INTRODUCTION

Effervescent granules are one of the most popular oral dosage forms; most of the pharmaceutical products like analgesics, antacid and cough formulation were prepared as effervescent granules. Effervescent granules are soluble, dissolve quickly and provide a palatable formula which can avoid the bad bitter taste of drugs. It is convenient, stable dosage forms [1].

The addition of effervescent granules into a cup contains 250 ml of water exactly before taking by the patient, the granules will be dispersed readily in the water, and they are dissolved by releasing of carbon dioxide gas. This occurs due to the interaction between acidic ingredients and basic bicarbonates in the presence of water. The libration of carbon dioxide will enhance the dissolution of the drug and mask the bitter taste effect of the drug [2]. Ibuprofen is a propionic acid derivative. It’s a non-steroidal anti-inflammatory agent used for treating rheumatoid arthritis and osteoarthritis. Ibuprofen considers insoluble substance in water (0.078µg/ml) with pKa 4.5. Due to the low solubility of ibuprofen, the dissolution profile of ibuprofen may be considering the rate-limiting step for the absorption process of the ibuprofen drug [3].

This study aimed to enhance the release profile of ibuprofen by using the wet granulation method to prepare effervescent granules of ibuprofen.

MATERIALS AND METHODS

Ibuprofen (Samarra Drug Industries, Iraq), citric acid (Evonik Degussa Ltd., India), tartaric acids (Aldrich, USA), Sodium bicarbonate, hydroxyl propyl methylcellulose (HPMC E5), (Gainland chemical company, U. K), Microcrystalline cellulose (Riedel-De-Haen AG seelze, Germany), croscarmellose sodium (Hyperchem, China).

Methods

Formulation of effervescent granules of ibuprofen

The wet granulation method was used to prepare the effervescent granules of ibuprofen [4]. The quantity of each ingredient used is shown in table 1. According to geometrical dilution, all ingredients of the formulation will be mixed thoroughly to maintain good distribution of the drug with other ingredients, and then pass the powder mixture to fabricate a moist mass. Then moisten mass was passed through sieve no. 20 to get granules. These granules were be dried at 40°C overnight in a hot air oven.

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 |
|-----------------|----|----|----|----|----|
| Ibuprofen       | 600| 600| 600| 600| 600|
| Citric acid     | 217| 217| 217| 217| 217|
| Tartaric acid   | 434| 434| 434| 434| 434|
| Sodium bicarbonate | 728 | 728 | 728 | 728 | 728 |
| Saccharine      | 15 | 15 | 15 | 15 | 15 |
| Croscarmellose sodium | — | 5 | — | 5 | 5 |
| Banana powder   | — | — | 5 | — | 5 |
| Microcrystalline cellulose | — | — | — | — | — |
| HPMC in alcohol 2% | 5 | 5 | 5 | 5 | 5 |

Evaluation of effervescent granules of ibuprofen

Determination of drug content

100 mg of effervescent granules were weighed and added to 100 ml of phosphate buffer solution (pH 6.8) and mixed thoroughly. Then the solution filtered and analyzed by using a UV-visible spectrophotometer (UV-1800 shimadzo, Japan) at 260 nm to detect the % of drug content of ibuprofen in the prepared granules. The drug content of each sample was estimated from their previously prepared Standard curve [5].
Fourier transforms infrared spectroscopy (FTIR) study

FTIR spectroscopy was used to detect the compatibility between ibuprofen and other ingredients. Disc of potassium bromide at wavelength 4000-400 cm⁻¹ was used to recorded FTIR spectra of ibuprofen, each ingredient in the formula and selected formula [6].

Flowability study

Bulk density and tapped density

Two types of density were determined (bulk density (BD) and tapped density (TD)). In a 100 ml measuring cylinder, an appropriate amount of granules was weighted and put; then the initial volume was recorded. After that, the measuring cylinder was tapped at the height of 2.5 cm at 2-second intervals until no further change was noted in the volume [7]. From the equation below, bulk density and tapped density were calculated.

\[
BD = \frac{\text{granules weight}}{\text{packing volume}} \\
TD = \frac{\text{granules weight}}{\text{tapped volume of the packing}}
\]

Where BD is the bulk density and TD is the tapped density

Carr’s index for ibuprofen granules was measured to evaluate the bulk density and tapped density [8]. The values of Carr’s index of ibuprofen granules were compared with references as shown in table 2.

\[
\text{Carr's index} = \frac{[\text{TD} - \text{BD}] \times 100}{\text{TD}}
\]

Hausner’s ratio of ibuprofen granules was calculated by using the equation below. Hausner’s ratio which is less than 1.25 shows good flowing properties more than higher ones. Hausner’s ratios which are from 1.25 to 1.6 show moderate flowing properties. Hausner’s ratio which is more than 1.6 will show more cohesive powders [9].

\[
\text{Hausner ratio} = \frac{\text{tapped density}}{\text{bulk density}}
\]

The angle of repose determination

To estimate the flow properties of ibuprofen granules, the funnel method was used to measure the angle of repose. When granular materials are poured onto a horizontal plane; a conical pile will be formed. The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose. The tan of the angle of repose was measured by height (H) of the cone and diameter of the base cone (D) [10]. The values of the angle of repose were compared with references as shown in table 3.

\[
\tan \theta = \frac{H}{0.5 + D}
\]

Table 2: Flow properties and compressibility index

| Flow characters | Carr’s index |
|----------------|-------------|
| Excellent      | 1-10        |
| Good           | 11-15       |
| Fair           | 16-20       |
| Passable       | 21-25       |
| Poor           | 26-31       |
| Very poor      | 32-37       |
| Very, very poor| >38         |

Table 3: Flow properties of the angle of repose

| The angle of repose value | Flow properties |
|---------------------------|-----------------|
| <20                       | Excellent       |
| 20-30                     | good            |
| 30-34                     | passable        |
| >40                       | Very poor       |

Effervescence time

The effervescence time of ibuprofen granules was measured by adding one dose of granules to a glass containing 250 ml of water when a clear solution is obtained the effervescent time will be recorded [11]. The arithmetic mean of triplicate readings was recorded.

Dissolution study

The dissolution study of ibuprofen granule was done by using the USP type II dissolution test apparatus. The dissolution test was performed by using a dissolution medium made of phosphate buffer with pH 6.8 and at a temperature of 37±0.5°C and 50 rpm. A sample of 5 ml will be drawn every 1 min interval and then replenished with 5 ml to maintain the constant volume. After that, the sample was filtered through Whitman filter paper, and then the absorbance of drug released was calculated from a previously prepared calibration curve of ibuprofen [12].

Statistical analysis

By using Microsoft Excel 2007, the results of the investigation are given as a mean sample (of three results) ± standard deviation (SD).

RESULTS AND DISCUSSION

The results of the flowability study are shown in table 4. The values of bulk density were in the range of 0.45 -0.51. The tapped density values of the prepared granules were in the range of 0.52-0.59. The values of the angle of repose were found in range 25.2-28.98. While the result of the carr’s index of the prepared granules was in the range of 1.13-1.16. The results indicate that all five formulas had good flow properties. The good flow properties may be attributed to the successful method of preparation by wet granulation [13].

Table 4: Flow properties of ibuprofen effervescent granules

| Formula no. | Bulk density | Tapped density | Angle of repose | Carr’s index | Hausner’s ratio | Flow property |
|-------------|--------------|----------------|-----------------|--------------|----------------|--------------|
| F1          | 0.5±0.15     | 0.57±0.12      | 28.9±0.98       | 12.28±0.13   | 1.14±0.03      | good         |
| F2          | 0.49±0.20    | 0.57±0.09      | 27.9±0.16       | 14.03±0.15   | 1.16±0.04      | good         |
| F3          | 0.45±0.18    | 0.52±0.11      | 27.7±0.17       | 13.46±0.18   | 1.15±0.72      | good         |
| F4          | 0.51±0.08    | 0.58±0.12      | 25.2±0.18       | 12.1±0.99    | 1.13±0.11      | good         |
| F5          | 0.51±0.12    | 0.59±0.13      | 26.8±0.87       | 13.55±0.12   | 1.51±0.89      | good         |

*Results are expressed as a mean±SD, n=3.
Compatibility study

The results of the FTIR study are shown in fig. 1. Fig. 1 (A) represents the peaks of ibuprofen drug, it detects intense band at 1720.56 cm\(^{-1}\), 2956.97 cm\(^{-1}\), 1645.33 cm\(^{-1}\), for C=O, C-H, and C=C respectively. Fig. 1 (B) represents the FTIR spectra of the selected formula (F5). The result demonstrates no chemical interaction between ibuprofen drug and other ingredients [14].

![Fig. 1: Spectra of ibuprofen and the selected formula F5, where (A): IR spectrum of ibuprofen, (B): IR spectrum of selected formula F5](image)

Determination of % drug content

The results of % of drug content were shown in table 5. The values of % drug content were in range 90.6±0.12 – 97.5±0.12. All five formulas were qualified for the IP specification for assay of ibuprofen granules which should be not less than 90% and should not more than 110%.

| Formula | Drug content% (w/w) | Amount of drug released % | Effervescent time (sec) |
|---------|---------------------|---------------------------|-------------------------|
| F1      | 93.9±0.14           | 90.2±0.12                 | 110±0.09                |
| F2      | 95.6±0.13           | 96.6±0.13                 | 104±0.13                |
| F3      | 95.1±0.99           | 95.3±0.98                 | 100±0.11                |
| F4      | 90.6±0.14           | 92.4±0.12                 | 113±0.13                |
| F5      | 97.5±0.11           | 99.1±0.1                  | 80±0.12                 |

*Results are expressed as a mean±SD, n=3.

Effervescence time determination

The results of the effervescence time were shown in table 5. The values of effervescence time were in the range of 80 – 113 sec. The resulted ranges were acceptable for this study according to USP [15].

Dissolution study

The % amount of drug released after 5 min obtained for the five formulations of effervescent granules of ibuprofen are presented in table 5. The results show that all five formulas had a good release profile within 5 min. The improvement of ibuprofen dissolution occurs due to bursting of the granules into minute particles which was facilitated by the production of effervescence. F5 shows the highest percentage of drug released, 99.1% within 5 min. The good release profile of F5 may be attributed to the presence of the combination of disintegrant banana powder and croscarmellose sodium [16, 17].

Table 5: Drug content, amount of drug released and effervescent time of ibuprofen granules

| Formula | Drug content% (w/w) | Amount of drug released % | Effervescent time (sec) |
|---------|---------------------|---------------------------|-------------------------|
| F1      | 93.9±0.14           | 90.2±0.12                 | 110±0.09                |
| F2      | 95.6±0.13           | 96.6±0.13                 | 104±0.13                |
| F3      | 95.1±0.99           | 95.3±0.98                 | 100±0.11                |
| F4      | 90.6±0.14           | 92.4±0.12                 | 113±0.13                |
| F5      | 97.5±0.11           | 99.1±0.1                  | 80±0.12                 |

*Results are expressed as a mean±SD, n=3.
In comparison with other studies used croscarmellose sodium and banana powder as a disintegrant, the results show the same enhancing effect of drug release of tramadol, meloxicam, and ibuprofen [18, 19]. That is the ability of both croscarmellose sodium and banana powder to act as disintegrates [20-22].

CONCLUSION
Ibuprofen was prepared and evaluated successfully as effervescent granules by wet granulation method. Effervescent granules of ibuprofen were well prepared by using citric acid, tartaric acid, sodium bicarbonate, saccharine, croscarmellose, banana powder, microcrystalline cellulose and HPMC in ethanol alcohol.

AUTHORS CONTRIBUTIONS
All the author have contributed equally

CONFLICT OF INTERESTS
Declared none

REFERENCES
1. Aulton ME. Pharmaceutics: the science of dosage form design. 2nd ed. New York: Churchill Livingstone; 2002.
2. Diy ASM, Thom NV. Formulation and evaluation of metronidazole effervescent granules. Int J Pharm Sci Res 2018;9:2525-9.
3. Parikh, Dilip M. Effervescent granules. Handbook of pharmaceutical granulation technology. Edn 3. Informa Healthc; 2005. p. 365-84.
4. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vitro bioavailability. Pharm Res 1995;12:413–20.
5. Lachmann L, Liberman H, Kanig J. The theory and practice of industrial pharmacy. Edn 3. Verghese Publishing House, Bombay; 1991. p. 320-1.
6. Bhosale AV, Hardikar SR, Patil N, Patel U, Sumbe Y, Jagtap R. Formulation and in vitro evaluation of microbially triggered ibuprofen. Int J PharmTech Res 2009;1:328-33.
7. S Patel, Natvaral M Patel. Development of directly compressible co-processed excipient for dispersible tablets using 32 full factorial design. Int J Pharm Res Sci 2009;1:125-48.
8. Senthil P, Suresh Kumar CH, Narasimha Raju, S Mohideen. Formulation and evaluation of gastro oral floating tablet of glipizide. Int J Biol Pharm Res 2010;1:108-13.
9. Wells J. Pharmaceutical preformulation: the physicochemical properties of drug substances. In: Aulton M. The science of dosage form design by Michael. 2nd ed. Churchill Livingstone; 2004. p. 133-4.
10. Kaerger S, Edge S, Price R. Influence of particle size and shape on flowability and compatibility of binary mixtures of paracetamol and microcrystalline cellulose. Eur J Pharm Sci 2004;22:173-9.
11. Sandhya S, Gowthami G, Vinod KR, Vidyasravanthi E, Sai Kumar P, Rao K, et al. Formulation and evaluation of herbal effervescent granules incorporated with linomophila indica extract for bacillary dysentery. Ann Bio Res 2012;3:63-72.
12. R Margret chandra, Debjit Bhowmik, Rahul Yadav, B Jayakar, K Sampath Kumar. Formulation and evaluation of the oral tablets ibuprofen. Pharma Innovation 2012;1:32-42.
13. Abolfazl Aslani, Fatemeh Fatnahi. Formulation characterization and physicochemical evaluation of potassium citrate effervescent tablet. Adv Pharm Bull 2013;3:217–25.
14. Eter latin. Infrared and Raman spectroscopy. 1st edition; 2011.
15. The United State Pharmacopeia (USP). 30, NF28, USA: The United State Pharmacopeia Convention Inc; 2010.
16. RB Saudagar. Formulation and characterization and evaluation of mouth dissolution tablet of lisinopril by using dehydrated banana powder as a natural polymer. WJR PR 2015;4:763-74.
17. Nayan Parz, Pramod Kumar. FDA-Approved natural polymers for fast-dissolving tablets. J Pharm 2014;1:6.
18. Shah SJ. Formulation and evaluation of mouth dissolving tablet of tramadol hydrochloride. AJPCR 2013;6:31-6.
19. J Ham, S Parthiban, A Vikneswari, GP Sentilkumar, T Tamiz Mani. Formulation and evaluation of orodispersible liquidosold compacts of meloxicam using banana powder as natural super disintigrentes. AJPRS 2015;3:25-38.
20. Gopinath E. Evaluation of musa acuminum fruit as a natural super disintegrant for tablet formulation. AJPCR 2018;11:167-71.
21. Hiola R, Tunadi R. Development of effervescent granules of corn milk supplemented with probiotic lactobacillus strain shirotia. Int J Appl Pharm 2018;10:71-5.
22. Masaad AMA, Shayouby MEA, Maghrabi IA, Masaad NMA. In vitro-in vivo correlation study of a newly formulated effervescent ciprofloxacin tablets with reference tablets. Int J Curr Res Chem Pharm Sci 2016;3:1-12.