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Concept, Manufacturing and Characterization of Effervescent Tablets: A Review

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Introduction

Effervescent tablets are easy to consume due to this they are getting popular over other oral dosage forms. Effervescent tablets get break when they are put in water or juice which causes tablet to dissolve and form a solution. USFDA redefined the definition to Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. Effervescent tablets consists of acids/acid salt, carbonates and hydrogen carbonates, flavour, sweetener, etc. which release carbon dioxide when it is added to water. Following chemical reaction takes place in effervescent tablets [1].

$C_6H_8O_7$ (aq) + $3NaHCO_3$ (aq) → $Na_3C_6H_5O_7$ (aq) + $4H_2O$ + $3CO_2$ (g) ↑

Citric acid + Sodium bicarbonate → Sodium citrate + Water + Carbon dioxide

The above reaction occurs due to presence of water, because water is one of the reaction product which accelerates the reaction, leading to difficulty in stopping the reaction. Due to this reason manufacturing and storage of effervescent product is planned by minimizing their contact with water [2,3].

Advantages of Effervescent Tablets

- Administered as palatable sparkling solution
- Readily absorbed because it has to consume in solution form.
- No need to swallow tablet
- Drugs that are unstable in aqueous solution when stored shows more stable state in effervescent granules or tablets forms.
- Better/good intestinal and stomach tolerance
- Large amount of active ingredients can be easily incorporated
- Better or accurate dosing.
- Rapid onset of action
- Good in taste.

Limitations of Effervescent Tablets

- Excipients are costly
- Special production facilities is required.
- High sodium or potassium makes it inappropriate for patients with heart failure or cardiac insufficiency
- Difficult to formulate drugs with unpleasant taste sufficiently palatable as an effervescent product [4-7].

Excipients Used in Effervescent Tablets

Excipients used in effervescent formulation is mentioned below [8]:

Acids

- Citric acid
- Tartaric acid
- Adipic acid
- Fumaric acid
- Malic acid

Carbonates/Bicarbonates

- Sodium carbonate
- Potassium carbonate
- Calcium carbonate
- Sodium bicarbonate

- Potassium bicarbonate

Lubricants

- Sodium benzoate
- Polyethylene glycol
- Adipic acid
- Magnesium stearate

Inders

- Lactose
- Sorbitol
- Xylitol
- Dextrose

Sweeteners

- Acesulfame potassium
- Sodium saccharin
- Aspartame
- Sucralose

Flavours

- Powdarome Lemon
- Powdarome Orange
- Strawberry Flavour
- Tutti Frutti Flavo

Various Formulation Method (Figure 1)

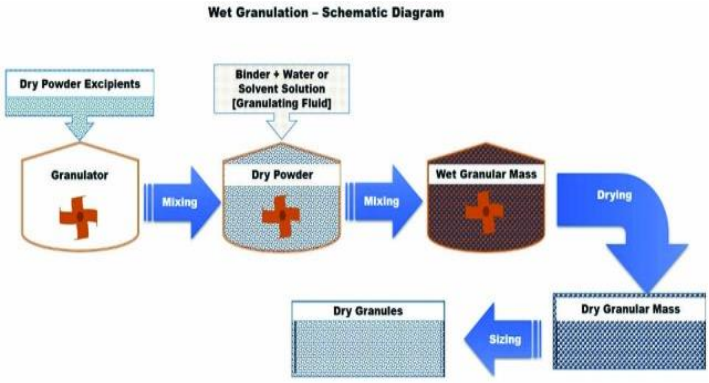

Figure 1: *Wet Granulation process for effervescent tablets.*

Wet Granulation [9-21]

Wet granulation is most common granulating process among other granulation method. In this method material is wetted by addition of binder solution and then drying is performed to get dry granules.

Wet granulation process involves following steps:

- Dry mixing of drug and excipients
- Addition of binder solution to form a wet mass
- Drying of wet mass to get the dried granules
- Blending with extra granular material and with lubricants
- Blend or granules are now ready for compression

Wet Granulation through fluid bed Process

Fluid bed granulation can also be used for effervescent tablets. In this method material is added into it and the binder solution is sprayed on that material, simultaneously hot air is blown from the bottom to make the granules dry. Thought requires high amount of granulation fluid which makes the process time higher and also makes it expensive.

Wet Granulation through fusion method

In this method acid and base (alkali) is mixed which is then heated due to which water is released from it. This released water of crystallization will act as a granulating agent so there is no need of addition of external water as a granulating agent. In this method chain reaction can occur which can produce excess moisture, so it is necessary to terminate this chain reaction. In rare cases, lower carbon dioxide content is observed in effervescent composition if it is produced by this method. Lower mechanical strength of product (tablets) is observed which the disadvantage of this method is.

Advancement Wet Granulation Techniques

Steam granulation: Steam granulation process do not require water, it utilizes steam instead of liquid water as a granulating agent. Steam provides higher diffusion rate into powder due to which it forms a hot thin film of water on the powder particles, requires small amount of heat to make it evaporate and thus dry granules are obtained [21-24] (Figure 2).

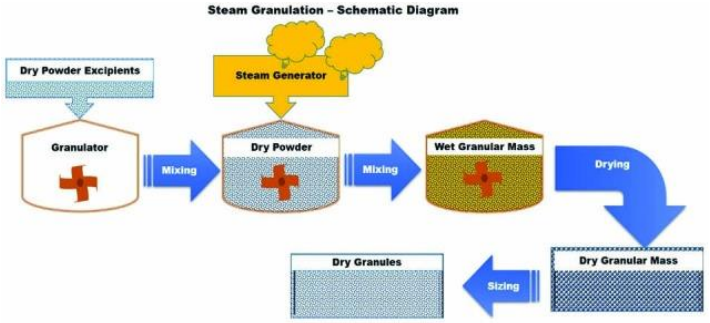

Figure 2: *Steam granulation process for effervescent tablets.*

TOPO granulation: TOPO vacuum granulation is a patented technology for the moisture sensitive component like effervescent dosage forms. In this technology, a small amount of water is added during process. Due to the chain reaction initiated by reaction between acid and base, additional water is generated which has to be eliminated by applying vacuum repeatedly for some time during the process. Due to vacuum, material is allowed to dry at low

temperature; also less drying time is required. This makes the process more beneficial for the components or API that are heat sensitive so it is a cost effective production process.

Continuous flow: Continuous flow technology is an advanced step of TOPO granulation which is designed for the continuous manufacturing of effervescent products. With the help of this technology manufacturers can produce up to 10 tons of granules every day. In this process powder is fed from one end and granules are collected from the other end and the entire process is carried out in an inclined drum. This technology is more useful when large amount of product is required to manufacture, especially sensitive materials or API like calcium or vitamin D3 [25].

Dry granulation: In dry granulation method the powder mixture is compressed without heating as there is no use of solvent. It is the least desirable method among various granulation method. The two basic procedures are to form a compact of material by compression and then to mill the compacted material to obtain a granules. Two methods are commonly used for dry granulation. The more widely used method is slugging, where the powder is recompressed and the resulting tablet or slug are milled to get the granules. Another method is to recompress the powder with pressure rolls using a machine such as Chilsonator.

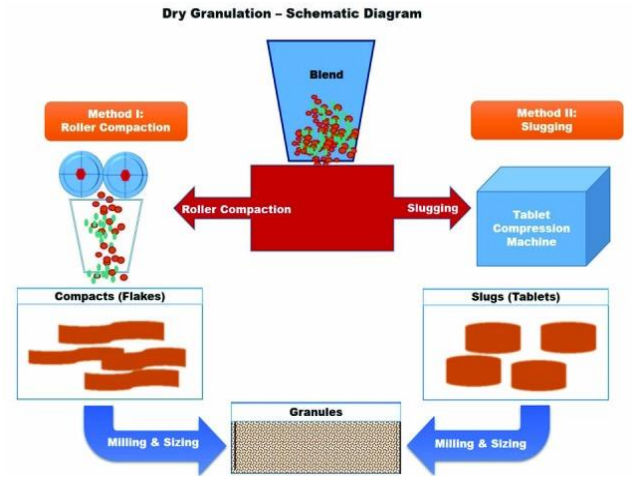

Figure 3: *Dry granulation process for effervescent tablets.*

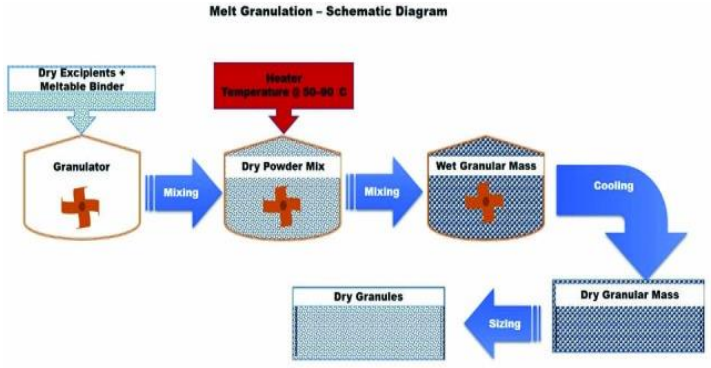

Figure 4: *Melt granulation process for effervescent tablets.*

Dry granulation using roller compaction: Materials are fed from the hopper which then goes to pressure rolls, this pressure rolls will compact the material into flakes which is milled or cut to obtain the granules. Similarly in slugging process materials are compressed in tablet machine to tablets and then milled to obtain the granules [26-32].

Melt Granulation / Thermoplastic Granulation: Melt granulation is similar to wet granulation only the difference is of use in binder (moldable). In melt granulation, binder which is in solid state is allowed to melt at temperature range of 50-80°C. This melted binder will now be used as a granulating liquid. As there is no need of drying phase because as we cool it at room temperature dried granules are obtained [33] (Figures 3,4).

Evaluation of Effervescent Tablet

Pre-compression parameters

Angle of repose (θ): To measure angle of repose, powder materials are allowed to flow from the funnel which is fixed with the stand at definite height. The radius and height of heap of powder formed is measured. Apart from flow property, Frictional force between powder and granules can be measured with the help of it.

$$\theta = tan^{-1}\, {}^{H}/_{R}$$

Where, θ is the angle of repose

H is height of pile

R is radius of the base of pile

Relation between angle of repose and flow property of powder is shown in below table (Table 1).

Table 1: *Type of flow of granules based on angle of repose.*

Angle of repose (degrees)	Type of flow
< 25	Excellent
25-30	Good
30-40	Moderate flow
> 40	Poor

Flow Rate: Flow rate is defined as rate at which material or powder emerges out from the orifice of funnel having suitable diameter. Weighed quantity of granules are allowed to poured into funnel having orifice of diameter 8mm and then flow rate is measured using stopwatch by noting the required by granules to emerge out from the orifice.

Flow rate = weight of granules/ time in seconds

Bulk density: Bulk density is obtained dividing weight of powder to bulk volume in cm3. Powder of about 50cm3 is taken and poured into the 100ml graduated cylinder and is allowed to dropped at 2 second interval for three times from a height of 1 inch onto a hard wooden surface. Bulk density is then calculated by using below equation.

$$D_b = {}^{M}/_{V_f}$$

Where
Db = bulk density
M = weight of samples in grams
Vf = final volumes of granules in cm^3 in cylinder

Tapped density: The tapped density can be obtained by dividing the mass of a powder by the tapped volume in cm^3. The sample of about 50 cm^3 of powder previously been passed through a standard sieve no. 20, has to carefully introduced into a 100 ml graduated cylinder. The cylinder has to drop at 2-second intervals onto a hard wood surface 100 times from a height of 1 inch. The tapped density of each formulation can then obtained by dividing the weight of sample in grams by the final tapped volume in cm3 of the sample present in the cylinder. Equation for tapped density is given below:

$$D_b = {}^{M}/_{V_f}$$

Where
Db= bulk density
M = weight of samples in grams
Vf= final volumes of granules in cm3

Carr's Index: Carr's Index also known as Carr's compressibility index is an indirect method of measuring powder flow from bulk density was developed by Carr. The percentage compressibility of a powder is a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation can be calculated according to equation given below:

%Compressibility = D2 – D1/D2 ×100

Where,
D2 = Poured bulk or bulk density.
D1= Tapped or Consolidated bulk density (Table 2).

Table 2: Carr's Index indicating flow of powder.

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair
23-28	Slightly Poor
28-35	Poor
35-38	Very Poor
>40	Extremely poor

Evaluation of Effervescent Tablets

Weight variation: Twenty tablets from every batch is randomly selected to check their uniformity. These tablets are weighed individually and their avg. weight is calculated. From this average weight, percent deviation each tablet is obtained. Limit for weight variation as per I.P and USP is mentioned below (Table 3).

Table 3: *Weight variation specification.*

IP/BP	Limit	USP
80 mg or less	10%	130mg or less
More than 80mg or Less than 250mg	7.5%	130mg to 324mg
250mg or more	5%	More than 324mg

Tablet thickness and diameter: Thickness and diameter of tablets are important for uniformity of tablet size. It is measured using Vernier Callipers.

Tablet hardness: Resistance of tablets is generally depend on the hardness of tablets which is an important factor as tablet may get break during transportation, storage and handling if it does not have proper hardness. Monsanto hardness tester is used to measure the hardness of tablet. Hardness is measured in kg or N.

Friability (F): Friability of tablet is measured to know the effect of shock or abrasion on tablets. To determine the friability of tablet Roche Friabilator is used. In this device pre weighed tablets are placed inside the friabiator and are allowed to rotate at 25 rpm for 4minutes, tablets are dropped from height of 15.6 cm in each revolution. According to USP friability limit should be within 0.5-1%.

Measurement of effervescence time: To measure the effervescence time, one tablet is placed inside the beaker containing 200 ml of water having temperature 20 °C ± 1 °C, while placing the tablet in beaker time should be noted in stopwatch. Final time is noted when the clear solution is obtained or tablet is completely dispersed. About mean of 3 tablets should be measured of each formulation.

Determination of effervescent solution pH

pH of solution should be checked immediately after completing the dissolution time of tablet using pH meter. Mean of 3 measurements is taken into consideration.

Measurement of CO_2 content

One tablet is placed in 100ml of 1N sulfuric acid and weight changes are determined. The difference obtained is in amount of carbon dioxide (mg) in one tablet. Measurement of 3 tablets is taken into consideration.

Moisture content

10 tablets are dried in desiccators which contain activated silica gel and let it remain for 4 hours. Moisture content of 0.5% or less is accepted for effervescent tablets.

Uniformity of content

10 tablets are selected randomly. Each tablet has to place into a 50mL volumetric flask, dissolved and diluted to 50 mL with phosphate buffer pH 6.8. One ml of this solution is diluted to 100 ml with phosphate buffer pH 6.8. The amount of drug present in each tablet can be determined by UV spectroscopy at 246 nm. Standard limit for uniformity of content is as follows;

- 10 tablets are randomly selected and placed into 50ml volumetric flask, dissolve it in 50ml of phosphate buffer having pH 6.8. One ml from this is taken and diluted with 100ml of phosphate buffer of pH 6.8. Amount of drug present in it can be measured by UV spectroscopy at 246nm. Standard limit is shown as below:

IP: Active less than 10mg or 10%,

BP: Active less than 2 mg or 2%,

USP: Active less than 25mg or 25%.

- 10 tabs limit not more than (NMT) one tablet deviate from range 85 – 115% & no tablet is outside 75 – 125% of the Avg value of /IP/BP/USP (Relative Standard Deviation less than or equal to 6%).
- If 2 or 3 tablets are within range of 85-115% and none of the tablet is outside the range of 75-125% repeat again with 20 tablets.
- The preparation complies the test if NMT one tablet is outside 85-115% limit and no tablet is outside the range of 75-125% of avg. content [34].

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