

## FORMULATION AND EVALUATION OF EFFERVESCENT TABLETS OF GLUCOSAMINE SULPHATE IN COMBINATION WITH IBUPROFEN AND VITAMIN- E FOR THE TREATMENT OF OSTEOARTHRITIS

Senthil Kumar Krishnan\*, Chidananda B, Mohammed Gulzar Ahmed

Department of Pharmaceutics, SAC College of Pharmacy, Karnataka -571448, India.

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### \*Correspondence for

#### Author

Senthil Kumar Krishnan

Department of

Pharmaceutics, SAC

College of Pharmacy,

Karnataka -571448, India.

### ABSTRACT

**Background and purpose of the study:** Osteoarthritis (OA) is the most common joint disorder worldwide. Generally, oral dosage forms are used for the treatment of OA but they have some disadvantages like slow absorption and thus, onset of action is prolong. This can be overcome by administrating the drug in liquid form but, many APIs have limited level of stability in liquid form. Recently, effervescent drug delivery systems have started gaining popularity, because they are easy to administer and lead to better compliance. The aim of this study is to formulate effervescent tablet with sufficient mechanical integrity and to achieve faster disintegration in water. **Method:** They are

intended to be dissolved or dispersed in water before use. The study was designed to assess the treatment for osteoarthritis by using combination of drugs such as Ibuprofen, Glucosamine and Vitamin E in an effective way. The dosage of Ibuprofen is reduced by addition of glucosamine sulphate (nutraceutical) on an assumption that the activity of ibuprofen may be enhanced by nutraceutical. The formulations were subjected to various evaluation tests. **Results:** All the formulations have shown good effervescence when placed in 100 ml of water. The resultant solution appeared clear indicating the solubility of ingredients in water. The friability and hardness of formulations are in the acceptable range. The Angle of Repose ( $\theta$ ), Hausner's Ratio and Carr's Compressibility Index (%) revealed that the formulations have good flow property. The solution time, CO<sub>2</sub> and moisture content of all the formulations are in the acceptable range. **Conclusion:** All the results concluded that effervescent tablet preparation containing ibuprofen in combination with glucosamine

sulphate and Vitamin-E can be formulated as marketed product for the treatment of osteoarthritis.

**KEYWORDS:** Osteoarthritis, Effervescent, Ibuprofen, Glucosamine sulphate, Vitamin-E.

## INTRODUCTION

OA can be defined as a heterogeneous group of conditions characterized by a combination of joint symptoms and signs stemming from defects in the articular cartilage and changes in the adjacent tissues, such as bone, synovial joint, muscles, and ligaments.<sup>[1]</sup> The oral dosage forms are the most popular way of taking medication, despite having some disadvantages like slow absorption and thus, onset of action is prolonged. This can be overcome by administering the drug in liquid form but, many APIs have limited level of stability in liquid form. So, effervescent tablets act as an alternative dosage form. The tablet is added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The tablet is quickly broken apart by internal liberation of CO<sub>2</sub> in water due to interaction between tartaric acid and citric acid with alkali metal carbonates or bicarbonates in presence of water.<sup>[2]</sup> Without appropriate pain relief, strengthening and maintaining joint mobility is rarely achievable. Relief is achieved by treating with non-steroidal anti-inflammatory drugs.<sup>[3,4]</sup> Next to NSAIDs, nutraceuticals are the fastest growing group of healthcare products. The effectiveness of glucosamine sulphate is to improve joint physical function in mild to moderate knee OA, and to ensure the therapeutic efficacy and safety as a disease-modifying agent in osteoarthritis compared with a combination of glucosamine sulfate and NSAIDs (Ibuprofen) in mild to moderate knee OA,<sup>[4-6]</sup> A number of studies have examined the effect of vitamin E on both symptoms and structural changes in OA. Antioxidant supplements and diets have long been advocated for the treatment of rheumatoid arthritis, osteoarthritis and other inflammatory arthritis.<sup>[7]</sup>

Hence, the aim of present work is to formulate different effervescent tablet preparations of ibuprofen in combination with glucosamine sulphate and Vitamin-E for the effective treatment of osteoarthritis.

## MATERIALS AND METHOD

### MATERIALS

Glucosamine sulphate, Ibuprofen and Vitamin-E were procured from Yarrow chem. Products (Mumbai). All the other chemicals used were of analytical grades.

**Calibration curve of ibuprofen**

Accurately weighed 100 mg ibuprofen was dissolved in 100ml of phosphate buffer pH 7.2 to get the stock-I solution of 1 mg/ml. From this stock solution, 10 ml is taken and diluted to 100 ml with phosphate buffer pH 7.2 to get stock-II solution of 100µg/ml. From this stock-II solution, aliquots of 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4 & 1.6ml were withdrawn and further diluted to 10 ml with buffer solution to obtain a concentrations range of 2 to 16µg/ml. The absorbance of the solutions was measured at 222 nm by using UV-Vis spectrophotometer. A graph of Concentration vs. Absorbance was plotted.<sup>[8]</sup>

**Calibration curve for glucosamine sulphate**

Four millilitres of glucosamine sulphate having different concentrations (i.e. 0.1%, 0.2%, 0.3%, 0.4%, 0.5%, 0.6% and 0.7%) was supplemented with 0.5 ml of 0.8% ninhydrin and 0.5 ml of 0.2M phosphate buffer (pH 6.0) as standard samples. For blank sample, glucosamine was replaced with water. Standards and blank solutions were heated at 100°C in a water bath for 30 min. Reaction was stopped by placing the test tubes into cold-water bath, and the colour changes were detected at 570 nm after they were held at room temperature for 20 minutes.<sup>[9]</sup>

**Calibration curve of vitamin E**

Accurately weighed 100 mg vitamin E was dissolved in 100ml of ethanol solution to get the stock-I solution of 1 mg/ml, Serial dilutions of standard solutions are prepared by pipetting out 0.5 to 2 ml solutions into 10 ml volumetric flask and brought the volume up to mark with ethanol to obtain concentration range of 0.05 to 0.2mg/ml. The absorbance of each dilution was recorded on spectrophotometer at 285 nm and calibration graphs were prepared by plotting absorbance against concentration.<sup>[10]</sup>

**Identification****Angle of repose**

The angle of repose of each powder blend was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of the funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated using the following equation,

$$\tan \theta = h/r$$

$$\theta = \tan^{-1}(h/r)$$

Where,  $\theta$  = angle of repose

h = height of the pile and,

r = radius of the powder cone respectively.

Angle of repose affects particle size distribution, as larger the particle size, it will flow freely and vice-versa. For good flowing materials, the angle of repose should be less than  $30^\circ$ .<sup>[11]</sup>

### **Bulk tapped density**

granules were poured gently through a glass funnel into a graduated cylinder exactly to 10 ml mark. Excess granules were removed using a spatula and the weight of the cylinder with pellets required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2 cm until the time when there was no more decrease in the volume. Bulk density and tapped density were calculated. Hausner's ratio and Carr's index were calculated.

### **Compressibility Index**

The Carr's index of the powder was determined by using formula:

$$\text{Carr's index (\%)} = [(TBD - LBD) \times 100] / TBD$$

Where, TBD is the total bulk density and LBD is the loose bulk density.

### **Hausner's Ratio**

The Hausner's ratio and Carr's index are measures of the flow properties of powders.

A Hausner's ratio of  $<1.25$  indicates a powder that is free flowing

Whereas  $>1.25$  indicates poor flow ability.<sup>[8]</sup>

$$\text{Hausner's ratio} = \text{tapped density} / \text{Bulk density}$$

### **Formulation of effervescent tablets**

#### **Wet Granulation**

The Wet granulation process performed into three steps:

- A) Dry Mixing & Granulation
- B) Lubrication of Granules
- C) Compression of Lubricated Granules

#### **Dry Mixing & Granulation**

##### **Acid granulation**

In the first step, weighed citric acid, tartaric acid were blended and passed through sieve no.40#. In second step, binding agent PVP-K-30 dissolved in ethanol. The above organic

solvent was mixed with acid portions i.e. citric acid & tartaric acid. The obtained wet mass was passed through sieve no.20# and dried at 60°C for 30 min.

### **Base granulation**

In base granulation, the sodium bicarbonate, sodium carbonate were blended and passed through sieve no.40#. In the second step, the binding agent PVP-K-30 was dissolved in organic solvent i.e. ethanol. The above organic solvent was mixed with active ingredients, sodium bicarbonate & sodium carbonate. The obtained wet mass was passed through sieve no.20# and dried at 60°C for 30 min.

### **Lubrication of acid and base granules**

After drying at room temperature, both granules i.e. acid granules and base granules were mixed. After mixing both granules, flavour and lubricating agent like sodium benzoate added to the granules and well mixed.

### **Compression of Lubricated Granules**

The lubricated granules were compressed into tablet by using rotary tablet punching machine.<sup>[8]</sup>

### **Evaluation of effervescent tablet**

#### **Tablet Hardness**

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Pfizer hardness tester.<sup>[8]</sup>

#### **Tablet thickness**

Thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauge on three randomly selected samples.<sup>[8]</sup>

#### **Friability**

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets through a distance of six inches with each revolution. After 100 revolutions, the tablets were reweighed and the percentage loss in tablet weight was determined.<sup>[11]</sup>

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}}$$

### Weight variation

Twenty tablets were weighed individually and the average weight was determined. Then, percentage deviation from the average weight was calculated. Just two tablets can be out of the 5% of the average weight.<sup>[11]</sup>

### Carbon dioxide content

Tablet was placed in 100 ml of 10% sulphuric acid solution, difference in weight after and before was calculated the resulted weight was the amount of CO<sub>2</sub> released.<sup>[12]</sup>

### Moisture content

10 tablets of each formulation were dried in a desiccator containing of activated silica gel for 4 hours. Water content of 0.5% or less is acceptable.<sup>[13]</sup>

### Drug content

100 mg tablet powder was weighed and dissolved in 100 ml of buffer solution which gives a stock-I solution. From stock-I solution, 10 ml is taken and diluted to 100 ml with buffer solution to give a stock-II solution. From stock-II required amount is taken and diluted to get desired concentrations. Simultaneous estimation of drugs were performed.

### Formation of two simultaneous equations

Set of two simultaneous equations were

$$Cx = \frac{A_2ay_1 - A_1ay_2}{ax_2ay_1 - ax_1ay_2}$$

and

$$Cy = \frac{A_1ax_2 - A_2ax_1}{ax_2ay_1 - ax_1ay_2}$$

Where, A<sub>1</sub> and A<sub>2</sub> are the absorbance of sample solutions at C<sub>x</sub> and C<sub>y</sub> are concentration of Ibuprofen and Glucosamine sulphate/Vitamin E in mg/ml in sample solution. By substituting the values of A<sub>1</sub> and A<sub>2</sub>, the values of C<sub>x</sub> and C<sub>y</sub> can be calculated by solving the two equations simultaneously. Here, ax<sub>1</sub> and ax<sub>2</sub> are the absorptivity coefficient of Ibuprofen; ay<sub>1</sub> and ay<sub>2</sub> are the absorptivity coefficients of Glucosamine sulphate/Vitamin E.

**For three drugs**

The first derived wave length for glucosamine sulphate (GS) was 570 nm at which Ibuprofen (IBU) and vitamin E (Vit-E) show zero absorbance. The estimation of IBU and Vit-E was carried out at 222 nm and 285 nm by employing simultaneous equation method at which GS shows zero absorbance.

Estimation of IBU and Vit-E was done by framing and solving simultaneous equations, for two drugs mentioned as above.<sup>[12]</sup>

**Content uniformity**

In this test, 30 tablets were randomly selected contained for sample, and 10 tablets should contain not less than 85.0 % and not more than 115.0 % of the label claim. If one unit outside the range of 85 to 115% of the label claim and no units is outside 75 to 125% or if RSD>6% or if both conditions prevail, test 20 additional units.<sup>[8]</sup>

**Solution time**

Solution time is the time required for 2 tablets to dissolve in 180ml of water at  $17.5 \pm 2.5^{\circ}\text{C}$  .<sup>[11]</sup>

**RESULTS AND DISCUSSION****Standard curves of active ingredients****Calibration data of Ibuprofen**

The absorbance was measured in a UV spectrophotometer (Shimadzu UV"1700) at 222 nm against buffer as blank. The absorbances were obtained and Calibration curve was plotted as shown in the figure 1.

**Calibration data of Glucosamine sulphate**

The absorbance was measured in a UV spectrophotometer (Shimadzu UV"1700) at 570 nm against buffer as blank. The absorbances were obtained and calibration curve was plotted as shown in the figure 2.

**Calibration data of Vitamin E**

The absorbance was measured in a UV spectrophotometer (Shimadzu UV"1700) at 285 nm against buffer as blank. The absorbances were obtained and calibration curve was plotted as shown in the figure 3.

**Evaluation of effervescent tablets****Angle of Repose ( $\theta$ )**

The values obtained for angle of repose all formulations are tabulated in Table 4. All formulation has value in the range of 25.4 to 31.37. This indicates good flow property of the powder blends.

**Density****Loose bulk Density (LBD)**

The values obtained for loose bulk density of formulations are given in Table 4. The maximum value of LBD was found to be 0.66 and minimum value was found to be 0.52 which indicates good flow property. LBD value of all formulations ranges between 0.52-0.66.

**Tapped density**

The values obtained for tapped bulk density of all formulations are tabulated in Table 4. TBD value of all formulations ranges between 0.60-0.75

**Hauser's Ratio**

The values obtained for Hauser's ratio for all formulations are in Table 4. Hauser's ratio value of all formulations ranges between 1.13-1.20 indicating that the powder blends have good flow property.

**Carr's compressibility index**

The values obtained for compressibility index for all formulations are tabulated in Table 4. Compressibility index of all formulations was found between 12% - 16.9% indicating that the powder blends have good flow property.

**Drug content and content uniformity**

The values obtained for drug content for all formulations are tabulated in Table 6. Drug content of all formulations was found between 85%-98.3%.

**Moisture content**

Ten tablets of each formulation were dried in a desiccators containing of activated silica gel for 4 hours. Water content of formulations was found to be acceptable (0.28-0.41%).



**Carbon dioxide content**

Tablet was placed in 100 ml of 10% sulphuric acid solution, difference in weight after and before was calculated and the CO<sub>2</sub> content of formulations was found to be between 84.2-147.3 mg.

**Table.1 Relationship between Angle of Repose and Flowability**

Angle of Repose	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

**Table 2: Relation of Carr's Index and Hausner's Ratio with Powder Flow**

Carr's Index	Flow Characteristics	Hausner's Ratio
< 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
>38	Extremely Poor	>1.60

**Table.3 Formulation design**

Sl.no	Ingredients	F1 (500mg)	F2 (1g)	F3 (1g)	F4 (1.2g)
1	Ibuprofen	200	200	-	200
2	Glucosamine sulphate	-	500	500	500
3	Vitamin E	-	-	100	100
4	Citric acid	47.68	47.68	77.68	77.68
5	Tartaric acid	75.51	75.51	105.51	105.51
6	Sodium bicarbonate	119.6	119.6	139.6	139.6
7	Sodium carbonate	20.23	20.23	36.27	36.27
8	PVP K 30	9.52	9.52	19.52	19.52
9	Sodium benzoate	1.56	1.56	3.56	3.56
10	Sucrose	25.86	25.86	37.86	37.86
11	Flavour(mint)	qs	qs	qs	qs
12	Alcohol	qs	qs	qs	qs

**Table.4 Evaluation of powder blend**

Formulations	Angle of Repose (θ)	Loose bulk Density (LBD)	Tapped bulk density (TBD)	Hausner's Ratio	Carr's Compressibility Index (%)
F1	25.4	0.52	0.60	1.15	13.3
F2	26.96	0.66	0.75	1.13	12.0
F3	28.05	0.63	0.72	1.14	12.5
F4	31.37	0.59	0.71	1.20	16.9

**Table.5 Evaluation of formulations for hardness, friability, solution time and pH**

Formulations	Hardness (kg/cm <sup>2</sup> )	Thickness (mm)	Friability (%)	Wt. Variation %	Solution time(sec)	pH of solution
F1	2.3	4.5	0.82	2.3	50	6.25
F2	2.8	4.2	0.61	2.5	52	6.80
F3	3.3	4.1	0.57	2.8	40	6.53
F4	3.0	4.4	0.53	3.0	55	6.38

**Table.6 Drug content and content uniformity**

Formulations	Content uniformity %		
	Ibuprofen	Glucosamine sulphate	Vitamin E
F1	98.3	-	-
F2	97.82	98.3	-
F3	-	96.8	85
F4	93.3	91.2	87.2

**Table.7 Moisture content of formulations**

Formulations	Moisture content %
F1	0.32
F2	0.28
F3	0.37
F4	0.41

**Table.8 Carbon dioxide content of formulations**

Formulations	CO <sub>2</sub> content (mg)
F1	84.2
F2	118.5
F3	105.2
F4	147.3

## CONCLUSION

In the present work, an attempt was made to formulate four different effervescent tablet preparations of Ibuprofen in combination with glucosamine sulphate and Vitamin-E were prepared for the effective treatment of osteoarthritis. The prepared effervescent formulations were thought to be patient friendly in case of swallow ability and show better therapeutic effect due to fast release.

As Ibuprofen not completely soluble in a glass of water at the time of taking medicines. To overcome Ibuprofen solubility problem it is mixed with base part granulates. Developed formula by above method has shown good evaluations parameters. The dosage of ibuprofen is reduced by addition of glucosamine sulphate (nutraceutical) on an assumption that the activity of ibuprofen may be enhanced by nutraceutical. As osteoarthritis include oxidative

stress, exogenous vitamin E supplementation ameliorates the modifiable indexes via regulation of free radical production and the consumption of antioxidant reserve. As ibuprofen cannot be used for long time treatment of osteoarthritis, the further treatment is continued with glucosamine and vitamin-E tablets. All the formulations have shown good effervescence when placed in 100 ml of water. The resultant solution appeared clear indicating the solubility of ingredients in water. The friability and hardness of formulations are in the acceptable range. The Angle of Repose ( $\theta$ ), Hausner's Ratio and Carr's Compressibility Index (%) revealed that the formulations have good flow property. The solution time and moisture content of all the formulations range in between 40-55 sec and 0.28-0.41% respectively. The carbon dioxide content of all formulations range from 84-147 mg. From the above results, it was suggested that the formulations should be stored in air tight container and in a dry place.

Hence, from the above results, conclude that it is possible to formulate effervescent tablets of ibuprofen in combination with glucosamine sulphate and vitamin-E for treating osteoarthritis.

## SUMMARY

Osteoarthritis (OA) is the most common joint disorder worldwide. Radiographic evidence of OA is present in the majority of people by 65 years of age and in about 80% of those older than 75 years. Approximately 11% of people older than 64 years have symptomatic knee OA, which can be prevented or cured by using proper medication.

In the present work, an attempt was made to formulate four different effervescent tablet preparations of ibuprofen in combination with glucosamine sulphate and Vitamin-E were prepared for the effective treatment of osteoarthritis. Effervescent tablets ensures many advantages like fast onset of action, good stomach and intestinal tolerance, more portability, more consistent response, accurate dosing, improved therapeutic effect.

In this study, preparation of effervescent tablet was carried out by wet granulation method using various ingredients like citric acid, tartaric acid, sodium bicarbonate, sodium carbonate, etc. The formulations were subjected to various evaluation tests like angle of repose, bulk tapped density, compatibility study, hardness, tablet thickness, friability, weight variation, carbon dioxide content, moisture content, drug content, content uniformity, solution time. All the results were found to be satisfactory.

Hence, it is concluded that effervescent tablet preparation containing ibuprofen in combination with glucosamine sulphate and Vitamin-E may be used for the treatment of osteoarthritis.

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