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RAPIDLY DISINTEGRATING TABLETS CONTAINING TASTE MASKED CLARITHROMYCIN

Ashish Kumar[1], Mittal Vinit[2] and Kaushik Deepak[2*]

[1]Research Scientist, Ranbaxy Research Labs, Gurgaon, India.

[2]Department of Pharmaceutical Sciences, Maharshi Dayanand University, Rohtak-124001, Haryana, India.

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ABSTRACT

The objective of this study was to mask the bitter taste of clarithromycin and to formulate rapidly disintegrating tablets (RDT) of the taste masked drug. Taste masking was achieved by melt granulation method using cetyl alcohol as meltable binder. Dissolution aid (KollidonCL) was added in the formulation to improve the dissolution rate of taste masked granules as the lipids are known to retard the dissolution. The formulation having drug-lipid-dissolution aid ratio of 1:1:0.15 showed significant taste masking, confirmed by drug release study in phosphate buffer pH 6.8 and taste evaluation. Taste evaluation of taste masked granules in human volunteers revealed considerable taste masking within 10s, whereas claritromycin was rated as very bitter with a score of +4 for 10s. The taste masked granules were formulated as rapid disintegrating tablets using disintegrant addition approach. Tablets were evaluated for various parameters such as hardness, friability, drug content, in-vitro and in-vivo disintegration time and dissolution rate. Tablets of batch F6 containing Kollidon CL as superdisintegrating agent showed faster disintegration. Dissolution profile of optimized RDT in phosphate buffer pH 6.8 showed reduction in dissolution rate initially but more than 85% drug was dissolved after 45 min. The release profile thus obtained proved that the tablet could provide effective taste masking characteristics without compromising with dissolution rate.

Keywords: *Clarithromycin; melt granulation; taste masking; rapidly disintegrating tablets.*

INTRODUCTION

The bitter taste of medicaments results in poor compliance from the patients especially infants, children and elderly. The macrolide antibiotic, clarithromycin is extremely bitter in taste and effective in the treatment of various infections in children and elderly patients, which often experience difficulty in swallowing solid oral dosages forms. The bitter taste of clarithromycin needs to be masked in order to provide a more palatable dosage form.

Numerous techniques have been described in academic and patent literature for masking of bitter or undesirable taste of drugs like addition of flavors and sweetener, microencapsulation, inclusion complexation with cyclodextrin, complexation with ion exchange resin, salt preparation, group alteration and prodrug approach[1-5]. The high bitterness intensity of clarithromycin has led to development of various approaches for its taste masking in pharmaceutical formulations[6-8]. In the present study the taste masking of clarithromycin was achieved using melt granulation technique. Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations[9].

Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets. A melt granulation process efficiently agglomerates pharmaceutical powders for use in both immediate- and sustained-release solid dosage forms. The process utilizes materials that are effective as granulating fluids when they are in the molten state. Cooling of the agglomerated powders and the resultant solidification of the molten materials completes the granulation process[10]. In this technique neither solvent nor water is used and fewer processing steps are required as the time consuming drying step is eliminated. Moreover there are no requirements on the compressibility of active ingredients and the entire procedure is simple, continuous and efficient resulting in a uniform dispersion of drug in the meltable carrier. The lipids are often used as meltable binder and their use for taste masking is also described in patent literature. Menjoge et al. employed lipids in combination with the pH dependent polymer which are either acid soluble or swellable. The lipid-polymer matrix delivered substantial amount of the bitter drug immediately at the gastric pH with improved palatability[11].

In the present work, the technique of melt granulation was applied to prepare the taste masked granules of clarithromycin using cetyl alcohol as meltable binder.

***Correspondence :** deepkaushik@rediffmail.com

Cetyl alcohol was chosen for the study as it is hydrophobic, stable under ordinary conditions, nontoxic at the concentration used and having a melting point of 56º which meets the process requirements. Since lipids retards the dissolution and hence bioavailability of clarithromycin therefore a dissolution aid was used so that taste masking is achieved without affecting the dissolution rate. The taste masked granules were formulated as rapidly disintegrating tablets using disintegrant addition approach.

MATERIALS AND METHODS

Materials

Clarithromycin USP, Ac-di-Sol and Kollidon CL were received as gift sample from Ranbaxy PDR, Gurgaon, India. Cetyl alcohol was purchased from Loba Chemie, India. All other chemicals were of analytical grade and used as received.

Preparation of taste masked granules

Melt granules of clarithromycin with cetyl alcohol was prepared in the drug: cetyl alcohol ratio of 1:1, 1:1.5 and 1:2. The granules were prepared by first melting cetyl alcohol 5ºC above its melting point in a beaker and then the drug and the dissolution aid were uniformly dispersed into the melt for 15min. and the dispersion was then transferred to rapid mixer granulator(RMG of 2.5 lit. capacity), Sainath Boilers and Pneumatics, Mumbai make. The dispersion was then cooled at room temperature with continuous stirring at 1000 rpm for 10 min and using the chopper to obtain uniform granules. The drug lipid matrix was finally passed through sieve #. 40 to obtain melt granules of clarithromycin.

Taste evaluation of the granules

The bitterness evaluation test was performed with human volunteers according to a previously described method[12] which was duly approved by the ethical committee. Test was carried out on a trained taste panel of 6 human volunteers (3 males and 3 females, with a mean age of 25 years), from whom informed consent was first obtained. The volunteers rinsed their mouths thoroughly before and after the tasting. Each sample was held in the volunteers' mouths for 30s and then expectorated, and the taste was evaluated and assigned a numerical value according to the following scale: 0- Tasteless, 1- Slight bitter, 2- Moderate bitter, 3- Strong bitter. The lower score indicated a greater masking effect.

In-Vitro Dissolution of the granules

Drug release was determined by adding taste masked granules equivalent to 125 mg of drug in 900 ml of dissolution media phosphate buffer pH 6.8 in a USP Apparatus II dissolution apparatus(Electrolab, India) using a paddle at 50 rpm. The samples were withdrawn after 30 minutes. After suitable dilution filtrate were then analyzed by HPLC (Jasco, UV-2075 plus).). The HPLC set up used for analysis consisted of mobile phase (mixture of methanol and 0.067 M KH_2PO_4 (650:3500, pH adjust 4.0 with phosphoric acid), column 4.6mm X 15cm, packaging L1 (of USP), 1ml/min flow rate, 20µl dose applied, UV detector and wavelength of 210nm.

Preparation of diluting granules

Diluting granules were prepared using an accurately weighed quantity of microcrystalline cellulose (60%w/w) and mannitol (35%w/w). The granulating agent used was PVP K30 (5%w/w). All three ingredients were granulated with water as granulating liquid using a rapid mixer granulator (Sainath Boilers and Pneumatics, Mumbai). The granules were then passed through sieve #.22 and dried at 60°C using fluid bed dryer (Retsch, Germany). Dried granules were sized by passing through sieve # 40 to obtain free flowing granules.

Formulation of rapidly disintegrating tablets

Taste masked granules equivalent to 125mg of clarithromycin, diluting granules and other tablet excipients were then accurately weighed and mixed thoroughly using a double cone blender (2.5 lit. capcity, Karnavati engineering Ltd. Mumbai) for 15min. Finally magnesium stearate and talc were added and tablets were compressed on 7mm flat faced punches using 16 station rotary tablet making machine(CMD3-16, Cadmach Machinery Co. Pvt. Ltd., Ahmedabad).

Evaluation of tablets

The prepared tablets were tested as per standard procedure for hardness, friability, disintegration, uniformity of dispersion, and drug content

Hardness

Hardness of tablet was determined using Monsanto hardness tester.

Friability

Ten tablets were used from each batch for friability test using Electrolab tablet friability tester. The weight of tablets was compared before and after 4 minute test (100 rotations). Tablet friability was reported as percentage weight loss

In-vitro Disintegration study

Randomly six tablets were selected for disintegration test. The test was performed without disc in simulated gastric fluid (37±0.5°C) using automated disintegration test apparatus (Electrolab).

Uniformity of dispersion test

Two tablets were dropped in 100 ml water (at 25ºc in a beaker).The tablet were allowed to disintegrate and the dispersion was then stirred for 30s with a glass rod until a smooth dispersion was obtained. The dispersion was passed through 710µm sieve (#.22). Sieve screen was checked for any portion remains above the sieve.

Particle size analysis

The particle size distribution of taste masked granules and final blend was carried out using Jaysons sieve shaker. The sieve shaker was operated for 15min using sieve #60, #80, #100 and pan and the % weight retained was determined.

In-Vitro dissolution rate study

Dissolution studies of tablets were performed according to USP XXIII Type II apparatus in phosphate buffer pH 6.8 (simulating salivary pH) by adding randomly selected tablets in 900 ml of dissolution media. The temperature was maintained at 37±0.5°C and the rotation speed was 50 rpm. The samples were withdrawn at various time intervals and analyzed by HPLC.

Taste Evaluation study

Bitterness of formulated dispersible tablets was evaluated by same method as was used in case of evaluation of taste in taste masked granules and compared with marketed dispersible tablet.

Stability studies

Optimized tablets were subjected to accelerated stability studies at 40°C±2°C/75%±5%RH for three months in environmental test chamber by ThermoLab and analyzed for taste, drug content and drug release after suitable time intervals

RESULT AND DISCUSSION

Matrix of clarithromycin with cetyl alcohol was prepared by using different ratio of clarithromycin: cetyl alcohol i.e. 1:1(G1), 1:1.5(G2) and 1:2(G3). Bitterness was evaluated by trained taste panel and the results as shown in (Table 1) revealed that there is slight bitterness felt by human volunteers in case of 1:0.5 after 10s and 20s as evident by their bitterness score of (1) after 10s and (2) after 20s. In case of 1:1 and 1:2 there was considerable taste masking within 10s, whereas clarithromycin was rated very bitter with a score of +4 for 10s. The ratio of 1:1(G2) showed good taste masking abilities which was comparable to that 1:2(G3). Hence the ratio of 1:1 was selected for further studies as the there is no advantage in selecting the ratio containing higher lipid amount which will add to the cost of formulation.

Table 1: *Bitterness evaluation of TMGs by taste panel*

Type of Product		Volunteers Score					
		I	II	III	IV	V	VI
Pure drug	10s	4+	4+	4+	4+	4+	4+
G1	10 s	1	0	0	1	0	1
	20 s	1	2	1	1	2	1
	30 s	2	1	2	2	2	1
G2	10 s	0	0	0	0	0	0
	20 s	0	0	0.5	0	0	0.5
	30 s	1	0	0	0	0	0
G3	10 s	0	0	0	0	0	0
	20 s	0	0	1	0	0	1
	30 s	0	0	0	0	0	1

0-tasteless, 0.5-very slight, 1.0-slight, 2.0-moderate, 3.0-strong, 4.0-very strong

Since lipid retards the dissolution rate and hence bioavailability of clarithromycin, it was necessary to use dissolution aid (water swellable) intragranularly so that taste masking is achieved without affecting the dissolution rate. The various dissolution aids such as Kollidon CL and Sodium Starch Glycollate were used for the study. More than 99 % of drug was released in case of granules which were prepared using Kollidon CL and amount of drug released was much higher than in other preparations and hence Kollidon CL was selected as dissolution aid. Different Ratio of clarithromycin: cetyl alcohol: Kollidon CL were used (1:1: 0.10(TMG1), 1:1: 0.15(TMG2) and 1:1: 0.20 (TMG3) for the preparation of granules (Table 2) and dissolution was carried out in phosphate buffer pH 6.8.

Table 2: *Ratio of drug, lipid and dissolution aid*

Preparation code	Clarithromycin :cetyl alcohol:kollidon CL
TMG1	1:1: 0.10
TMG2	1:1: 0.15
TMG3	1:1: 0.20

Dissolution rate studies in phosphate buffer pH 6.8 showed that more than 75 % of pure drug was dissolved in 5 minutes, while in the same period the dissolution of clarithromycin from different taste masked granules was below 50% (Fig. 1). The dissolution of clarithromycin is thus reduced at salivary pH from the granules. This reduction of dissolution rate of clarithromycin from the granules is responsible for reduction of the bitterness of drug. The reduction in dissolution rate in case of TMG1 was less than TMG2 and TMG3. The batch TMG2 having good taste masking property and contating less concentration of dissolution aid as compared to TMG3 , was selected for further evaluation.

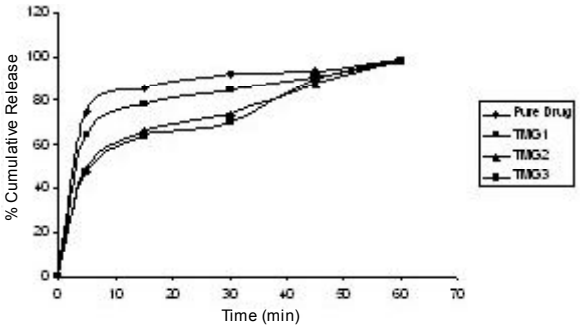

Fig.1: *Dissolution profiles of pure drug and taste masked granules*

Table 3: *Formulation Compositions of Rapidly disintegrating tablets*

Parameters*	F1	F2	F3	F4	F5	F6
Ingredients(mg)	F1	F2	F3	F4	F5	F6
Taste masked granules*	275	275	275	275	275	275
Diluting granules	62	44.5	27	62	44.5	27
Ac-di-Sol	17.5	35	52.5			
Kollidon CL				17.5	35	52.5
Aspartame	21	21	21	21	21	21
Raspberry dry flavor	14	14	14	14	14	14
Magnesium stearate	3.5	3.5	3.5	3.5	3.5	3.5
Talcum	7	7	7	7	7	7
Total	400	400	400	400	400	400

* Equivalent to 125mg of claritromycin

The taste masked granules were formulated as rapidly disintegrating tablets by using super disintegrating agents. Six trials as shown in (Table 3) were taken in which different super disintegrating agents in different concentration were used to optimize the formulation. The optimized formulation was decided on the basis of disintegration time of tablet. From the evaluation of tablets as shown in (Table 4), formulation F6 containing Kollidon CL disintegrated quickly than other formulations (In-vitro disintegration time of 44.33±0.25). The other tablet properties such as hardness (3.38±0.21), friability (0.18±0.25) and weight variation (398.54±0.32) were found to be well within the limits.

Table 4: *Evaluation of rapidly disintegrating tablets of taste masked granules*

Parameters*	F1	F2	F3	F4	F5	F6
Hardness	3.18±0.18	3.58±0.26	3.68±0.14	3.08±0.12	3.18±0.32	3.38±0.21
% Friability	0.18±0.25	0.18±0.25	0.18±0.25	0.18±0.25	0.18±0.25	0.18±0.25
In-Vitro disintegration time,s	58.33±0.25	54.33±0.25	62.33±0.25	52.33±0.25	62.33±0.25	44.33±0.25
Weight Variation	398.14±0.46	401.52±0.24	397.32±0.25	400.01±0.42	398.64±0.18	398.54±0.32
Content Uniformity,%	99.14±0.46	98.24±0.22	99.04±0.16	100.14±0.28	98.14±0.26	100.08±0.23
Uniformity of Dispersion	Pass	Pass	Pass	Pass	Pass	Pass

**Mean±S.D. (n=3)*

The particle size analysis of taste masked granules and the final blend for compression was determined as the particle size could affect not only the dissolution rate, but also the grittiness. There was uniformity in the particle size distribution of taste masked granules and the granules of final blend (Table 5).

Table 5. Mesh analysis of taste masked granules and the final blend

Sieve No.	% Weight Retained	
	Taste masked Granlules	Final blend
60#	47 ±2.56	51 ±2.76
80#	13 ±1.64	9± 0.98
100#	22 ±2.06	21 ±1.22
Pan	18 ±0.86	19 ±1.08

The dissolution rate study was designed to assess whether the dissolution rate is retarded or not during the initial period in order to suppress the bitterness. The dissolution rate studies of optimized RDT in phosphate buffer pH 6.8 showed that approximately 40% of drug was dissolved in 5 minutes, while in the same period the dissolution of clarithromycin from marketed RDT was more than 75% (Fig.2). The dissolution of clarithromycin is thus reduced at salivary pH from the optimized tablets and this reduction of dissolution rate is responsible for reduction of the bitterness of the drug which is further proved by the taste masking studies. By virtue of suppression of dissolution rate in the initial period, the benefits achieved of taste masking and better patient acceptance might outweigh a slight delay in drug release. Bitterness of optimized dispersible tablet (F6) of clarithromycin was evaluated and compared with marketed dispersible tablet for taste characteristics by trained taste panel. Taste of F6 was found to be acceptable, while the marketed formulation was found to have unacceptable taste with moderate to strong bitter taste.

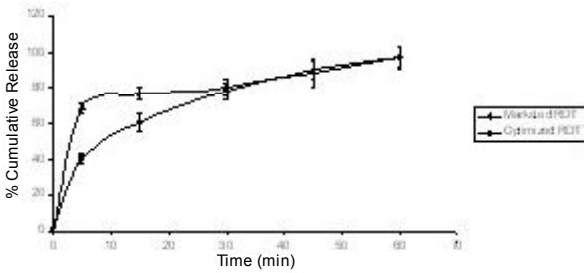

Fig. 2: *Comparative dissolution profile of optimized and marketed RDT*

The optimized tablets were subjected to accelerated stability testing in an environmental test chamber (ThermoLab) at 40°c/75%RH for 3 months .The samples were withdrawn after 30 days and analyzed for taste, drug content, disintegration time and dissolution rate. The accelerated studies revealed that the optimized RDT were stable and the dissolution rate profile after 3 months was found to be comparable with initial dissolution rate profile (Fig. 3).

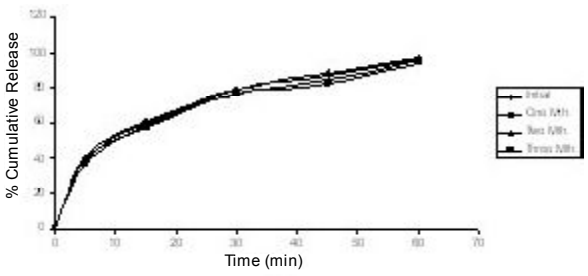

Fig. 3: *Comparitive dissolution profile after stability studies*

CONCLUSION

An effective taste masking was achieved for clarithromycin using the technique of melt granulation. Cetyl alcohol proved to be an effective meltable binder and incorporation of Kollidon CL as dissolution aid ensured good dissolution of taste masked granules. The optimized rapidly disintegrating tablets of clarithromycin were highly satisfactory and can be recommended for the evaluation of bioavailability.

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