



Research Article

Enhancement of taste masking by a newly formulated effervescent ciprofloxacin tablets

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ABSTRACT

Oral administration of pharmaceuticals is one of the most popular methods of drug delivery. Many orally administered drugs elicit bitter taste. Palatability is an extremely important factor in ensuring the likelihood that the recipients will intake the pharmaceuticals. A constant problem in treatment of patients is their inability or unwillingness to swallow solid dosage forms such as tablets especially in children and the elderly. These types of dosage forms permit perceptible exposure of active drug ingredient to the taste buds. Accordingly, masking of unpleasant taste characteristics of drug ciprofloxacin HCL is an important factor in formulation of this The mask of the taste of this important drug was carried out by many techniques to enhance bitterness reduction. In the present work, the technique for masking the drug bitter taste was the use of the effervescent base in the drug formulation, guar gum, flavor and saccharin. The method proved to be successful mechanical taste of the formulated tablet. The aim of this study is to develop an effective and pH stable taste masked ciprofloxacin hydrochloride tablet formulation using effervescent technology.

Key words: Taste masking; Taste bud; Ciprofloxacin HCl; Effervescent technique.

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INTRODUCTION

Undesirable taste is one of several important formulation problems that is encountered with certain drugs. Oral administration of bitter drugs with an acceptable degree of palatability is a key issue for health care providers. Patients expect oral pharmaceutical dosage form to be pleasantly flavored and palatable, because taste is one of the most important parameters governing patient compliance. This change in patient attitude is due to the advances made by flavoring and pharmaceutical industries. Therefore, taste masking technologies

are very crucial factors for better patient compliance and therapeutic value^{1,2}.

Ciprofloxacin HCl (shown in figure 1) is effective against many gram-negative enteric bacteria especially in typhoid fever, tissue abscess, and upper respiratory tract and urinary tract infections¹¹.

Ciprofloxacin HCl is one of several oral pharmaceuticals having unpleasant, bitter- taste characteristics. Thus, development of a newly formulated ciprofloxacin HCl oral dosage product with a pleasant taste would definitely be preferred in giving a unique identity to the product and adding value/timeline to the patient.

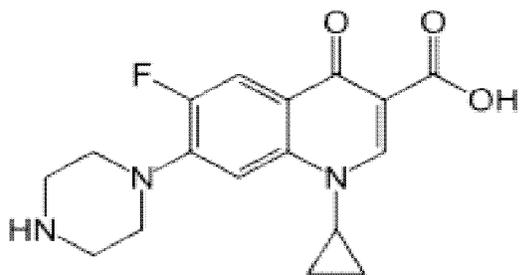


Figure 1. Structure of Ciprofloxacin

Ciprofloxacin HCl is one of several oral pharmaceuticals having unpleasant, bitter-taste characteristics. Thus, development of a newly formulated ciprofloxacin HCl oral dosage product with a pleasant taste would definitely be preferred in giving a unique identity to the product and adding value/timeline to the patient.

The Sense of Taste: Taste is the ability to respond to dissolved molecules and ions-(gate keeper to the body). Human detects taste with taste receptor cells

that are clustered in to onion-shape organs called taste buds. Each taste bud has a pore that opens out to surface of the tongue enabling molecules and ions taken into the mouth to reach the receptor cells inside. Human have around 10,000 taste buds which appear in fetus at about three months. A single taste bud contains 50 – 100 taste cells. Each taste cells receptors on its apical surface. These are trans membrane proteins which bind to the molecules and ions- that give rise to the four primary taste sensations namely - salty, sour, sweet and bitter (figure 2)³⁻⁵.

Recently, a fifth basic taste umami has been discovered. The umami is the taste of certain amino acids (e.g. monosodium glutamate)³.

There is often a correlation between the chemical structure of a compound and its taste. Low molecular weight salts tend to taste salty where as high molecular weight salts tend toward bitterness. Nitrogen containing compounds, such as alkaloids tend to be quite bitter. Organic compounds containing hydroxide groups tend to be increasingly sweet as the number of OH increases⁶. Receptor mechanism involves initial depolarization atypical receptor site, which causes local action potential in receptor cell. This in turn causes synaptic activation of the primary sensory neuron (figure 3).

Table 1: Specific area of tongue and threshold concentration for primarytastesensations¹⁷

Taste	Area of Tongue	Threshold Concentration
Sweet(sucrose)	Tip of tongue	0.5%
Salt (NaCl)	Tip and sides of tongue	0.25%
Sour (HCl)	Sides of tongue	0.007%
Bitter (Quinine)	Back of tongue	0.00005%

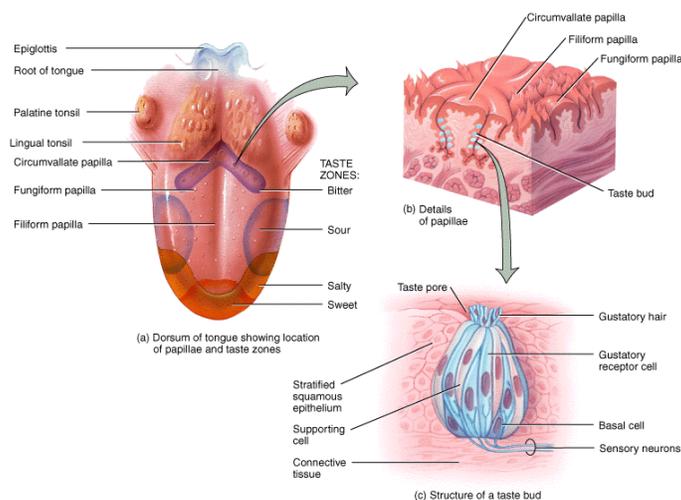


Figure 2. A taste bud and taste receptor cell⁴

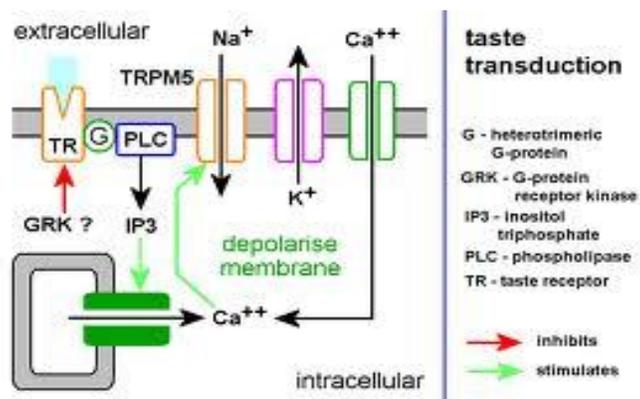


Figure 3. A taste transduction in taste receptor cell⁴

Four basic tastes are confirmed to specific regions of tongue (Table1).However, some works deny the presence of specific regions of the tongue for a particular taste and consider it as a misconception⁷.Threshold value (is a minimum concentration of substance that evokes perception of a taste).The following table gives the threshold concentration of four primary taste sensations. It can be seen that positive tongue is 10,000 times more sensitive to the bitterness of quinine than to sweetness of sugar. Saccharine, on this scale would rate about 0.001 %^{8,9}.

Ciprofloxacin hydrochloride effervescent tablets (figure 2 and 3)were formulated as a good example for masking the bitterness of this drug. In this study, Ciprofloxacin hydrochloride tablets were taken as an example for taste masking due to its extensive use in treatment of *Salmonella typhi* and *Salmonella para typhi*, UTI and most gram negative infection in tropical countries^{9,10}. In general, effervescent tablets (which itself is a technique of masking taste) was a type of palatable dosage forms which is much preferable by the patient. It might be due to its effectiveness and ease to swallow, thus the efforts was done to formulate ciprofloxacin to this effective dosage form and the masking of taste was critical step during working in this formula^{11,12}.

So major taste masking efforts are required before bitter drugs are acceptable for market trials. Major masking technologies are based on the reduction of solubility of the drug in the saliva or competing the receptor of the bitterness, so the drug concentration on saliva will remained below taste threshold value (is a minimum concentration of substance that evokes perception of a taste).the desire for improved palatability of formulations has prompted the development of various new technologies for taste abatement many of this technologies have been successfully commercialize .But the ideal solution of taste masking would be the discovery of universal inhibitor of bitter taste of all drug¹⁴. Techniques used in the masking of the taste in ciprofloxacin HCl effervescent tablets included.

A) Taste masking with flavors and sweeteners:

This technique is the simplest approach for taste masking. However, this approach is not very successful for highly bitter drugs. Thus artificial sweeteners and flavors are generally being used along with other taste masking techniques to improve the efficiency of these techniques. Saccharin (which is used in this formula) is most sweetness of commonly used sweeteners is equal 450 times unit of sucrose is unpleasant after taste¹⁴. Cooling effect of certain flavoring agent (table 2) aids in reducing perception

of bitterness (vanilla which is used in this formula is very stable and also masks effect of bitterness). The physiology involved is merely to numb taste buds, either rapidly or over period time, so that the cooling effect actually builds up after ingestion. The brain perceives the coolness even though physically the temperature of the product has not changed¹⁵.Some generalization concerning the selection of flavors to mask specific types of taste have been suggested by Janovasky and Wesley¹⁶.Such recommendations are listed in (table 3).

Table 2: Classification of flavoring agent¹⁶

Type	Example	Comment
Natural	Peppermint	Less stable
Artificial	Vanilla	Very Stable
Natural	Strawberry	Effective at low concentration

Table 3: Flavor selection¹⁶

Taste Sensation	Recommendation Flavor
Salt	Butterscotch, apple, apricot, peach, vanilla
Bitter	Wild cherry, walnut, chocolate, mint combination fruit
Sweet	Fruit and berry, vanilla
Sour	Citrus flavor, licorice, root beer, raspberry

A survey of taste preferences of human race, as a whole, indicates that sweet taste is very agreeable to our species. Hence, for controlling the taste qualities efforts are directed to make the prepared formula sweet to different decrease.

Sweeteners are commonly used for this purpose (saccharin was used in effervescent ciprofloxacin formula). Table 4 presents a compilation of the most common artificial and natural sweeteners used in pharmaceutical products, their relative sweetness levels, and pertinent comments¹⁸.

B) By effervescent agents: Effervescent agents have been shown to be useful and advantageous for oral administration of drugs and have been employed for use as taste masking agent for ciprofloxacin HCl (in ratio 1:2:3.4)¹⁹. It comprises effervescent base, an orally administrable medicament, a taste masking generator of carbon dioxide, and optionally a taste bud desensitizing composition by other non active material such as sweeteners, flavoring components and fillers¹³. Recently, effervescent

tablets of fentanyl and brochlorperazine were developed to supply these drugs to the oral cavity for buccal, sublingual, and gingival absorption, and from these researches, ciprofloxacin HCl was formulated as an effervescent tablets (figure 5). The formulation contains the drug in combination with effervescent agent to promote its absorption in the oral cavity and to mask its bitter taste¹².

Table 4: Relative sweetness of commonly used sweeteners¹⁸

Sweetening agent	Relative sweetness*	Comment
Aspartame	200	Not very stable in solution
Acesulfame potassium	137 – 200	Bitter after taste if used in higher concentration
Cyclamate	40	Banned
Glycyrrhizin	50	Moderately expensive
Lactose	0.16	Large amount required
Manitol	0.60	Negative heat of solution
Saccharin	450	Unpleasant after taste
Sucrose	1	Most commonly used
Sucralose	600	Synergistic sweetening effect

* Sucrose is taken as standard of 1 for comparison



Figure 5. Ciprofloxacin HCl tablets manufactured using effervescent base technique as taste masking.

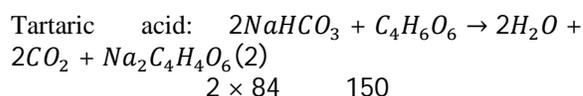
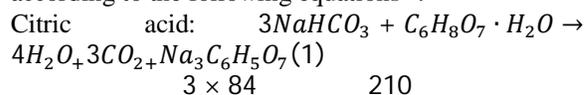
B) **Rheological modification:** Increasing the viscosity with rheological modifier such as gums or carbohydrates can lower the diffusion of bitter substances from the saliva to the taste buds. Ciprofloxacin HCl effervescent suspension can

be formulated with guar gum (0.1 – 1%) and microcrystalline cellulose (avicell 5%) to reduce bitter taste of the ciprofloxacin HCl according to previous research on acetaminophen^{20,21}.

METHODOLOGY

2.1 Formulation of Tablets:

Effervescent tablets were prepared by two methods. In both methods, the ratios of the effervescent ingredients were taken as (1:2:3.4) for citric acid: tartaric acid: sodium bicarbonate, respectively, according to the following equations¹⁵:



2.1.1. Wet Granulation:

The most widely used and most general method of tablet preparation is the Wet Granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved as well as the time and labor necessary to carry out the procedure, especially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluents, and disintegrate were mixed or blended well¹⁶.

Specific amount of ciprofloxacin and saccharin were weighed and divided into two pestles in equal amounts and well mixed. Citric and Tartaric acid were added to one pestle and sodium bicarbonate in the other, as effervescent bases, to avoid reaction. The binder combination (Guar and Poly vinyl pyrrolodine) were then added slowly after dissolving in a very small amount of water and the mixtures were blended continuously to make the paste, then granulated using mesh (10), and left in oven (60°C) for twenty hours to dry. The mixture was passed through mesh after drying¹⁵. The microcrystalline cellulose, which was added before granulation was used as disintegrate and after granulation as glident. Talc powder and magnesium stearate were both added as lubricant and glident. Granules were compressed into two types; one tablet (250 mg active ingredient) using 20mm die and 125 mg ingredient, using 13 mm die¹⁶.

2.1.2 Calculations:

Formula (1) (high binder concentration):

Guar: 1% and PVP: 4% (w/w).

Formula (2) (low binder concentration):

Guar: 0.005% and PVP: 2% (w/w)

Guar gum with polyvinyl pyrrolidone as binder indifferent ratios for the two formulae

Saccharin was used from three to five time of active ingredient and the best one it was used in ratio five times to active ingredient.

Saccharine may also be used as a binder.

The two Tablets weight in these two formulae were 1600 mg and 2000 mg.

Microcrystalline cellulose (Avicil) 5% is used as disintegrating agent, glident and lubricant.

Magnesium stearate and Talc powder combinations were used as lubricant and glident.

Vanillin was used as flavoring agent.

2.1.3 Direct Compression:

As its name implies, direct compression consists of compression of tablets directly from powdered material without modifying the physical nature of the material itself. Formerly, direct compression as the method of tablet manufacture was reserved for small group of crystalline chemicals having all the physical characteristics required for the formation of a good tablet¹⁶. Ciprofloxacin is mixed with lactose in a mortar to improve compression characteristic then sodium bicarbonate (NaHCO₃) and saccharine sodium (four times the amount of active ingredient) were added, mixed well and named as mixture (A). In another mortar, specified amount of tartaric acid and citric acid were weighed accurately and named (B). Then (A) and (B) were mixed together and specified amounts of banana and vanillin flavor were added and then the whole mixture was passed through a sieve for more mixing. One percent of guar was used in dry form for all weight formulae of ciprofloxacin effervescent tablets. The mixed powder was then placed in an oven for drying (at 60°C) and then compressed in tableting machine¹⁶.

RESULTS AND DISCUSSION

Table 5 summaries the Quality Control Tests Undertaken for the two types of the ciprofloxacin Effervescent Tablets. Two values of hardness were found in result due to variation in binder (saccharin) concentration because PVP and guar were used in the two concentrations. In wet granulation method, mesh number ten was used for first granulation for resizing

and mesh number fourteen was used for enhancing uniformity of distribution and mixing.

In the two types of effervescent tablets (wet granulation method and direct compression method) the zone of inhibition was slightly larger in wet granulation method than in direct compression method. This might be due to good distribution of active ingredient in the tablet formulation. In wet granulation, saccharin was employed as a sweetening agent and binder. To overcome bitterness problem, saccharin was four to six times in weight to active ingredient in the effervescent formula.

Effervescent tablet formula was used to enhance solubility and might increase the palatability and mask taste, effectiveness and bioavailability. The Flavoring agent (vanillin) was employed to mask taste beside shaving a good odor. Wet granulation is very good for production of effervescent tablet rather than dry compression method (Tables 5 and 6). Guar gum in a 1% w/w concentration is a strong binder when it was used in combination with PVP 4% w/w in formula. Ten times dilution of guar gum, PVP were needed for binder (0.1 guar gum and 0.4 PVP) with saccharin to avoid high hardness value in compression. The addition of Avicil 5% before resizing to avoid stickiness and enhanced disintegration and worked as glident and lubricant. In the effervescent formula, potassium carbonate was used in state of sodium bicarbonate for hypertensive patient and for patient taking digoxin. Tablet weight in these two formulas 1.600 gm was used in two divided tablets to be handled easily and stand packaging and transportation. Potassium citrate was used with effervescent base to give unique combination as cleaning renal ducts and as antisalt. The minimum concentration of saccharin used in the formula help to inhibit bitterness.

The weight variation of effervescent tablet (both wet granulation method and direct compression method) complies with the monograph requirements and this gave an indication for homogeneity and uniformity of the active ingredient distribution.

Wet granulation effervescent formulation gave more tablet hardness compared to direct compression method and thus it was easy to handle (Table 5 and 6). Compression of wet granulation tablet was better compared to direct compression method. This was due to the presence of granules in wet granulation method. In addition, friability of wet granulation method was less than direct compression effervescent tablet, due to the presence of granules.

Both types of formula pass the thickness and diameter test and this indication for good tablet compression.

Table 5: A Summary of the Quality Control Tests Undertaken on the two types of the Ciprofloxacin Effervescent Tablets

Effervescent Tablet	Friability	Hardness (Kg/cm ²)	Deviation %	pH	Assay %	Mean of Dissolution Time (min)
Direct Compression	3.5	4.5	1.045	6.02	98	1.43
Wet Granulation 13mm tablet	1.9	7.82	1.22	6.15	97	3.09
Wet Granulation 20mm tablet	2.6	5.2	0.84	6.17	96	2.8

Table 6: A comparison of two types of effervescent tablets on different bacteria

Effervescent Tablet	Diameter(mm)			Surface Area (mm ²)		
	<i>E. Coli</i>	<i>Staph aureus</i>	<i>Salmonella</i>	<i>E. Coli</i>	<i>Staph aureus</i>	<i>Salmonella</i>
Direct Compression	17	15	14.8	266.9	176.7	172
Wet Granulation	18	15.5	15.4	254.3	188.6	186.2

The dissolution time of direct compression effervescent tablet was 91second, and that of wet granulation effervescent tablet was 115second. The two types of effervescent formulas complied with the European pharmacopeia specifications¹⁹.

CONCLUSION

Considering all the above-mentioned factors in formulating the newly effervescent ciprofloxacin HCl tablets, as an ideal taste masking formulation, characterized the following properties:

- Involvement of least number of equipments and processing steps.
- Requirement of minimum number of excipients for an optimum formulation.
- No observed adverse affects on drug bioavailability.
- The formulation requires economical and easily available excipients.
- Least manufacturing cost.
- Can be carried out at room temperature.
- Require excipients that have high margin of safety.
- Rapid and ease tablets preparation.

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