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EFFERVESCENT GRANULES – A REVIEW

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ABSTRACT

Effervescent granules are dosage form composed of dry aggregates powder particle; it contain one or more active pharmaceutical ingredient with or without excipients. Due to its low toxicity and onset action will be get fast, so effervescent granules are mostly used. Effervescent granules are uncoated granules containing drug, acid substances, carbonates or hydrogen carbonate which rapidly react with water and liberate CO_2. In this review, it gives us information regarding basic mechanism of effervescent granules and its fundamentals and excipients used, different formulation development strategies of effervescent granules with suitable pictorial representation and evaluation of effervescent granules. Additionally packaging, advantages, disadvantages and some marketed formulation details also added. Effervescent granules are prepared by various methods such as wet method, dry method, hot melt extrusion method and non-aqueous method. The above mentioned methods are briefly explained in this review.

KEYWORDS: Effervescent granules, effervescent mechanism, wet method, dry method, non-aqueous method.

1. INTRODUCTION

Effervescent granules are the most popular granular dosage form; which administered orally having drug and effervescent base composed of Sodium bicarbonate, citric acid and tartaric acid.(1) Effervescent granules are used in many pharmaceutical products such as analgesics, antacids and cough formulation.(2) Effervescent Granules are highly soluble, highly stable and having fast dissolving property and are convenient dosage forms.(3) The effervescent granules are added into a cup of water, readily granules dispersed in water and they are dissolved by releasing CO_2.(4) Due to interaction between the acid and base in presence of water, the CO_2 is evolved then granules are quickly dispersed. Due to liberation of CO_2, the dissolution of API in water can be observed as well as taste masking effect also enhanced.(3)

$$3NaHCO_{3\,(aq)} + H_3C_6H_5O_{7\,(aq)} \rightarrow 3H_2O_{\,(aq)} + 3CO_2 + Na_3C_6H_5O_{7\,(aq}$$

(Sodium bicarbonate) (Citric acid) (Water) (Carbon dioxide) (Sodium citrate)

Fig. 01: Effervescent granules direction of use.

2. MECHANISM OF EFFERVESCENCE[5]

As we already know that Effervescent granules contain acid (citric acid) and base (Sodium bicarbonate) it rapidly reacts in water by releasing CO_2.

Due to liberation in CO_2 gas, the API is dissolved in water as well as taste masking effect is enhanced.

The reaction between the citric acid and Sodium bicarbonate it results in liberation of CO_2 shown as follows

$C_6H_8O_7.H_2O + 3NaHCO_{3\,(aq)} \rightarrow Na_3C_6H_5O_7 + 4H_2O + 3CO_{2\,(aq)}$

(Citric acid) (Sodium bicarbonate) (Sodium citrate) (Water) (Carbon dioxide)

$C_4H_6O_6 + 2NaHCO_3 \rightarrow Na_2C_4H_4O_6 + 2H_2O + 2CO_{2\,(g)}$

(Tartaric acid) (Sodium bicarbonate) (Sodium carbonate) (water) (Carbon dioxide)

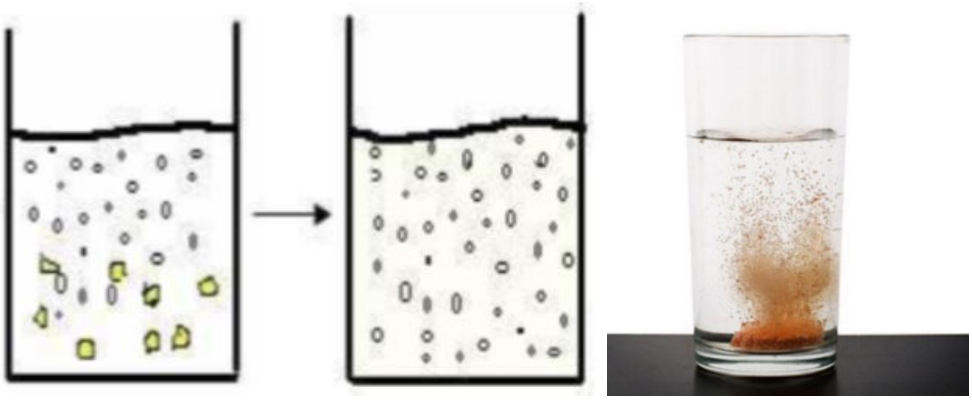


Fig.02: Mechanism of Effervescent granules.

3. FUNDAMENTALS OF EFFERVESCENT

Effervescence consists of soluble organic acid and an alkali metal carbonate salt, one of which is often the API.

When it comes into contact with water, CO_2 is liberated.[6-7]

The required ingredient for effervescent granules is acid and base, additionally it also requires a sweetener and a binding agent.[3]

1. **Acid** - It includes Citric acid, Tartaric acid, Malic acid, Adipic acid and Fumaric acid.
2. **Base** – It includes Sodium carbonate, Sodium hydrogen carbonate, Potassium bicarbonate, Sodium sesquicarbonate.
3. **Sweetener** – Mannitol, Sucrose.
4. **Binding agent** – Starch paste.
5. **Vehicle** – Ethanol (Non- aqueous method).[3]

3.1. Excipient used in effervescent granules[8]

Table 01: Excipients used in effervescent granules.

S.No	Excipient	Category
1.	Citric acid	Acidifying agent
2.	Tartaric acid	Acidifying agent
3.	Fumaric acid	Acidulant
4.	Ascorbic acid	Antioxidant
5.	Sodium bicarbonate	Alkalizing agent
6.	Sodium carbonate	Alkalizing agent
7.	Polyvinylpyrrolidone-30	Binding agent
8.	Polyethyleneglycol-6000	Binding agent
9.	Mannitol	Binding agent
10.	Sodium citrate	Buffering agent
11.	Sodium lauryl sulphate	Lubricant
12.	Sodium benzoate	Lubricant
13.	Acesulfame potassium	Lubricant

4. FORMULATION DEVELOPMENT-EFFERVESCENT GRANULES[9]

4.1. Common Procedure

Sieve the powder through sieve No. 60

↓

Mix the powder and transferred to hot porcelain dish

↓

The mixture was heated on the boiling water bath without stirring or pressing the powder

↓

Then the resultant mixture sieved through sieve No. 8

↓

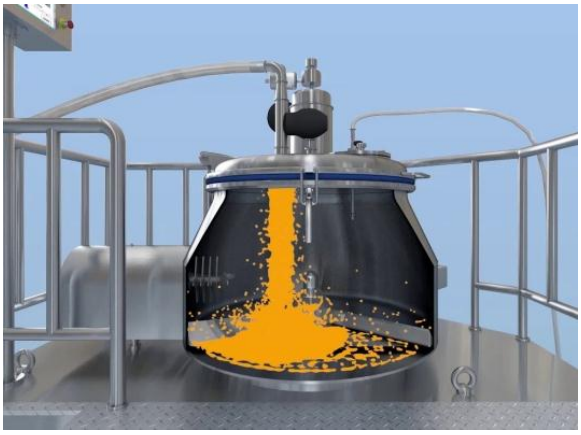
Dry the granules at 40˚C

↓

Dried granules passed through the sieve No. 14 and retained over Sieve No. 20

↓

Then these granules were packed in wide mouth container.



(1) Wet Granulator **(2) Hot Melt Extrusion Equipment**

Fig. 03: Equipment used for Effervescent granules preparation.

Fig. 04: General preparation method of Effervescent granules.

4.2. Preparation of effervescent granules

The effervescent granules are prepared using various methods like wet method, dry method or fusion method, hot melt extrusion techniques and non-aqueous method.

1. Wet method

It is the oldest method of granule preparation. Initially, all the ingredients are powdered and passed through a sieve to induce uniform, particle size.[10]

Table 02: Sieve number with granule size.

Sieve No	Granule size
4	Large granules
8	Medium size granules
10	Small granules

In wet granulation process, wet massing is the important step. During this process, granulating agent is added in the powdered mixture, it gets moistened.[11]

The moistened powdered mixture is passed through a mesh screen to produce desired size granules. Then these granules are dried by using a hot air oven.[12]

All ingredients are mixed thoroughly for uniform distribution
↓
Pass the powder through sieve to obtain uniform particle size
↓
Add suitable amount of binding agent
↓
Molten mass is passed through the sieve to obtain desired size granules
↓
These granules are dried in hot air oven.

2. Hot melt extrusion technique[13,5]

Initially 'required quantity' of ingredient is weighed and passed through sieve No.18. Heat it at 50 - 80˚C temperature until a molten mass obtained. Then the obtained mass is cool down at room temperature and pass it through the sieve No. 8 or sieve No.10 to obtain granules. Finally dry the granules at a temperature not exceeding 60˚ C.

Weigh the ingredients and pass it through sieve No. 18
↓
Heat at 50 – 80 ˚C temperature to obtain molten mass
↓
Cool it to room temperature
↓
Then pass it through sieve No. 8 or 10 to obtain granules
↓
Granules dried at temperature not exceeding 60˚C

3. Fusion method or dry method[14]

This method is most significant for effervescent granules preparation. In this method, compression step is eliminated. Here, powders are heated using an oven or any other heat source. It uses monohydrate citric acid as binding agent. Then the mixture is stirred to obtain uniform mass, cool it to room temperature which is then passed through a sieve to obtain granules and finally dried in an oven.

4. Non-aqueous method[15]

Weigh the ingredients and taken in a china dish. Add drop by drop of alcohol (ethanol) until it forms a mould, pass the mould through sieve no.10, granules are obtained and these granules are kept in an oven at a temperature of 55˚ C for 12 hrs. The granules are again passed through the sieve to obtain uniform sized granules. The granules are packed and stored.

5. EVALUATION OF EFFERVESCENT GRANULES

1. Angle of repose[3]

Using fixed funnel method, the angle of repose can be determined by passing the prepared granules in funnel. The measurement of height(h) and radius(r) of granule pile gives angle of repose which indicates the flow property of granules.

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

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

Where, h = Height of pile
r = Radius of pile

Table 03: Angle of repose with its flow nature.

Angle of repose	Type of flow
<20	Excellent
20 – 30	Good
30 – 34	Passable
>40	Very poor

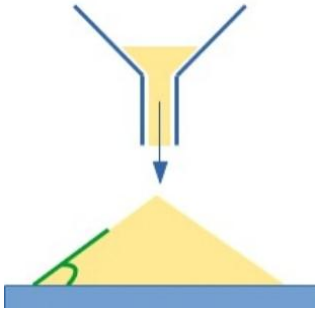


Fig 05: Angle of repose in funnel method.

2. Bulk density[3]

In a measuring cylinder, a certain quantity of prepared granules were taken without compacting. The volume occupied by the granule is noted as V_1 (bulk volume). Bulk density can be calculated by using the following formula,

$$\text{Bulk density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}}$$

Fig 06: Bulk density determination.

3. Tapped density[3]

The volume occupied by the granule is noted as V_2 (tapped volume). In a measuring cylinder, a certain quantity of prepared granules were taken and tappedfor 100 timesTapped density can be calculated by using the following formula,

$$\text{Tapped density} = \frac{\text{Weight of granules}}{\text{Tapped volume of granules.}}$$

Fig. 07: Tapped density apparatus.

4. Carr's index[3]

The percentage compressibility index of a granule was a direct measure of the potential strength and stability of granule. The Carr's consolidation index can be calculated by using the following formula,

$$\text{Carr's index} = \frac{\text{(Tapped density – Bulk density)}}{\text{(Tapped density)}} \times 100.$$

Table 04: Carr's index with its flow properties.

Carr's Index	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

5. Flow rate[16]

Flow rate of granule has been defined as the rate at which the particular mass emerges through the orifice in funnel of suitable diameter. It can be determined by pouring the weighed quantity of granules in funnel with an orifice of 8mm diameter.

The time required for complete granule mass to emerge out of the orifice was recorded using a stopwatch.

The flow rate was calculated from following formula,

$$\text{Flow rate} = \frac{\text{Weight of granules}}{\text{Time in seconds.}}$$

6. Hausner's ratio[17]

Flow property of the granule can be determined using hausner's ratio. Lower the hausner ratio better the flow property or vice versa. It is calculated using,

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

7. Effervescence time[18]

In vitro effervescence time was measured by dissolving some quantity of granules in a beaker containing 50 ml of water. Granules were randomly selected from the batch. In vitro effervescence time was measured. Repeat the procedure for all the prepared formulation and measured the effervescent time for all batches.

8. Disintegration test[20]

One dose of effervescent granules is poured in the beaker containing water at 15- 25˚, numerous bubbles of gas is liberated. When the liberation of gas around the granules stop, granules get disintegrated, being either dissolved or dispersed in water. Repeat the operation on 5 other doses. If each of 6 doses disintegrate within 5 minutes, then the preparation complies with this test.

Fig 08: Disintegration time of Effervescent granules

9. In vitro dissolution studies[19]

The effervescent granules were placed inside the dissolution vessel. The USP Type – II dissolution apparatus (paddle type), Type – I (If granules is floating) was set up at a speed of 75 rpm. Then the sample of 1ml were withdrawn at time interval 10, 20, 30,40, 50 and 60 minutes. The volume of dissolution fluid is adjusted to 900ml by replacing 1ml of fresh dissolution medium

after each sampling and the sink condition was maintained. The dissolution media used is 0.1 N HCl and the temperature of 37 ± 0.5˚ C was maintained in the apparatus.

Fig. 09: Dissolution apparatus.

6. PACKAGING OF EFFERVESCENT GRANULES[21]

Effervescent packaging on market,

1. **Primary packaging:** blisters, bottles, tubes, sachets, and stick packs;
2. **Secondary packaging:** paperboard cartons, side sealed bags, and wallet packs;
3. **Product type:** tablets, powders, granules;
4. **Material type:** plastic [PE, PP, PVC], aluminium, metal).

For effervescent granules, packaging should provide suitable protection from moisture. Effervescent granules are labelled to indicate that they are not to be swallowed directly. Granules may be stored at controlled temperature. Effervescent granules should be stored in air tight container.

Fig 10: Packaging of Effervescent granules.

7. ADVANTAGES[22-25]

1. Easy to administer
2. Easily portable and Marketing aspects.
3. Onset of action is faster
4. Gentle on the digestive tract
5. It mask unpleasant taste also.
6. More stable than liquid dosage form

8. DISADVANTAGES[22]

1. It is not given to children due to CO_2 gas toxicity.
2. If the packaging is not done properly then there might be chances of physical degradation.
3. It has shorter shelf life compared to the other dosage form.

9. MARKETED FORMULATIONS

Table 05: Marketed formulation of effervescent granules.

S.NO	NAME OF THE PRODUCT	INGREDIENTS	THERAPEUTIC USES
1	Eno	Sodium bicarbonate, Citric acid	1. Acidity 2. Flatulence
2	Cranberry	Cranberry extract	1. Urinary bladder infection
3	Citravescent	Sodium carbonate anhydrous, Citric acid, Tartaric acid	1. Urinary and systemic alkaliniser
4	Ibuprofen	Ibuprofen, Croscarmellose sodium, Banana powder	1. Analgesic 2. Anti-inflammatory 3. Antipyretic
5	Citro-soda	Sodium bicarbonate Sodium citrate Citric acid	1. Urinary alkalizer Antacid

		Tartaric acid	
6	Proximol	Hexamine Proxymadiol Piperazine citrate Halfa bar extract	1. Uric acid dissolvent 2. Urinary antiseptic 3. Propulsive for ureteric stone

10. CONCLUSION

Effervescent granules are designed to release carbon dioxide upon contact with water, promoting their disintegration, within a couple of minutes the granules completely dissolve and the drug becomes available in solution. So effervescent granules produces quicker action. Effervescent granules are prepared by Wet method, Fusion method or dry method, hot melt Extrusion method, in which the Fusion method is the most important method for the formulation of Effervescent granules. This review paper will be a very useful reference for future researches about effervescent granules.

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12. BIBLIOGRAPHY

1. Salomy, Monica, Diyya et.al., "Formulation and Evaluation of Metronidazole Effervescent Granules". *Int. J. of pharmaceutical sciences and research*, 2018; 9(6): 2525-2529.
2. Sayani Bhattacharya, Swetha G. "Formulation and evaluation of Effervescent granules of Fexofenadine hydrochloride". *The Pharma Innovation Journal*, 2014; 3(3).
3. K.Divya, G.Vamshi, T.Vijaykumar et.al., "Review on Introduction of Effervescent tablets and granules". *Kenkyu journal of pharmacology*, 2020; 6: 1-11.
4. Jinan Al-Mousaury, Zahraa Al-Hussainy et.al., "Formulation and Evaluation of effervescent granules of Ibuprofen". *Int. J. of Applied Pharmaceutics*, 2019; 11(6): 66 -69.
5. Solanki H.K, Basuri T, Thakkar J.H and Patel C.A. "Recent advances in granulation technology". *Int. J. of pharmaceutical science review and research*, 2010; 5(3): 48-54.
6. Foldvari M. "Nanopharmaceutics innovation in gene therapy: moving towards non viral and non invasive delivery methods." *J. of nanomedine biotherapeutics discovery*, 2014; 4: 135.
7. Maurya S.D, Rawal R.K, Jha S, Chauhan P.S, Kumar A. "Drug loaded beads: Current status". *American J. of pharm tech Research*, 2013; 3(1): 331-337.
8. Srinath K.R et.al., " Formulation and evaluation of Effervescent Tablets of paracetamol". *Int, J. of pharmaceutical research and development*, 2011; 3(3): 76-104.
9. Polli J.E, Rekhi S.G et.al., "Methods to compare dissolution profile and a rationale for wide dissolution specification for metoprolol tartrate tablets". *J. pharm science*, 1997; 86(6): 690-700.
10. Bhusan S.Y, Sambhaji S.P, Anant R.P et.al., " New drug delivery system for elderly. *Indian Drug*, 2000; 37: 312-318. (google scholar).
11. Juti Rani Devi, Bidyut Das. "preparation and evaluation of Ibuprofen effervescent granules", 2019; 12(8).
12. Ansel H.C, Popovich N.G, Allen L.V.J.R. "Pharmaceutical Dosage Form and Drug Delivery system". *B.I Waverly pvt. ltd.* NewDelhi., 1999; 6: 469-471.
13. Moghimipour E, Akhgari A and Ghassemian Z. "Formulation of Glucosamine Effervescent Granules". *Science Med. Journal*, 2010; 9(1): 21-34.
14. A Review of Patents on Effervescent granules.
15. CVS. Subramanyam unit operations textbook. Effervescent granules by non aqueous method, 127.
16. Patel Salim G, SiddaiahM. "Formulation and Evaluation of Effervescent Tablets: a review". *Journal of drug delivery and therapeutics*, 2018; 8(6): 296-303.
17. Diyya A.S, Thomas N.V. "Formulation and Evaluation of Metronidazole Effervescent Granules". *Int. J. of pharmaceutical sciences and research*, 2018; 9: 2525-2529.
18. Sandhya S, Gowthami G et.al., "Formulation and evaluation of herbal effervescent granules incorporated with Limnophilaindica extract for bacillary dysentery". *Annals of Bio Research*, 2012; 3(1): 63-72.
19. Raymond M: Effervescent tablets; Libermann H.A, Lachman L and Schwartz TB: pharmaceutical dosage forms, marcel dekker, Inc, New York, 2008; 2(1): 285-328.
20. Indian pharmacopeia, 2018; 1094.
21. LoydV. Allen, "Ansel's pharmaceutical dosage forms and drug delivery systems".11th Edition, 182-183.
22. Shet N, Vaidya I, Banerjee N. "Formulation and evaluation of aceclofenac sodium Effervescent taste masked granules". *Int. J. of Bio Pharm*, 2014; 5: 50-58.
23. Palanisamy P, Rabi A, Kumar D.Y. "Formulation and evaluation of Effervescent tablets of aceclofenac." *Int. Res. J. Pharm.*, 2011; 2: 185-190.
24. Aslani A, Jahangiri H. "Formulation, characterisation and physicochemical evaluation of Ranitidine Effervescent tablets. *Adv. Pharm Bull*, 2013; 3: 315-322.

25. Nagendrakumar D, Raju S.A, Shirsand S.B, Para M.S Rampure M.V. "Fast dissolving tablets of Fexofenadine hydrochloride of Effervescent method". *Indian J. pharm science,* 2009; 77(22): 116-119.