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Research Article

MIRACULOUS TASTE MASKING OF CLARITHROMYCIN

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ABSTRACT

Clarithromycin has poor acceptance by pediatric and geriatric patients due to very bitter taste. Usually, in dry syrup formulations, high concentration of sugar is used for taste masking purpose. But high consumption of sugar has been related to several chronic diseases and several times is unable to mask the extreme bitter taste. Therefore this study aimed to investigate taste masking capacity of excipients other than sugar. For this purpose, several granulating material were evaluated for masking the bitter taste of clarithromycin. The best way to achieve pleasant taste was developed by using combination of sucralose and hydroxyl propyl cellulose. Combination of sucralose with hydroxyl propyl cellulose provided high intensity sweetness, miraculously reduced product biterness and absence of aftertaste. These taste masked granules can be used in formulation of dry syrup which can be easily accepted by pediatric as well as by geriatric patients. The result of this study provided important information for future applications of sucralose in combination with hydroxyl propyl cellulose for taste masking purposes.

Key words: Clarithromycin, sucralose, bitter taste, granulation.

INTRODUCTION

The macrolide antibiotic, clarithromycin is extremely bitter in taste and effective in treatment of various infections in children and elderly patients, which often experience difficulty in swallowing solid oral dosage forms. For these patients, the drug are mostly provided in liquid dosage forms, which lead to perceptible exposure of active ingredient to the taste buds. Taste masking is an important factor in these dosage form for better patient compliance[1].

Traditionally, taste masking in dry syrup formulations is done by using high concentration of sucrose, however, high sugar consumption has been a matter of great public and scientific interest[2]. These adverse effects have been associated with obesityand risk of cronic disease like type 2 diabetes and cardiovascular diseases. As a results, many alternative taste masking agents have been extensively investigated. Non nutritive sugar can facilitate reduction in added sugar intake and promote beneficial effects on metabolic related parameters[3].

Sucralose is the only commercial sweetener derived from sucrose and is an intense sweetener made by selective substitution of the hydroxyl groups of sucrose with chlorine. Sucralose has a taste profile very close to that of sucrose, presenting very low level of bitterness and sourness[4].

The study was planned to mask bitter taste of clarithromycin without use sucrose. Different granulating materials were used to prepare clarithromycin granules by wet granulation technique and were dried, milled to obtain granule of desired particle size. Extent of bitterness was evaluated by taste panel. It was recognized that clarithromycin granules prepared by HPC+ Sucralose mixture not only masked the bitter taste but also created a pleasant taste.

MATERIALS AND METHODS

Clarithromycin was received as gift sample from Amneal Laboratories Ltd.
Two different techniques were followed for taste masking:

Solid dispersion technique: Solid dispersions of clarithromycin were prepared using Polyethylene glycol 4000 (PEG 4000) and with Polyvinyl Pyrollidone K 30 (PVP 30).

Using PEG 4000
Solid dipersion of clarithromycin with PEG 4000 were prepared in 4 different ratios i.e. 1:1, 1:2, 1:3 and 1:4. Clarithromycin was mixed with PEG 4000 in the ratio of 1:1, 1:2, 1:3 and 1:4. Sufficient quantity of acetone was added to dissolve the mixture and mixture was stirred on magnetic stirrer at 60°C-70°C to allow formation of solid dispersion. Solid dispersion obtained were further dried in fluid bed processor to obtain dried material which was further milled and passed through #16 to obtain granules.
Similarly, solid dispersions were also prepared using Polyvinyl pyrollidone K30 in the ratio of 1:1, 1:2, 1:3 and 1:4.

Granulation Technique: Wet granulation is one of the best technique to mask the bitter taste of solid oral dosage forms. 5 Different excipients were used separately for preparation of taste masking granules v.i.z. lactose, mannitol, sorbitol, starch, hydroxyl propyl cellulose. Using each excipient, granulation was performed in the ratio of 1:1, 1:2, 1:3 and 1:4.

Granulation with Lactose: Clarithromycin and lactose were sifted through # 30 sieve. Sieved lactose along with clarithromycin granulated in using purified water as granulating agent. Wet granules were passed through # 10 screen and were dried in fluid bed processor to form dried granules. Dried granules were milled and passed through # 16 screen. Similarly granules were prepared in the ratio of 1:2, 1:3 and 1:4 ratio.
Similarly, granules were also prepared separately using mannitol, sorbitol, starch and hydroxyl propyl cellulose. With each excipient, granules were prepared in the ratio of 1:1, 1:2, 1:3 and 1:4.

Taste Evaluation: The bitterness evaluation was performed on a taste panel of 6 human volunteers with mean age of 30 years. The volunteers rinsed their mouth thoroughly before and after the tasting. Granulated powder equivalent to 250 mg of clarithromycin was held in the mouth for 30 sec and then expectorated. Taste was evaluated and was assigned a numerical value ranging from 1 to 5, where high score indicated better taste masking (refer table 1).
Results observed for taste evaluation score are mentioned in table 2.
Further different combinations of hydroxyl propyl cellulose were used along with intense sweetener sucralose to further conceal the bitter taste. Results of taste evaluation mentioned in table 3.

Micromeritic properties
The granule size separation was carried out by using vibratory sieve shaker at medium vibration level for 20 min using fie standard sieves ranging from #8 to #100. Refer table 4 and tab1e 5.

In vitro dissolution testing

The USP apparatus 1 (rotating basket) has been used to study in-vitro drug release. Granules of ratio 1:2+2 (Clarithromycin : Hydroxy Propyl Cellulose + Sucralose) equivalent to 500 mg of clarithromycin were placed in basket of dissolution test apparatus with 6.8 ph phosphate buffer as dissolution media. Dissolution medium was maintained at temperature of 37±0.5°C and basket was rotated at 100 rpm. 5 ml of aliquots were withdrawn by single mark pipette after every 30 min interval and volume withdrawn was replaced with fresh equal quantities of dissolution medium. Cumulative drug release obtained is shown in table 6.

RESULTS

Solid dispersion were prepared by solvent evaporation method in which drug and inert excipients were dissolved in common solvent which was evaporated leading to the formation of solid dispersion. However, solid dipersion prepared with PEG 4000 or with PVP K 30 were unable to mask the bitter taste.

Taste masking by granulation technique was found to be comparatively better, inexpensive and quicker technique. Granulation lower the effective surface area of the bitter substance that comes in contact the tongue. However taste masking effectiveness of different granulating agents was observed in the following order

Clarithromycin + PEG 4000 ≤ Clarithromycin + PVP K 30 < Clarithromycin + Sorbitol ≤ Clarithromycin + Mannitol ≤ Clarithromycin + Lactose Clarithromycin + Starch <Clarithromycin + Hydroxy Propyl Cellulose.

Reason for different taste masking capacity can be attributed to the solubility of granules in the saliva. Granules prepared with sorbitol and mannitol being easily soluble in saliva were not able to effectively mask the bitter taste, while granules prepared with hydroxyl propyl cellulose being less soluble had better ability to prevent the interaction of clarithromycin with taste receptors.
An interesting development in the taste masking was observed by using mixture of hydroxyl propyl cellulose with sucralose. Miraculously, granules were found to have no bitter taste when formulated with mixture of hydroxyl propyl cellulose with sucralose. Instead granules were having sweet and pleasant taste.

It can be observed from the physical properties of granules that hausner ratio varied from 1.14 to 1.18, while Carr's index varied from 12.3 to 15.27, indicating good flow properties.

Drug release profile of granules was studied in Ph 6.8 phospahate buffer. It can be noted that more than 85.0 % of drug got released within 60 min, hence these granules can be used in formulation of pediatric and geriatric dry syrups.

Table 1: Taste scale

Value	Parameter
5	Tasteless
4	Very Less Bitter
3	Moderate Bitter
2	Bitter
1	Strongly Bitter

Table 2: Results of taste evaluation score

Combination	Score				Mean Score
	1:1 ratio	1:2 ratio	1:3 ratio	1:4 ratio	
Clarithromycin + PEG 4000	1	1	1	1	1
Clarithromycin + PVP K 30	1	1	1	1	1
Clarithromycin + Lactose	2	2	2	3	2.25
Clarithromycin + Mannitol	2	2	2	2	2
Clarithromycin + Sorbitol	2	2	2	2	2
Clarithromycin + Starch	2	2	3	3	2.5
Clarithromycin + Hydroxy Propyl Cellulose	4	4	4	4	4

Table 3: Results of taste evaluation score

Combination	Score			Mean Score
	1:3+1 ratio	1:2+2 ratio	1:1+3 ratio	
Clarithromycin: Hydroxy Propyl Cellulose + Sucralose	4	5	5	4.66

Table 4: Physical property of granules

Sieve size	% Retention Combination (Clarithromycin : Hydroxy Propyl Cellulose + Sucralose)		
	1:3+1 ratio	1:2+2 ratio	1:1+3 ratio
#8	0	0	00
#16	02	02	01
#22	38	34	38
#60	86	81	88
#100	93	92	91

Table 5: Physical properties of granules

Parameter	% Retention Combination (Clarithromycin : Hydroxy Propyl Cellulose + Sucralose)		
	1:3+1 ratio	1:2+2 ratio	1:1+3 ratio
Bulk Density (g/ml)	0.63	0.64	0.61
Tapped density (g/ml)	0.72	0.73	0.72
Hausner ratio	1.142	1.140	1.180
Carr's Index	12.5	12.3	15.27

Table 6 Dissolution release profile

Time points (min)	% Dissolution (mean of 6 samples)
	Granules ratio 1:2+2 (Clarithromycin : Hydroxy Propyl Cellulose + Sucralose)
0	0
30	78.4
60	87.8
90	88.0
120	92.8

DISCUSSION

From the taste evaluation studies, it was concluded that miraculous taste masking for clarithromycin was achieved by granulation technique using combination of hydroxypropyl cellulose along with sucralose. These granules can be used for further formulation of tablets, dry syrups and can also be taken for scale-up studies.

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