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A Comprehensive Review on Effervescent Tablets

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ABSTRACT

In the recent world oral dosage forms preparing themselves more popular methods of drug administration. e.g. Slow absorption of the medicament which is nothing but overcomes by administrating the drug in liquid dosage forms, therefore possibly allowing the use of lower dosage whereas instability of many drugs in liquid dosage forms preventing its use. The effervescent technique is nothing but an alternate method that is accelerating disintegration and dissolution timing of the drug, along with the recent developments of new pharmaceuticals techniques. So, effervescent tablets are the most extensively to adjust the behavior of the drug. e.g. Controlled release preparations, sustained release preparations, and also pulsative drug delivery systems. The article is demonstrated for new applying effervescent techniques in effervescent tablets.

INTRODUCTION:

Pharmaceutical products of different dosage forms are given by various routes for systemic delivery of the drugs. The reason is that the oral route of drug administration is achieving such popularity because of its ease of administration. (07, 49) Rapid GI transit can prevent complete drug release in the zone of drug absorption and reduces the efficacy of the administered dose (50, 47).

Effervescent tablets are becoming most popular in diverse sectors due to its ease in which they are consumed. The effervescent tablets are a special type of the tablets which are specially designed as it breaks which comes into contact with juice or the water. This Buoyant Delivery System (08) uses the matrices which are prepared by swellable polymers e.g. Chitosan or with effervescent components e.g. Citric acid or the tartaric acid and sodium bicarbonate (48) and also the matrices which contains chambers of liquid thus gasifies at body temperature (46, 25).

Incorporation of the floating chamber which is filled with air, vacuum, or inert gases achieves flotation of the drug delivery system. (09) The needed gas can be incorporated into the floating chamber by CO_2 (Produced as a result of reaction happening between the effervescent components like organic acids and bicarbonate salts or by volatilization of organic solvents. (e.g. Ether or cyclopentane). These matrices are fabricated so that when it arrives in the stomach the carbon dioxide gets liberated by the acidity of gastric contents and it is entrapped in jellified hydrocolloids. This reaction produces an upward movement of dosage forms and also maintains its buoyancy. The dosage forms float on the chyme due to a decrease in the specific gravity. (44, 10) Recently multiple unit types of floating pills are developed which generates carbon dioxide gas. The system consisting of sustained released pills that are seeds which are surrounded by double layers. The inner layer was the effervescent layer which contains $NaHCO_3$ and tartaric acid and the outer layer was a swellable membrane layer which is mainly made up of purified shellac and polyvinyl acetate.

Furthermore, the effervescent layer was divided into two sub-layers to avoid direct contact between the tartaric acid and $NaHCO_3$. Tartaric acid was the outer layer and sodium bicarbonate tartaric acid was the outer layer. Sodium bicarbonate was kept in the middle layer. When the system was immersed in the buffer solution at 37 degrees Celsius, it sank at the one time in the solution and forms swollen pills like balloons with lower density. (Less than 1gm/ml). This reaction was happened due to the formation of CO_2 by neutralization in

inner effervescent layers with the diffusion of the water through the swellable membrane which was the outer layer. The system was found that floats within 10 minutes and approximately 80% remained floating for five hours irrespective of P^H and viscosity of the test medium.

The drug benzoic acid (P-amino benzoic acid) was released when the system was floating. The approach of this test utilizing citric acid (anhydrous) and sodium bicarbonate (which were used as the effervescing agent and HPC-H grade as a release controlling agent has also gets reported. The *in-vitro* results indicated that a linear decrease in FT of the tablet with a decrease in the amount of effervescing agent in the range of 0-20%. (24)

Figure No. 1: An effervescent tablet in the glass of water

Effervescent tablets are tablets that are designed to dissolve in water and to release carbon dioxide. (43, 11) These are products of compressing components in the form of powders which are packed in a blister pack with incorporated desiccant in the cap. To use the effervescent tablet they are dropped into the water to make the solution. The powdered ingredients are also packed and also sold as effervescent powders or may be granules and sold as effervescent granules. Generally, powdered ingredients are firstly granulated before it is made into tablets. Effervescent tablets are designed to break when it comes in contact with liquid such as juice or the water. This could make a preferable choice for many people who were taking tablets from medicinal as well as a dietary supplement. (41)

BENEFITS OF EFFERVESCENT TABLETS OVER THE REGULAR TABLETS (22):

(1) The pleasant taste of effervescent tablets as compared with other regular used tablets: Effervescent tablets are going to be more popular since when they come in contact with liquid (Water or fruit juice) they give a better taste as compared to other regular used tablets. Conventional tablets also have a reduced absorption rate than effervescent tablets.

(2) Distributes more evenly: Conventional tablets dissolve slowly in the stomach. Sometimes it gets only partially dissolved which can leads to irritation in some cases. The benefit of an effervescent tablet over a conventional tablet is that it gets completely dissolved. It also has lower chances of irritation and also it is very easy for ingestion.

(3) Increased liquid intake: Effervescent Tablets provide nutritional benefits and also increases water intake. This is also useful for you when you are dehydrated effervescent tablet is a fantastic way of rehydrating.

(4) An easy alternative to regular tablets: The people who may have troubling in swallowing either due to age or illness, it is the best alternative for them. Taking effervescent tablets is the best way for ingesting medicine for people who have a sore throat or medical issues that make swallowing difficult.

(5) Simple and easy to measure: Effervescent tablets easily dissolve into the water or the liquid of your choice. After mixing it is ready for use or drink. Conventional tablets or powders need to measure and stir in repeatedly to avoid inconsistent drink with lumpy bits. So effervescent tablets are more efficient. Simply drop in liquid and it gets completely dissolved. After the dissolution, it is ready for use.

(6) To sum up: Effervescent tablets are becoming popular in the day today as it is easy to intake. They also have the best taste and can be added to the liquid of your choice.

As per the revised definition published by USFDA effervescent tablet is the tablet that is intended to dissolve in water before administration. Effervescent tablets are uncoated tablets that generally contain acid or acid salts (citric, tartaric, malic acid, and carbonates or bicarbonates) (sodium or potassium or any other suitable alkali metal carbonate or hydrogen carbonate) which reacts rapidly in the presence of water and releases CO_2. Due to the liberation of CO_2 gas, the dissolution of API in water and taste-masking effect is increased.

(16-20) The reaction between citric acid and sodium bicarbonate and tartaric acid and sodium bicarbonate which results in the liberation of carbon dioxide is shown below.

$C_{16}H_8O_7.H_2O$ $+3NaHCO_{3\,(aq)}$ = $Na_3C_6H_5O_7+$ $4H_2O+$ $3CO_{2\,(g)}$

Citric acid Sodium bicarbonate Sodium citrate water

$C_6H_6O_6$ $+2NaHCO_3$ = $2H_2O+$ $2CO_{2\,(g)}$

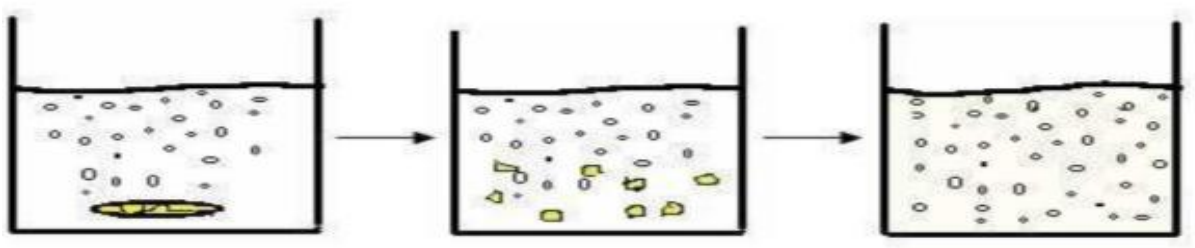

Figure No. 2: Mechanism of effervescence

FUNDAMENTALS OF EFFERVESCENCE (22, 13):

The composition of effervescence is of soluble organic acid and an alkali metal carbonate salt, one of which is API. If this mixture comes into contact with water then there is a formation of effervescence. Following are some examples of acids and alkali metals that are used in the formation of effervescent tablets:

- Tartaric acid
- Citric acid
- Fumaric acid
- Malic acid
- Adipic acid
- Sodium bicarbonate
- potassium bicarbonate
- Potassium carbonate

ADVANTAGES OF EFFERVESCENT TABLETS (21, 40):

1. Its onset of action is fast.
2. There is no need to swallow a tablet.
3. The tablet has a good stomach and intestinal tolerance.
4. More palatability.
5. It has super stability.
6. The tablet gives a more consistent response.
7. Accurate dosing can be achieved.

DISADVANTAGES OF EFFERVESCENT TABLETS (21, 40):

1. The tablet which contains more bulk is larger which also requires special packaging material.
2. There is pleasant taste of some active pharmaceutical ingredients.
3. The effervescent tablets are relatively expensive to produce because of the large amount of the excipients and special production facilities.

METHODS TO FORMULATE EFFERVESCENT TABLETS (14, 17, 18, 15, 19, 20, 16, 06, 39, 05, 38):

(1) Wet Granulation: The most widely used process of agglomeration in pharmaceutical companies is nothing but wet granulation. This granulation process simply involves wet massing of the powders blend with a suitable granulating liquid, wet sizing, and drying.

The important steps involved in wet granulation are given below:

1. Mixing of drugs and the excipients
2. Firstly formulate the binder solution
3. Formation of wet mass with the help of the powder mixture and binder solution
4. Drying of the formed moist granules

5. Mixing of screened granules with glidant, disintegrant, and the lubricants

Advantages of Wet Granulation Process:

(1) It permits the mechanical handling of powders without loss of mixed quality.

(2) This method is useful to improve the flow of powders by increasing particle size and sphericity. This process is also useful for improving the uniformity of powder density.

LIMITATIONS OF WET GRANULATION:

1. Due to labor, time, the equipment is an expensive process.

2. There is also loss of material during various stages of processing.

(2) Dry granulation: In this process, the powder mixture is compressed without the use of solvent and heat. It is a less desirable method in between all the methods of granulation. Two basic procedures are used to form a compact of material by compression and then the compact is milled and granules are obtained. Generally, two methods are used for dry granulation. The most widely used method is slugging. In this method, the powder is recompressed and the resulting slug is milled to yield the granules. The other method involves recompression of powder with pressure rolls using a machine. e.g. Chilsonator (05, 38, 04, 26, 37, 03, 27, 02).

Roller Compaction:

The compaction of powder may be accomplished by the special machine called a chilsonator. It gives out compacted mass in steady continuous flow.

The machine contains a hopper in which a spiral auger is fitted to feed the powder into the compaction zone. Like slugs, The formed aggregates are then screened or milled for the production of granules. (40-43)

Use: It is used in the production of directly compressible excipients. The compaction process of the drug and is also useful for the granulation of inorganic materials. It is also used to formulate sustained release formulations.

Advancement in Granulation:

Steam granulation: Steam granulation is an advanced modification of wet granulation. In this technique, steam is used instead of water as a binder. It has several benefits which include high distribution uniformity, higher diffusion rates of powders. During drying, the processing time is shorter, no health hazards to operate. (28, 32)

Melt granulation or thermoplastic granulation: In this method, granulation is achieved by the addition of a moldable binder. (at room temperature) Binder is in the solid state at 50-80 degrees Celsius it gets melted. So there is no need for the drying phase. So that granulation is obtained by cooling it to room temperature. (33, 29, 34)

EVALUATION OF EFFERVESCENT TABLETS:

Precompression parameters:

(1) The angle of repose: - It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. The force of friction in loose powder or granules can be measured by using the angle of repose. It is also indicative of the flow property of powder.(31,30)

$$\mathrm{Tan}\Theta = H/R$$

Where,

Θ= Angle of repose

H=Height of the pile of powder

R=Radius of the base of the pile

The powder mixture was allowed to flow through the funnel which was fixed to a stand at a definite height (H).

By measuring the height, the radius of a heap of powder formed the angle of repose is being calculated.

Table No. 1: Relationship between the angle of repose and powder flow property

Angle of repose	Type of flow
Less than 20 degree	Excellent
20-30 degree	Good
30-34 degree	Passable
Greater than 40 degree	Very poor

(2) Flow rate: The flow rate of the powder may be defined as the rate at which the particular mass emerges through the orifice of the funnel of a suitable diameter.

Each formulation that contains granules has a specific flow rate and it is determined by the pouring accurately weighed quantities of granules in a funnel with an orifice of 8 mm diameter. The requiring timing for the complete granule mass to emerge out of the orifice is being recorded by using a stopwatch. The flow rate was calculated using the following equation (49).

Flow rate=Weight of granules/Time in seconds

(3) Bulk density: The ratio of the mass of the powder and bulk volume in cm^3 is called bulk density.

1. Measurement method:
2. Take the sample (50cm^3 of powder).
3. Pass it through standard sieve No. 2.
4. Introduced into 100 ml graduated cylinder
5. The cylinder was dropped at 2 sec intervals onto a hardwood surface three times from a height of one inch.
6. The bulk density of each formulation is obtained by using the following formula.

$$D_f = M/V$$

Where,

D_f=Bulk density

M= Weight of the sample in gm.

V_p= Final volume of granules in cm^3

(4) Tapped density: The ratio of the mass of powder to the tapped volume in cm^3 is nothing but tapped density.

Measurement of tapped density:

1. A sample of about 52 cm^3 of powder is taken.
2. Passed through standard sieve No. 20.
3. Introduced into 100 ml graduated cylinder.
4. The cylinder was dropped at 2 sec intervals onto a hardwood surface 100 times from a height of one inch.
5. The tapped density of each formulation is then calculated by using the following formula.

$$D_0=M/V_p$$

Where D_0= Tapped density

M= weight of sample in gm.

V_p= Final volume of granules in cm^3

(5) Carr's index:

Carr developed a special method (Indirect method) of measuring powder flow from bulk densities. The percentage compressibility of the powder was a direct measure of potential powder arch or bridge strength and stability.

Carr's index is calculated by the following equation:

$$\% \text{ compressibility} = d_f\text{-}D_0/D_f\times100$$

Where,

D_f= Fluff or poured bulk or bulk density

D_0= Tapped density.

Table No. 2: Carr's index and an indication of the flow of powder

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
Greater than 40	Extremely poor

EVALUATION OF EFFERVESCENT TABLETS:

(1) Weight variation: It was determined to find out that different batches of tablets have uniformity in their weight. 20 tablets are weighed individually. The average weight is calculated. Compare the individual tablet weight with the average.

If NMT 2 tablets are outside the % limit and none of the tablets differ by more than two times the % limit the tablets meet this test.

Table No. 3: Weight variation specifications as per Indian Pharmacopoeia.

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

(2) Tablet thickness and the diameter: The diameter and thickness of the tablet were measured to check the uniformity of the tablet and size. It was measured by using the vernier calipers.

Tablet hardness: The hardness of the tablet was measured by using the Monsanto hardness tester. It was tested to check the resistance of the tablet during shipping and transportation.

The hardness is measure in terms of kg/cm^2.

(3) Friability: This was determined by using Roche friabilator. It is the device that keeps the effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at

a height of 6 inches in each revolution. The pre-weighed sample is kept in the friabilator and subjected to 100 revolutions. The tablets were dusted by using soft muslin cloth and reweighed. Its USP limit is 0.5-1.

The friability is calculated as,

$$F= W_{initial}-W_{final}/W_{initial}\times 100$$

(4) Measurement of effervescence time: A single effervescence tablet is placed in a beaker containing 200 ml of purified water at 20 degrees celsius±1 degree Celsius. Whenever a clear solution appears then the effervescence time is finished. For each formulation, 3 measurements are carried out.

(5) Determination of effervescent solution P^H: The P^H of the solution is determined with the help of one tablet in 200 ml of purified water at 20 degrees Celsius by using a P^H meter. After completion of dissolution time for each formulation, the experiment is repeated.

(6) The measure of CO_2 content: One effervescent tablet is inserted into 100 ml of 1N sulphuric acid solution and weight changes are noted after completion of dissolution end. The obtained weight difference shows the amount of CO_2 per tablet (mg). Three determinations are carried out to report the drug.

(7) Evaluation of water content: 10 tablets of each formulation are taken and dried completely in the desiccator containing activated silica gel for four hours. 0.5% or less of water control is acceptable.

(8) Uniformity of control: Randomly select the 10 tablets. Transfer each tablet into a 50 ml volumetric flask. Dissolve it and dilute it with 50 ml phosphate buffer at P^H 6.8. One ml of this solution is again diluted to 100 ml with phosphate buffer at P^H 6.8. By using UV spectroscopy at 246 nm the amount of drug present in each tablet is noted. The standard limit for uniformity of content is, IP=Active less than 10 mg or 10%.

BP= Active less than 2 mg or 2%

USP=Active less than 25 mg or 25%

(9) *In-vitro* disintegration timing: The process by which the breakdown of a tablet into smaller particles is achieved is called disintegration. The *in-vitro* disintegration timing of the tablet was determined by using the disintegration test apparatus as specified in IP. The

standard limit for disintegration timing is within 3 minutes in water at 25 degrees Celsius (IP) and 15-25 degrees Celsius (BP).

RELEASE KINETIC MODELING (21, 40, 17, 35, 31, 30):

In recent years the drug release from pharmaceutical dosage form has been subjected to profitable scientific developments when the new dosage form is developed then it is necessary to ensure that the drug has to release appropriately. Drug dissolution of the dosage form is described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time (t). Some analytical definitions of Q (f) function are commonly used as zero order, first order, Higuchi and Korsmeyer-Peppas.

In vitro dissolution is also recognized as an important pharmaceutical dosage form which cans influence the release in drug development. Under certain circumstances, its kinetic may be used as a surrogate for the assessment of bioequivalence.

ZERO ORDER KINETICS: Drug dissolution from dosage forms couldn't be disaggregated and release the drug slowly can be represented as,

$$W_0 - W_t = K_t$$

Where,

W_0= Initial amount of drug in dosage form

W_t= Initial amount of drug in dosage form at time (t)

K= Proportionality constant

On simplification,

F_t= Fraction of drug dissolve in time t.

K_0= Zero order release constant.

$$Q_t = Q_0 + K_0 t$$

Where,

Q_t= Amount of drug dissolved in time t.

Q_0= Amount of drug in solution.

FIRST ORDER KINETICS:

In 1967 Gibaldi and Feldman and 1969 Wagner proposed the application of their model to drug dissolution studies. The dissolution concept of solid particles into the liquid media implies surface action as can be seen by the Noyes-Whitney equation.

$$DC/at = K (C_s - C)$$

Where,

C= Concentration of solute in time t.

C_s= Solubility in the equilibrium at expression temperature

K= first order proportionality constant.

Higuchi equation: for the study of the release of water soluble and low soluble drops which are incorporated into the matrices Higuchi developed theoretical models.

The obtained relation is,

$$F_t = Q - \sqrt{D (2C - C_s) C_s t}$$

Where,

Q= Amount of drug released in time t per unit area.

C= Drug initial concentration.

C_s= Drug solubility in matrix media.

D= Diffusivity of a drug molecule.

On simplification,

$$d_Q = Cdh - 1/2(C_s d_h)$$

But according to the first law,

$$dq/dt = DC/h$$

Again on simplification,

$$Ft = K_H^{1/2}$$

K_H= Higuchi dissociation constant.

Korsmeyer gave an equation:

$$Ft=at^n$$

A= constant

N= release exponent

$$T= M_t-M_o \text{ (Fractional release of the drug)}$$

Table No. 4: Mathematical models which are used to describe drug release mechanism

Sr. No.	Mathematical model	Equation
1	Zero	$Q_t=Q_0=K_ot$
2	First	$lnQ=lnQ_0=K_1t$
3	Higuchi	$Qt=K_H\sqrt{t}$
4	Korsmeyer Peppas	$Qt/Q_0=K_kt$

CONCLUSION:

Nowadays most of the drugs formulated in the form of effervescent floating dosage form because of some added advantages over traditional tablet formulation. These dosage forms provide potential approaches for gastric retention. The density of effervescent floating dosage form is lower than gastric fluid. So it can be concluded that these dosage forms provide the best treatment for GIT disease.

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