Research Article

Study the effect of wet granulation and fusion methods on preparation, characterization, and release of lornoxicam sachet effervescent granules

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ABSTRACT

The present work is based on the formulation of effervescent granules of lornoxicam unit dose. Six such formulations were prepared using citric and tartaric acids and sodium bicarbonate as effervescent base at different ratios. Mannitol and aspartame were used as sweetening agents since lornoxicam has a bitter taste. The granules were prepared by the wet and fusion method, and they were evaluated for flow property (such as angle of repose, bulk density, tapped density, and Carr's index), particle size, pH, effervescence time, *in vitro* dissolution studies, and drug content. The formulated effervescent granules exhibited excellent flow properties and bulk density suitable for a unit dose. All the formulations exhibited effervescence time <60 s and dissolution profile was found to be >75% in 5 min. F2 formulation was selected as the best formulation because of their physicochemical characteristics; it is concluded that the wet method resulted in better granules compared to fusion method.

KEY WORDS: Effervescent granules, Lornoxicam, Preparation methods

INTRODUCTION

The oral dosage forms are the most popular method of drug administration, in spite of some disadvantages like slow absorption, and thus, the onset of action is time consuming. This can be overcomed by administrating the drug in liquid form, but many active pharmaceutical ingredients have limited level of stability in liquid form.[1] Hence, effervescent granules are formulated to reduce these effects which are intended to be dissolved or dispersed in water before use. This dosage form includes a mixture which when incorporated in water produces an immediate rate of release of the therapeutic compound for instant release.[2]

According to the European Pharmacopoeia, granules are defined as preparations of solid dry aggregates of powder particles able to withstand handling. Very often, they are used for oral administration. They can be prepared in single or multidose presentation with several types of use.[3]

Formulation of effervescent preparation mainly consists of three components: Active ingredients (drug), acid source, and alkaline source constituted by carbonate and bicarbonate. Acid substance and carbonates or a bicarbonate substance reacts rapidly in the presence of water by releasing carbon dioxide. They are usually dissolved or dispersed in water before administration. They provide a pleasant taste due to carbonation which helps in taste masking of objectionable medicaments. This is a unique advantage of this dosage form over other fast release dosage forms which required the use of method of taste masking. Other excipients are diluents, binders, disintegrating agent, sweetener, flavors, colors, surfactants, and antifoaming agents (if required).

The active ingredients are either present in the effervescent formulation as readily soluble compounds or they are solubilized by salt formation during the dissolution process. However, it is also possible to disperse poorly soluble active ingredients.

Effervescent granules are usually prepared from a combination of citric and tartaric acid rather than from a single acid because the use of either acid alone causes difficulties. When tartaric acid is the sole acid, the resulting granules readily crumble and lack mechanical strength. Citric acid alone results in a sticky mixture which is difficult to granulate during the manufacturing process. The reaction between

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citric acid, tartaric acid and sodium bicarbonate results in liberation of carbon dioxide.

Lornoxicam is a nonsteroidal anti-inflammatory drug of the enolic acid class of oxicam derivatives; it is used in a wide range of painful and inflammatory conditions. Lornoxicam was thought to display its effects by inhibition of cyclooxygenase isoenzymes and thus to inhibit prostaglandin synthesis from arachidonic acid.[4] It belongs to biopharmaceutical classification system - Class II substance with low solubility and high permeability. It was reported to be practically insoluble in water and has low to variable bioavailability, and it is characterized by bitter taste.[5] The chemical structure of lornoxicam is shown in Figure 1.

In the present work, an attempt has been made to formulate a unit dose of effervescent granules containing immediate release of lornoxicam. The prepared granules were evaluated for drug content, particle size, pH, effervescence time, and *in vitro* drug release.

MATERIALS AND METHODS

Materials

Lornoxicam was purchased from Wuhan Senwayer Century Chemical Co., Ltd., China. Sodium bicarbonate, citric acid, and tartaric acid were purchased from HiMedia, India. All the ingredients used were of analytical grade.

Methods for Preparation of Lornoxicam Effervescent Granules

Effervescent granules were prepared by two methods: Wet method and fusion method. We prepared three formulas with different base ratio; F1 was prepared at ratio 1:2:4.8 of citric acid, tartaric acid, and sodium bicarbonate, respectively, while F2 was prepared at ratio 1:2:3.4 and F3 at ratio 1:2:3.67. These formulas were prepared by wet method and fusion method, so the total number of the formulas was six with the same ingredients, as shown in Table 1. The amount of acids and bases was determined by stoichiometric calculation[6] sufficient to prepare 20 g of powder containing 16 mg of lornoxicam in one dose.

Wet Method

The wet method differs from the fusion method in that the source of binding agent is not the water of crystallization from the citric acid but ethanol was used as the moistening agent, forming the pliable mass for granulation. In this method, all of the powders (anhydrous) were weighed and placed in a mortar, and then, ethanol was added drop by drop until we get a wet mass to pass the ball test. Then, the wet mass was sieved and the granules were dried in an oven at temperature 40°C for 10 min; then, the granules were placed in containers and tightly sealed.

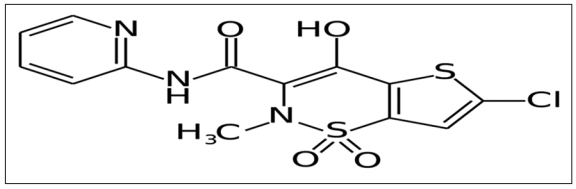

Figure 1: Chemical structure of lornoxicam

Table 1: Composition of lornoxicam effervescent granules

Material	F1 (g)	F2 (g)	F3 (g)
Lornoxicam	0.32	0.32	0.32
Citric acid	2.5	3	3
Tartaric acid	5	6	6
$NaHCO_3$	12	10.2	11
Mannitol	0.3	0.3	0.3
Aspartame	0.2	0.2	0.2

Fusion Method (Dry Method)

In the fusion method, the one molecule of water present in each molecule of citric acid (monohydrate) acts as the binding agent for the powder mixture. The required quantity of citric acid monohydrate was placed in a mortar and on hot plate. During the heating process, the heat releases the water of crystallization from the citric acid, and then, all the other materials were added with continuous mixing. The mixture was sieved and dried at room temperature, and then, the granules were placed in containers and tightly sealed.

Evaluation of Lornoxicam Effervescent Granules

Particle size distribution[7]

The size and size distribution of the granules produced were determined by agitation for 5 min using a sieve shaker fitted with a progression of standard sieves. From the weight retained on each sieve, a particle size distribution graph was plotted from which the mean diameter was determined for each formula.

Angle of repose[6]

The angle of repose was determined by allowing granules to flow through a funnel and fall freely onto a graph paper on a horizontal surface. The height and diameter of the resulting cone were measured, and the angle of repose is calculated from this equation:

$$\text{Tan } Ø = h/r \qquad \text{Equation 1}$$

Where h is the height of the powder cone and r is the radius of the powder cone.

Bulk density[8]

20 g granules blend introduced into a dry 100 ml cylinder, without compacting. The granules were carefully leveled without compacting, and the unsettled

apparent volume, Vo, was read. The bulk density was calculated using the following formula:

$$\rho bulk = M/Vo \quad \text{Equation 2}$$

Where ρbulk = Apparent bulk density, M =Weight of the sample, Vo = Apparent volume of powder.

***Tapped density*[8]**

A suitable amount of granules was placed in a 100 ml measuring cylinder using densitometer instrument, the sample was tapped 1000 times, and then, tapped volume was measured to the nearest graduated unit. Tapped density was calculated using Equation 3.

$$\rho tab = M/Vf \quad \text{Equation 3}$$

Where ρtab = Tapped Density, M = Weight of the sample, and Vf = Tapped volume of powder.

***Carr's index*[9]**

The compressibility index of granules can be calculated by the following equation:

$$\text{Carr's} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Equation 4

***Effervescence time and pH*[10]**

In vitro effervescence time was measured by pouring the one dose of granules (1 g) in a beaker containing 50 ml of water. Granules from each batch were randomly selected and *in vitro* effervescence time was measured from the beginning of effervescence until we get clear solution, and then, the pH of solution was measured by pH meter.

Drug Content

A dose of the effervescent granules was accurately weighed and mixed in 100 ml phosphate buffer pH 6.8 in a volumetric flask. Subsequent dilution was made from the stock solution, and the concentration of the dilution was measured at λ max 376 nm in spectrophotometer (ultraviolet [UV]-visible, Cary).

In Vitro Dissolution Study

The *in vitro* dissolution studies for F2 and F′2 were carried out in the USP dissolution test apparatus Type 2 (paddle). A 900 ml of the dissolution medium of 0.1N HCl (pH 1) was taken, and the temperature was maintained at 37 ± 0.5°C. The speed of the paddle was set at 50 rpm. Sampling was done at every 1 min interval. For each sample, 1 ml of the dissolution medium was withdrawn and the same amount of dissolution medium at 37±0.5ºC was replenished to the dissolution medium. The sample withdrawn was filtered and analyzed in the UV spectrophotometer.

RESULTS AND DISCUSSION

Particle Size Distribution

In our experiment, we used sieving method over microscopic method; since microscopic method can measure particle size up to 100 µm, it is time consuming and tedious, and it needs an experienced person, whereas sieving method is fast, automated (does not need an experienced person), and easy to perform, gives a wide range of particle size especially for coarse particles, and inexpensive. The results of particle size are shown in Table 2; the particle size was ranged from 335 to 594 µm. In general, the formulas prepared by fusion method had lower particle size than formulas prepared by wet method since water of crystallization produced from fusion method was not sufficient to form pliable mass and granules, so there is a lot of powder not converted to granules. During drying stage in the fusion method, the unbound water in granules evaporated, which resulted in lower moisture content than granules produced by wet granulation method. Granulation by fusion method produced granules with lower tendency for adhesion, due to their lesser moisture content.

The particle size distribution is shown in Figure 2.

Flow Property of Granules

The values obtained for bulk density, tapped density, angle of repose, and Carr's index are tabulated in Table 2. All the formulations showed good flow properties. The angle of repose was <30°, indicating excellent flow property of the granules, while Carr's index results indicated flow properties ranged from fair to excellent.

Effervescence Time and pH

The effervescence time of all formula was ranged from 33 to 52 s as shown in Table 2. A high concentration of sodium bicarbonate reduces the effervescent time, so F1 and F′1 have the lowest effervescent time. The pH of solution [Table 2] after effervescence was <6 due to the liberation of CO_2 and complete consumption of sodium bicarbonate. The unreacted citric acid resulted in the acidic pH of the solution which improved taste perception.

F1 prepared by wet method had the highest pH due to high concentration of sodium bicarbonate. In general, the pH of effervescent granules prepared by dry method was less than granules prepared by wet method because the heat releases the water of crystallization from the citric acid, which, in turn, dissolves a portion

Table 2: Evaluation parameters of lornoxicam effervescent granules

Formula	Type of test							
	Particle size (µm)	Angle of repose	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	Effervescence time (s)	pH	Drug content (%)
F1	419.525	22°	0.6	0.75	20	33.16	5.1	99
F2	594.069	24.3°	0.6	0.75	20	48.84	4.7	98
F3	575.303	27.6°	0.6	0.75	20	52.31	4	98
F′1	335.218	29.4°	0.9	1	10	35	2.7	91.7
F′2	388.427	25.2°	0.81	1	19	46.91	3.4	90
F′3	442.184	21	0.75	0.8	6.25	42.55	3	90

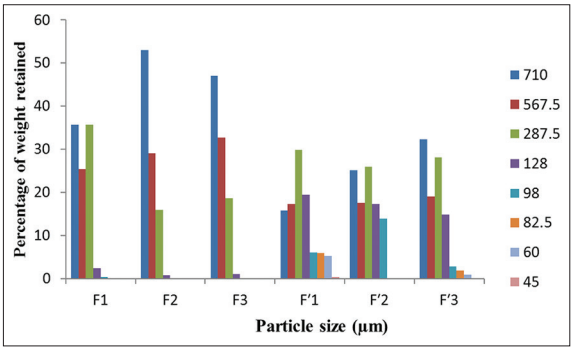

Figure 2: Particle size distribution

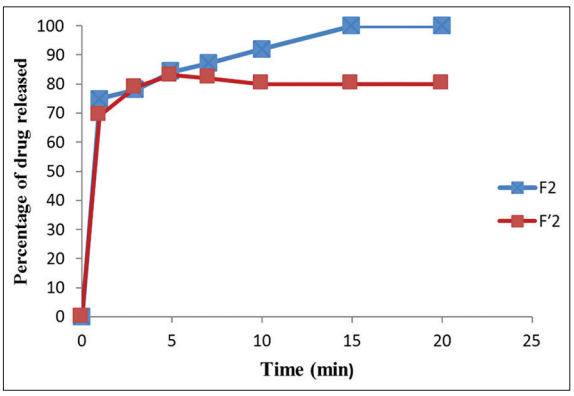

Figure 3: Dissolution profile of lornoxicam effervescent granules

of the powder mixture, setting the chemical reaction and consequently releasing some carbon dioxide.

Ratios of effervescent components in the formulations of F2–F′2 led to a better solubility with no sedimentation, a pH <6, and an appropriate effervescent reaction so that F2–F′2 were selected as the best formulas with ratio 1:2:3.44 of citric acid, tartaric acid, and sodium bicarbonate, respectively.

Drug Content

The drug content was in the range of 96.81 ± 0.01–99.44 ± 0.01 for all the six formulations as shown in Table 2. Hence, it qualified the IP specifications for assay of drug content which should not be <90% and should not be >110%.

In Vitro Dissolution Study

F2 and F′2 showed >75% release within 5 min in 0.1 N HCl as shown in Figure 3. The bursting of the granules into minute particles was facilitated by the production of effervescence. The formulations showed the good bursting effect and hence promoted rapid dissolution, and F2 gave 100% drug release in around 15 min, while F′2 prepared by fusion method gave 80% drug release in 15 min.

CONCLUSION

Lornoxicam effervescent granules were prepared successfully by the wet and dry method containing citric acid and tartaric acid as acid components and sodium bicarbonate as base source. Formulated granules had given satisfactory results for various physicochemical properties, i.e. bulk density, tapped density, angle of repose and drug content, uniform granule size, and good effervescence time.

F2 formulation was selected as the best formulation because of their physicochemical characteristics with 100% release within 15 min. It is significant that wet method resulted in better granules compared to fusion method.

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