REVIEW ARTICLE

A Bird Eye View on Effervescent Drug Delivery System

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ABSTRACT

Effervescent drug delivery systems (EDDS) have gained significant attention in the pharmaceutical industry due to their unique characteristics and potential advantages over conventional dosage forms. This comprehensive review aims to provide an in-depth understanding of EDDS, including their formulation strategies, underlying mechanisms, and diverse applications in drug delivery. EDDS are effervescent dosage forms that release drugs upon water dissolution, leading toward carbon dioxide gas generation. The effervescence, resulting from the reaction between an acid and a base, facilitates rapid drug dissolution and enhances drug bioavailability. The primary components of an EDDS include an active pharmaceutical ingredient (API), effervescent agents (e.g., organic acids and bases), binders, disintegrants, and other excipients. Effervescent tablets, granules, powders, and effervescent-coated dosage forms are commonly employed formulations. Several factors, such as pH, temperature, solubility, and particle size, influence the drug's effervescence process and subsequent release kinetics. The drug release mechanisms from EDDS can be attributed to various phenomena, including effervescence-driven disintegration, gas evolution, and solubilization. The effervescence-induced carbon dioxide bubbles mechanically disrupt the dosage form, leading to enhanced drug dissolution and subsequent release. Additionally, the carbon dioxide gas acts as a propellant, providing rapid drug delivery and potentially improving patient compliance. EDDS find applications in diverse therapeutic areas, including analgesics, antacids, dietary supplements, and antiviral agents. They offer several advantages, such as improved drug stability, enhanced bioavailability, increased patient convenience, and ease of administration, particularly for populations with swallowing difficulties.

Furthermore, EDDS can be tailored to achieve controlled release, targeted drug delivery, and taste masking through appropriate formulation modifications. However, challenges associated with EDDS include their sensitivity to environmental conditions, potential drug degradation during effervescence, and the need for specialized packaging to maintain stability. The selection of suitable effervescent agents, excipients, and manufacturing processes is crucial to overcome these limitations and ensure consistent product performance. In conclusion, effervescent drug delivery methods offer an auspicious approach instead of enhancing drug delivery and patient compliance. Their formulation versatility, rapid drug release, and potential for controlled release make them an attractive option for various therapeutic applications.

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INTRODUCTION

Effervescence has been proven to be a valuable method of delivering medications and dietary supplements orally in the pharmaceutical and dietary industries for many years. The use of effervescent granules and tablets is widespread in Europe and the United States, and its popularity is also growing in other countries.[1] Effervescent granulation plays a crucial role in producing effervescent dosage forms, essential for achieving the anticipated features of effervescent tablets. This step is of utmost importance in the aspect of stability of the finished product. The history of effervescent formulations dates back more than two centuries, when powdered forms were officially mentioned as cathartic salts. A patent published in 1815 defined the development of "Seidlitz Powders," consisting of effervescent excipients including sodium potassium tartrate, sodium bicarbonate, and tartaric acid at a 3:1:1 ratio.[2]

Effervescent tablets and granules have gained increasing popularity as dosage forms due to their rapid solubility, ease of administration, and ability to provide quick therapeutic action. Pharmacopeias define effervescent forms as granules or tablets that need to be dissolved in water before being given in the direction of patients. They are particularly useful for delivering water-soluble active ingredients, especially when a high dosage is required. In some cases, an effervescent drug for oral administration may contain over 2 grams of the active ingredient, and the tablets can weigh up to 5 grams with a diameter of 25 mm, or sachets may be used for larger dosages.

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Effervescent tablets or granules are usually not coated and are composed of acidic substances combined with carbonate or bicarbonate elements. These components react rapidly upon dissolution in water, releasing carbon dioxide. Effervescent tablets quickly disintegrate, typically within two minutes or even faster, because of the release of carbon dioxide bubbles. They are frequently prescribed for pain relief and anti-inflammatory treatments. In some instances, these formulations can considerably accelerate drug absorption in the body associated with regular tablets, leading to a faster therapeutic response.[3]

Among the various routes employed and developed to treat various disease conditions, oral drug delivery is widely recognized and utilized for several decades. Its popularity can be attributed, in part, to its convenient administration.[4,5] However, achieving sustained drug delivery through the oral route is challenging due to the limited time drugs spend in the stomach (known as gastric residence times or GRTs). When gastrointestinal transit occurs rapidly, it can impede the comprehensive release of the drug at the absorption site and lead to a decrease in the drug's efficacy.[6,7] Effervescent formulations, such as tablets, are gaining popularity in multiple segments, comprising supplements and pharmaceutical applications, primarily because of their ease of consumption. The design of effervescent tablets is such that they react when they come into contact with liquids, for example, water or juice, instigating the tablet in the direction of dissolving and forming a solution.[8]

Granules are a unique form of medication consisting of dehydrated aggregates of solid powder particles. They encompass either one or any active pharmaceutical ingredients (APIs) and may include other ingredients as well.[9] Effervescent granules are particularly advantageous as they exhibit high solubility, stability, and fast dissolution properties, making them suitable dosage forms. These granules should be mixed with a glass of water just before consumption. Upon contact with water, they undergo a reaction in which carbon dioxide is released due to the interaction between an acid and a base. The resulting solution or dispersion should be promptly ingested. This rapid evolution of carbon dioxide gas disperses the granules quickly in the water. As a result of this process, the API contained in the granules dissolves in water, and the taste masking effect is also enhanced. The presence of carbon dioxide gas due to the effervescent system gives a good taste to the formulation.[10,11]

Effervescence Reaction

Effervescence refers to the formation of gas bubbles in a liquid due to a chemical reaction. In pharmaceutical oral solid dosage 3NaHCO3(aq)[252g(3 mol)] + H3C6H5O7(aq)[192g(1 mol)] =3H2O(aq)[54g(3 mol)] + 3CO2[132g(3 mol)] + 3Na3C6H5O7(aq)[258g(1 mol)]

forms, the commonly observed reaction is an autocatalytic acid-base interaction between sodium bicarbonate and citric acid. The reaction between sodium bicarbonate and citric acid, which triggers effervescence, initiates even with a minimal presence of water, acting as a catalyst. Since water is also a product of this reaction, it speeds up the process and becomes challenging to halt. As a result, the entire production, packaging, and storage of effervescent products need to be carefully designed to minimize water contact. Considering the stoichiometric ratios involved in the reaction, it becomes clear why effervescent doses are typically large.

Recently, certain effervescent systems have been developed not only for oral use but also as penetration enhancers in topical products, including applications for the skin and vagina. In these instances, the effervescence occurs directly after administration, triggered by factors such as saliva in the mouth,[12] blood serum on wounds,[13] or the moisture of the vaginal mucosa in suppositories utilized for treating vaginal infections.[14] The purpose of effervescence in these cases is to adjust the pH or facilitate drug absorption.[15] other types of effervescent formulations rely on a different reaction leading to the formation of carbon dioxide. These formulations utilize reactants that generate hydrogen peroxide and oxygen during effervescence. While these reactants may not be appropriate for oral ingestion, they can be safely utilized in formulations intended for external use, such as antibacterial products used to clean dental plates.[16]

Buoyant drug delivery systems use matrices comprising expandable polymers like methocel or polysaccharides such as chitosan combined with effervescent components like $NaHCO_3$, citric, and or tartaric acid. Another approach involves matrices comprising chambers filled with liquids that produce gas at body temperature.[17-19] To facilitate buoyancy within the stomach, these delivery systems include a floating chamber filled with either a vacuum, air, or an inert gas.[20] To introduce gas into the floating chamber, one of two methods is employed: the volatilization of an organic solvent such as ether or cyclopentane or the initiation of an effervescent reaction involving organic acids and carbonate-bicarbonate salts, resulting in the production of carbon dioxide (CO_2).[21] Upon reaching the stomach, the matrices respond to gastric acid, causing the release of carbon dioxide. This gas becomes ensnared within the gel-like hydrocolloid, resulting in an upward propulsion of the dosage form, thereby sustaining its buoyancy. As the specific gravity diminishes, the dosage form continues to float atop the gastric chyme.[22,23]

Essentials of Effervescent

Effervescence takes place when water interacts with a soluble organic acid and an alkali metal carbonate salt, typically with one of them serving as the API. This reaction leads to the formation of carbon dioxide. Commonly utilized acids and alkalis in effervescent formulations for example, citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, sodium bicarbonate, sodium carbonate, sodium sesquicarbonate, potassium bicarbonate, and potassium carbonate.

Advantages of Effervescent System

- Effervescent tablets offer numerous advantages, including fast onset of action, as they dissolve quickly in water, eliminating the need to swallow a tablet.
- They are well-tolerated by the stomach and intestines, making them suitable for use in geriatric and pediatric patients.
- Effervescent tablets also provide benefits such as taste masking, enhancing drug permeation, and improving bioavailability.
- They offer increased portability, improved palatability, and superior stability compared to other dosage forms.
- Effervescent tablets allow for precise dosing and can integrate larger amounts of active ingredients. These tablets provide a more consistent therapeutic response and an enhanced therapeutic outcome.
- In addition, effervescent tablets might be a good option in remote areas where parenteral forms might not be accessible because of the expense or a shortage of trained medical personnel.[24]

Disadvantages of Effervescent System

- Undesirable flavor of certain active ingredients.
- Superior tablets that necessitate specialized packaging materials.
- Comparatively high production costs because of the significant quantity of potentially costly excipients and specialized manufacturing facilities.
- A clear solution is typically ideal for administration, while a finely dispersed solution is currently generally accepted.[24]

Ideal Drug Candidates for EDDS

- Rapid absorption through the upper gastrointestinal tract.
- Drugs with low pKa values which exhibit a predominantly non-ionized form.
- Drugs with lower solubility at higher pH levels.
- Local action of drugs, for example, the treatment of *Helicobacter pylori* in ulcerative conditions.
- Drugs that undergo degradation in alkaline pH conditions can improve their bioavailability by formulating them into gastro-retentive forms.
- Reducing gastric irritation prevents increased drug concentration levels in the stomach.[24]

Formulation Development Approaches of EDDS

Effervescent products require a careful selection of raw materials, similar to conventional granules and tablets. The main goals are to ensure good flowability, compressibility, and compactibility. However, effervescent forms have unique characteristics that require additional considerations, particularly regarding the choice of active ingredients. Moisture content is a crucial factor as it distresses tablet compressibility and stability. It is preferred to use raw materials with very low moisture content to prevent premature effervescent reactions during processing or after packaging the granules or tablets. Another important aspect is the solubility and rate of solubility of the raw materials since effervescent forms must dissolve quickly, typically within two minutes, in a standard glass of water (around 100 mL).

When dissolved in water, the active ingredient in effervescent products should be soluble, water-dispersible, or capable of solubilizing through salt formation. Likewise, the excipients used, for example, sweeteners, coloring agents, and flavors, must also be water-soluble. While the list of excipients for this dosage form has remained largely unchanged, recent advancements in the physical properties of these raw materials have addressed crucial manufacturing aspects and ensured consistent high quality. Each material has various commercially available grades, including pre-formulated grades, which, in some cases, eliminate the need for granulation as they are specifically designed for direct compression.[25]

The selection of excipient grades for effervescent granules or tablets depends on various factors, including the properties of the active ingredient, desired dosage, release profile, and available process technology. The specific purpose of the effervescent formulation has a significant impact on the choice of raw materials. When developing an effervescent formula, it is crucial to consider the stoichiometric ratios in the reaction and the solubility of carbon dioxide in water. Under standard temperature and pressure conditions (0°C and 1 atm. pressure), the solubility of carbon dioxide in water is approximately 90 mg/100 mL. The recommended ratio amongst the acid and alkaline constituents is typically around 0.6, although there may be cases where increasing the acid content is necessary to achieve a pleasant taste. The alkaline-acid ratio plays a dual role in determining the effervescence capacity and the taste of the resulting solution. When the solubility of the active ingredient is independent of pH, the alkaline-acid ratio can be adjusted accordingly, considering the desired pH for liquefying the active ingredient. If the active ingredient's solubility is enhanced under acidic conditions, an additional acidic agent can be added to lower the solution's pH. Conversely, an excess of alkaline sources should be incorporated if the active ingredient is more soluble at higher pH levels.[26]

An alternative method to improve the solubility of the active ingredient in effervescent formulations is to raise the amount of carbon dioxide produced through accumulative the alkaline component in the formulation. However, formulators have limited flexibility when it comes to other excipients like diluents or binders due to the larger tablet size inherent in effervescent systems. Additional binders cannot significantly improve compressibility since the tablets are already large and must maintain a rapid dissolution rate when placed in water. In recent times, there have been notable developments in effervescent formulations focusing on creating formulations capable of regulating the effervescence rate, providing options for rapid, intermediate, or slow rates. The rate control primarily depends on the ratio of the acid and alkaline components. Still, it can also be influenced by the specific chemical belongings of the effervescent excipients or their blends, especially when a slower effervescence rate is desired.[24]

Excipients used in EDDS

Acid materials

Effervescence relies on obtaining acidity from three foremost foundations. The food acids like citric, tartaric, and ascorbic acids are widely used. These are preferred because that of their pleasant taste, lack of odor, cost-effectiveness, and ease of handling.

Citric acid

It is the preferred acidic component in effervescent products due to its exceptional solubility as well as extremely good taste. It is a colourless, white, crystalline powder. Different particle sizes are available, including coarse, medium, fine, and powder (for the anhydrous form). Citric acid dissolves well in water and also in ethanol.[27] According to the selected machinery and the circumstances of the procedure, it can be used as either a monohydrate or an anhydrate. The anhydrous form of citric acid is less susceptible to moisture absorption than the monohydrate.[28] However, if stored under high humidity (over 70%), the anhydrous version may clump together. Citric acid monohydrate is commonly utilized in preparing effervescent granules, although the anhydrous form is extensively utilized in formulating effervescent tablets. The monohydrate variant undergoes a melting process at 100°C and liberates its water of hydration at 75°C, rendering it a fitting choice for use as a binder in hot-melt granulation procedures.

Tartaric acid

It is highly soluble in water and is more very hygroscopic in nature. When reacting with sodium bicarbonate in effervescence reactions, tartaric acid behaves similarly to citric acid, producing noticeable effervescence. However, due to its diprotic nature (having two acidic hydrogen atoms), tartaric acid needs to be utilized in a high quantity to achieve the appropriate stoichiometric proportions compared to citric acid, which is a triprotic acid. Regarding compression, tartaric acid exhibits equivalent properties in the direction of citric acid.[29]

Ascorbic acid

In its crystalline form, it appears as white crystals, while in fine powder form, it is light yellow. Unlike some other acids, it is not hygroscopic, which can be advantageous during production as it is easily handled. It demonstrates high solubility in water (approximately 1 gram dissolves in about 3 mL of water) and absolute ethanol.[30] However, when exposed to light, it gradually darkens. When sodium bicarbonate is used in an effervescent reaction, the rate at which carbon dioxide is released is equivalent to other acids like citric acid and tartaric acid.

Acid anhydrides

Food acid anhydrides can serve as a viable source of acidity in effervescent formulations because they can be hydroxylases in water to produce the corresponding acid. This hydroxylation process ensures a strong and sustained effervescence effect through continuous acid production in the solution. Avoiding water throughout the entire process when anhydrides are included in a formulation is crucial. If water is present, the anhydrides would undergo hydrolysis and convert into the corresponding acids before their intended use.[31]

Acid salts

Effervescent formulations commonly incorporate acid salts such as sodium dihydrogen phosphate, amino acid hydrochlorides, and acid citrate salts. These acid salts are preferred due to their water solubility and rapid reaction with alkaline sources. When combined with one of the mentioned acids, they act as pH buffering agents during drug administration. This buffering effect helps enhance the absorption of the active ingredient while minimizing potential adverse effects on the stomach.[32]

Additional acid sources

Unlike the others mentioned, fumaric acid and nicotinic acid are not hygroscopic and have lower water solubility. Malic acid, on the other hand, is extremely hygroscopic and soluble but possesses fewer acidity compared to tartaric or citric acids. Despite this, it is sometimes preferred for its mild and light taste. Acetylsalicylic acid, a commonly used active ingredient in effervescent preparations, is combined with other acid sources due to its low water solubility. While adipic acid has low water solubility and is not utilized as an acid source, it can be found in effervescent formulas as a lubricant. It has demonstrated satisfactory outcomes as a lubricant in effervescent calcium carbonate tablets.[33]

Carbon dioxide's sources

Carbonate salts are widely favored as the primary cause for generating effervescence in formulations. Bicarbonate forms of carbonate salts are particularly preferred due to their higher reactivity, resulting in a more potent effervescence effect.

Sodium bicarbonate

In effervescent formulations, sodium bicarbonate is the main component of carbon dioxide, providing a carbon dioxide yield of about 52%. It is commercially available in various forms, ranging from free-flowing even granules to fine powder, and is odorless with a somewhat alkaline taste. When heated to approximately 50°C, sodium bicarbonate starts in the direction of breaking down into carbon dioxide, sodium carbonate, and water. At higher temperatures of 250 to 300°C for a short duration, it undergoes complete conversion into anhydrous sodium carbonate. The conversion procedure depends on time and temperature, achieving around 90% conversion within 75 minutes at 93°C.[34] While sodium bicarbonate has low compressibility and is non-elastic, this limitation is addressed through techniques like spray drying. Moreover, there are now directly compressible grades available, incorporating additives like PVP or silicone oil.[35]

Sodium carbonate

Sodium bicarbonate is commercially supplied in three diverse formulae: anhydrous, monohydrate, and decahydrate. All of these forms exhibit high solubility in water. Sodium bicarbonate is relatively resistant to the effervescent reaction, making it suitable for certain formulations where it can be

utilized as a stabilizing agent. However, its usage for this purpose should not exceed 10% of the batch size, as it has a tendency to preferentially absorb moisture, thus preventing the effervescence reaction from initiating. Among the different forms, the anhydrous form is particularly preferred for this stabilizing function.[36] Additionally, a specific grade of modified sodium bicarbonate is commercially available, featuring a carbonate layer coating on the surface. This modification enhances bicarbonate stability and makes it suitable for direct compression applications.[36,37]

Potassium bicarbonate and potassium carbonate

The solubility of these salts is lower compared to their equivalent sodium salts, and they are also further costly. However, they can be used as partial substitutes for sodium salts when there is a need to reduce the amount of sodium ions in a formulation.[38]

Calcium carbonate

Precipitated calcium carbonate is a fine, white, odorless, and tasteless powder or crystals. It exhibits very limited solubility in water and is insoluble in ethanol or isopropanol. Due to its high density and lack of appropriate compressibility, it is not appropriate for direct compression. Typically, it is utilized as a calcium supplement in effervescent tablets for individuals with calcium deficiency. Additionally, it can serve as an alkaline source, contributing to the stability of the effervescent system.[39]

Sodium glycine carbonate

It produces a gentle effervescent reaction that promotes very fast disintegration in tablet dosage forms. As a result, it is commonly employed in the formulation of fast-dissolving sublingual tablets. It possesses higher compressibility than other alkaline compounds, making it suitable for direct compression.[39]

Binders

In general, using a binder is often necessary to provide effervescent tablets with the desired hardness for handling. However, the usage of binders in effervescent preparations needs to be improved due to their tendency to slow down tablet disintegration and absorb moisture. Finding the right balance between granule strength and disintegration time is crucial when determining the quantity of binder in a formulation. Water can act as an effective binder in wet granulation when all the constituents are granulated together. A minor quantity of water, disseminated evenly on the powder bed, partially dissolves the raw materials and facilitates agglomeration. Alternatively, solvents like ethanol and isopropanol can be utilized as granulating liquids in the direction of dissolving dry binders.

The choice of binder in wet granulation also depends on the production technique and the quantity of granulating liquid used. For instance, when alkaline and acidic components are granulated together with water, adding a binder to the formulation would be unnecessary as the small amount of water is insufficient to activate it. The most commonly used binder for effervescent tablets is polyvinylpyrrolidone (PVP) due to its strong binding properties, even at low concentrations (typically 2%). PVP K25 and K30 are favored variants due to their good water solubility and ability to maintain the desired dissolution rate of the active ingredient, aligning with the goals of effervescent tablets. They can be used in water, alcohol, and hydroalcoholic solutions, and they can also be utilized in dry granulation processes.[40]

Binders commonly employed in dry granulation, for instance, lactose, mannitol, and dextrose, are generally unsuitable for effervescent formulations as they would require larger amounts than what is permitted.

Lubricants

Tableting is a crucial step in producing effervescent products, and selecting an appropriate lubricant is highly important due to the unique chemical and physical characteristics of lubricants. Since many lubricants have low water solubility, they tend to hinder tablet disintegration, which needs to be rapid for effervescent tablets. Effervescent tablets need to produce a clear and transparent solution without any insoluble film or residue on the water surface. When selecting a lubricant, careful consideration is required regarding its water solubility and compatibility with the therapeutic action of the active ingredient. Several lubricants have been tested to find the most suitable conditions for effervescent tablets; including the possibility of external lubrication of the granules directly in the tablet press dies.[40] Commonly used lubricants in effervescent manufacturing include sodium benzoate, sodium acetate, L-leucine, and carbowax 4000. Combinations of lubricants have also been explored, such as calcium and potassium sorbates, as well as micronized polyethylene glycol (PEG) with calcium ascorbate or trisodium citrate, as reported in the literature.[41] A successful combination involves spray-dried L-leucine and PEG 6000.[42] Other lubricants with lower solubility are still employed in effervescent tablet formulation, but finding a balance between compression effectiveness and water solubility is crucial for effective lubrication. Commercially available magnesium stearate is often used in combination with sodium lauryl sulfate, a surfactant agent that aids in dispersion.[43]

Additives

Small quantities of additives are included in the formulas to enhance the taste and appearance of effervescent preparations. Water-soluble flavors like lemon, orange, and fruit essences are commonly used to meet sensory requirements. Typically, these flavors constitute around 0.5 to 3.0% of the final dosage. Sweeteners such as sorbitol, sucrose, aspartame, stevia, and saccharin sodium are often combined with flavors for desired sweetness. Coloring agents, including artificial FD & C dyes and natural coloring substances, can be included in amounts ranging from 0.1 to 3.5% of the dosage. Surfactants or antifoaming agents may also be employed to improve the performance of the effervescent preparation during use.[44]

Manufacturing of Effervescent Dosage Forms

During the manufacturing process of effervescent products, careful attention must be given to the conditions to ensure product stability even after packaging. Since most of the raw materials utilized in effervescent manufacturing are highly hygroscopic, it is crucial to prevent moisture absorption from the surrounding air. This is necessary to avoid the initiation of the effervescent reaction before usage and to maintain a reliable shelf life. The entire production process, including the dispensing and sieving of raw materials, granulation, blending of other ingredients (if required), lubricant addition, compression, in addition to packaging, can be effectively acted upon within a closed and integrated handling system. Utilizing intermediate bulk containers and a dedicated blender for materials handling helps minimize product transfers and reduce exposure. In cases where open handling and pneumatic transfer systems are employed, it is highly recommended to maintain the moisture content in the manufacturing area at a minimum level by controlling the airflow. The recommended working conditions throughout the manufacturing facility include maintaining a relative humidity (RH) under 20% and an even constant temperature of 21°C. However, maintaining an RH of 25% at a controlled room temperature of 25°C is adequate for preventing the granules or tablets from sticking to the machines and preventing them from absorbing moisture from the environment.[45,46] The granulation process in effervescent product manufacturing is typically performed in batch mode and significantly impacts the final products' characteristics, primarily granules but also tablets. It is crucial to carefully address the lubrication of granules, as well as the compression and packaging of both granules and tablets. Compressing effervescent granules poses several challenges. Due to the large proportion of effervescent components in the tablets, which typically have low compressibility themselves, the tablets need to have larger dimensions. The raw materials used in effervescent formulations occupy a significant portion of the formulation, leaving limited space for other excipients that could contribute to compression improvement. Additionally, the selection and quantity of lubricants used can present challenges. Poorly balanced lubricants can adversely affect the final product's dissolution time, taste, and appearance. Consequently, the compression phase must be carried out meticulously and may require pre-compression and high compression forces. To address lubrication issues within the formulation, tablet presses can sometimes be equipped to perform external lubrication of the granules as shown in (Figure 1)[46].

To prevent granules from sticking to the dies and punches during the tableting process, anti-adherent or lubricant ingredients can be sprayed directly into the tablet press dies using ancillary dosing equipment (as shown in Figure 2) just before the filling phase.[47] This technique, commonly employed in the Nutraceuticals industry, allows for the use of a smaller quantity of lubricant compared to intrinsic lubrication methods. It improves the tensile strength of the tablets while reducing the force required for tablet ejection. In addition

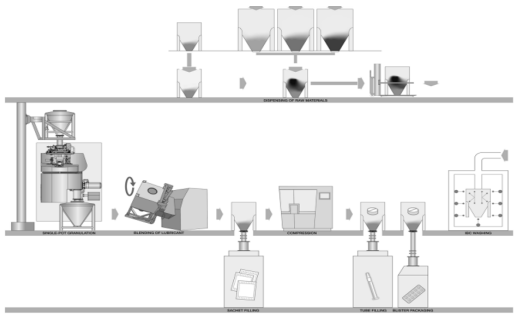

Figure 1: Typical process flow diagram for effervescent forms (Source: From IMA S.P.A., Bologna, Italy)

to this technique, there is an alternative method that is not extensively described in the literature but is sometimes used in practice to enhance the quality of effervescent tablets. This method involves compressing the granules that are remaining a little moist. Subsequently, the tablets are dried and brought to the desired moisture content for stability through a phase in a static-ventilated oven or a fluid bed. For packaging effervescent granules and tablets, operating in an environment with strict humidity control is essential. Choosing packaging materials that provide an effective moisture barrier is crucial to ensure product stability.

Packaging is crucial to maintain the stability of the effervescent dosage forms. The main goal is to safeguard them during packaging processes and maintain their stability over their shelf life, even after the package is opened. Previously, effervescent preparations were commonly packaged by separately wrapping the acid and alkaline constituents to prevent premature effervescence before use. Nevertheless, contemporary effervescent medications can be conveniently packaged in individual dosage units within hermetically sealed containers crafted from protective materials like aluminum foil or plastic laminates. Another packaging option for tablets is to stack them one by one into tubes made of plastic or metal. These tubes have a diameter almost identical to that of the tablets, minimizing the amount of air in contact with the tablets. It is important to reseal the tubes after removing each tablet. An alternative approach for packaging tablets is to either wrap them in aluminum foil before filling them into tubes or place them directly into tubes with silica gel present on the internal side of the cap. These methods are considered the most effective for achieving long-term stability.[48] In the case of tablets packed in aluminum strips or blisters, it is crucial to have precise temperature control in the packaging machine's welding unit. This ensures accurate sealing while preventing overheating, which could trigger the release of residual water from the tablets and potentially initiate the effervescence reaction at a later stage.[49]

Methods of Manufacturing of EDDS

Wet granulation

It is the most frequently utilized granulation technique. A powder mixture is wet massed with a granulating liquid in this procedure, which proceeds through wet sizing and drying.[50]

Figure 2: LUMS, dosing equipment for external lubricant addition in a tablet press (Source: From IMA S.P.A., Bologna, Italy)

Benefits of wet granulation includes

- Allowing for the mechanical handling of powders without compromising the quality of the mixture.
- Improving powder flow via sphericity and particle size optimization.
- Improving the uniformity of powder density.

Limitations

- It is a costly process
- Material damage throughout numerous processes phases is possible.[50]

Dry granulation

It is a type of granulation in which a powder combination is compressed without including heat or solvents. Of all granulation techniques, it is regarded as having the least favor. The procedure involves two main phases: first, the powder combination is compressed to form a solid object, and then the compact is ground towards producing granules. Slugging and compressing the powder utilizing pressure rolls are two frequently used techniques for dry granulation; the latter is frequently carried out using a device like the chilosonator.[50]

Rollar compaction

A device called the chilsonator can be used to condense powder utilizing pressure rolls. The chilsonator produces a compact mass while operating continuously, unlike a tablet machine. A hopper with a spiral auger that makes it easier for the powder to enter the compaction zone feeds the powder between the rollers. The accumulated particles have been filtered or crushed to generate granules, much like slugs.[50] The chilsonator has a variety of uses, including the granulation of inorganic materials, compaction of the excipients, and natural products to develop immediate as well as sustained release formulations.

High shear granulator

To produce granules on a big scale, the pharmaceutical industry frequently uses this setup. It includes a wet mill alongside the granulator and dryer and allows seamless connection with both upstream and downstream machinery. A second batch can be easily loaded, mixed, and granulated in the extreme shear granulator. In contrast, the first batch is dried in the fluid bed before being discharged, thanks to sophisticated control systems. Additionally, as part of a single operation, every instrument can be automatically cleaned in place.[51]

Fluid bed granulation

Fluidized bed granulation is commonly used to create effervescent granules for effervescent tablet manufacturing. In this procedure, a fluidized bed that is constantly stirred up is developed by suspending a dry combination of powdered acid and carbonate sources in a stream of heated air. The introduction of a granulating fluid, often water in a precisely dispersed form, causes a brief reaction before the fluid vaporizes. The substances partially react as a result of this reaction, resulting in the formation of separate granules made up of the two reactive constituents. Since these granules are more significant than the original powder particulates, they can be pulverized into tablets after being dried in the fluidized bed system. This method can achieve component mixing and granulation, which is drying in one piece of equipment with a lower emission of carbon dioxide gas.[51]

Hot melt granulation

The standard binder solution utilized during wet granulation is swapped out in the melt granulation procedure with a binder that can melt. Although the high shear procedure gives the advantage of introducing the binder in its solid state, it can also be applied in its molten form. The friction between the mixer and the heated bowl jacket produces the heat needed for melting.[51]

Environmental Controls During the Manufacturing of EDDS

Because the formulation's basic components are hygroscopic, they cannot experience an effervescent reaction throughout production by absorbing moisture from the air. It is essential to keep processing environments cool and low humidity to avoid problems like effervescent reactions and the clinging of granules or powder to equipment. As a result, stringent control and a well-equipped manufacturing facility are used to manufacture. All equipment needs to be meticulously cleaned when the procedure is finished, including dried with low-moisture air to remove any leftover materials and moisture. Failure to do so could result in processing issues throughout consecutive batch manufacturing and machine surfaces that are too rough. Open handling of the goods enables the use of less complicated equipment, but it is crucial to keep the manufacturing area's moisture levels low. The humidity must be kept at no higher than 20% throughout the plant, and a constant temperature of 25°C is also preferred. Typically, problems brought on by atmospheric moisture can be avoided with a maximal relative humidity of 25% at a controlled temperature of 25ºC or lower.[51]

Assessment of EDDS

Weight variation

Twenty tablets were chosen at random and weighed one by one. The computed mean weight was compared to the tablet weights.

The pharmacopeia restrictions of 5% of the target weight should not be exceeded during this process for deviations of less than two tablets.[52]

Friability test

Using a friabilator, the tablets' friability was assessed. A tablet was dropped from a height of 6 inches after each turn of the rotating plastic chamber, which combined abrasion and stress on the tablets for 4 minutes. After dusting the pills with a soft muslin towel, they were reweighed. It was determined what percentages of the tablets were friable, and an acceptable friability value is less than 1%.[52]

CO_2 content

Three tablets were put in separate beakers with 100 mL of 1N sulfuric acid solution. The amount of emitted CO_2 (in mg) was determined based on the weight difference between the pills before and after they had been dissolved.

pH determination

Using a pH meter, the solution's pH can be determined.

Effervescence time

Three tablets were dissolved in various water beakers, and the duration of the effervescence was timed using a stopwatch. The moment a transparent solution became available was referred to as the effervescence time.

Assay

Twenty tablets were weighed and then finely powdered for the assay. In a suitable volumetric flask, a sufficient volume of pure water was added to a precise weight of powder equal to 200 mg of ranitidine HCl. The mixture was shaken ferociously for around 20 minutes. The flask was refilled with purified water, and the mixture was well blended. With the first 10 mL of the filtrate being discarded, the resultant solution was passed through using a Whattman no. 42 filter paper. The filtrate was next submitted to titrimetric examination using an appropriate aliquot. To create a 100 g/mL solution, the filtrate, which had an equivalent concentration of 2 mg/mL, was properly diluted. A spectrophotometer was used to do additional research on this diluted solution.[52]

Content uniformity

The content of every distinct tablet was determined after arbitrarily picking ten tablets.

Moisture content

Three tablets have been placed in independent desiccators with saturated salt solutions at various relative humidities (60, 71, and 90%) to calculate the equilibrium moisture content. The moisture content was assessed on the first and seventh days using the following method: A dry magnet and methanol were added to an autotitrator. To get the endpoint, the solution was titrated with Karl Fischer reagent. The tablets were crushed into a powder, which was then swiftly and precisely measured at 100 mg before being added to the titration tank. Up until the point of no return, the mixture was mixed. The volume (V) and factor (F) of the Karl Fischer reagent utilized throughout the sample titration were then used to compute the equilibrium moisture content.[52]

Effervescent Drug Delivery System for Paediatric and Geriatric Population

Due to their unique characteristics and advantages, effervescent drug delivery systems can be particularly beneficial for pediatric and geriatric populations.

Pediatric Population

Swallowing ease

Children, especially young ones, often have difficulty swallowing tablets or capsules. Effervescent formulations provide a convenient alternative as they dissolve quickly in water, creating a pleasant-tasting effervescent solution that is easier for children to consume.

Taste masking

Many pediatric medications have a bitter taste, making it challenging to administer them. Effervescent systems can incorporate flavors and sweeteners into the formulation, effectively masking the bitter taste and making the medication more palatable for children.

Compliance enhancement

The appealing taste and ease of administration of effervescent formulations can improve medication compliance in pediatric patients. Children are more likely to take their medication willingly when it is more enjoyable and doesn't cause discomfort during administration.[53]

Geriatric Population

Swallowing difficulties

The geriatric population often experiences swallowing difficulties, known as dysphagia, due to age-related conditions or medication side effects. Effervescent formulations can provide a solution by transforming solid dosage forms into liquid form, reducing the risk of choking and making medication ingestion easier for older adults.

Bitter taste avoidance

Geriatric patients may also be more sensitive to the bitter taste of certain medications. By using effervescent systems, medications can be formulated with flavors and sweeteners to enhance palatability and improve medication acceptance among older individuals.

Hydration promotion

Effervescent formulations typically require dilution in water before ingestion. This encourages older adults, who may be at higher risk of dehydration, to consume adequate fluids, promoting hydration while delivering the necessary medications.

Convenience and safety

The simplicity of dissolving an effervescent tablet or powder in water makes it easier for geriatric patients to self-administer

medications without the need for complex preparation or manipulation. This convenience, coupled with the reduced risk of swallowing difficulties, improves medication adherence and safety.[54]

Effervescent DDS for Taste Masking and Permeation/ Bioavailability Enhancement

Taste masking with EDDS

Effervescent formulations can effectively mask the unpleasant taste of drugs through the following mechanisms:

Effervescence

The effervescence generated when an effervescent tablet or powder is melted in water can deliver a sensory distraction and mask the taste of drugs. The fizzy sensation and bubbles created in the mouth can help reduce the perception of bitterness or unpleasant taste.

Flavoring and sweetening agents

EDDS can incorporate flavoring agents and sweeteners to enhance palatability and mask the taste of drugs. These additives can provide pleasant flavors and sweetness, effectively camouflaging the undesirable taste. Example, effervescent paracetamol tablets flavored with cherry or orange have been developed to improve taste and patient acceptability, particularly for pediatric populations.[55]

Permeability/Bioavailability Enhancement with EDDS

EDDS can enhance drug permeability and bioavailability through the following mechanisms:

pH modification

Effervescent formulations can modify the pH of the gastrointestinal (GI) environment. By adjusting the pH to more favorable drug solubility and absorption conditions. EDDS can improve drug dissolution and enhance permeation in specific regions of the GI tract.

Carbon dioxide release

The effervescence generated by EDDS leads to the release of carbon dioxide bubbles. This gas release can create pressure within the GI tract, increase their absorption rate by increasing the penetration of active substances into the paracellular pathway, improve drug dissolution, enhance contact between the drug and the absorptive surfaces, and facilitate drug absorption and bioavailability.

Enhanced dissolution

Effervescent formulations generally exhibit rapid and complete dissolution. This increased dissolution rate can enhance drug solubility and improve the overall bioavailability by increasing the amount of drug available for absorption. Example effervescent rizatriptan benzoate tablets have been developed to enhance the bioavailability of rizatriptan, a selective serotonin receptor agonist used to treat migraines. The effervescent formulation demonstrated improved drug release and increased bioavailability compared to conventional tablet.[56]

Effervescent DDS considering BCS III and IV

EDDS can be particularly beneficial for drugs categorized under BCS III and IV. It classifies drugs according to their attributes of solubility and permeability. BCS Class III drugs exhibit high solubility but poor permeability, whereas BCS Class IV drugs display both low solubility and low permeability. Both of these classes encounter difficulties in terms of drug absorption and achieving desired levels of bioavailability. Effervescent DDS can address these challenges through various mechanisms:

Enhancing solubility

Effervescent formulations can increase the solubility of poorly soluble BCS Class IV drugs. The effervescent reaction and rapid dissolution of the formulation increase the drug's apparent solubility, ensuring a higher concentration of the drug in solution, which can enhance its absorption.

Modulating pH

Effervescent systems can adjust the pH of the gastrointestinal (GI) environment to create conditions that improve drug solubility and absorption. This pH modification can enhance the dissolution and permeability of BCS III and IV drugs, leading to increased bioavailability.[57]

Effervescent DDS offers Several Advantages for BCS III and IV Molecules

Enhanced dissolution

Effervescent formulations generally exhibit rapid and complete dissolution. This increased dissolution rate can improve drug solubility, particularly for BCS IV drugs with low solubility, and increase the amount of drug available for absorption.

Improved bioavailability

EDDS's improved solubility and dissolution can enhance the bioavailability of BCS III and IV drugs, which typically face absorption challenges due to their low permeability.

Patient compliance

Effervescent formulations often provide improved taste and ease of administration, which can enhance patient compliance, especially for drugs with low solubility or other formulation-related challenges.[58]

BCS III and IV Molecules Formulated as EDDS

Ondansetron

Ondansetron is a BCS Class III antiemetic drug utilized in lieu of the anticipation of nausea and vomiting. Ondansetron has been formulated in the effervescent form to increase its overall bioavailability, solubility, and rate of dissolution.[57]

Itraconazole

Itraconazole is a BCS IV antifungal agent with low solubility and bioavailability challenges. Effervescent formulations of itraconazole have been developed to enhance its solubility and dissolution, thereby improving its oral absorption and therapeutic efficacy.

Application of EDDS

The EDDS are dosage forms that contain effervescent agents, typically a combination of an acid and a carbonate or bicarbonate, which react upon contact with water or gastric fluids to release carbon dioxide gas. This effervescence leads to disintegration or dissolution of the dosage form, facilitating drug release and enhancing patient compliance. EDDS has several applications in pharmacy, like following

Oral drug delivery

Effervescent tablets and powders are commonly used in oral drug delivery. The effervescence generated upon contact with saliva or gastric fluids helps to disintegrate the tablet or dissolve the powder, resulting in rapid drug release and improved bioavailability. This formulation approach is beneficial for drugs that have poor solubility or require fast onset of action.

Pediatric and geriatric formulations

Patients who, like youngsters and the elderly, struggle to consume standard tablets or capsules can benefit from EDDS. Effervescent dosage forms can be dissolved in water, providing a convenient and palatable solution for administration. This improves medication adherence and patient acceptance, especially in populations with swallowing difficulties.

Nutritional supplements

Effervescent formulations are widely used in the production of dietary and nutritional supplements. They offer a pleasant sensory experience due to the effervescence, which can

Table 1: Recent advancements and research work done in E

Author	*Conclusion*
Agarwal *et al.*, 201562	The goal of this research was to create effervescent tablets of risperidone, a medication used for mental disorders, in order to enhance patient adherence. To address the drug's limited solubility in water, various combinations of nanoemulsions were loaded with risperidone and then adsorbed onto Aeroperl. The formulation that exhibited the highest drug dissolution was selected for development into effervescent tablets. A factorial design approach was employed to explore different variables in tablet formulation, and several formulations were prepared accordingly. These formulations were contrasted with preparations lacking the nanoemulsion formulation and assessed using a variety of criteria. The best tablet composition based on the Carr index, effervescence time, and drug release was found using statistical analysis.
Pradhan *et al.*, 201563	This research aimed to create a controlled-release drug delivery approach for Samchulkunbi-tang (ST), a traditional Korean herbal remedy used to address chronic gastritis and stomach ulcers. The objective was to devise a gastroretentive drug delivery system utilizing a hydrophilic matrix. Scanning electron microscopy analysis was conducted to examine the surface characteristics of the swollen tablet, which exhibited the presence of gas bubbles. The optimized formulation established favorable in vitro drug release, with controlled release lasting for more than 8 hours. Additionally, the tablet exhibited excellent buoyancy properties, indicated by a floating lag time (FLT) of 30 seconds and a total floating time (TFT) exceeding 12 hours. These findings suggest that ST's established floating tablet formulation could provide effective gastroprotection and offer a promising approach for delivering the drug to the upper gastrointestinal tract.
Collins *et al.*, 201964	This study aimed to develop a metformin drug delivery system that floats in the stomach and releases the drug gradually, utilizing Grewia mollis gum. The objective was to enhance the absorption of metformin at its target site and provide extended-release. In the development of gastro-floating matrix tablets containing metformin, Grewia mollis gum was employed. This method holds potential advantages for drugs that exhibit limited absorption in the upper gastrointestinal tract, particularly in cases where their absorption window is constrained.
Sari *et al.*, 202065	The primary objective of this research was to determine the optimal formula for producing effervescent granules that meet the overall requirements of effervescent pharmaceutical formulations. This was achieved by exploring different concentrations of effervescent salts in the formulations. The extract underwent screening for secondary metabolites, revealing the presence of alkaloids, saponins, phenolics, and flavonoids. The prepared effervescent granules were evaluated, and it was found that F1 and F2 did not meet the required standards for granule flowability, whereas F3 m*et al.* the evaluation criteria. Based on these findings, it can be concluded that F3 exhibited the most desirable characteristics among the effervescent granule formulations, meeting the general standards for effervescent dosage forms.
Sawant *et al.*, 202166	The formulation of effervescent tablets utilizing the wet granulation technique is preferred over dry granulation and direct compression due to its ability to provide a even distribution of the active ingredient. In this study, the taste of diclofenac sodium solution was improved by incorporating saccharin into an effervescent formula, effectively masking the taste of the drug.
Al-Mousawy *et al.*, 201967	The findings indicate that the granules formulated in this study exhibit favorable flow properties and have an appropriate bulk density for the desired dosage. The FTIR analysis results indicate that there are no detectable drug interactions with the other components in the formulation. Across all five formulations, the effervescent time remains under 3 minutes, with Formula 5 showcasing the most favorable drug release rate at 99.1%±1% and an impressively short effervescent time of around 80 seconds. The effective development and assessment of ibuprofen in the form of effervescent granules were accomplished through the strategic combination of croscarmellose sodium and banana powder.
Rosch *et al.*, 202168	The formulations based on mannitol exhibited the fastest disintegration and satisfactory hardness values, leading to their selection for subsequent development and stability testing. Conversely, formulations utilizing dextrates exhibited impressive tablet hardness, ensuring efficient and swift hydrogen production. As expected, this specific formulation displayed sensitivity to moisture. Hence, it is recommended to maintain vigilant oversight over processing and storage conditions and exercise caution when selecting primary packaging materials.

Table 2: Patents related to EDDS

Patent Number	*Title*	*Year*
WO2016042372A169	Effervescent composition and method of making it	2016
EP2309998A170	Effervescent tablets/granules	2016
EP1091732A171	Effervescent drug delivery system for oral administration	2006

Table 3: Marketed formulations of EDDS

Product Name	*Drug Name*	*Manufacture*
HISTAC	Ranitidine HCL	Ranbaxy, India
NEXX-DT	Loratidine	Anthiea, India
LORID	Loratidine	Finecure India
CUCET-DT	Cetirizine	Cubit, India
EZE-DT	Cetirizine	Saga Lab, India
EKON-DT	Cetirizine	Blue Cross, India
INCEZ	Cetirizine	Intra lab, India

enhance patient compliance. Additionally, effervescent tablets or powders can contain a higher concentration of active ingredients, such as vitamins or minerals, as they provide better solubility and absorption.

Combination therapy

EDDS can be used to formulate combination products containing multiple active ingredients. Formulating the ingredients as effervescent tablets or powders can achieve their simultaneous release and synergistic effects. This approach is particularly useful in situations where multiple drugs or supplements need to be administered together, simplifying the dosing regimen for the patient.[59]

Gastrointestinal drug delivery

The EDDS is commonly used for drugs that require rapid disintegration and dissolution in the stomach or intestine. The effervescence generated by the reaction between acid and carbonate or bicarbonate components helps in the dispersion of drug particles, leading to enhanced drug dissolution and absorption. This is particularly useful for drugs with poor aqueous solubility or those that exhibit pH-dependent solubility.

Controlled release formulations

Effervescent systems can be designed to provide a controlled release of drugs by modifying the effervescence properties. By adjusting the composition and ratio of the acid and carbonate or bicarbonate components, the rate of effervescence can be controlled, thereby influencing drug release kinetics. Effervescent systems allow for the tailoring of release profiles to achieve desired therapeutic outcomes.

Taste-masking

Effervescent dosage forms can help mask the unpleasant taste of drugs, especially in the case of pediatric or geriatric patients. The effervescence and the resulting effervescent solution can taste palatable, improving patient acceptability and compliance.

Targeted delivery

EDDS can be utilized for targeted drug delivery to specific regions of the gastrointestinal tract. By formulating the drug into an effervescent system with appropriate excipients, the effervescence can act as a driving force to propel the drug to the desired site of action, such as the colon or specific regions of the small intestine.[60,61]

Recent advancement in EDDS

Recent advancements and research work done by various researchers are presented in Table 1.

Patent in system related to EDDS

Some patents related to EDDS are captured in Table 2.

Marketed formulations of EDDS[51,71,72]

Numerous marketed formulations of EDDS are summarised in Table 3.

CONCLUSION

In conclusion, a bird's eye view of the EDDS reveals its significant impact and potential in the field of pharmaceuticals. EDDS offers a versatile and innovative approach to drug delivery, addressing various challenges associated with conventional dosage forms. Through the effervescence generated by the reaction between acid and carbonate or bicarbonate components, EDDS enables rapid disintegration, enhanced drug dissolution, and improved bioavailability. The application of EDDS extends to diverse areas within pharmacy. It has been successfully employed in oral drug delivery, particularly for drugs with poor solubility or those requiring fast onset of action. EDDS has found particular value in pediatric and geriatric populations, where swallowing difficulties can be overcome by providing medications in effervescent tablet or powder form, ensuring patient compliance and acceptance.

Furthermore, EDDS serves as an efficient platform for combination therapy, enabling simultaneous release and synergistic effects of multiple active ingredients. The controlled release capabilities of EDDS make it a valuable tool in tailoring drug release profiles, thereby optimizing therapeutic outcomes. Additionally, the taste-masking properties of effervescent formulations contribute to improved patient experience and adherence. With its ability to target specific gastrointestinal tract regions, EDDS holds promise for site-specific drug delivery, improving treatment effectiveness while reducing potential adverse effects. The efficacy of EDDS in diverse applications reflects its potential to address the evolving needs of the pharmaceutical industry and advance patient care.

In summary, the effervescent drug delivery system provides a promising avenue for pharmaceutical formulation development. Its ability to enhance drug dissolution, improve bioavailability, overcome taste challenges, and offer controlled and targeted drug release makes it a valuable and versatile option in modern drug delivery. Continued research and

development in this field holds the potential for further advancements, expanding the horizon of therapeutic options and ultimately improving patient outcomes.

REFERENCES

1. GME. Effervescent products market size, trends & analysis - forecasts to 2026. January 25, 2020. Available at https://www.globalmarketestimates.com.
2. Homan P. Seidlitz — the morning-after powder. The Pharmaceutical Journal 2001; 267(7179):911–936.
3. Moeller PL, *et al.* Time to onset of analgesia and analgesic efficacy of effervescent acetaminophen 1000 mg compared to tablet acetaminophen 1000 mg in postoperative dental pain: a single-dose, double blind, and randomized, placebo-controlled study. Journal of Clinical Pharmacology 2000; 40(4):370–378
4. Gharti KP, Thapa P, Budhathoki U, Bhargava A, Formulation and in vitro evaluation of floating tablets of hydroxypropyl methylcellulose and polyethylene oxide using ranitidine hydrochloride as a model drug, Journal of Young Pharmacists, 2009; 4(4):201-208.
5. Singh BN, Kim KH, Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention, Journal of Controlled release, 2000; (63):235–59.
6. Khairnar SV, Pagare P, Thakre A, Nambiar AR, Junnuthula V, Abraham MC, Kolimi P, Nyavanandi D, Dyawanapelly S. Review on the scale-up methods for the preparation of solid lipid nanoparticles. Pharmaceutics. 2022;14(9):1886.
7. Ghugarkar PG, Khulbe P. Formulation, Development, Evaluation and Optimisation of pH Dependent Drug Delivery System Containing Proton Pump Inhibitor. International Journal of Pharmaceutical Quality Assurance. 2022;13(1):21-25.
8. Agyilirah GA, Green M, DuCret R, Banker GS, Evaluation of the gastric retention properties of a cross-linked polymer coated tablet versus those of a non-disintegrating tablet, International Journal of Pharmaceutics, 1991; 75:241–47.
9. Patel SK, Kumar D, Waghmode AP, Dhabale AS. Solubility enhancement of ibuprofen using hydrotropic agents. International Journal of Pharmaceutical and Life Sciences. 2011; 2:542-5.
10. Patel SG, Siddaiah M. Formulation and evaluation of effervescent tablets: a review. Journal of drug delivery and therapeutics. 2018 Nov 15;8(6):296-303.
11. Parikh, Dilip M. Effervescent granules. Handbook of pharmaceutical granulation technology. Edn 3, Informa Healthcare, 365-384.
12. Pather SI, *et al.* Sublingual buccal effervescent. US Patent US2011/0212034 A1 2011.
13. Rapp M. Fibrin-based glue granulate and corresponding production method. WO Patent WO/2000/ 038752 2000.
14. Sánchez MT, Ruiz MA, Castán H, Morales ME. A novel double-layer mucoadhesive tablet containing probiotic strain for vaginal administration: design, development, and technological evaluation. European Journal of Pharmaceutical Sciences 2018; 112:63–70.
15. Metronidazole, clotrimazole, and chlorhexidine vaginal effervescent tablet and preparation method. CN Patent CN101406463B 2012.
16. Effervescent tablet for false teeth as well as preparation method and application of effervescent tablet. CN Patent CN102552054B 2013.
17. Mohrle R, Liberman L, Schwartz L. Pharmaceutical Dosage Form, Vol. 1, Marcel Decker Inc., New York, 2005, 285- 292.
18. Lachman L, Liberman HA, Kanig JL. The theory and practice of industrial pharmacy. 3rd Edn, Philadelphia, lea and febiger, 1986.
19. Swarbrick J, Boylan JC. Encyclopaedia of pharmaceutical technology. New York: Marcel Dekker; 2002.
20. Harald S, Effervescent Dosage, Pharmaceutical Technology Europe, 2003; 15(4): 25–28.
21. Srinath KR, Formulation and Evaluation of Effervescent tablets of Paracetamol, International Journal of Pharmaceutical Research & Development. 2011; 3(3):76- 104.
22. Indian Pharmacopoeia, Government of India Ministry of Health and Family Welfare. Delhi: Controller of Publications 1996; 2: 35, 448, 554.
23. Howard CA, Lloyd A, Nicholas and Popovich, Effervescent granules. Edn 8, Pharmaceutical Dosage From and Drug Delivery International Student Edition, 2000, 172-178.
24. Bhange M, Jadhav A. Formulation and development of Novel Matrix Dispersion System based on Phospholipid Complex for Improving Oral Bioavailability of Ferulic Acid. International Journal of Drug Delivery Technology. 2022;12(4):1489-1495.
25. Popescu C, Zhou L, Nienow C, Lefevre Ph. Ascorbic acid stability in effervescent tablets formulated with direct compressible maltitol. AAPS Annual Meeting, San Diego, CA, 2014.
26. Merrifield DR, Laurence P, Doughty G. Pharmaceutical formulations. US Patent US6,077,536 2000.
27. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Edn 6, Royal Pharmaceutical Society of Great Britain, London, UK. 2009:181–183.
28. Gothoskar AV, Kshirsagar SJ. A review of patents on effervescent granules. Pharmaceutical Reviews. 2004; 2(1):11-15.
29. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Edn 6, Royal Pharmaceutical Society of Great Britain, London, UK. 2009:731–732.
30. Rowe RC, Sheskey PJ, Quinn ME. Handbook of Pharmaceutical Excipients. Edn 6, Royal Pharmaceutical Society of Great Britain, London, UK. 2009:43–46.
31. Repta AJ, Higuchi T. Synthesis, isolation, and some chemistry of citric acid anhydride. Journal of Pharmaceutical Sciences 1969; 58:1110–1113.
32. Bilgic M, *et al.* Effervescent formulations comprising second-generation cephalosporin. WO Patent WO2011/093833 A2 2011.
33. Hoss Carr G. Adipic acid as a tableting lubricant. Us Patent US3, 584, 099 1971. https://patentimages.storage.googleapis.com/49/80/96/3d3dfbf6cab564/US3506756.pdf.
34. Chemical Book. 2017. Sodium bicarbonate Available at: https://www.chemicalbook.com/productchemicalpropertiescb7492884_en.htm.
35. Saleh SI, Boymond C, Stamm A. Preparation of direct compressible effervescent components: spraydried sodium bicarbonate. International Journal of Pharmaceutics. 1988; 45(1–2):19–26.
36. Mohapatra A, Parikh RK, Gohel MC. Formulation, development, and evaluation of patient-friendly dosage forms of metformin, Part-III: soluble effervescent tablets. Asian Journal of Pharmaceutics 2008; 177–181.
37. Effer Soda® Technical Sheet. Available at https://www.spipharma.com/en/products/functionalexcipients/effer-soda/.
38. Duvall RN, Gold G. Effervescent analgesic antacids composition having reduced sodium content. EP Patent EP0377906 A2 1993.
39. Tritthart W, Piskernig MA, Kölb G. Effervescent formulations. US Patent US 6,242,002 B1 2001.
40. Chiesi P, *et al.* Pharmaceutical compositions containing an

effervescent acid-base couple. US Patent US 6,284,272 2001.
41. Alexander TA. Lubricant for use in tableting. US Patent US 5,843,477 1998.
42. Daher LJ. Lubricant for use in tableting Bayer Corporation, USA. US Patent US 5,922,351 1999.
43. Rotthaeuser B, Kraus G, Schmidt PC. Optimization of an effervescent tablet formulation using a central composite design optimization of an effervescent tablet formulation containing spray-dried l-leucine and polyethylene glycol 6000 as lubricants using a central composite design. European Journal of Pharmaceutics and Biopharmaceutics 1998; 46(1):85–94.
44. Rudnic EM, Schwartz JD. Oral solid dosage forms. The Science and Practice of Pharmacy 21st Edition, In: Remington JP, Beringer P. Lippincott Williams & Wilkins, eds. Philadelphia, PA, USA 2006:891–893.
45. Armandou J-P, Mattha AG. Establishment of a geographical and chronological map for relative humidity (RH) in an effervescent tablets manufacturing and storage building. Pharmaceutica Acta Helvetiae 1982; 57:287–289.
46. Mohrle R. Effervescent tablets. In: Lieberman HA, Lachman L, eds. Pharmaceutical Solid Dosage Forms. Vol 1. Marcel Dekker, Inc., New York 1980:225–258.
47. Daher LJ. Lubricant. US Patent US 5,922,351 13 1999.
48. Özer YA, *et al*. Evaluation of the stability of commercial effervescent ascorbic acid tablets by factorial design. STP Pharma Science 1993; 3(4):313–317.
49. Yadav AV, Yeole PG, Gaud RS, Gokhale SB. Text Book of Pharmaceutics. Pragati Books Pvt. Ltd., India 2016:208.
50. Narala S, Nyavanandi D, Mandati P, Youssef AA, Alzahrani A, Kolimi P, Zhang F, Repka M. Preparation and in vitro evaluation of hot-melt extruded pectin-based pellets containing ketoprofen for colon targeting. International Journal of Pharmaceutics: X. 2023 Dec 1;5:100156.
51. Narala S, Komanduri N, Nyavanandi D, Youssef AA, Mandati P, Alzahrani A, Kolimi P, Narala N, Repka MA. Hard gelatin capsules containing hot melt extruded solid crystal suspension of carbamazepine for improving dissolution: Preparation and in vitro evaluation. Journal of Drug Delivery Science and Technology. 2023 Apr 1;82:104384.
52. Foldvari M, Nanopharmaceutics Innovations in Gene Therapy: Moving Towards Non-Viral and Non-Invasive Delivery Methods. J Nanomedine Biotherapeutic Discovery. 2014; 4:135.
53. Aulton ME, Taylor K, editors. Aulton's pharmaceutics: the design and manufacture of medicines. Elsevier Health Sciences; 2013.
54. Shetty A, Saini R, and Shetty S. Geriatric Formulations: A Review. Journal of Young Pharmacists. 2017; 9(2):157-162.
55. Gupta SU and Yadav SK. Taste Masking of Paracetamol in Effervescent Tablets for Pediatric Use. Indian Journal of Pharmaceutical Sciences. 2018; 80(3):452-458.
56. Roy S, Pare A, Bhattacharjee A. Kesharwani, P. Formulation and Evaluation of Effervescent Rizatriptan Benzoate Tablets for Rapid Onset of Action. Journal of Young Pharmacists. 2013; 5(2):48-53.
57. Bhaskar K, Anwar S, Prabhakar C. Formulation and evaluation of effervescent floating tablets of ondansetron hydrochloride. International Journal of Pharmaceutical Sciences Review and Research, 2012; 16(1):146-151.
58. Patel VM and Patel NM. Formulation development and evaluation of floating effervescent tablets of itraconazole. International Journal of Pharmaceutical Sciences and Research. 2010; 1(9):52-58.
59. Obeidat WM, Schwabe K, Müller-Goymann CC. Pharmaceutical Aspects of Effervescent Dosage Forms: A Review. Pharmaceutics. 2020; 12(9):853.
60. Inamdar N, Elango K, Prasad CV, Chintamaneni M, Gannu R, Raju AB. Effervescent Drug Delivery System - A Review. Research Journal of Pharmacy and Technology. 2008; 1(3):234-238.
61. Patel DM, Shah TH, Shah SR, Chakraborty S, Mishra R. Effervescent Systems as Versatile Drug Delivery Technology: A Comprehensive Review. Adv Pharm Bull. 2016; 6(4):495-502.
62. Agrawal AG, Kumar A, Gide PS. Self-emulsifying drug delivery system for enhanced solubility and dissolution of glipizide. Colloids Surf B Biointerfaces. 2015;126:553-560.
63. Pradhan R, Lee HH, Kim JO, Moon SO, Choi HM, Kim JB, Yong CS, Lee HD, Kim JO. Preparation and evaluation of gastroretentive effervescent floating drug delivery system of Samchulkunbi-tang. Journal of Pharmaceutical Investigation. 2015; 45:423-31.
64. Airemwen CO and Uhumwangho UM. Formulation and Evaluation of Effervescent Floating Matrix Tablets of a Biguanide Using Grewia mollis Gum. Asian Journal of Applied Sciences. 2019; 1291-98.
65. Maysarah H, Sari I, Faradilla M, Kwok K. Formulation of effervescent granule from robusta green coffee bean ethanolic extract (Coffea canephora). Journal of Pharmacy and Bioallied Sciences. 2020; 12:S743-6.
66. Savant PB, Qureshi MA, Kshirsagar N, Kareppa M, Thalkari AB, Karwa PN. Preparation and Evaluation of Diclofenac Sodium Effervescent Tablet. Research Journal of Pharmaceutical Dosage Forms and Technology. 2021; 13(4):305-1.
67. AL-MOUSAWY JI, AL-HUSSAINY ZA, ALAAYEDI M. Formulation and evaluation of effervescent granules of ibuprofen. International Journal of Applied Pharmaceutics. 2019; 7:66-9.
68. Rosch M, Lucas K, Al-Gousous J, Pöschl U, Langguth P. Formulation and Characterization of an Effervescent Hydrogen-Generating Tablet. Pharmaceuticals. 2021; 14(12):1327.
69. https://patents.google.com/patent/WO2016042372A1/en
70. https://patents.google.com/patent/EP2309998A1/en
71. https://patents.google.com/patent/EP1091732A1
72. Chaudhari, R.N., Jain, A.K., Chatap, V.K. An Overview on Phyto-chemistry, Traditional and Pharmacological aspects of Pyrostegia Venusta. Research Journal of Pharmacy and Technology, 2022,15(5):2339–2345