

Efferescent tablets: a safe and practical delivery system for drug administration

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Abstract

Efferescence is defined as the evolution of gas bubbles from a liquid as a result of a chemical reaction. For medicinal use, efferescent tablets have specific characteristics that allow rapid adsorption of the intended drug. In this manner, a medication can be absorbed easily and effectively if it dissolves easily in water and is present at a sufficient dose. Common acids utilized for efferescent reactions are citric, malic, tartaric, adipic and fumaric acids. Citric acid is most commonly used for this application, which also adds a citrus-like taste to the products. Tartaric, adipic and fumaric acids are usually used in small amounts, due to their low water solubility. Efferescent tablets are used to simplify the handling of doses, provide optimal compatibility, promote superior and rapid absorption, increase a patient's liquid intake and circumvent the difficulty of swallowing large pills. This review defines efferescent tablets in terms of the technology and describes the advantages and disadvantages.

Keywords: Efferescent, tablet, advantages, disadvantages.

Özet: Eferesan tabletler: ilaç kullanımı için güvenli ve pratik bir uygulama sistemi

Eferesans, bir sıvı içinde oluşan kimyasal reaksiyon sonucu, çözünme ve gaz kabarcıklarının oluşması olarak tarif edilmektedir. Tıbbi kullanımda eferesan tabletler, verilen ilacın hızlı emilimini sağlamaya yönelik bir özellik taşımaktadır. Verilen ilaç, eğer su içinde yeterli dozda ve kolayca çözünürse daha hızlı ve etkin şekilde emilim sağlanacaktır. Köpürme reaksiyonu için genellikle sitrik, malik, tartarik, adipik veya fumarik asitler kullanılmaktadır. En sık tercih edilen, ürüne hafif bir limon aroması da veren sitrik asittir. Tartarik, adipik ve fumarik asitler, suda çözünürlükleri daha düşük olduğu için daha az miktarlarda kullanılırlar. Uygun ilaç dozu alınımın sağlanması, ilaca uyumun kolaylaştırılması, hızlı ve daha iyi emilim, hastanın sıvı alımının artırılması ve büyük tabletlerin yutulma zorluğunun ortadan kaldırılması için eferesan tabletler kullanılmaktadır. Bu derlemede, teknolojik açıdan eferesan tabletler değerlendirilmiş, avantaj ve dezavantajları tanımlanmıştır.

Anahtar sözcükler: Eferesan, tablet, avantaj, dezavantaj.

Medications such as pills are the forms generally used, whereas they have some disadvantages. Slow absorption is the important disadvantage as the onset of action gets pro-

longed. In liquid forms of the medication, the delay is avoided. Many drugs do not have enough stability levels in the suspension form. Gastric residence also affects drug delivery

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which is predicted before. Gastro-retentive preparations are created to manage gastric residence. Another form of the drugs is effervescent tablets.^[1] Effervescent mixtures and powders, and compound effervescent powders including saline cathartics are also used.^[2]

In effervescent technology, gas bubbles occur from the liquid after chemical reaction. Alkali metal bicarbonates and acids (mainly citric or tartaric) are used to make effervescence. The reaction occurs after adding water.^[3-5] The main issue is acid-base reaction. The basic component is sodium bicarbonate and acidic component is citric acid.^[5]

Effervescent tablets have specific characteristics that allow rapid adsorption of the drug. The drug can be absorbed easily when it displays adequate dissolution in water and is present at a sufficient dose.^[6] Potassium citrate has these characteristics. In case of kidney stones containing urate and calcium, Potassium citrate is used which is helpful to decrease the prevalence of the stones.^[7] Patients with kidney stones should take too much water to use effervescent easily. Potassium citrate powders are given with packages and the dose is measured. Therefore, a study has been aimed to design and formulate potassium citrate effervescent tablets. They decrease calcium oxalate and urate stones.^[8]

Definition of Effervescent Tablets

The chemical reaction occurs in effervescent tablets. It is related to acid-base reaction. At the end, carbon dioxide is released. Tartaric, malic, fumaric, citric and adipic acids are utilized. Due to the citrus-like taste, citric acid is usually preferred for effervescent. Malic acid is expensive, whereas it adds smoother taste. The low water-soluble agents are fumaric, malic and tartaric acids. So, they can be consumed in small amounts.^[9]

In effervescent technology, when organic acid and bicarbonate get together in the water, carbon dioxide is released. The solving process is seen in 17–20°C water. They may be easily carried and used. Their taste is pleasing. The foam of them helps to kill the local bacteria. In traditional Chinese Medicine, similar techniques and materials are used to prepare similar medicine.^[10]

After the reaction of effervescent tablets, simultaneous carbon dioxide is produced. Their contents are compressed mixture of acids and sodium bicarbonate.^[11] They rapidly dissolve in the water. When the patients have problem with capsule or tablet swallowing, these agents can be used easily.^[12,13] These tablets are also absorbed faster.^[14] The main acid used is citric acid. The other acids

of adipic, tartaric, malic and fumaric are also used. Alkali sources are Potassium carbonate and bicarbonate, and sodium carbonate and bicarbonate. When considering low cost, high solubility and intensity of reaction, sodium carbonate is preferred.^[15] Excipients, water-soluble lubricants and colors, flavorings and sweeteners are also added.^[15]

Polyvinylpyrrolidone (PVP) is used as binder in effervescent. Its form is as dry powder or wet forms of aqueous or hydroalcoholic solutions. Mannitol and PEG 6000 are other effective binders.^[15,16] When using tablet press machine, relative humidity should be low ($\leq 25\%$) and temperature should be at room temperature (25°C).^[5] To obtain excellent flowability, production is made by direct compression method. Size of the particles should be equal. In granules, particle size should be small.^[13,17] To achieve agglomeration of the particles, monohydrate citric acid is released in the fusion method (at 54°C). Using a nonreactive solution, such as ethanol or isopropanol, granulation is achieved. 0.1–0.5% water is enough for active solution.^[15] The control of effervescent tablets is performed by conventional similar tablets. The control parameters are weight, hardness, pH, solution time and friability.^[8,15]

Potassium citrate is soluble in water, but insoluble in alcohol.^[7] It is used in metabolic acidosis and replaces sodium bicarbonate. It can also be used in urinary tract infections as an alkalizing agent. It decreases the formation of kidney stone induced by calcium oxalate and urate.^[18-21] Therefore, oral supplements with potassium citrate prevent hyperkalaemia, because it can be absorbed from gastrointestinal tract highly.^[8,21]

Effervescent tablet solution was compared with standard tablets in 242 patients. The formulations contained 1000 mg acetaminophen. The patients had moderate or severe pain due to the dental surgery. Both of them were evaluated in terms of pain intensity and relief. They were both effective compared to placebo. Onset of analgesia was 20 min in effervescent tablet and 45 min in standard tablet. Median pain relief time was 15 min faster in the effervescent tablet.^[22]

Recently, effervescent antibiotics have been launched on the market. Consumption of the drug as a half glass of liquid seems easier than swallowing a large tablet. Particularly in patients with a sore throat or swallowing disorder, this delivery method improves the quality of life with easier and faster uptake of the drug. Furthermore, effervescent tablets have storage advantages for keeping the drug dry, stable and safe compared with syrup or suspension forms.

Effervescent Tablet Technology

The technology of the effervescent tablets was based on chemical reaction. Acid neutralize a carbonate salt. At the end, carbon dioxide gas is released which produce the fizzing.^[23] To initiate the reaction, water is important. If there is no water in the medium, acid or carbonate cannot dissociate and the reaction cannot be initiated. After the reaction begins, more water is generated. Effervescent tablets should be produced in optimum environment and packaged carefully. Therefore, stability is created. During the production, anhydrous raw materials are used. They should be kept in dry environment. Relative humidity ratio must be less than 10%. In effervescent tablets, the source of carbon dioxide is carbonate. Sodium carbonate and bicarbonate are the commonly used carbonate salts.^[23]

In sodium carbonate, CO₂ percentage is lower than bicarbonate. In bicarbonate, CO₂ proportion is higher than soda ash. Its' reaction time is more quickly and it is less stable. In most of the products, both carbonate and bicarbonate are used in 50/50 ratio. Reaction time and stability are acceptable in this form. In effervescent products, magnesium and potassium carbonate are also used. Acids are the other and important part in effervescent which react with carbonates.^[23] Citric acid is a trivalent and has good neutralizing effect. Fumaric acid is a divalent and more effective than citric acid. Fumaric acid reacts slowly and less soluble than citric acid. Stability of the fumaric acid is more than citric acid. The other acids are malic acid and adipic acid.^[23] The weight ratio of the acid and total carbonate is 1:1 for ideal for effervescent. When this ratio is 1:10, the system will be highly soluble and reactive. Essential oils and fragrances are included as 0.5–3% in effervescent. The oil should not contain glycol solvents which can cause instability.^[23]

Dyes or lake pigments can be added to produce colored solutions or products. Color stability is also important. They should be chosen as anhydrous material. Dried flower bud, herbs, chamomile extract maybe used for this purpose. The percentage may be lower than 1–2%. Another 0.1–2% of the effervescent should be consisted of vitamin E, squalene, almond oil and cosmetic esters. Foamers are surfactants. PEG-30 castor oil, laureth 4, polysorbate 80 or 85 are emulsifiers.^[23]

Polymers are added as 0.2–4 percentage. PEG or polyquaternium are usually used. For solid effervescent tablets, binders are used as 10–20% (maltodextrin, lactose and sorbitol). The materials that help flowing are calcium silica, talc, fumed silica or cornstarch.^[23] Production is completed with exact ratios of different materials.^[3]

During production, hygroscopic materials are used to absorb moisture. Moisture may cause effervescent reaction. The production is performed in closed systems and ended by split valve technology. To achieve high level safety, low moisture should be present in ventilated air.^[3]

Granulation and drying

The tablets are produced as equal weight and homogeneous. They compressed in high-speed rotary presses. Wet granulation is avoided, because it may initiate reaction.^[3] Roller compaction and direct compression are used for drying.^[2] Ventilation of the machines is also controlled.^[3]

Wet granulation

The wet granulation is performed by two steps. Initial step is done by alkaline or acid components, subsequently dry blending is performed.^[2] A high shear granulator is used for drying.^[2] These methods need running time and cleaning processes. This is a critical step and homogeneity of the tablets is obtained with this method.^[3]

Organic solvents

Effervescent reaction is not started in inorganic solvents. These agents are used as a granulation fluid. In this method, evaporation occurs at lower heat. Drying is obtained at lower temperatures. The fluid bed is necessary because of created organic gas and non-condensable process.^[3]

Water

Water is used as a granulation fluid. It is used in very small amount, because water may initiate pre-effervescent reaction. In this reaction, carbon dioxide is released. Drying process of the production reduces the water amount. A high shear granulator is used for this purpose. In larger bath sizes, the drying time takes longer.^[3] For drying, microwave technology or batches (small or medium) are used. In larger batches, the process takes more time.^[3]

Fluid bed spray granulation

In this process, simultaneous granulation and drying are performed. Low moisture levels are obtained and the risk of pre-effervescent reaction is limited to minimum. For more granulation fluid, it is necessary to have high shear process.^[3]

Lubricants

After granulation, lubricant should be added to the tablets. To improve flowing, magnesium stearate is used. It prevents tablets from sticking. When magnesium stearate is used, a film will be present on the water after dissolving of

the tablets. L-leucine plus polyethylene glycol mixture are also used for this purpose.^[4,5]

Tablet compression

Moisture ratio is different in effervescent tablets and normal tablets. It is <0.3% and 2%, respectively. Effervescent tablets are commonly larger than normal tablets; and they may be easily broken or damaged. For the packaging, these details are very important to keep in mind. Dwell time should be increased to solve this problem.^[3]

During filling, powder pressure is obtained by rotary valves. When lubricant is absent, the tablets can stick the walls. Lubricants may be solid or liquid.^[3] During press procedure, surface materials are forced to be pressed into the tablets and moisture, absorbed from the air, is decreased.^[3]

Blister packs and tube arrangements used for packaging

Packing materials have a relatively stable shelf life. Aluminum is used instead of polymer blister materials. Because its water permeability is lower. In a package, ten or more tablets are placed. Environment should have low humidity, because humidity may destroy the tablets. Drying agents such as silica gel is incorporated into the tubes.^[3]

Advantages and Disadvantages of Effervescent Tablets

Oral forms are more preferred way of medication. In this form, slow absorption maybe the most important disadvantages. When taking the liquid form, the lower dosages can be used. Stability of active pharmaceutical ingredients is lower in liquid form. As effervescent tablets are dissolved in water just before administration, it provides advantage for the stability of these medications.^[9]

Taking big tablets of capsules is difficult for the patients. Effervescent technology provides an alternative to them. Dissolving and break-down of standard tablets also takes additional time in the stomach. In effervescent, ingredients are distributed in the solution and they are not localized in certain point.^[9] They can be taken in liquids and promotes patients to take more liquid. Absorption is improved and usage is easy in effervescent tablets.^[9]

Advantages of effervescent tablets:^[3] Improved taste, faster absorption, presentable fizzy tablets.

Disadvantages of effervescent tablets: Larger tablets, complex production process, delicate packaging process.

Fundamentals of effervescent: There are organic acid and alkali metal carbonate salts.^[3]

Why Effervescent Tablets Are Used?

The doses can be taken easily. The ingredients (carbonate and acid) serve as buffer for the stomach with optimum pH. The absorption occurs at 15 min.^[24] Effervescent tablets are uncoated tablets.^[6,25,26] They are susceptible to the stomach.^[25,27] They may be taken in liquid form. If patients have swallowing difficulty, they can take these medications easily. It is well-tolerated in the stomach. After effervescent reaction, CO₂ is produced and it increases the penetration of active substances into the paracellular spaces.^[28,29]

Lubricants are used to prevent adhesion of the tablets. Sucrose is added as hygroscopic material and cause to increase the tablet bulk. Aspartame and sucralose are the other sweeteners.^[1,30] Aspirin is the most commonly used effervescent tablet.^[6,31]

Effervescent tablets are used for:

- **Rapid and enhanced absorption:** It is dissolved in liquid and the ingredients are absorbed quickly. Conventional tablets are dissolved slowly and absorption is reduced.^[24]
- **Optimal compatibility:** The effervescent tablet contains a balanced ratio of acids and carbonates forming a buffer. It has optimal compatibility with the stomach.^[24]
- **Increase in liquid intake:** Effervescent tablets provide both the medicinal value intended and additional liquid intake. In diarrhea and high temperature in summer, intake of effervescent table with water contributes to daily liquid intake.^[24]
- **Advantages in case of swallowing problems:** Effervescent tablets present an alternative for these patients.^[24]
- **Simple handling and measuring into exact doses:** Effervescent tablets are dissolved quickly and the patients can obtain exact doses.^[24]

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