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DEVELOPMENT AND EVALUATION OF TASTE MASKED CLARITHROMYCIN ORAL SUSPENSION

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ABSTRACT

Most of the pharmaceuticals are administered by the oral route which is the popular route of drug delivery. Taste is an essential and critical parameter in administering formulations which have relation with taste buds. Several drugs have bitter taste, consequently there is a consistent problem in the treatment of the patients because of their inability to swallow such formulations. Four formulations of taste masked granules of clarithromycin were thus prepared by wet granulation and enteric-coating techniques using different concentrations of taste masking agent and two coating materials. The resulting clarithromycin granules were characterized for size distribution, content determination, dissolution at phosphate buffer (pH 6.8), release in 0.1N HCl and taste evaluation. Among these formulations, Formulation D showed minimum bitterness, better dissolution profile at phosphate buffer at pH 6.8 and higher resistance to the acidic medium comparing to other formulations. The formulation D presented showed to be a good base for preparing an oral reconstitutable suspension, which was evaluated for various parameters like drug content, dissolution at phosphate buffer at pH 6.8 and taste evaluation. The oral taste masked suspension prepared disposed respectable decline in the sour taste of clarithromycin and similar dissolution profile in comparison with marketed suspension.

INTRODUCTION

Bitter, sour or unsweetened tastes are intensely unacceptable if using the oral route of delivery, especially in the case of drugs for pediatric use (Szejtli and Szente, 2005; Ernest *et al*., 2007). The majority of the orally administered drugs including antibiotics such as sparfloxacin or clarithromycin are bitter in taste (Shirai *et al*., 1994; Shirai *et al*., 1993; Yajima *et al*., 1999). However, such drugs are not easy to swallow, resulting in non patient compliance and a decrease in therapeutic efficacy. Solid preparations such as capsules and tablets are not proposed for pediatric patients, preferably liquid preparations are used. It is common that dissolved substances educe taste sensation, therefore, the drugs are highly astringent (Szejtli and Szente, 2005). To surmount this problem, masking of bitterness becomes essential and done by masking the bitter taste of drugs by either decreasing its oral solubility or the amount of drug particles exposed to taste, therefore reducing the perception of bitter taste. Many techniques used for taste masking are based on coatings (Douroumis *et al*., 2011), complexation (Arima *et al*., 2012), granulation (Pawar and Joshi, 2014), solid dispersion system (Shah *et al*., 2007) and microencapsulation techniques (Lorenzo-Lamosa *et al*., 1997) such as simple and complex coacervation (Hashimoto *et al*., 2002), solvent evaporation (Al-Omran *et al*., 2002) and spray- drying (Vehring, 2008; Elversson and Millqvist-Fureby, 2006) or spray congealing (Robson *et al*., 1999).Taste masking is the major factor in the development of the dosage form. It not only improves the taste of molecule (Douroumis, 2007) but also the formulation and performance of the substance, patient compliance and better therapeutic efficacy (Matsui, 2007). The dose of a drug may edict if a selective formulation strategy would be convenient to realize taste masking. In pediatric, the dose is limited in order to grant the use of flavoring substances to mask the taste of the molecule. In our case, coating is the most efficient method to achieve taste masking in order to obtain an adequate eventual dosage framework size (Joshi and Petereit, 2013). Clarithromycin (CLM) (6-0-methyl-erythromycin A) is a 14-membered macrolide antimicrobial agent widely used to treat many different types of bacterial infections affecting the skin and responsible for respiratory tract diseases (Langtry and Brogden, 1997; Carbon and Poole, 1999). It is also used together with other medicines to treat stomach ulcers caused by helicobacter pylori (Rajinikanth and Mishra, 2008), pharyngitis, maxillary sinusitis, pneumonia and acute bacterial intensification of chronic bronchitis (Neu and Chick, 1993).This drug is stable in the gastric acid and well absorbed from the gastrointestinal tract, but its bioavailability is relatively little (55%) due to first-pass metabolism (Chu *et al*., 1992 ; Davey, 1991). Clarithromycin (CLM) has a very

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bitter taste and therefore presents as a model drug to estimate taste-masking efficiency for many kinds of oral formulations. The purpose of this work was to develop clarithromycin taste masked pharmaceutical granules from which a stable oral reconstitutable suspension can then be prepared . In the present study, our initial goal was to prepare clrithromycin granules using granulation technique and to apply enteric coating by using two different coating materials to mask the bitter taste of clarithromycin. The granules of formulations were then evaluated for various parameters like granule size distribution, granules content determination, granules release in HCl 0.1N and dissolution at phosphate buffer at pH 6.8. The oral suspension was prepared by using the clarithromycin granules selected to which was added suitable excipients like a preservative, a diluent, a sweetener, a suspending agent, a lubricant and aromas.

MATERIALS AND METHODS

Materials

Clarithromycin (CLM) was purchased from Alembic Pharmaceuticals Limited (India). Carbopol 974P was procured from Noveon company (Mumbai, India). Acrycoat L-30D and hydroxypropyl methylcellulose phthalate 55 (HPMCP 55) were obtained from Colorcon (West Point, PA, United States). Polyvinylpyrrolidone (PVP K90) was purchased from Suan Pharma (Madrid, Spain). Potassium sorbate, maltodextrin, Xanthan gum and titanium dioxide were purchased from Kirch Pharma (Salzgitter, Germany). Aroma blueberry and aroma masking were received from International pharmaceutical flavours and Fragrances (New York, United States). Potassium dihydrogen phosphate was obtained from Sigma-Aldrich (Darmstadt, Germany) as well as phosphoric acid. Water used was double distilled and filtered through 0.45µm filter. Other chemicals used were of analytical or HPLC grade.

Preparation of clarithromycin granules

The quantities of all ingredients used for the different formulations are given in Table-1 .The batch size was 1 Kg for each formulation. Clarithromycin granules for oral suspension are made by mixing clarithromycin with Carbopol 974P (formulations A and B) and with Acrypol 934 (formulations C and D). Purified water was taken in a clean stainless container and then PVP-K90 was added under continuous stirring. This solution of PVP-K90 was used to granulate the blend of clarithromycin and carbopol 974P.The granules formed were dried at 70°C until loss on drying is NMT 5% .In order to coat the formulated granules (Table 1), two coating materials namely HPMCP-55 and Acrycoat L-30D were employed. Finally, the granules were dried at 70°C and then sifted to obtain clarithromycin granules 27%.

Characterisation of Granules

Granule size distribution

The granule size distribution was determined using a sieving apparatus (Sieving AS 200 basic, Retsh, Haan, Germany). Four standard sieves (Linker, Kassel, Germany) were used in the range of 250-850 µm. The retained particles percent for each fraction collected was calculated using the following expression:

$$\text{Retained particles percent (\%)} = \frac{Wfs - Wes}{Wes} \quad 100$$

Where, Wfs is weight of full sieve in g and Wes is weight of empty sieve in g.

Granules content determination

Granules (50 mg) were dissolved in methanol (10 mL) and made up to the volume with mobile phase (50 mL) which consisted of methanol - buffer in the ratio 65:35. The buffer was prepared by weighing 9.12 g of potassium dihydrogen phosphate in 1000 mL of water. The contents of clarithromycin in each formulation were determined using HPLC system, a Waters Alliance e2695 Technology (E10SM4327A, United States). The system supplied with auto sampler, quaternary pump, degasser and a PDA Detector. The column used was a Kromazil C_{18}, 5µm particle (4.6 x 150 mm), column temperature was maintained to 50°C. The flow rate of mobile phase was kept 1 mL/min. The injection volume was 50 µl and ultraviolet (UV) detection was at 210 nm. The final pH was adjusted to 4 with dilute phosphoric acid 0.05 M.

Dissolution at Phosphate buffer Study (pH 6.8)

Dissolution tests were performed using the USP apparatus 2 paddle method (Sotax-Type AT7 smart dissolution apparatus, Switzerland) rotating at 50 rpm. A volume of 900 ml of pH 6.8 phosphate buffer solution was used at a temperature of 37°C±1°C. Each sample contained the equivalent to about 250 mg of clartithromycin. The samples (10 ml) were withdrawn at time intervals: 10, 20, 30, 45 and 60 min, filtered and analyzed by HPLC. The chromatographic conditions were the same used for the granules content determination. The dissolution tests were performed in sixtuplicate and the amounts of clarithromycin released were calculated.

Granules release in 0.1 N HCl

The procedure follows the same method given for the dissolution at pH6.8 phosphate buffer but, the medium of the dissolution used was 0.1 N HCl. The samples (10 ml) were withdrawn at time intervals: 10, 20, 30, 45 and 60 min. The amounts of clarithromycin dissolved were then determined.

Taste evaluation of granules

Taste evaluation was made by six volunteers using time intensity procedure. About 15 mg granules of the four formulations was kept in mouth for 1 min. These volunteers were demanded to evaluate the granules for taste and were informed not to swallow the granules, which were located on the tongue. Bitterness levels were registered at 2, 10 and 60 sec. The bitterness level of granules of each formulation was determined against 15 mg of pure clarithromycin using a scale (0: No Bitter, X: Threshold Bitter, 1: Slight Bitter, 2: Moderate Bitter, 3: Strong Bitter). After the realization of test, volunteers were informed to completely wash their mouth with distilled water.

Formulation of developed oral taste masked suspension of clarithromycin

Taking into account the characteristics of formulated coated granules, the oral reconstitutable suspension (125 mg clarithromycin / 5 ml) was formulated. All ingredients used for the preparation of oral suspension are presented in Table-2. In a separate vessel, the amount of potassium sorbate was dissolved in purified water and then granulated with the mixture of sucrose and maltodextrin .The granules were dried until humidity content is less than 1% and passed through sieve 10 # to get the same particle size. The above granules were mixed with clarithromycin granules. Titanium dioxide, aroma blueberry, aroma masking, xanthan gum, citric acid and colloidal silicon dioxide were added to the mixture. The oral suspension formed is reconstituted up to 37.5 ml with water before use.

Evaluation of oral taste masked suspension of clarithromycin

Dissolution at Phosphate buffer (pH 6.8)

Dissolution parameters and the chromatographic conditions follow the same method given for the granules. The dissolution profile of prepared suspension was compared with marketed preparation.

Taste evaluation of developed oral suspension

Taste evaluation was done by six volunteers using time intensity technique. 5 mL of oral prepared suspension and 10 mL of marketed preparation (Zeclar, Abbott) were located on the tongue. Bitterness levels of the two preparations were noted after 10 sec, 1 min and 2 min.

RESULTS AND DISCUSSION

Granule size distribution and content of clarithromycin granules

All the formulations had produced granules of good quality and regular shaped. The cumulative frequency for formulations of group 1 was 12,4 , 15,3 ,56.4 and 9,2 % for granules having a size range of 125, 250, 355 and 425 µm, respectively. For group 2 formulations, the cumulative frequency was 10,3% for the 250 µm size range, 53,2% for 355 µm and 49,8 % for 425 µm. Overall group 2 formulations produced larger granules comparing to group 1 formulations essentially due to the addition of a lower amount of PVP (Al-Omran *et al*., 2002, Albertini *et al*., 2004). The yield of granules from granulation group1 and group 2 was 90% (w/w) and 95% (w/w).

Table 1. Formulation and process variables for the preparation of clarithromycin granules 27%

Ingredients	Group 1		Group 2	
	Formulation A	Formulation B	Formulation C	Formulation D
Clarithromycin (g)	270	270	270	270
Acrypol 934 (g)	110	120	140	155
PVP K90 (g)	50	40	40	35
Purified water (mL)	q.s	q.s	q.s	q.s
HPMCP-55 (g)	470	480	-	-
Acrycoat L-30D (g)	-	-	465	465
Triethyl citrate (g)	100	90	85	75
Acetone (mL)	q.s	q,s	q.s	q.s
Ethanol (mL)	q.s	q.s	q.s	q.s

Table 2. Formulation of oral taste masked suspension

Ingredients	Quantity (g) for 125mg Clarithromycin/5ml of suspension
Clarithromycin granules	5.555
Potassium sorbate	0.24
Sucrose	32.460
Maltodextrin	3.13
Xanthan gum	0.0456
Aroma blueberry	0.124
Aroma masking	0.304
Colloidal silicon dioxide	0.06
Citric acid	0.050
Titanium dioxide	0.428
Purified water	q.s.
Weight of each bottle	42.39

Table 3. Content of CLM granules as a function of particle size

Granules Size (µm)	Theoretical amount of CLM per 100mg of granules (mg)	Actual amount of CLM calculated in mg (% drug loading)	
		Group 1	Group 2
125<x<250	27	23,65 (87,59)	25.33 (93,81)
250<x<355	27	24,02 (88.96)	24.56 (90,96)
355<x<425	27	23,33 (86.40)	26.48 (98,07)
425<x<1000	27	25,45 (94.25)	25.15 (93,14)

Table 4. Results of Taste evaluation of formulations

Volunteers	Bitterness level after														
	Pure drug			Formulation A			Formulation B			Formulation C			Formulation D		
	2 sec	10 sec	60 sec	2 sec	10 sec	60 sec	2 sec	10 sec	60 sec	2 sec	10 sec	60 sec	2 sec	10 sec	60 sec
1	3	3	3	X	3	3	X	2	3	X	2	3	0	0	0
2	3	3	3	1	3	3	X	2	3	1	3	3	0	0	0
3	3	3	3	1	2	3	1	3	3	X	3	3	0	0	0
4	3	3	3	1	3	3	1	2	3	1	2	3	0	0	0
5	3	3	3	X	3	3	1	3	3	X	2	3	0	0	0
6	3	3	3	1	3	3	X	3	3	0	2	3	0	0	0
Mean Human Response	10	10	10	56.67	13.33	10	60	20	10	66.67	23.33	10	90	90	90

Score: 3=0-20%; 2=20-40%; 1=40-60%; X=60-80%; 0=80-100%

Table 5. Comparative in vitro release of clarithromycin suspension with marketed suspension in phosphate buffer pH 6.8

Time in min	CLM oral suspension	Marketed suspension
0	21.36	24.21
20	74.30	77.40
30	90.44	91.45
45	97.85	94.65
60	98.20	95.12

Table 6 . Difference factor (f1) and similarity factor (f2) at phosphate buffer pH6.8

Test comparison	Factor	pH 6.8 phosphate buffer
CLM oral suspension versus marketed suspension	f1	3
	f2	76.52

Table 7. Results of Taste evaluation of oral suspension compared with marketed suspension

Volunteers	Bitterness level after					
	Oral suspension			Marketed suspension		
	10 sec	1 min	2 min	10 sec	1 min	2 min
1	0	0	0	0	0	0
2	0	0	0	0	X	0
3	0	0	0	0	0	X
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	0	0	0	0	X
Mean Human Response	90	90	90	90	86.67	83.33

respectively, which indicates a very small loss of material throughout the granulation process. The actual amounts of clarithromycin of each fraction in the two groups of formulations as well as the contents of clarithromycin were determined. (Table 3)

Dissolution at phosphate buffer (pH 6.8)

The in vitro release profile of clarithromycin granules of different formulations was studied comparing to pure clarithromycin.The plots of % cumulative drug release v/s Time (min) for developed granules are represented (Fig. 1). After 60 min, the percentage of clarithromycin released from formulations A, B, C and D and pure clarithromycin was 91.13, 92,56, 98,67, 100,3 and 100,5 , respectively. Formulation D revealed better dissolution profile than other formulations, which could be related not only to the higher amount of Acrypol 934 which enhanced the release of the drug and also the lower amount of PVP (Shahbaziniaz *et al*., 2013).

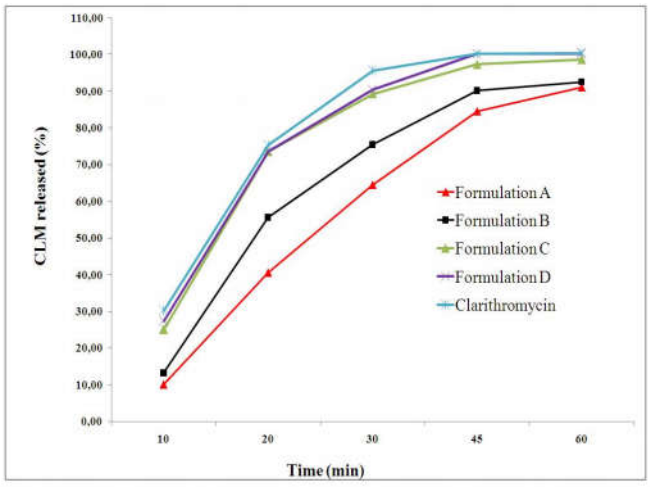

Fig. 1. In vitro release profile of clarithromycin granules in phosphate buffer pH 6.8

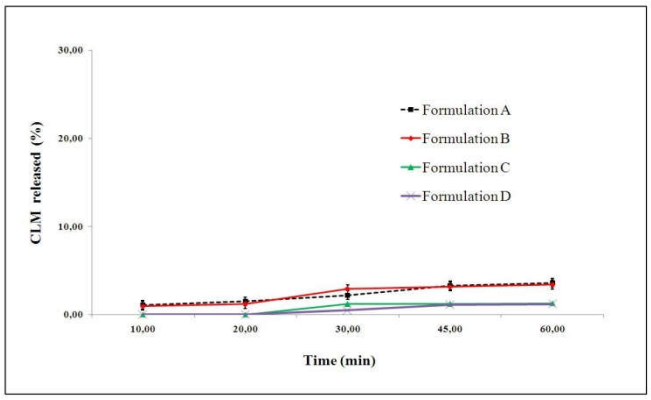

Fig. 2. Dissolution behavior of clarithromycin granules in 0.1N HCl

Granules release in 0.1 N HCl

The dissolution behavior of the prepared granules in 0.1N HCl was observed (Fig.2).The percentage of clarithromycin released from formulations A, B, C and D was 3.6, 3.4, 1.3 and 1.2 , respectively after 60 min. These results indicate that the granules of formulation D show higher resistance to the acidic medium comparing to other formulations. Therefore, Acrycoat L-30 D which is used as an enteric coating agent for formulations C and D has been shown to be more effective than HPMC Phthalate for formulations A and B.

Taste evaluation of granules

Results of taste evaluation of pure drug as well as of the different formulations are given in Table-3 and show the great taste masking suitability of the granules of formulation D comparing to other formulations. Formulation D did not reveal any bitter taste when the granules were kept on the tongue using time intensity procedure, mainly due to the higher concentration of the taste masking agent (Ameye *et al*., 2002; Albertini *et al*., 2004).Bitterness was perceived by the six

volunteers in case of pure drug and formulations A, B and C. The results obtained indicates that the not only the granulation method but also the use of Acrycoat L-30D as a coating substance and the choice of suitable formulation were efficient in masking the clarithromycin's bitter taste.

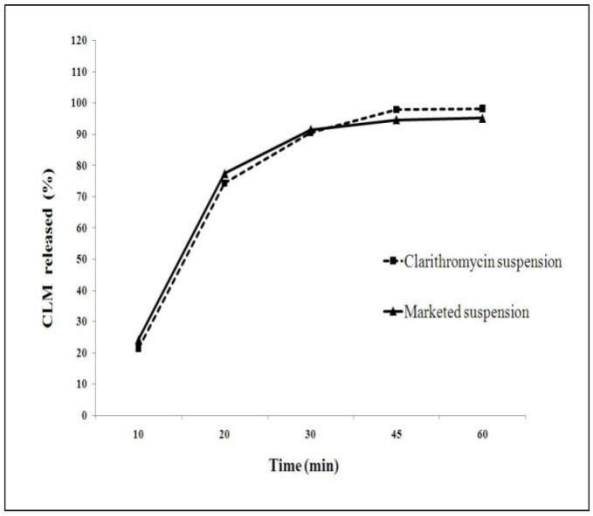

Fig. 3. Comparative in vitro release of clarithromycin suspension with marketed suspension

Evaluation of oral taste masked suspension

The assay of the oral suspension was found to be 102.11 % (required limit: 90-110%) and pH was 4.86 (required limit:4.0-5.4)

Dissolution at phosphate buffer (pH 6.8)

Comparison of dissolution profile is based on a difference factor (f1) and a similarity factor (f2) that compare the oral suspension prepared with the marketed suspension and establishes similarity profile. The factors f1 and f2 play a very important role in comparing the formulations' release profile. Two dissolution profiles are considered similar when the f2 value is between 50 and 100 and the f1 value is less than 10.The results (Table 5 and Fig. 3) indicate that the dissolution profile of the oral suspension in phosphate buffer pH6.8 was found to be similar comparing to marketed suspension .The values of f1 and f2 factor calculated are presented in Table-6.

Taste evaluation of developed oral suspension of clarithromycin

Results of taste evaluation of prepared oral suspension against the marketed suspension are given in Table-8. These results reveal the considerable decline in the bitter taste of prepared oral suspension comparing to marketed suspension which could be possibly due to the formulation composition of the granules of clarithromycin adopted (Yajima *et al*., 2002).

Conclusion

The trials for the formulation of clarithromycin granules using different concentrations of taste masking agent , also the trials for coating of these granules using two different coating substances have been analyzed. The granules prepared were characterized using various parameters and found that, clarithromycin granules of formulation D prepared by a higher amount of Acrypol 934 , a lower quantity of PVP K90 and coated by Acrycoat L-30D had efficiently reduced the bitterness of clarithromycin with suitable drug release profile. The formulation explored was successfully used for preparing oral suspension which which showed the same dissolution profile and better taste as compared to marketed suspension.

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