 50rpm sample (5 mL) was withdrawn from the

dissolution apparatus every 2 min. for 30 min, and it was replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper no. 41. Absorbance of these solutions was measured at 267nm UV spectrophotometer Shimadzu 1700.

Taste evaluation

Single blind study was designed for the taste masking test and disintegration time in the buccal cavity. Six volunteers participated in the test. They were asked to rate the bitter taste of the three formulations (formulation 1–3) using a scale of 0–3. When the score was 1 or less, the taste was considered as acceptable. If the score was higher than 1, the bitterness of the formulation was not acceptable [21].

Mouth feel

The same human volunteers who 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 [22].

Wetting time

The wetting time of tablets was measured using a simple procedure [23]. A piece of tissue paper folded twice was placed in a small Petri dish containing 10 ml of distilled water. A tablet having amaranth powder on the upper surface was placed on the filter paper. Time required to develop red color on the upper surface of tablet was recorded as wetting time.

Stability studies

Stability studies were carried out at 25±5°C/60±5%RH; 30±5°C/65±5%RH and 40±5°C/75±5%RH for a period of 1, 2 and 3 months for the formulations as per ICH guidelines.

Result and discussion

IR spectroscopy was used as means of studying drug-excipients compatibility which indicates no drug-excipients interaction.

The value of compressibility index below 15% indicates a powder which usually gives rise to excellent flow characteristics, whereas above 25% indicate poor flowability. Lower Hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25). The following table shows the characterization of each formulation.

The size and shape of the tablet can also affect the disintegration time and subsequent dissolution profile. The size of the tablet was 8 mm and shape of tablet was flat round oval. The color of the tablet was white and the flavor is which on the basis of flavor added which is patient compliant. Tablet crushing strength, the critical parameter was controlled as the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness for all formulation batches i.e. F1 to F6 was found to be between 3.2-5.6 Kg/cm^2. Thickness for all formulation batches i.e. F1 to F6 was found to be between 3.21 to 3.46 mm.

Drug content for all formulation batches i.e. F1 to F6 was found to be in the range of 98.43and 103.36%. Uniformity of content for all formulation batches i.e. F1 to F6 was found to be in the range of 98.00 to 101.99%. Uniform weight due to uniform die fill with acceptable variation as per standards was obtained since blend of material was free-flowing. The percent deviation in weight variation for all formulation batches i.e. F1 to F6 was found to be 150mg ± 1.0%. Hence, weight variation test for all batches of tablets comply specifications. The % friability values for all formulation batches i.e. F1 to F6 were found to be between 0.200 to 0.500%.

Disintegration time is an important criterion for selecting an optimum CDT formulation. Several methods have been described for evaluating in vitro disintegration time of CDT formulations. It was observed that decreasing the concentration of Precirol-ATO resulted in a decrease in disintegration time. The in-vitro disintegration of CDTs shows disintegration time from 540-148 seconds. From this result it was concluded that the disintegration time of the formulated batches is in the range.

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a chewable-dispersible tablet, mouth dissolving, oro-dispersible tablets. The in-vitro dispersion time shows better chewable and dispersion of tablet in the salivary fluid pH 6.8.

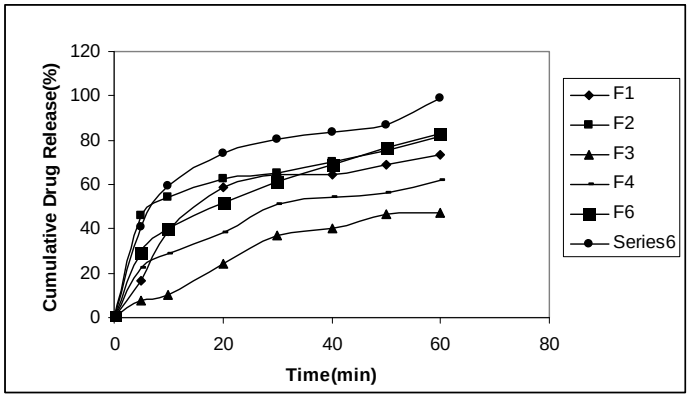

Figure 1. Comparative dissolution profile of HCTz formulations.

The mean score less than 1 for the formulation 6 indicated that the formulation containing Precirol ATO-05 sufficiently alleviate the bitterness of CDT tablets. F6 formulation 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 Precirol ATO-05. The Precirol in 1:2 proportions with drug gives better taste masking, which did not show any result on drug release.

All formulations show smooth and pleasant mouth feeling, but formulation F6 shows better mouth feel as compare to other formulations thus fulfill the requirements of chewable-dispersible tablets. As increase the concentration of the Precirol there is bitterness of the formulation as reduces the concentration better mouth feeling effect. The wetting time was rapid in Crosspovidone followed by Sodium starch glycol ate. Here also it was observed that as the concentration of disintegrant increased the time taken for wetting was reduced. As the concentration of

Crosspovidone was increased from formulation F4 to F6 the wetting time was reduced.

There was no color, and odor change at any temperature. There is no change in the *in vitro* dispersion time, *in vitro* disintegration time, and *in vitro* dissolution profiles after three months of stability studies for F6 formulation at different temperatures.

Precirol ATO-05 could not retard the release in optimized formulation but it acts as taste masking agent. The amount of Precirol ATO-05 used affects the taste masking and drug release profile. So the optimized formulation is suitable for geriatric patients in treatment of epilepsy and for bipolar diseases in patients older than 2 yrs of an age. which gives better taste masking and fast onset of action as compared to conventional tablet.

Conclusion

In conclusion, we achieved our objective of preparing chewable dispersible tablets of Lamotrigine by melt granulation. Also a prerequisite, taste masking of Lamotrigine by preparing a taste masked granules of Lamotrigine with Precirol ATO-05. These patient compliant tablets that had a good taste and are useful for pediatric and geriatric populations and can be commercialized

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