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Recent advances in the technology of effervescent tablets: lessons learned and future perspectives

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Effervescent tablets are solid pharmaceutical dosage forms that are widely accepted due to their advantages. The improvement in patient compliance results from a combination of factors related to both the extrinsic characteristics of the tablet and the effects it produces. An important reason is the possibility of avoiding swallowing whole tablets, as a large part of the population, such as the elderly, children, and dysphagic patients, find it difficult to swallow them. The aim of this investigation is to review the recent literature on the technology and application of effervescent tablets and investigate their added value towards upgrading of such dosage forms and in general of pharmaceutical technology. Special attention is given to the excipients that are used for the design and development of efficacious systems, as well as their added value for the drug release studies having in mind the patients' unmet needs.

Introduction

Effervescent tablets are pharmaceutical dosage forms that are widely accepted due to their advantages. Their applications include not only pharmaceutical products but also dietary supplements. Even though oral administration is widely known as the most popular route for non-invasive systemic drug delivery, simplicity in usage and patient compliance are not the only assets that effervescence technology offers.[1,2] They are favored in dysphagic patients or special populations such as the elderly.[3,4] The general population prefers them for their good taste and palatability. Furthermore, they permit the incorporation of a high amount of the Active Pharmaceutical Ingredient (API) and enable enhanced solubility of the API, faster therapeutic efficacy, and fewer adverse effects such as gastrointestinal irritation.[1,4–7] A good example of their superiority over regular tablets is paracetamol effervescent tablets.[4] The improved pharmacokinetic profile in comparison with those of conventional solid oral formulations is due to their ability to be rapidly dissolved in water.[1,4–6] In particular, the main mechanism of drug release and dissolution involves the reaction between specific excipients—an acid and an alkali carbonate or bicarbonate—in an aqueous environment that leads to the production of carbon dioxide.[1,8]

On the other hand, effervescent medication has disadvantages as well. Apart from the necessity for specific packaging due to tablets' size, the main concern is the exposure to large amounts of sodium when the usage is daily.[1] The utilization of effervescent tablets in supplements or unprescribed medication without health care supervision should also be considered. Real world data demonstrate that the use of specific sodium salts—fortunately not the excipients of choice—is more likely to have an impact on patients' health, while healthy people are not at a serious risk of cardiovascular diseases with effervescent treatment.[4,9] As far as their production is concerned, the manufacturing process requires controlled conditions due to sensitive excipients in moisture.[7] Additionally, there are problems such as sticking, inadequate hardness, and hygroscopicity of the tablets, resulting in unmet quality requirements. There have been efforts to overcome these limitations, with the most promising one being a coating *via* the fluid bed technique.[8]

From a regulatory aspect, effervescent tablets should be uncoated and dissolved in an aqueous solvent prior to their usage.[4] However, recent research has exploited the effervescence technology to form novel formulations with prolonged or targeted release properties. The main principle is still gas liberation, as mentioned earlier, in order to induce or intensify floating in the stomach or saliva.[10–12] In fact, a respective orodispersible formulation has already been marketed with encouraging results for targeted treatment of esophagitis.[13] These dosage forms are typically used as per os tablets that are activated by gastric fluids in a slow-release pattern, accelerating the residence time in the upper gastrointestinal tract. Moreover, they are an effective solution for APIs that are insoluble in the alkaline pH of the intestine.[10,12,14] In general, other excipients are also added, usually polymers that are

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Table 1 The advantages and the limitations of effervescent tablets

Advantages	Limitations
• Improved therapeutic effect • Incorporation of larger amounts of the API • Stability during storage. • Improved oral bioavailability (a) Controlled–sustained drug release. (b) Targeted release in the gastrointestinal tract (c) Fast absorption and onset of action. (d) Enhanced dissolution rate of hydrophobic and lipophilic APIs. (e) Enhanced stability of APIs in an acidic environment. (f) Enhanced disintegration of the tablet as well as quick and complete dispersion in water. • Improved patient's compliance (a) Decreased administration frequency of formulations with prolonged or targeted release properties. (b) Suitable for patients with swallowing problems (older patients, infants, and dysphagia patients). (c) Minimization of undesirable side effects. (d) Taste and smell masking. (e) Good stomach and intestinal tolerance. • Adapting the 3D printing technology advantages	• Susceptible to humidity • Controlled environmental conditions during the manufacturing process • Special packaging materials • Relatively high cost of production

hydrophilic and create a matrix for CO_2 entrapment and slow drug release.[10–12] In this perspective, the combination of these features permits the fabrication of innovative formulations with the scope of reaching patients' unmet needs.

Taking into account all the above, the technology of effervescent tablets is a promising method for the formulation of APIs and presents many advantages and applications in the pharmaceutical industry.[1,8] A very important advantage is the formulation of both hydrophilic and lipophilic APIs, which could be applied to the administration of many different active substances. The application and study of effervescence technology remain promising areas for future investigation. The improvement in patient compliance results from a combination of factors related to both the extrinsic characteristics of the tablet and the effects it produces. An important reason is the possibility of avoiding swallowing whole tablets, as a large part of the population, such as the elderly, children, and dysphagic patients, find it difficult to swallow them. Also, the ability to mask the taste and smell of tablets makes them more accessible to patients. The gastro-retentive forms, although they must be swallowed by the patient, have the advantages of reducing the frequency of administration, as they have the ability to float for more than 24 hours, and of minimizing the unwanted effects that are presented by the repeated administration of conventional tablets.[10,12] In addition, they cause less irritation and show good tolerance in the gastrointestinal system. Furthermore, the method of preparation of effervescent tablets with 3D printing is time saving during production as the time-consuming steps of granulation and tableting are omitted, enabling the production of small batches, and avoiding the use of excessive amounts of excipients. Environmental humidity control is not required, and premature effervescence reactions are avoided, too. The advantages and limitations of effervescent tablets are summarized in Table 1.

The main purpose of this work is to emphasize on effervescent systems by reviewing the recent literature and investigating the added value of novel effervescent formulations developed in order to highlight the exceptional results and conclusions of their research work towards the enrichment and upgrading of pharmaceutical technology having the ultimate goal of fulfilling patients' unmet needs. Special attention is given to the excipients that are used for the design and development of the efficacious systems, as well as their added value for the drug release studies.

Methods

An extensive search was performed in the electronic databases PubMed, Scopus, and Google scholar for English-language publications. The publications from the past five years (2018–2023) served as a comprehensive guide for the systematic investigation of effervescent tablets. The authors performed literature search excluding the studies with full text unavailable, publication language other than English, and conference abstracts. After the screening of titles and abstracts, 30 full-text studies were included in the section Recent advances of effervescent tablets.

Recent advances of effervescent tablets

Effervescent tablets of nateglinide were prepared as a prolonged-release formulation for the treatment of diabetes mellitus type II. The list of excipients used consists of ethyl cellulose, Carbopol 930, sodium bicarbonate, citric acid, PVP k-30, talc, and magnesium stearate, while the optimal method of preparation was direct compression. As for the preformulation

studies, the physicochemical characteristics were determined, whereas the drug–excipient compatibility study was conducted using Fourier transform infrared spectroscopy (FTIR) and differential scanning calorimetry (DSC). Based on DSC, it is confirmed that there is no interaction between nateglinide and the excipients. Afterwards, post-compression studies indicated rapid and constant floatation with drug release that reached 99% at 24 hours and exhibited a stable formulation with temperature, humidity, and light changes. The authors declared that the problem of rapid onset and short duration of insulinotropic action can be solved by using this gastro-retentive formulation that can reduce drug waste and dose frequency, enhance solubility and bioavailability, and prolong the duration of action.[15]

The formulation of effervescent floating tablets of fluoxetine took place for the treatment of depression. The tablets were prepared by direct compression and were composed of HPMC K4M, Carbopol 934, sodium bicarbonate, citric acid, magnesium stearate, and lactose. Moreover, their chemical properties and thermodynamic characteristics were investigated *via* FTIR and DSC, respectively, highlighting that there are no compatibility issues. The rheological characteristics were also studied and it was found that the powder blend is easily compressible. Identification tests were also conducted regarding the organoleptic features, the melting point, IR spectroscopy, and solubility analysis. Except for drug release and stability studies, floating capacity and *in vitro* disintegration time were examined as well. The release kinetic data demonstrated that all formulations follow the Korsmeyer–Peppas model, drug release could reach 96% in 12 hours, and there was no significant variation after placing the tablets under various temperature and humidity conditions for a period of 3 months.[16]

Reddy and Kumar[17] formed antiemetic floating tablets of domperidone and probed their characteristics. HPMC K4M, Carbopol 934, sodium CMC, sodium bicarbonate, talc, lactose, and magnesium stearate were selected as the other components. According to preformulation studies, the powder blend had good flow properties, whereas no chemical interaction between the drug and the polymers was detected. Direct compression was the optimal preparation method in this case as well. Besides, the post-compression studies indicate that the formulation containing Carbopol p934 displayed a desirable sustained effect with 98% release at the end of a 12-hour period. The suggested system with prolonged release properties may improve oral drug delivery, especially for drugs that have an absorption window in a particular region of the GIT.[17]

In another study, silymarin flavonolignan (silybin, silydianin, and silychristin) tablets were formulated with the intention of gastro-retentive and sustained release.[18] The direct compression approach was preferred due to its affordability and production convenience, while the excipients of choice were HPMC K4, Carbopol 934P, HPMC K15, sodium bicarbonate, citric acid, and magnesium stearate. Referring to the preformulation outcomes, the mixture had excellent flow characteristics and compressibility, while the formulation's constituent parts were compatible with each other. The post-compression results pointed out adequate mechanical strength, retarded release of the drug for more than 12 hours, and zero-order kinetics. At 16 hours, the formulation showed a drug release of about 95%. Hence, the proposed technology can possibly improve a drug's pharmacokinetic profile in the treatment of acute and chronic hepatic diseases (Fig. 1).[18]

Effervescent tablets of methocarbamol were developed as a patient friendly skeletal muscle relaxant drug. The tablets were prepared by direct compression and consisted of citric acid, sodium bicarbonate, PVP k30, PEG 6000, mannitol, sucralose, and sour cherry flavor. Regarding the preformulation studies, the rheological characteristics indicated that the powder blend had good flowability. In addition, post-compression parameters highlighted that the hardness of tablets was mostly affected by the amount of PEG 6000, while the effervescence time was mostly influenced by the sodium bicarbonate/citric acid molar ratio. Eventually, the optimization of the study was carried out using the Design of Experiments (DoE) approach. Because there were right number of excipients in this formulation, the hardness, pH, friability, and effervescence time were all appropriate for futher experiments for evaluation of the bioavailability of these effervescent tablets.[19]

Mishra[20] fabricated antibiotic effervescent tablets of low-solubility cefpodoxime proxetil. The tablets were formulated by direct compression, and the selected excipients were HP-β-cyclodextrin, sodium bicarbonate, citric acid, mannitol, sodium starch glycolate, polacrilin K, sodium saccharine, talc, and magnesium stearate. No interaction between the drug and the excipients was observed. Moreover, the hardness test revealed good strength, which can be attributed to the adhesive nature of the HP-β-cyclodextrin used. Furthermore, post-compression tests pointed out consistent drug release (more than 80% in 30 minutes) and drug content of more than 98%. Hence, the suggested formulation enhanced the solubility and disintegration of the drug, achieving a quick and complete dispersion in water.[20]

Floating tablets of ciprofloxacin HCL were prepared for antibiotic therapy, by the Tadros[21] scientific team. The excipients

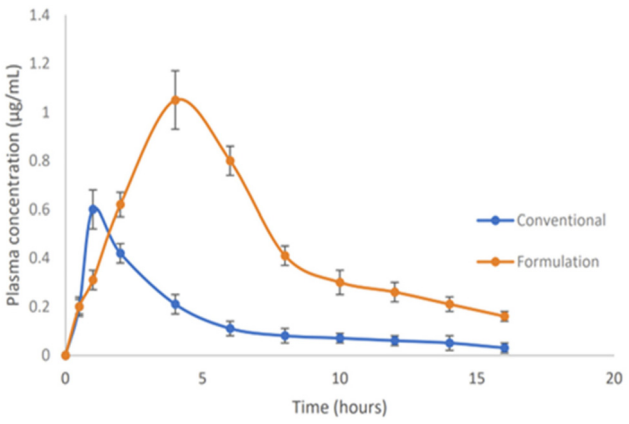

Fig. 1 Pharmacokinetic study overlay.[18]

of choice were HPMC K15M, sodium alginate, microcrystalline cellulose, magnesium stearate, sodium bicarbonate, and calcium carbonate, and the optimized formulation method was found to be direct compression. The physicochemical features demonstrated that the drug content ranged from 97 to 102% and the friability was less than 1%, indicating good mechanical resistance. Referring to post-compression studies, the tablet exhibited buoyant behaviour and controlled drug release for more than 12 hours. This promising gastro-retentive system displayed excellent floating properties and extended adhesion periods. The authors declared that the difficulty of a short elimination half-life and narrow absorption window can be improved by using a formulation that can prolong the presence of the dosage form within the GIT, while exhibiting better physical stability and antibacterial activity.[21]

An interesting study by Akhtar *et al.* (2020) showed how to develop levocetirizine effervescent tablets, as an antihistamine drug. The list of excipients consists of sorbitol, sodium bicarbonate, citric acid, mannitol, crospovidone, CCS, aspartame, aerosol, and magnesium stearate. Firstly, the properties of the powder were determined by identifying the angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio, while the drug–excipient compatibility study was conducted using FTIR. Based on the results, it was confirmed that the drug and the proposed excipients are compatible. After the direct compression of the granules, the tablets were subjected to external evaluation. Furthermore, post-compression tests demonstrated a stable formulation with changes in temperature, humidity, and light, whereas more than 90% of the drug was released within 1 min. The selected formulation can overcome swallowing problems and therefore improve patients' compliance. Rapid absorption, onset action, good stomach and intestinal tolerance, enhanced safety, and stability are among its advantages.[22]

Kumar and Shrivastava[23] formulated slow-release floating tablets of verapamil HCL as a potent antiarrhythmic drug. Karaya gum, HPMC K15 M, sodium bicarbonate, PVP K30, magnesium stearate, and lactose were selected as the optimal components. The drug–excipient compatibility was examined by FTIR and DSC, and it was confirmed that no chemical interaction took place. Direct compression was chosen as the most suitable method of preparation. Additionally, post-compression studies like water uptake, *in vitro* buoyancy, *in vitro* drug release, mathematical model fitting of obtained drug release data, and stability studies were conducted. The results indicated constant drug release, while more than 75% drug release was achieved in 12 hours. Besides, the tablets were floating for more than 8 hours, whereas complete swelling was achieved by the end of 8 hours. No significant changes occurred in the physical appearance or drug content during the study period. The suggested effervescent formulation extended the gastric residence time of the drug and thus enhanced its absorption.[23]

Buccal effervescent tablets of ropinirole HCL were formed by Smail and his colleagues,[24] for the treatment of Parkinson's disease. The aim of this study was to prepare fast disintegrating tablets using four different types of super-disintegrants; in particular, kyron T-314, crospovidone, croscarmellose sodium, and sodium starch glycolate, to improve drug permeation through oral mucosa. The tablets were prepared by direct compression, and the rest of the excipients that were utilized were sodium bicarbonate, citric acid, sodium carbonate, microcrystalline cellulose, and magnesium stearate. According to the flowability study, the powder mixture presented good flow characteristics. Moreover, the drug release was almost 100% within 6 min, while the drug content was determined to be equal to 99%. The proposed technology assists in fast onset action by sublingual administration, improving the drug's intestinal absorption and pharmacokinetics.[24]

The main goal of the Rahamathulla[25] study was to formulate neratinib sustained release floating tablets for breast cancer therapy. The added value of this work is the evaluation of the anticancer efficacy of neratinib, in addition to the use of the HPMC-90SH 15 000 polymer. Direct compression was chosen as the ideal method of preparation. The list of excipients comprises HPMC-90SH, microcrystalline cellulose, sodium bicarbonate, talc, and lactose. Furthermore, the physicochemical interactions and the rheological and thermodynamic features were investigated, highlighting that the powder is easily compressible and that there are no compatibility issues. Additionally, floating and sustained release lasted for more than 24 and 12 hours, respectively, while the floating lag time was 120 s. The authors indicated that the problem of poor solubility can be solved by using this gastroretentive formulation, which can enhance the bioavailability and absorption of the drug.[25]

Taymouri[26] prepared effervescent tablets of bismuth subcitrate, and the final formulation was optimized by using an irregular factorial design. The tablets were prepared by direct compression and consisted of citric acid, sodium bicarbonate, mannitol, sucrose, polyvinylpyrrolidone K 30, polyethylene glycol 6000, and flavoring agents. Five dependent variables were optimized to obtain the levels of each variable which maximized CO_2 content and hardness, minimized disintegration time and friability, and permitted targeting at a specific pH (pH 6.0). The suggested tablet exhibited adequate stomach and intestinal tolerance and can be used as a potent drug for the treatment of peptic ulcers. The incorporation of larger amounts of active pharmaceutical ingredients and the improvement of patient compliance are among the benefits that this effervescent form can provide.[26]

A study performed by Zhao and colleagues[27] focused on fabricating effervescent tablets containing a combination of probiotic lactobacilli and root powders of two medicinal plants, namely Chinese ginseng and *Polygonatum sibiricum*, for multiple uses. Citric acid, sodium bicarbonate, povidone, and polyethylene glycol 6000 were selected as the other components. The most efficient method of preparation was found to be direct compression. The bacterium viability studies pointed out that the presence of the two herbs has a slow-releasing effect on disintegration. Furthermore, they have a dose-dependent protective influence on the lactobacilli in the

GIT. Hence, this probiotic tablet can disintegrate rapidly while effectively protecting the viability of lactobacilli after tableting and in the gastrointestinal environment, along with its high antibacterial ability.[27]

Metronidazole gastro-retentive floating tablets were formulated for the treatment of *Helicobacter pylori*. The tablets comprised Carbopol 934P, chitosan, guar gum, sodium alginate, HPMC, microcrystalline cellulose, lactose, NaHCO3, talc, and magnesium stearate. Direct compression was selected as the manufacturing process, and preformulation tests were conducted, showing excellent flowability and ingredient compatibility. Additionally, post-compression parameters were examined, indicating increased drug release in release media containing NaCl 0.5% and 0.9%, during which the swelling process and polymer viscosity had a linear relationship. The authors concluded that these osmotically controlled bioadhesive effervescent tablets are expected to enhance the stomach-specific action of anti-*H. pylori* agents based on their buoyancy and swelling behavior and therefore decrease administration frequency and increase patient compliance (Fig. 2).[2]

The objective of the Thapa and Jeong[11] study was to develop sustained-release effervescent tablets (EFTs), utilizing an experimental design approach. For this purpose, they used a hydrophilic matrix loaded with a highly water-soluble model drug, in particular metformin HCl. The amounts of polyethylene oxide WSR 303 (PEO) and sodium bicarbonate, as well as tablet compression force, were deemed independent variables, while drug release time, tablet tensile strength, floating lag time (FLT), tablet ejection force, and tablet porosity were selected as the responses. The tablets were prepared by direct compression, and the excipients of choice were polyethylene oxide WSR 303, sodium bicarbonate, lactose monohydrate, microcrystalline cellulose, and magnesium stearate. The results demonstrated that the kinetic model was the Korsmeyer–Peppas model. FLT increased with the increasing amount of PEO and compression force level but decreased with the increase in sodium bicarbonate. In conclusion, PEO could control drug release, improve gel strength, and improve tablet properties, while sodium bicarbonate exhibited a dual function of improving tablet floating and enabling controlled release by retarding the drug release from the hydrophilic matrices (Fig. 3). Overall, the work of Thapa and Jeong provided a Quality by Design perspective by systematically fabricating EFTs for loading high-water-soluble drugs.[11]

Gastro-retentive effervescent tablets of superparamagnetic iron oxide nanoparticles (SPIONPs) were prepared by Zhou *et al.*[28] When the tablets interacted with the acidic microenvironment, carbon dioxide was generated and captured by ultrasound (US) imaging. The selected method of preparation was direct compression, and the excipients used were lactose, mannitol, sodium bicarbonate, and HPMC/carbomer. Furthermore, the post-formulation studies indicated that the presence of foaming agents enabled stable CO_2 bubbles *in situ* in an acidic environment, and thus ultrasound sensing could be applied. Meanwhile, the presence of the adhesive ingredient prevented the tablet from rapid disintegration, which verifies the controlled release of SPIONPs. The released SPIONPs were pushed by ultrasound to the deeper muscle layer and dis-

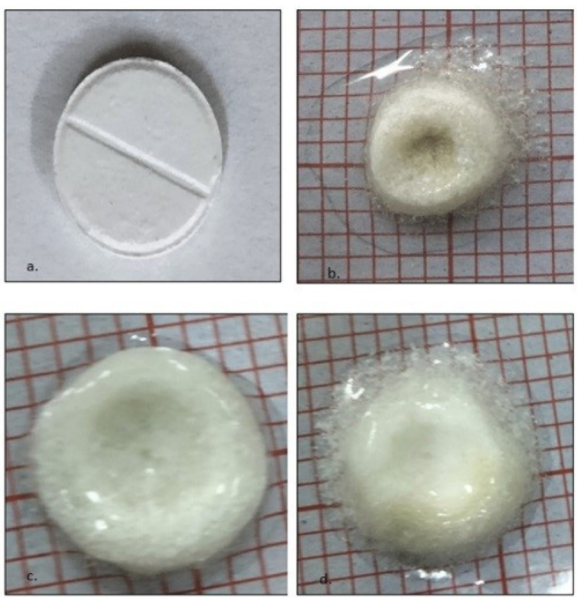

Fig. 2 Swelling behavior of an effervescent floating tablet of metronidazole (F3): (a) tablet at 0 h, (b) tablet swelling after 2 h, (c) tablet swelling after 4 h and (d) tablet swelling after 8 h.[2]

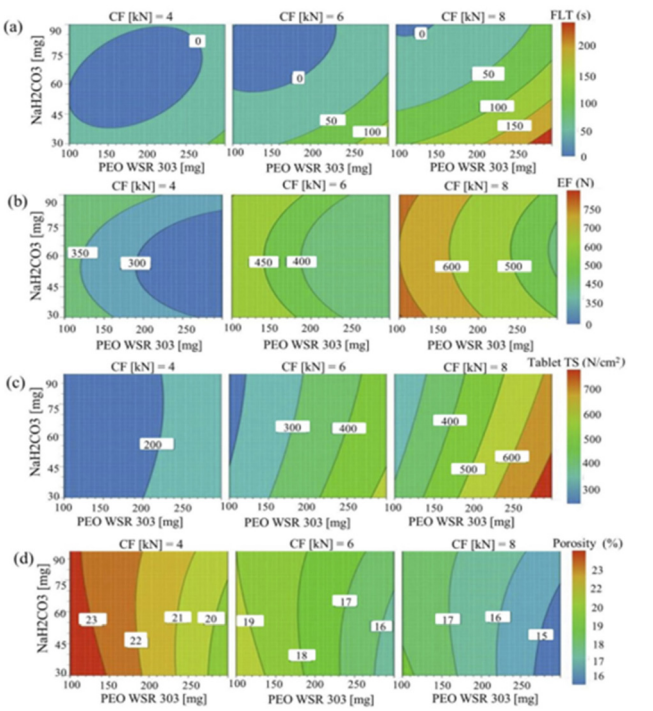

Fig. 3 Contour plots showing the effects of the hydrophilic polymer (PEO) and sodium bicarbonate on (a) floating lag time (Y4), (b) tablet ejection force (Y5), (c) tablet tensile strength (Y6), and (d) tablet porosity (Y7).[11]

tributed more dispersedly. This proves that the absorption of released nanoparticles was promoted by ultrasonic energy in the tissue. Hence, the suggested technology offers targeted delivery, effective release, and absorption of nanoparticles in the gastric area, which can be imaged by MRI and US.[28]

Suksaeree and colleagues[29] formulated expectorant effervescent tablets with Semha–Pinas (SHPN) extract. The development of SHPN tablets was based on process and formulation optimization using the Box–Behnken design. Four levels of three independent variables, including compressional force, quantity of the effervescent base, and quantity of fumed silica, were screened using the "one factor at a time" method. The list of excipients consists of sodium bicarbonate, anhydrous citric acid, tartaric acid, fumed silica, sucralose, magnesium stearate, and microcrystalline cellulose. The present work also used fumed silica as an adsorbent to prevent unwanted effervescent reactions. The plant extraction took place by freeze-drying, and the tablets were prepared by direct compression. Additionally, post-compression studies highlighted that increasing compressional force resulted in more tablet compaction. In this perspective, tablet friability was decreased, and disintegration time was prolonged. The developed tablets can ameliorate patient convenience and decrease the time needed to disperse the extract compared with the traditional dosage form.[29]

Another scientific group[30] prepared floating tablets of losartan potassium for the treatment of hypertension. The direct compression approach was selected, while the excipients of choice were HPMC 90SH 15 000, lactose, microcrystalline cellulose, magnesium stearate, sodium bicarbonate, and karaya gum. Moreover, the material compatibility, their interactions, as well as their thermodynamic and morphological characteristics were investigated *via* FTIR, DSC, and scanning electron microscopy (SEM), respectively. The results indicated that there is no compatibility issue while the rheological evaluation revealed that the powder is easily compressible. Additionally, post-compression tests exhibited adequate floating and swelling capability, controlled release for over 24 hours with 100% drug release at the end of 24 hours, and non-Fickian diffusion. Consequently, this formulation may substantially extend the stomach residence time in comparison with an oral solution, enhance its intrinsic features through good gastric floatation, and regulate the release into the acidic environment.[30]

Effervescent bilayer tablets of clarithromycin and esomeprazole were developed as a controlled-release formulation for the treatment of *Helicobacter pylori* infection by Israr *et al.*[14] Direct compression was the method of choice, and the list of excipients comprised two layers of Eudragit® RS 100, Carbopol 934 P, talc, magnesium stearate, avecil 102, and sodium bicarbonate. Besides, the physicochemical interactions were examined by FTIR, highlighting that there were no van der Waals or hydrogen bonds between the components, while the powder had excellent flow as determined by the rheological evaluation. In addition, floating, buoyancy, drug release kinetics, and dissolution studies were performed and the floating lag time and total floating time under 25 seconds and 24 hours, respectively, were found. The release of both drugs started simultaneously by anomalous non-Fickian diffusion, and the polymeric materials extended the drug release rate up to 24 hours. Subsequently, such tablets may be efficiently used in clinical practice to reduce dosage frequency and increase patient compliance, which ultimately might enhance therapeutic efficacy and reduce side effects.[14]

Effervescent tablets of albendazole were prepared, for the treatment of helminthiasis, by Vani and colleagues.[31] The tablets were prepared by the wet granulation method, and the utilized excipients were sodium bicarbonate, sodium carbonate, citric acid, tartaric acid, PVP, simethicone, saccharine sodium, sodium benzoate, magnesium stearate, and microcrystalline cellulose. According to preformulation studies and the FTIR technique, the powder had sufficient flow and there was no interaction between the drug and the polymers used. Referring to post-compression studies, the optimized formulation exhibited faster and better release over a period of 15 minutes in comparison with the chewable formulation, which dissolved completely in 30 minutes. In conclusion, this formulation improved the release of the drug by a minimum of 80% in 10–15 minutes.[31]

In the work of Partama *et al.*,[32] antiseptic effervescent tablets of Papaya leaf extract were formulated by varying the amounts of citric and tartaric acid. The list of excipients comprises citric acid, tartaric acid, sodium bicarbonate, lactose, magnesium stearate, PVP K30, and talc. The ethanol extract was recovered by maceration, and the tablets were prepared by wet granulation. Furthermore, the evaluation of the granules indicated that the powder had good flow and was easily compressible. The final formulation was tested for its effectiveness, and the results pointed out that the extract contains flavonoid compounds, whereas the tablets can be dissolved within 2 minutes and possess antibacterial activity against *Escherichia coli*. Regarding the variation of citric and tartaric acids, it did not affect the physical properties of the tablet. However, it seems that it influenced the tablet's hardness. The suggested formulation can improve the dissolution rate and enhance the stability of the product, increasing its shelf life.[32]

Savant *et al.*[33] prepared effervescent tablets of diclofenac sodium that can be used as an analgesic. The tablets were prepared by wet granulation, and sodium bicarbonate, tartaric acid, propyl alcohol, lactose or sucrose, mannitol, sodium benzoate, propylene glycol, and citrus oil were the excipients of choice. Moreover, the rheological characteristics were determined by identifying the angle of repose, bulk density, tapped density, Carr's index, and Hausner ratio. The powder had acceptable flow properties and was easily compressible. Additionally, post-compression tests demonstrated good distribution of the active pharmaceutical ingredient and fast absorption. The proposed technology can be used by dysphagic patients displaying tolerability while enhancing the bioavailability, dissolution time, and taste of the drug.[33]

Korde *et al.*[34] prepared immediate-release effervescent tablets of acetaminophen by wet granulation. The optimal combination of excipients was sodium bicarbonate, citric acid,

lactose, gelatin, starch, and talc. Besides, the results of the rheological study showed that the powder blend had good flow and compression properties. Afterwards, post-compression tests such as disintegration time, content uniformity, and *in vitro* drug release took place, resulting in fast on-set action as well as rapid absorption and disintegration of the drug. The authors declared that the effervescence technology eliminated the need to swallow tablets, increased the penetration of the drug into the paracellular pathway, exhibited good tolerability in GIT, and improved the palatability and dissolution time of the drug.[34]

The purpose of the Mohapatra *et al.* study,[3] was to formulate effervescent tablets of metformin that can be utilized in the management of non-insulin-dependent diabetes mellitus, especially for dysphagic patients. The optimized method of preparation was wet granulation because both metformin and the effervescent ingredients are poorly compressible. The list of excipients included citric acid, tartaric acid, sodium bicarbonate, saccharin sodium, mango flavor, glycine powder, and talc. Moreover, it was established that using treated sodium bicarbonate in a stoichiometric ratio led to substantially stable tablets in a short-term stability study, as sodium carbonate preferentially absorbs moisture. The effervescent formulation exhibits good storage stability and rapid disintegration, and most importantly, it can enhance patient compliance.[3]

Effervescent tablets of poorly water-soluble glipizide were developed for the treatment of diabetes by Aklima *et al.*[35] PVP K30, corn starch, sodium bicarbonate, citric acid, ascorbic acid, sodium saccharine, lactose, magnesium stearate, sodium metabisulphite, Congo red, and raspberry flavor were the excipients of choice. Referring to preformulation studies, the rheological features of the granules exhibited excellent flow properties and compressibility. The optimized method of preparation was found to be wet granulation. Additionally, drug content studies indicated that the mean disintegration time was 95–105 seconds. After the dissolution of the drug, a dispersed phase is formed, which can cause higher permeability through the biological membrane. Hence, enhanced bioavailability and dissolution in GIT, improved patients' compliance, and long stability are among the advantages that this formulation can provide.[35]

Taymouri *et al.*[36] formulated effervescent tablets of valacyclovir that can be used for the treatment of herpes. The Design of Experiments methodology was utilized to find the optimal formulation using a full factorial design with four different variables: citric acid (A), sodium bicarbonate to citric acid molar ratio (B), PVP k30 (C), and PEG 6000 (D). The studied responses were hardness, friability, pH, and effervescence time. The tablets were prepared by dry granulation, while the excipients of choice were citric acid, sodium bicarbonate, mannitol, sucrose, povidone k-30, PEG 6000, and flavoring agents. Additionally, post-compression studies included effervescence time, water content, solution pH, carbon dioxide content, and taste evaluation.[36] The amount of sodium bicarbonate and citric acid in this formulation, along with the appropriate 3 : 1 ratio of sodium bicarbonate to citric acid, allowed for a good effervescence period (98.33 seconds) and a suitable pH (4.67). This formulation also exhibited good friability (0.55%) and hardness (77.25 N). Consequently, it was concluded that the prepared effervescent tablet had the ideal qualities to make oral valacyclovir delivery easier.[36]

A traditional Chinese medicine, Xianganfang, was fabricated with fresh juice, for the treatment of chronic gastritis by Dong.[6] The tablets were prepared using a semisolid 3D printer with three cartridge holders to separate acid and alkali sources by drug paste through model design. HPMC hydroalcoholic gel, PVP ethanol solution, sodium bicarbonate, tartaric acid, and mannitol were the other components. Moreover, a freeze-drying method was used to remove water from fresh juice to prepare the drug powder for 3D printing. Furthermore, physical and qualitative parameters such as the identification of *Phyllanthus emblica* and licorice as active substances from Chinese traditional medicine were examined. The results demonstrated that all tablets disintegrated completely within 5 minutes, the drug content did not change during storage, and the preparation by 3D printing did not require the environment's moisture control. The authors declared that 3D printing has the advantages of flexibility, less time consumption, and small batches, and can avoid the tedious steps of granulation, tableting, excessive excipients, and premature effervescence.[6]

Huang and colleagues[37] formed antioxidant-effervescent tablets of astaxanthin-loaded microcapsules. Firstly, microcapsules were prepared by layer-by-layer (LBL) self-assembly and freeze-drying techniques, while vitamin E acetate, astaxanthin oleoresin, sodium caseinate, and κ-carrageenan were the rest, apart from the active component, of the microcapsule's ingredients. The rheological and morphological features as well as the encapsulation efficiency (EE) of the microcapsules were examined. In particular, SEM images revealed that a block aggregate was formed consisting of the complex formed by sodium caseinate and κ-carrageenan that was 'wrapped' with astaxanthin oleoresin. Moreover, FTIR analysis highlighted that the self-assembly might be due to electrostatic adsorption and hydrogen bonding. In addition, good encapsulation ability was found based on the calculated EE of all the prepared astaxanthin-containing microcapsules that was greater than 85%. The tablets were prepared by wet granulation, and the list of excipients consisted of citric acid, sodium bicarbonate, PEG 6000, PVP K30 anhydrous sodium, carbonate, aspartame, strawberry essence, and magnesium stearate. Furthermore, post-compression studies exhibited a dissolution rate that reached 90% after 2 hours, whereas according to an *in vitro* cytotoxicity assay, the cell viability was greater than 90%. Microcapsules improved the water solubility, stability, and oral bio-accessibility of astaxanthin, which is a lipophilic drug. Also, effervescent tablets can further enhance the stability, smell, and taste of microcapsules and are easier to be accepted by patients.[37]

The scientific group of Wang[38] formulated delayed-release effervescent tablets of stiripentol enteric solid dispersions. Xanthone, Eudragit L100, lactose monohydrate, mannitol, povidone K30, sodium carboxymethylcellulose, anhydrous

citric acid, and sodium bicarbonate were the selected excipients. The solid dispersions were manufactured by solvent evaporation, and the tablets were prepared by dry granulation because of faster disintegration and greater hardness. Additionally, solid-state characterization, stability, and quantification studies were conducted. Post-compression tests indicated an approximately 90% dissolution rate within 30 minutes in intestine-simulated medium, while the bioavailability was as high as 139% compared to that of STP suspension. The oral formulations encompassing enteric solid dispersions combined with effervescence technology possess excellent performance in enhancing the dissolution rate, stability under acidic conditions, and drug absorption and are expected to become a promising approach to solving stability, solubility, and permeability problems.[38]

Hydrogen-generating tablets were prepared as an emerging treatment for diseases related to inflammation and oxidative stress by Rosch *et al.*[39] The study investigated the effects of different polysaccharides on the morphological, mechanical, and disintegration properties of the formulation. The list of excipients comprises magnesium powder, ascorbic acid, Citrocoat® N, maltose, mannitol, lactose, dextrates, sodium stearyl fumarate, and adipic acid. Moreover, the optimal method of preparation was dry granulation, as it is suitable for avoiding segregation during mixing. Afterwards, disintegration, porosity, hydrogen generation, magnesium content, and stability studies were conducted. Mannitol was found to be superior to other polysaccharides and promoted far more rapid hydrogen generation combined with acceptable mechanical properties. Data from the dynamic vapor sorption tech-

Table 2 Excipients used for the formulation of effervescent tablets

Excipient	Role	Added value for the encapsulated API	Ref.
Citric acid	Effervescent agent	Fast disintegration of the tablet	38
Sodium bicarbonate	Effervescent agent	Fast disintegration of the tablet	38
Eudragit L100	Polymer	Controlled release	38
Lactose monohydrate	Filler and binder	Sufficient hardness and good disintegration properties of the tablet	38
Povidone K30	Polymer and binder	Agent for dispersing and suspending APIs	38
Sodium carboxymethylcellulose	Binder	Agent for dispersing and suspending APIs	38
Magnesium powder	Effervescent reaction	Partition in the reaction to produce H_2	39
Citrocoat® N	Effervescent reaction	Partition in the reaction to produce H_2	39
Ascorbic acid	Antioxidant	Protection of the API from oxidation during manufacturing and storage	39
Maltose	Filler and sweetener	Fast disintegration and taste masking	39
Mannitol	Filler and sweetener	Fast disintegration and taste masking	39
Lactose	Filler and sweetener	Fast disintegration and taste masking	39
Dextrates	Filler and sweetener	Fast disintegration and taste masking	39
Sodium stearyl fumarate	Lubricant	Avoidance of delayed disintegration and tablet quality problems such as sticking	39
Adipic acid	Lubricant	Avoidance of delayed disintegration and tablet quality problems such as sticking	39
Eudragit® RS 100	Polymer	Controlled release and taste masking	14
Carbopol 934 P	Polymer and binder	Controlled release	14
Talc	Lubricant, glidant, and diluent	Enhancement of the powder flow properties and avoidance of tablet quality problems such as sticking	14
Magnesium stearate	Lubricant	Avoidance of tablet quality problems such as sticking, decrease in tablet hardness, and increase in disintegration time	14
Avecil 102	Direct compression filler	Efficient dry blending of ingredients and production of tablets with appropriate formulation properties such as high hardness and low friability	14
HPMC 90SH 15.000	Retardant and swellable hydrophilic polymer	Controlled release	30
Microcrystalline cellulose	Binder and diluent	Improvement of formulation characteristics of the tablets such as compressibility, disintegration time, hardness and friability	30
Karaya gum	Retardant and swellable hydrophilic polymer	Controlled release	30
Tartaric acid	Effervescent agent	Fast disintegration of the tablet	6
HPMC hydroalcoholic gel	Binder	Assistance in binding the pastes in the 3D printing method	6
Polyethylene oxide WSR 303 (PEO)	Polymer	Controlled release	11
Sodium bicarbonate	Effervescent agent	Retardation of the API release rate from the hydrophilic matrix and improvement of the tablet floating	11
Kyros T-314	Superdisintegrant	Fast disintegration of the API	24
PVP	Synthetic polymer and binder	Agent for dispersing and suspending APIs	19
PEG 6000	Polymer and solvent	Increase the aqueous solubility of APIs	19
Sucralose	Sweetener	Taste masking	19
Propyl alcohol	Solvent	Dissolving hydrophilic APIs	33
Sodium benzoate or propylene glycol	Lubricant	Avoidance of tablet quality problems such as sticking, decrease in tablet hardness, and increase in disintegration time	33
Citrous oil	Flavoring agent	Taste and smell masking	33

nique suggested that the investigated mannitol/adipic acid-based formulation was stable for at least 14 days at 25 °C and 60% relative humidity (RH). The experiments showed that the tablets need adequate packaging and controlled environmental conditions during processing and packaging.[39]

Three-dimensional (3D) printing technologies have been applied to effervescent and dispersible tablets. Recently, Hong *et al.* (2021) developed multicompartmental dispersible tablets containing levetiracetam-pyridoxine hydrochloride using the binder jet 3D printing technique. The printing layers played a key role in the control of the API dose due to the surface morphology and the porosity of the systems, which allowed the immediate disintegration in the mouth accompanied by rapid drug release.[40] Another example from the recent literature is the preparation of efavirenz dispersible formulation for children diagnosed with HIV using selective laser sintering 3D printing. The porous structure and the small dimensions of the final dosage forms allowed the parental route of administration in the feeding tubes.[41]

Conclusions

This review deals with the recent advances in the technology of effervescent tablets. It also summarizes their advantages and drawbacks. Besides, the latest literature examples are thoroughly presented emphasizing on novel developments that exploit effervescence technology to overcome existing limitations. The excipients that are selected for this purpose are also highlighted.

As has been already mentioned in the Introduction section, the main mechanism of action of effervescence technology is gas liberation using appropriate excipients. Considering the latest literature, the different developments could be separated into immediate and modified release. In the former case, the research focuses on fast disintegration of the dosage forms and suitable formulation characteristics *via* selection of specific excipients and optimization of their ratio by DoE or usage of innovative methodologies for their production such as 3D printing. In some cases, scientific works emphasize on specific dosage forms such as microcapsules or enteric solid dispersions to overcome the barriers of this technology. Regarding modified release formulations, prolonged retention in the stomach or saliva by floating or targeted delivery in the gastrointestinal tract is intended. Moreover, there are research works combining effervescence with the use of polymeric matrices or ultrasound technology. It was, also, highlighted that effervescence could be applied by producing H_2 bubbles instead of CO_2 as well.

The population graphics of the use of effervescent formulations by different ages are quite interesting in comparison with other formulations. For example, a French cross-section study showed that the effervescent formulations are the most popular formulations during self-medication for 95.3% of paracetamol, aspirin, vitamins, and betaine, especially for male patients in all age ranges.[42] According to the reflection paper, formulations of choice for the pediatric population, released from EMA, "As effervescent tablets normally contain high sodium and/or potassium ion concentrations, they may not be suitable for all patients, *e.g.*, those with renal insufficiency".[43] Last but not least, effervescent formulations are the choice for those patients with swallowing difficulties—dysphagia, which is a problem mainly associated with children and elderly.

These formulations could be utilized in various diseases, such as diabetes, improving the intrinsic properties of the APIs, manipulating their pharmacokinetic profile, and their overall therapeutic effect. Gastro-retention, prolonged drug release, as well as gastrointestinal targeted therapy were not only the main goal for most of the aforementioned developments but also their main asset. We believe that effervescence mechanisms in combination with innovative manufacturing processes could lead pharmaceutical technology a step forward towards meeting patients' needs (Table 2).

Author contributions

Paraskevi Chatzidopavlaki: formal analysis, investigation, and writing – original draft. Efstathia Triantafyllopoulou: writing – original draft and validation. Natassa Pippa: conceptualization, methology, validation, supervision, and project administration. Georgia Valsami: conceptualization, methology, validation, supervision, and project administration. Paraskevas P. Dallas: conceptualization, methology, validation, supervision, and project administration.

Data availability

This is a review article, and no new data were generated or analyzed in this manuscript. All data discussed in this review manuscript are available in the original published papers.

An extensive search was performed in the electronic databases PubMed, Scopus, and Google scholar for English-language publications. The publications from the past five years (2018–2023) served as a comprehensive guide for the systematic investigation of effervescent tablets. The authors performed the literature search excluding the studies with full text unavailable, publication language other than English, and conference abstracts. After the screening of titles and abstracts, 30 full-text studies were included in the part of recent advances of effervescent tablets.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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