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**Improvement in the Characters of a Newly formulated
Effervescent Ciprofloxacin Tablets by Enhancement
in the Excipient Properties of the Formula**

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Abstract

This research is a formulation of the drug as an effervescent tablet by two methods (direct compression and wet granulation). The bitter taste was masked by saccharine as sweetening agent but by little concentration in compared to previous effervescent formula, furthermore the effervescent effect of citric acid, tartaric acid and sodium bicarbonate lead to improve the taste of the drug. Also the Guar was used as binder agent lead to hide the taste in higher concentration with tragacanthum as mixture to improve rheological properties beside sustained release in compared to previous effervescent formula to enhance its therapeutics efficacy. The vanillin which was used as flavoring agent also enhances the palatability with more amount to previous formula. The formulated tablets were passed all the fundamental testes in the monograph, and also microbiological sensitivity test was done against (*Escherichia coli*, *Salmonella typhi*, *Salmonella paratyphi* and *Staphylococcus aureus*) and then the results were compared to select the suitable one.

Also compression was done between two formula of wet granulation method (the binder increase concentration and die cavity when was change). This study was found that formulating the drug as effervescent tablet by wet granulation method (with more binder of rheological gum less saccharin) concentration and die cavity No thirteen or twenty is the more better than previous effervescent ciprofloxacin formula.

Keywords: gums, improvement properties, ciprofloxacin, Effervescent tablets.

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, upper respiratory tract and urinary tract infections.

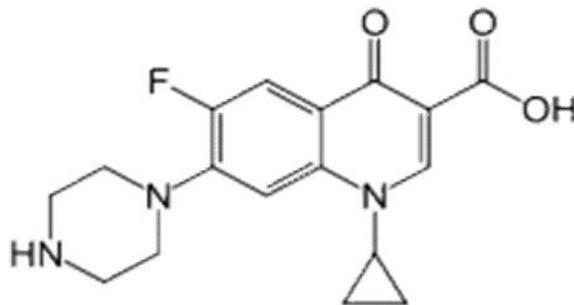


Figure 1. Structure of Ciprofloxacin

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 patent.

Ciprofloxacin was formulated previously as effervescent tablets⁽³⁻⁴⁾, so in this research more enhancement in formula was done to improve its characters and onset of duration.

Ciprofloxacin for systemic administration is available as immediate-release tablets, extended-release tablets, an oral suspension, and as a solution for intravenous administration. When administered over one hour as an intravenous infusion⁽⁵⁾, ciprofloxacin rapidly distributes into the tissues, with levels in some tissues exceeding those in the serum. Penetration into the central nervous system is relatively modest, with cerebrospinal fluid levels normally less than 10% of peak serum concentrations. The serum half-life of ciprofloxacin is about 4–6 hours, with 50-70% of an administered dose being excreted in the urine as unmetabolized drug. An additional 10% is excreted in urine as metabolites. Urinary excretion is virtually complete 24 hours after administration. Dose adjustment is required in the elderly and in those with renal impairment. Ciprofloxacin is weakly bound to serum proteins (20-40%), but is an inhibitor of the drug-metabolizing enzyme cytochrome P450 1A2, which leads to the potential for clinically important drug interactions with drugs metabolized by that enzyme. Ciprofloxacin is about 70% orally available when administered orally, so a slightly higher dose is needed to achieve the same exposure when switching from IV to oral administration. A 750-mg immediate-release oral tablet given every 12 hours produces about the same area under the serum concentration curve (AUC) and peak serum concentration (C_{max}) as

a 400-mg dose given every 8 hours IV^[5]. The extended release oral tablets^[6-7-8] allow once-daily administration by releasing the drug more slowly in the gastrointestinal tract. These tablets contain 35% of the administered dose in an immediate-release form and 65% in a slow-release matrix

Ciprofloxacin hydrochloride (effervescent tablets) (figure 1-2) was formulated as a good example for masking the bitterness of this drug⁽⁶⁻⁷⁻⁸⁾.

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 paratyphi*, UTI and most gram negative infection in tropical countries⁽⁹⁻¹⁰⁾.

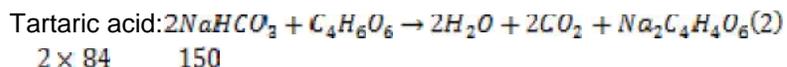
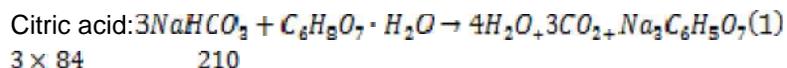
Effervescent tablets (which itself technique of the masking of the taste) it was more palatable dosage form which preferable for the patient, might be more effective and easy to swallow, thus the efforts was done to formulate the drug to this effective dosage form and the masking of taste was critical 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 compete to 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 drug.⁽¹¹⁻¹²⁻¹³⁻¹⁹⁾

Techniques used in the improving the properties of effervescent ciprofloxacin HCl tablets formula included:

Methodology

Formulation of Tablets:

Effervescent tablets were prepared by two methods. In both methods, the ratios of the effervescent



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 disintegrant were mixed or blended well⁽¹⁴⁻¹⁵⁻¹⁶⁻¹⁷⁻¹⁸⁾.

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 (Guargum, tragacanth 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 drying¹⁸. The microcrystalline cellulose, added before granulation, was used as disintegrant 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 die⁽¹⁴⁻¹⁹⁻²⁰⁾.

Calculations:

Formula (1) (high binder concentration):

Guargum, tragacanthgum: 1% (in combinatin0.2%-2%), and PVP: 3% (w/w).

ingredients were taken as (1:2:3.4) for citric acid: tartaric acid: sodium bicarbonate, respectively, according to the following equations¹³:

Formula (2) (low binder concentration):

Guargum with tragacanth: 0.005% and PVP: 2.0% (w/w)

Guargum with polyvinyl pyrrolidone as a 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 mayalso be used as a binder.

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

Microcrystalline cellulose (Avicil) 5-7% 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.

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 tablet¹⁴.

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 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 with natural flavors (strawberry, peppermint) 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 machine¹⁴.

Fundamental tests carried out on the effervescent tablets

Determination of uniformity of weight

20 tablets from effervescent tablet were weighed individually with an analytical weighing balance. The average weights for each effervescent tablet and the percentage deviation from the mean value were obtained.⁽²³⁾

Assay

A solution of 1% w/v ferric chloride was freshly prepared, as well as 100 mcg/ml of pure ciprofloxacin (HCl). Five effervescent tablets were crushed and 100 mg of the powdered samples were weighed. Dissolved in 100 ml 0,1N hydrochloric acid (HCl) and further dilution was made to obtain 100mcg/ml. To five ml of effervescent tablet and the pure sample, 1 ml of ferric chloride was added and made up to 50 ml with 0,1N HCl. The absorbance of each sample was taken at 438 (nm) against the blank reagent (1ml ferric chloride solution made up to 50 ml with 0,1NHCl) with an ultraviolet spectrophotometer (Jenway, UK). The percentage content was calculated for effervescent tablet by using calibration curve already prepared according to monograph.⁽²³⁾

Hardness test

The crushing strength was determined with a tablet hardness tester (Monsant, U.K). Four tablets were

randomly selected from effervescent tablet and then the pressure at which each tablet crushed was recorded and the hardness value obtained.⁽²⁴⁾

Friability test

Ten tablets of effervescent ciprofloxacin HCl were weighed and subjected to abrasion by employing a Roche friabilator (ErwekaGmbH, Germany) at 25 rev-min for four minutes. The tablets were then weighed and compared with their initial weights and percentage friability was obtained.⁽²⁴⁻²³⁾

Dissolution test

The tablets were dissolved in sink condition and the time of dissolution of effervescent tablet was recorded by stop watch.⁽²⁵⁾

pH adjustment

The effervescent tablets were dissolved and then filtered and the pH of resultant solution was read by pH meter.⁽²⁴⁾

Microbiological sensitivity test

Microbiological test was carried out for new formula in four species to inhibit and ensure the effectiveness of the antibiotics. And those species are *Salmonella typhi*, *Staph. aureus*, *Escherichia coli* using disc diffusion Kirby-Bauer.⁽²⁸⁾

Results and Discussion

Table 1: 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 2: 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

Table (3) Comparison between two types of effervescent formula

Effervescent formula additives	Modified effervescent formula	The improving in the formula
1.Guargum	Guargum with tragacanth gum	Enhancement in sustained release with more mask of the taste
2.Vanilla	Vanilla with strawberry and peppermint	More flavor effect and mask of the taste
3.Avicil 5%	Avicil 7%	Enhancement the tablets flowbidity
4. saccharin 4% active ingredient	saccharin 2% active ingredient	Decrease risk of increased amount of artificial sweeteners.
5. Tragacanth gum is not found Only guargum	Tragacanth gum in combination with guargum	Enhancement the sustained release properties.
6. powder was adjust by additives	Powder was adjust by additives and centrifugation.	Enhance flowbidity



Figure (2) newly modified effervescent ciprofloxacin tablets

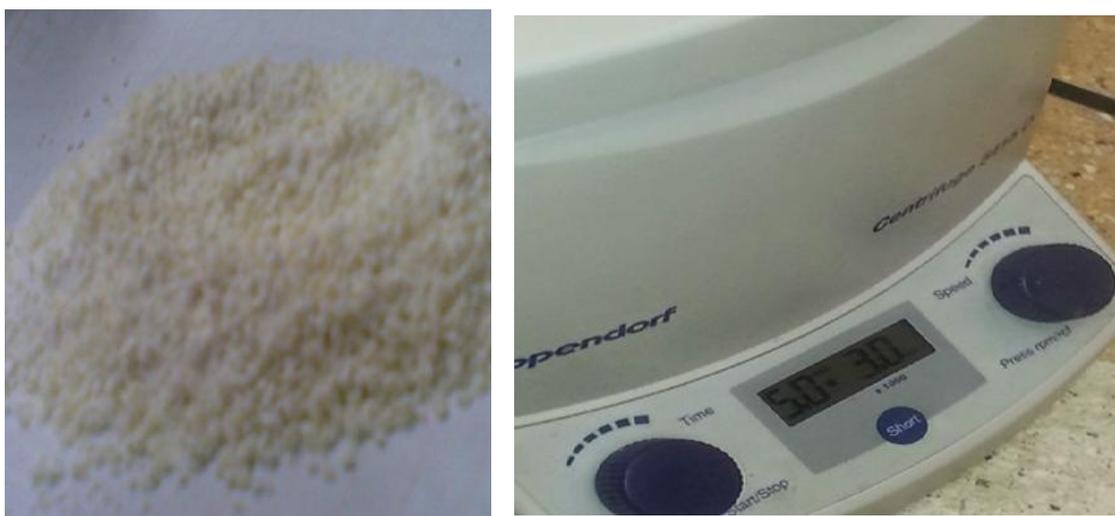


Figure (3) Granules of modified effervescent ciprofloxacin with centrifugator which used in adjustment the powder rheology.

A) Flavors and sweeteners:

This technique is the simplest approach for taste masking and improving hardness properties. But 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 taste, so more improving was done here by decreasing the amount of saccharin and replace it by vanilla and gums⁽¹²⁻¹⁸⁾. (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 changed.⁽¹³⁾ Some generalization concerning the selection of flavors to mask specific types of taste have been introduced in improvement effervescent formula by addition of Peppermint and Strawberry table (3) which agreed with Wesley et al.⁽²²⁾

B) 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).⁽¹⁸⁾ It comprise 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 fillers.⁽²¹⁾ Recently, effervescent tablets of ciprofloxacin HCl was formulated as an effervescent tablets (figure 2-3). The formulation contain more effervescent base amount the drug in combination with gums to promote it is absorption in sustained release manner and avoiding previous saccharin highly amounts and to mask it is bitter taste which agree with shayoub et al.⁽³⁻¹⁸⁾

C) 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 with tragacanthgum in combination (0.2 – 2%) and microcrystalline cellulose (avicill 7%) to reduce bitter taste of the ciprofloxacin HCl and to enhance sustained release characters.⁽¹⁹⁾

Conclusion

Considering all the above-mentioned factors in formulating the newly effervescent ciprofloxacin HCl tablets, as an ideal formula, 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 effects on drug bioavailability and give more effect with good manner.
- 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 with good rheology properties by gums.
- Rapid and ease of tablets preparation.
- Improvement and developing the effervescent formula enhance the pharmaceutical formulations and may be used for other drugs to enhance its efficacy.
- In this PhD study more developing in formula character to be acceptable for patients with enhancement efficacy⁽²⁶⁻²⁷⁾

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