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Research Article

Effect of Guargum on Dissolution and Sustained release of ciprofloxacin in newly formulated Effervescent tablets comparing with five marketed formulations

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ABSTRACT

This research studied the role of guargum in a prepared formulation of ciprofloxacin as effervescent tablet by two methods (direct compression and wet granulation) in dissolution rate. A comparison of this effect of guargum was compared with dissolution rate of five conventional ciprofloxacin tablets brands. Also, the guargum beside its binding effect has masking effect on the bitter taste of the drug. Furthermore, the effervescent effect of the added citric acid, tartaric acid and sodium bicarbonate lead to the improvement of taste of the drug. The vanillin was also used as flavoring agent to enhance the palatability. This study showed that formulating the drug as effervescent tablets by wet granulation method using guargum as a binder resulted in enhancement of the dissolution rate of the drug due to libration effect of guargum during dissolution. This enhancement may be due to the guargum surface activity as wetting, disintegrating agent and high viscosity effect. Compared to conventional drug brands, the amount of the formulated drug due to dissolution has higher resolution peak. This indicates better absorption and bioavailability of the formulated drug.

Key words: Guargum, Effervescent ciprofloxacin Tablets, Dissolution rate, Sustained Release, Taste masking.

1. INTRODUCTION

The Guar or cluster bean (Cyamopsis tetrago*noloba*) is an annual legume and the source of guar gum. It is also known as Gavar, Guwar or Guvar bean. It is principally grown in India and Pakistan, with smaller crops grown in the U.S, Australia, China and Africa. Guargum, also called guaran, is a galactomannan. It is primarily the ground endosperm of guar beans. The guar seeds are dehusked, milled and screened to obtain the guargum[1]. It is typically produced as a free-flowing, pale, off-white-colored, coarse to fine ground powder. Guar is a multi-purpose plant, mostly used today as a source of galactomannan gum, which is used as a thickener and stabilizer in foods such as salad dressings, ice cream and yoghurt. The gum and the water-soluble resin extracted from the seeds are also used in pharmaceutical manufacturing and other industries, including paper manufacturing, cosmetics, mining and oil drilling[2]. In 2008, India accounted for 80% of the world trade of guargum and guargum seed was among the top three traded agricultural commodity on Indian bourses[3]

Chemically, guargum is a polysaccharide composed of the sugars galactose and mannose, the back bone is the linear chain of β 1,4-linked mannose residues to which galactose residues are 1, 6-linked at every

second mannose, forming short side-branches [Fig. 1][4]. This is due to presence of more galactose branch points compared to other gums. Furthermore, it is not affected by ionic strength or pH, but will degrade at pH screams at high temperature (e.g. pH 3 at 50 °C)[4]. It remains stable in solution over pH range 5 – 7 like most effervescent formulas with pH 6.2[5]. Guargum is economical because it has almost eight times the water-thickening potency of cornstarch only a very small quantity is needed in effervescent ciprofloxacin HCl for producing sufficient binding effect, viscosity and masks solid particles in solution and furthermore works as stabilizer because it helps to prevent solid particles from settling and thus enhance solubility by effervescent base[4]. Manufacturers define different grades and qualities of guar- gum by the particle size. Modified forms of guargum that are available commercially include enzyme-modified, cationic and hydropropyl guargum[6]. 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[7-9].

Tablet formulations may be rendered effervescent for several reasons, including improvement of their disintegration characteristics, and increase in dissolution rate, thus enhancing the liberation of ciprofloxacin HCl, in addition to the masking taste property of guargum[10]. 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 tablets[11,19].

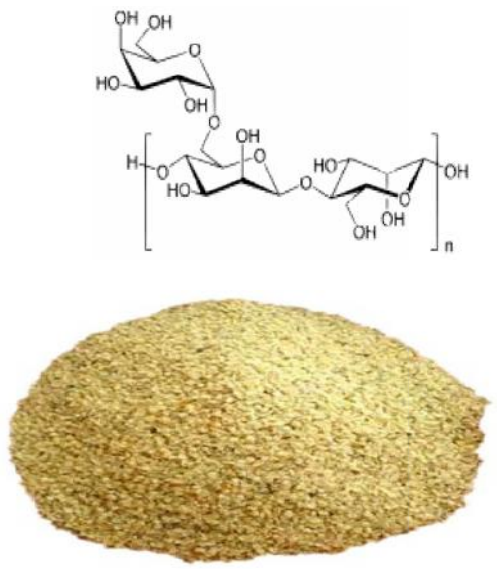

Figure 1
Chemical Structure of Polysaccharide Galactose and Mannose and Granules of Guargum

Ciprofloxacin hydrochloride [Fig. 2] was formulated with guargum as a good example for masking the bitterness of this drug[12].

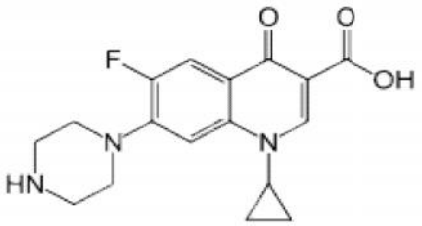

Figure 2
Structure of Ciprofloxacin

Guargum is more soluble than locust been gum and is a better stabilizer as a first choice for the formulation of effervescent ciprofloxacin tablets.

Recent similar studies of new formulations of effervescent tablets of other pharmaceutical products were quoted in references 20

The purpose of the present study is to formulate an effervescent ciprofloxacin tablet by two methods (direct compression and wet granulation). The success of the formula was contributed by the use of an effervescent base, a taste masking generator, a flavoring agent and a sweetening agent. This study found that formulating the drug as effervescent tablet by wet granulation method (low guargum concentration as binder) lead to improvement of the drug disintegration characteristics, and increase in dissolution rate. This consequently lead to increase in the drug effectiveness, therapeutic effect and decrease in the ciprofloxacin resistant as well as increase in patient acceptability as effervescent tablet compared to conventional ciprofloxacin brands.

2. 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 equations[13]:

Citric acid:

$$3NaHCO_3 + C_6H_8O_7 \cdot H_2O \rightarrow \underset{3\times 84}{4H_2O} + 3CO_2 + \underset{210}{Na_3C_6H_5O_7} \quad (1)$$

Tartaric acid:

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

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 disintegrant were mixed or blended well[14].

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 and Poly vinyl pyrollodine) 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 drying[15]. 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 20 mm die and 125 mg ingredient, using 13 mm die[14].

2.1.2 Calculations:

Formula (1) (high binder concentration):
Guargum: 1% and PVP: 4% (w/w).

Formula (2) (low binder concentration):
Guargum: 0.005% and PVP: 2% (w/w)
Guargum with polyvinyl pyrollodine as a binder in different 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 was also be used as a binder.
The two Tablets weights of the two formulae were 1600 mg and 2000 mg.
Microcrystalline cellulose (Avicil) 5% was 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 tablet[14].

Ciprofloxacin was mixed with lactose in a mortar to improve compression characteristic then sodium bicarbonate ($NaHCO_3$) 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 flavor were added and then the whole mixture was passed through a sieve for more mixing.

One percent of guargum 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 machine[14].

3. Result and discussion:

a. Effect of Guargum in Dissolution Profile of Effervescent Ciprofloxacin HCl Tablets

The effervescent tablets were prepared by two methods wet granulation method and direct compression method. In both methods, guargum was used as a binder; the difference between the two methods was that in wet granulation the binder was used in liquid form and in dry compression in dry form[10].

The use of guargum in wet granulation method in liquid form lead to increase in the tablet consistency and thus increased its hardness value which retarded the solubility process compared to direct compression method. However, wet granulation was generally applied for formulation of effervescent tablets. The high friability value in direct compression method lead to the use of guargum in liquid form to make the tablets easier for handling, packaging and transportation and this agreed with the study by Adegbolagun et al.[16] and Gtu et al[17].

The Role of Guargum in Dissolution Profile of the formulated effervescent ciprofloxacin HCl tablets compared to Conventional brands of ciprofloxacin tablets

Guargum shows high low-shear viscosity but is strongly shear-thinning. It is very thixotropic above 1% concentration thus in effervescent formula it was used in concentration ≤ 1 %. Guar gum is economically cheap and is used as stabilizer because it helps to prevent solid particles from settling. This may prevent fast liberation of the drug, explaining the increase of the liberated amount of the dissoluted drug in Fig. 4[4,9].

Guargum was used in low concentration to allow the particles of effervescent drug to separate easily in solution, and due to the high solubility of the effervescent ciprofloxacin the use of guargum did not hinder the solubility of the drug. Guargum also has stabilizing and coating effects of the solid particles in solution, in addition to its sweetening, flavor and taste masking beside its effervescent action. The guargum work as binder before compression and stabilizer with masking effect after dissolution of the ciprofloxacin HCl tablets, that explained the increase in the value of drug dissolution compared to conventional ciprofloxacin HCl tablets [Fig. 4][4].

The increased amount of the dissolved drug in effervescent tablets at (45 min) compared to the five brands may be due to the use of guar as binding agent which caught some effervescent granules and release them later at that time. This indicated the sustained release and stabilizer properties of guar gum.

The mean dissolution time of effervescent tablets using direct compression was 102.7 ± 5.8 seconds and that of wet granulation was 185 ± 8.0 seconds. The dissolution time of the two formulations of effervescent tablets complied with the pharmacopeia specifications for effervescent tablets (up to 300 seconds)[18]. Thus the guargum did not affect the dissolution and solubility of effervescent granules formulae (Figs. 5, 6), so the use of guargum should be in appropriate concentration (1 - 2%). The dissolution of tablet from direct compression is faster than that of wet granulation method; this might be due to the higher value of tablet hardness using wet granulation method. Also, it might be due to using guargum in liquid form which increased its viscosity and binding effect[18].

The effervescent formulation 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 (saccharine), flavoring agent, guargum and filers. Thus, all that contributes in success the formula.

Conclusion

Addition of 0.5% guargum before compression worked up as a binder and after dissolution of the drug as stabilizer with a taste masking effect. Tablet hardness results varied according to guargum concentration (as binder). The dissolution time results of the two effervescent formulae may be due to the enhancing guar effect on disintegration time, dissolution time, absorption and sustained release of the active ingredient of the formulated tablets.

Using guargum in liquid form as binder resulted in more tablet hardness value than guargum in dry form. This may be due to the increase in viscosity of the formula and improvement in compressibility of tablets. Furthermore, Guargum may delay liberation of some granules of drug and liberate them later, explaining increase in the dissolution time profile of effervescent ciprofloxacin HCl. Guargum and effervescent bases (citric acid, tartaric acid and sodium bicarbonate), in addition to saccharin were used to mask the bitter tastes of the two formulated ciprofloxacin effervescent tablets.

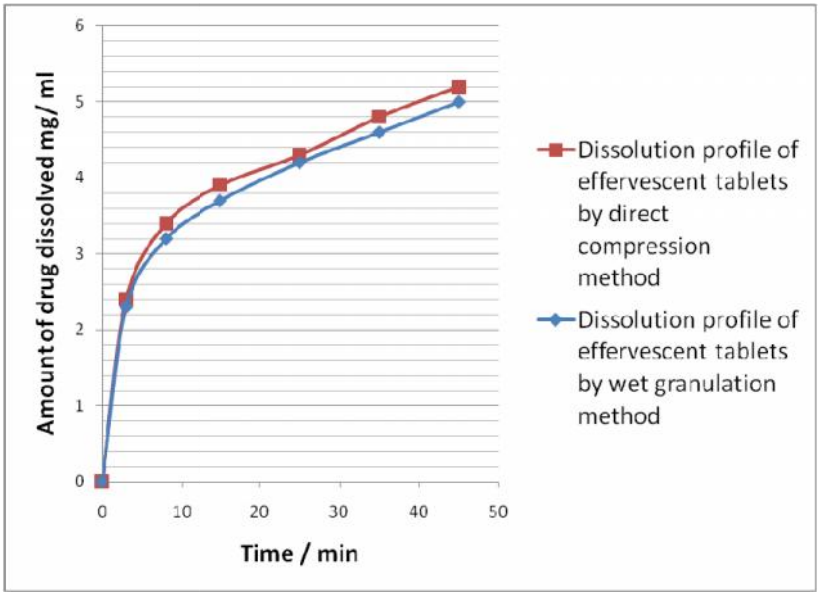

Figure 3
Dissolution Profile of Effervescent Ciprofloxacin Tablets by two Methods.

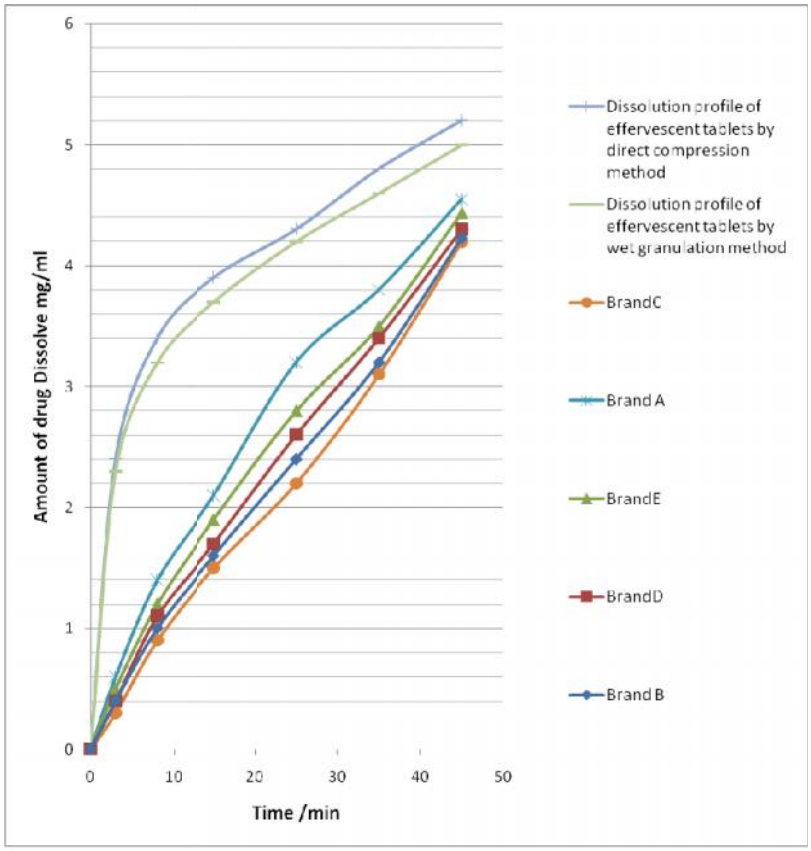

Figure 4
Dissolution Profiles of Conventional Brands and the two Types of the formulated Effervescent Ciprofloxacin HCl Tablets

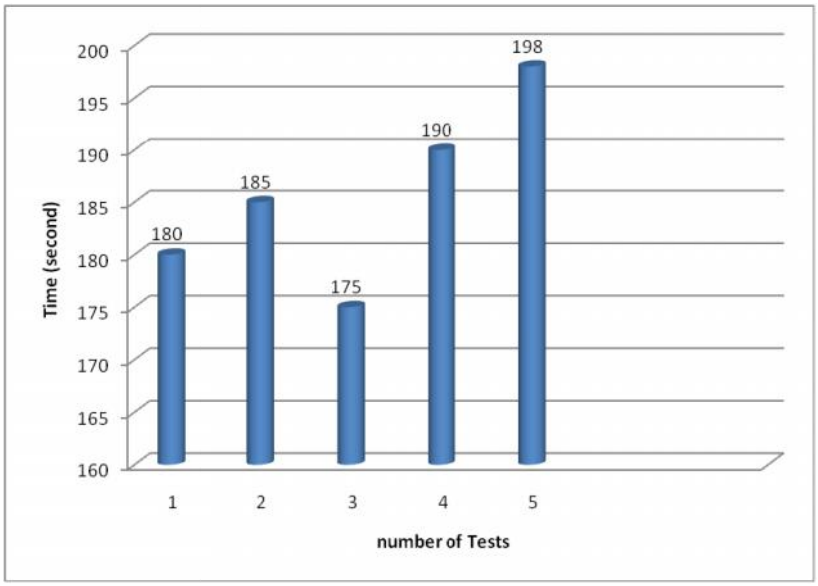

Figure 5
Dissolution Time of Effervescent Tablets using Wet Granulation Method.

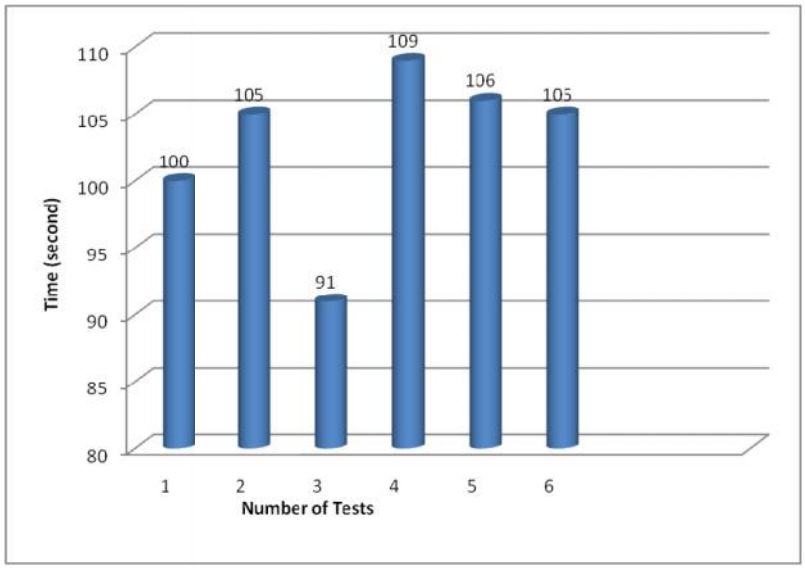

Figure 6
Dissolution Time of Effervescent Tablets using Direct Compression Method

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