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RESEARCH ARTICLE

COMPARISON STUDY BETWEEN TWO TYPE OF FORMULATION TAKING A NEWLY FORMULATED EFFERVESCENT CIPROFLOXACIN

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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 sweeting agent 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 (Blasé and Shah, 1993., Skraanga and Tully, 2000.). The vanillin which was used as flavoring agent also enhances the palatability (Hussain and Barcelon. 1991., Pather *et al*., 2002). The formulated tablets were passed all the fundamental testes in the monograph, and also microbiological sensitivity test was done against *(Escherichia coli, Salmonella typhi, Salmonellapara typhi 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 (low binder) concentration and die cavity thirteen or twenty is the suitable one and that might be lead to increase the drug effectiveness, therapeutic effect and decrease the ciprofloxacin resistant as well as increase patient acceptability ass effervescent tablet.

KEY WORDS: Direct Compression, Wet Granulation, Effervescent Ciprofloxacin Hc.

INTRODUCTION

Effervescent Tablets

Tablet formulations may be rendered effervescent for several reasons, including improvement of their disintegration characteristics and their taste. The first effervescent tablets were essentially derived from the mildly purgative effervescent mixture known as a Seidlitz powder, but today the most popular have acetyl salicylic acid as their main ingredient. Effervescence is derived by the reaction which takes place between alkali metal carbonates, or bicarbonates, and citric and/or tartaric acids, to release carbon dioxide. Most formulations call for an acid concentration in excess of the stoichiometric requirement, as this improves palatability because of its ability to solubilize the drug. (Nichols, 2000).

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) (Mohrle 1989). 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 filers. Thus all that contributes in success the formula (Niazi and Shamesh 1987).

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Ciprofloxacin Hcl

Ciprofloxacin hydrochloride (Effervescent Tablets) (Figure 1 and 2) was formulated as a good example for masking the bitterness of this drug. (WWW.Google.com).

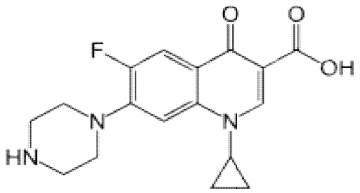

Figure 1. Structure of Ciprofloxacin

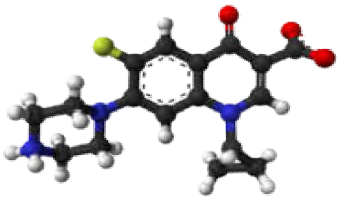

Figure 2. 3D Structure of Ciprofloxacin

This study Ciprofloxacin hydrochloride (monohydrate slat of 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid) Mwt 385.8 (C17H18FN3O3 HCl H2O) was taken due to it is very important drug especially in tropical countries. It used in treatment of Salmonella typhi and Salmonella para typhi ,UTI and most gram negative infection, it is part of a group of the fluroquinolones which introduced in

MATERIALS AND METHODS

Ciprofloxacin HCl powder usd as active ingredient (from India). Citric acid and Tartaric acid from Pharmaceutical Laboratory University of Khartoum. Sodium bicarbonate (lab chemic-India). Saacchrine as sweeting agent from India. Flavouring agent banana flavor Wafrapharma. Guar as compressing agent (binder) is gained from Pharmaceutical Laboratory University of Khartoum. Mueller Hinton Agar (Oxoid Ltd, England) from Omdurman Ahlia University. MacConkey Agar (Oxoid Ltd, England) from Omdurman Ahlia University. Nutrient Agar (Oxoid Ltd, England) from Omdurman Ahlia University. Microorganisms (Salmonella Sp, Staphylo coccus aureus, Escherechia coli).

Formulation of Tablets

Direct Compression

Tablet was prepared by two methods to achieve the most effective one and then compare between two methods. In the two methods the ratios of the effervescent ingredients were taken as (1:2:3.4) respectively for citric acid: tartaric acid: sodium bicarbonate according to the following equation.

Citric acid

$$3NaHCO_3 + C_6H_8O_7 \cdot H_2O \rightarrow 4H_2O_+ 3CO_{2+} Na_3C_6H_5O_7$$
$$3 \times 84 \qquad 210 \qquad (1)$$

One gram of citric acid (mwt=210) reacts with 1.2gm of sodium bicarbonate (mwt=84) as obtained from the following calculations: $\frac{1}{210} = \frac{x}{3} \times 84 \rightarrow 1.2\text{gm.}$

Tartaric acid

$$2NaHCO_3 + C_4H_6O_6 \rightarrow 2H_2O + 2CO_2 + Na_2C_4H_4O_6 \quad 2 \times 84 \quad 150 \qquad (2)$$

Since it desired to use a 1:2 ratio of citric acid to tartaric acid , two grams of tartaric acid (mwt=150) reacts with 2,24gm of sodium bicarbonate according to the following calculations:

$$\frac{2}{150} = \frac{x}{2} \times 84(\text{gm})$$

x=2,24

From the above calculations, 1, 2gm+2, 24 are required to react with 1+2gm of the citric: tartaric acid combination. Since it is desired to leave a small amount of the acid in excess to enhance palatability and taste, 2,24gm +1,2gm = 3,44gm only 3,4gm of sodium bicarbonate was utilized. Therefore, the ratio of effervescent ingredients used was (1:2:3.4) for the citric acid tartaric acid: sodium bicarbonate (Polli *et al*., 1997). All the component were blended togethe and then were compressed.

wet granulation

The most widely used and most general method of tablet preparation is the Wet Granulation method. It is popularity is due to the greater probability that the granulation will me*et al*l the physical requirements for the compression of good tablets. It is chief disadvantages are the number of separate steps involve as well as the time and labor necessary to carry out the procedure, specially on a large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication and compression. (Mohrle 1989).

Specific amount of ciprofloxacin and saccharine were weighted and were divided into two dishes in equal amount and well mixed to each one of dishes effervescent base was added Citric and Tartaric acid in one and sodium bicarbonate in another one to avoid reaction then the binder combination (Guar and PVP) was added slightly slow after dissolving in a very few amount of water and then the mixture was blended continuously well till become granules and then was put in oven for drying damp mass for twenty hours then the damp mass was passed through mesh ten for granulation and resizing

Figure 3. Granules in granulation method of effervescent tablet

and through mesh fourteen for enhancing uniformity of distribution of mixing. The MCC was added before resizing to avoid sticking and work further as disintegrated agent, lubricant and glident, after this talc powder and Mg stearate were added as lubricant and glident in combination. Granules were compressed into two types, one tablet 250 mg (0.25 gm) by punch 20 and 125 mg (0.125 gm) by punch 13 as divided dose. (Mohrle 1989).

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. (US Pharmacopeia National Formulary USP 23/NF 18 (1995)).

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 438λ(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. (US Pharmacopeia National Formulary USP 23/NF 18 (1995))

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. (British Pharmacopeia 1998).

Friability Test

Ten tablets of effervescent ciprofloxacin HCl were weighed and subjected to abrasion by employing a Roche friabilator (Erweka Gmbh, Germany) at 25 rev-min for four minutes. The tablets were then weighed and compared with their initial weights and percentage friability was obtained. (British Pharmacopeia 1998).

Dissolution Test

The tablets were dissolved in sink condition and the time of dissolution of effervescent tablet was recorded by stop watch. (European Pharmacopoeia, 4th Edition 2002).

Ph Adjustment

The effervescent tablets were dissolved and then filtered and the pH of resultant solution was read by pH meter. (European Pharmacopoeia, 4th Edition 2002).

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, Escherechia col using disc diffusion Kirby-Baueri. (Koletar 2000).

RESULTS AND DISCUSSION

A summary of the results of uniformity of weight, assay, hardness test, friability, pH and dissolution and microbiological sensitivity test according to the pharmaceutical monographs are as shown in Table 1 and Table 2. In two types of effervescent tablet (wet granulation method and direct compression method) the zone of inhibition is slightly larger in wet granulation method than in direct compression method this might be due to good distribution of active ingredient.

- In wet granulation method we can omit the binder when we use saccharin in any formula when it use with a very low quantity of water.
- We can overcome the problem of bitterness of soluble drug (ciprofloxacin) by using saccharin from four to six time's active ingredient in effervescent formula.
- Effervescent tablet formula can be use to enhance solubility and might increase the palatability and mask taste and bioavailability and activity.
- Flavoring agent (vanillin) might mask taste beside good odor.
- Weight granulation is very good for production of effervescent tablet rather than dry compression method.
- Guar 1% is very strong binder when it was used in combination with PVP 4% in formula.
- Ten times dilution were needed for binder (0.1 guar and 0.4 PVP) with saccharin to avoid very hardness value in compression in previous method in which we use guar 1% dry lactose PVP 1% we find weight granulation method give good compressibility rather than direct compression.
- Two values of hardness were found in result due to variation in binder concentration because PVP and guar were used in two concentrations.
- In wet granulation method mesh number ten was used for first granulation resizing and mesh number fourteen was used for enhancing uniformity of distribution and mixing.
- The addition of MCC 5% before resizing to avoid stickiness and enhance disintegration and might work as glidant and lubricant.
- Guar 0.5 with 4% PVP gives thick binder.
- The use of MCC is work as lubricant which intended to reduce the friction during tablet rejection between the wall of tablet and the wall die cavity in which the tablet was formed furthermore has glidant effect and disintegrating action.

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	1.71
Wet Granulation (Punch 13)	1.9	7.82	1.22	6.15	97	3.09
Wet Granulation	2.6	5.2	0.84	6.17	96	2.8

Table 2. Comparison between two types of effervescent tablet on different species of microorganisms

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

Figure 4.Tableting process of effervescent ciprofloxacin HCl

Figure 5. Inhibition zone of effervescent ciprofloxacin tablet in *Salmonella* species

- In effervescent formula potassium carbonate might be used in state of sodium bicarbonate for hypertensive patient and for patient taking digoxin.
- Tablet weight in this two formulas 1600 mg (1.600 gm) can be use in two divided tablets can be berryable easy to handle and stand packaging and transportation.
- Potassium citrate it might be used with effervescent ciprofloxacin to give unique combination as anti effective and cleaning and anti salts.
- In granulation method lubricant and glident were needed beside MCC, talc powder 1.5% from all formula and Mg stearate 0.75% from all formula putting increasing concentration of Mg stearate can impaired disintegration time because it is hydrophobic (might hinder solubility time and water contact) thus we need aluminum foils or glass tight container as package.
- Due to minimum concentration of saccharin was used to inhibit bitterness, thus suggested formula was put for more palatability.
- The weight variation of effervescent tablet (both wet granulation method and direct compression method) complies with the monograph requirements and this might be giving an indication for homogeneity and uniformity of the active ingredient distribution.
- Wet granulation effervescent tablet give more value hardness in comparison to direct compression method and thus it was easy to handle.
- Compression of wet granulation tablet is rather good in comparing to direct compression method this due to granules in wet granulation method.
- Friability of wet granulation method is bigger than direct compression effervescent tablet, this due to ability of granules to compress. Despite of the value is (1.9) but it could be acceptable for effervescent (Mohrle, 1989).
- All the types of formula pass the thickness and diameter test and this indication for good tablet compression.
- The dissolution time of effervescent tablet (direct compression) (91-115second) and the dissolution time of effervescent tablet (wet granulation) the two types of effervescent is complied with the pharmacopeia specifications for the effervescent tablets, which are up to 300 seconds (5min) (European pharmacopeia, 2002). (European Pharmacopoeia, 4th Edition. 2002). The dissolution of tablet from direct compression is faster than wet granulation method; this might be to the ability of granules to compress.
- On comparing the tablets were formulated as effervescent tablets (wet granulation) a zone of inhibition was found more than the direct compression this might be due to more distribution of the active ingredient by mixing (Mohrle, 1989).
- In effervescent tablet wet granulation method in comparison to dry compression method it gives more effect than direct compression method, this might be due to good mixing and distribution of granules.
- Due to the high solubility of the effervescent drug, ciprofloxacin was formulated as an effervescent tablets and to become more effectiveness, convenient easy to use and swallow. Premeasured dosage forms that are already in solution when ingested effervescent mixtures have been moderately popular, they offered republic ionic dosage form that was interesting to prepare (Quitin *et al*., 2004). In addition they provide a pleasant taste due to carbonation, (CO2 covering testing pables of the tongue) which helped to mask the unpleasant taste of objectionable materials (Mohrle, 1989).
- Ciprofloxacin when dissolve in water at first there was very bitter taste, to solve this problem, saccharin sodium powder was added to the formula and give a nice odor, together with vanillin flavor to mask the taste beside effervescent action in mask (Quitin *et al*., 2004).

The effervescent tablets is very effective in medicine this clear that the microbiological test was carried out against enterobacteriace and this might be solution of the problem of resistance. The zone of inhibition diameter is absolutely of pure ciprofloxacin when we use the suitable media for bacteria that emphases the effectiveness of drug (active ingredient). And there is no drug in compatibility of various component of formula and that clear after incubating of formula against selected microorganisms Table 2.and Figure 5.

Conclusion

- The study managed to improve the palatability of the drug solution, via the utilization of saccharin sodium and vanillin flavor and using effervescent formula. Formulation into effervescent tablet is suitable for larger dose size which has difficulty in production of a convention tablet due to the difficulty in swallowing, besides enhancing solubility, which masking the taste and may leads to higher bioavailability and compression.
- Formulating tablet as wet granulation method (when it is possible and applicable) is better than in direct compression method because of good distribution active ingredient.
- The effervescent formula is needed and sometimes it is a must to enhance palatability of certain drugs.
- The correlation can be made between dissolution rate of effervescent tablets as an indication for its effectiveness without in vivo studies and that by microbiological inhibition zone assay.
- Wet granulation method (when it is applicable) is better than the direct compression method; this due to good distribution of active ingredient.
- Effervescent tablet from ciprofloxacin might reduce the microbial resistance, and increase patient compliance, and the effervescent tablets need well tight container.
- The effervescent tablets which prepared by wet granulation method (punch13) two tablets must be used to give 250 mg

active ingredient (ciprofloxacin HCl) or four tablets to give 500 mg.

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