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 CO2. 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. Effervescent granules are used in many pharmaceutical products such as analgesics, antacids and cough formulation. Effervescent Granules are highly soluble, highly stable and having fast dissolving property and are convenient dosage forms. The effervescent granules are added into a cup of water, readily granules dispersed in water and they are dissolved by releasing CO2. Due to interaction between the acid and base in presence of water, the CO2 is evolved then granules are quickly dispersed. Due to liberation of CO2, the dissolution of API in water can be observed as well as taste masking effect also enhanced.

3NaHCO3 (aq) + H3C6H5O7 (aq) → 3H2O (aq) + 3CO2 + Na3C6H2O7 (aq)
(Sodium bicarbonate) (Citric acid) (Water) (Carbon dioxide) (Sodium citrate)

Fig. 01: Effervescent granules direction of use.

2. MECHANISM OF EFFERVESCENCE
As we already know that Effervescent granules contain acid (citric acid) and base (Sodium bicarbonate) it rapidly reacts in water by releasing CO2.

Due to liberation in CO2 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 CO₂ shown as follows
\[ C_6H_8O_7 \cdot H_2O + 3NaHCO_3(aq) \rightarrow Na_3C_6H_5O_7 + 4H_2O + 3CO_2(aq) \]

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).\[^{[3]}\]

### Table 01: Excipients used in effervescent granules

<table>
<thead>
<tr>
<th>S.No</th>
<th>Excipient</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Citric acid</td>
<td>Acidifying agent</td>
</tr>
<tr>
<td>2</td>
<td>Tartaric acid</td>
<td>Acidifying agent</td>
</tr>
<tr>
<td>3</td>
<td>Fumaric acid</td>
<td>Acidulant</td>
</tr>
<tr>
<td>4</td>
<td>Ascorbic acid</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>5</td>
<td>Sodium bicarbonate</td>
<td>Alkalizing agent</td>
</tr>
<tr>
<td>6</td>
<td>Sodium carbonate</td>
<td>Alkalizing agent</td>
</tr>
<tr>
<td>7</td>
<td>Polyvinylpyrrolidone-30</td>
<td>Binding agent</td>
</tr>
<tr>
<td>8</td>
<td>Polyethylene glycol-6000</td>
<td>Binding agent</td>
</tr>
<tr>
<td>9</td>
<td>Mannitol</td>
<td>Binding agent</td>
</tr>
<tr>
<td>10</td>
<td>Sodium laurel sulphate</td>
<td>Lubricant</td>
</tr>
<tr>
<td>11</td>
<td>Sodium benzoate</td>
<td>Lubricant</td>
</tr>
<tr>
<td>12</td>
<td>Acesulfame potassium</td>
<td>Lubricant</td>
</tr>
</tbody>
</table>

### 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.
Fig. 03: Equipment used for Effervescent granules preparation.

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

STEP - 1  STEP - 5
SIEVING THE POWDER  DRYING THE GRANULES IN HOT AIR OVEN

STEP - 2  STEP - 6
POWDER IN PORCELAIN DISH  SIEVED GRANULES

STEP - 3  STEP - 7
MIXTURE HEATED ON WATER BATH  PACKAGING

STEP - 4  STEP - 8
RESULTANT MIXTURE SIEVING  STORAGE

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.

<table>
<thead>
<tr>
<th>Table 02: Sieve number with granule size.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sieve No</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>10</td>
</tr>
</tbody>
</table>

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

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.

2. Hot melt extrusion technique
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
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
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
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.

\[ \tan \theta = \frac{h}{r} \]

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

<table>
<thead>
<tr>
<th>Table 03: Angle of repose with its flow nature.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angle of repose</td>
</tr>
<tr>
<td>&lt;20</td>
</tr>
<tr>
<td>20 – 30</td>
</tr>
<tr>
<td>30 – 34</td>
</tr>
<tr>
<td>&gt;40</td>
</tr>
</tbody>
</table>

2. Bulk density
In a measuring cylinder, a certain quantity of prepared granules were taken without compacting. The volume occupied by the granule is noted as V₁ (bulk volume). Bulk density can be calculated by using the following formula,

\[ \text{Density} = \frac{\text{Weight of granules}}{\text{Bulk volume of granules}} \]
3. Tapped density\textsuperscript{[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 tapped for 100 times. Tapped density can be calculated by using the following formula,

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

![Fig 06: Bulk density determination.](image)

4. Carr’s index\textsuperscript{[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,

\[
\text{Carr’s index} = \frac{(\text{Tapped density} – \text{Bulk density})}{\text{Tapped density}} \times 100.
\]

<table>
<thead>
<tr>
<th>Carr’s Index</th>
<th>Type of flow</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-15</td>
<td>Excellent</td>
</tr>
<tr>
<td>12-16</td>
<td>Good</td>
</tr>
<tr>
<td>18-21</td>
<td>Fair to passable</td>
</tr>
<tr>
<td>23-35</td>
<td>Poor</td>
</tr>
<tr>
<td>33-38</td>
<td>Very poor</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Extremely poor</td>
</tr>
</tbody>
</table>

![Table 04: Carr’s index with its flow properties.](image)

5. Flow rate\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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 effervescence time for all batches.

8. Disintegration test\textsuperscript{[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.

9. In vitro dissolution studies\textsuperscript{[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.

6. PACKAGING OF EFFERVESCENT GRANULES

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.

7. ADVANTAGES
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
1. It is not given to children due to CO₂ 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.

<table>
<thead>
<tr>
<th>S.NO</th>
<th>NAME OF THE PRODUCT</th>
<th>INGREDIENTS</th>
<th>THERAPEUTIC USES</th>
</tr>
</thead>
</table>
| 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 |
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.

11. ACKNOWLEDGMENTS
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