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Review

Flavor Microencapsulation for Taste Masking in Medicated Chewing Gums—Recent Trends, Challenges, and Future Perspectives

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Abstract: Chewing gum, being a pleasant formulation, requires effective taste-masking techniques, such as encapsulation methods along with an amalgamation of flavors and sweeteners. Taste-masked medicated chewing gum offers a palatable way of administering drugs and dietary supplements to children and old-aged people. The concept of chewing gum development provides a sustained and modified release of actives through various techniques, such as microencapsulation, cyclodextrin-complexation, buffering agents, ion exchange resin, solid dispersions, effervescent agents, etc. The taste, solubility, and stability of the active ingredient are the key parameters to be kept in mind, while formulating a medicated chewing gum. Flavor microencapsulation has been used as a crucial technology in the research and food industry to control sensory performance as demonstrated by the hefty number of chewing gum patents over the years. This manuscript provides an insight into conventional and novel taste-masking techniques employed in developing palatable chewing gums. Additionally, concepts of flavor microencapsulation, its applications, polymers, and patents have been discussed.

Keywords: flavor microencapsulation; upfront release; flavor-changing chewing gum; Tastech; Flavor8®; time-intensity sensory analysis

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1. Introduction

Many drugs are extremely bitter or have other aversive attributes, which can make formulating palatable drug products, such as medicated chewing gum, a daunting challenge. Furthermore, limited research associated with sensory principles within the pharmaceutical industry has hindered the development of palatable drug products. This leads to poor patient compliance [1]. Thus, taste disguising has become a precondition for unpleasant drugs to enhance patient compliance, particularly in the pediatric and elderly population [2].

Various physical and chemical methods frequently used for taste masking involve solid dispersion systems, ion exchange resin, complexation, effervescence, etc., which avoid contact of the taste palate with bitter drugs [3]. Simple incorporation of a sweetening agent/flavoring agent is not sufficient to mask the bitter taste of the drug. A perfect taste-masking method can be achieved by applying an amalgamation of special taste-masking techniques, such as microencapsulation and the use of flavors. The concept of microencapsulation of flavors in chewing gums has been a crucial technology to regulate sensory performance, such as taste masking, flavor enhancement, sequential, delayed, or controlled release and the long-term shelf-life protection, such as handling, and safety of

raw flavor materials [4]. This manuscript discusses the most common microencapsulation technologies used in medicated chewing gums, prospects of flavor microencapsulation, their patents, and patented technology platforms.

2. Taste Masking of Chewing Gums—Conventional Methods

Medicated chewing gum act as an extended-release formulation that delivers a constant release of the contained drug. This elegant, non-invasive drug delivery system could be a boon in treating localized oral disease. There is a monograph in European Pharmacopoeia that defined the term "chewing gum" as a pharmaceutical dosage form in 1991. It provides a sustained release of the drug after a normal chewing time, i.e., 15–30 min. However, it poses certain problems, as continuous chewing may cause temporomandibular joint disorder. Medicated chewing gum has been exploited for various drugs, such as cetirizine, dextromethorphan hydrobromide, dimenhydrinate hydrochloride, nicotine, antacids, miconazole, aspirin, caffeine, antimicrobial decapeptide, ondansetron hydrochloride, and nystatin, etc. [5]. It provides both local as well as systemic benefits after permeation through the buccal mucosal or from the GIT. The physiochemical characteristics of a drug, such as aqueous solubility, pKa value and partition between gum/saliva, chewing time, chewing frequency, and impacts to the release of drugs from the gum, are some important parameters that should be considered [6]. Chewing gums have a fast onset of action with pleasant taste and high bioavailability. The mechanism of drug release from chewing gum is shown in Figure 1. It contains two portions, one is a water-insoluble gum base portion (elastomers, plasticizers or fillers) and the other is a water-soluble bulk portion (active constituents, sweeteners, flavors, anti-tack agents). Elastomers offer flexibility and maintain the gluey texture. Fillers control chewability and impart texture. Various colorants and dyes are used to impart colors and aesthetic appearance to chewing gum. Sweeteners provide the taste masking for bitter drugs present in the gum and can be used as a softener to mix the constituents and preserve moisture. While, flavors are used to improve aroma [7].

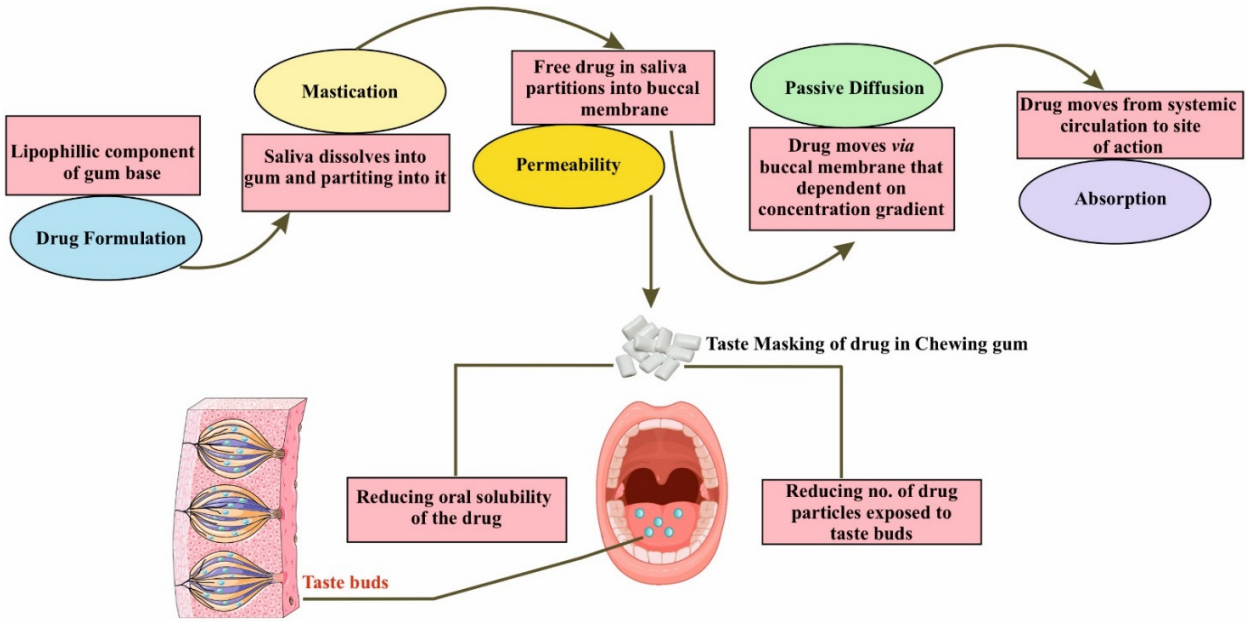

Figure 1. Mechanism of drug release and taste masking in chewing gums.

Taste masking may be described as minimizing the detection of a disagreeable taste that would somehow exist [8]. The poor palatability and bitter taste are one of the main reasons for noncompliance with chewing gum formulations [9]. On chewing, the drug partitions into saliva; making taste masking important is done so that the bitter perception of the drug can be reduced. Earlier, Guo and Singh [10] reviewed several emerging strategies, such as the structure of oral mucosa and the basic conditions of mucosal adhesion, and

several of the bio-adhesive materials commonly used for oral mucosal administration and oral mucosal adhesion products that have been released into the market. Several peripheral interactions can happen when one compound would interfere with the taste signal mechanism related to another compound, which might lead to taste modification [11]. The common methods are discussed below.

2.1. Sweeteners and Seasoners

It is imperative to understand that only the water-soluble portion of the drug can produce a taste sensation. The use of sweeteners and flavors is the underlying taste-masking technique, particularly for pediatric formulation. This method however is not very fruitful for extremely bitter water-soluble drugs, antibiotics, etc. [12]. These include dextrose, maltose, dextrin, sorbitol, starch hydrolysates, xylitol, sucrose, fructose, galactose, corn syrup, sucralose, aspartame-acesulfame salt, alitame, saccharin, glycyrrhizin, etc. Various natural and artificial flavoring agents used to improve aroma include spearmint oil, mint oil, clove oil, ginger oil, cola, fruit flavor, etc. A chewing gum formulation containing a gum base, active component, polymers, and one or more sweetening and flavoring agents was patented [13]. One study was done to evaluate the effect of sweeteners like stevia and xylitol chewing gums on salivary enzyme streptococcus mutans count [14]. Cho et al. [15] developed a sweetened masticatory chewing gum comprising antihistamines to alleviate its side effects, including dizziness and dryness of the mouth. Shaikh et al. [16] attempted to formulate a chewing gum for dolasetron containing a gum base with fillers, sweeteners, coloring agents, plasticizers, and antioxidants that provide elegance and stability. Almelh et al. [17] patented an anesthetic chewing gum to alleviate pain from orthodontic surgical treatment, which contains Prilocaine HCl and Lidocaine HCl as the anesthetic components, sweeteners, anti-adherents, lubricants, opacifiers, glidants, and flavoring agents. Birth control pills are being developed for women as spearmint flavored medicated gum, Femcon-Fe [18]. Parouha et al. developed a taste masked medicated chewing gum of Disulfiram using various compositions of dextrose and castor oil in order to enhance its taste, softness and release [19]. The limitations of this method open new realms for flavor and sweetener microencapsulation for prolonged palatability of the gum, which is discussed later.

2.2. Ion Exchange Resins

They are versatile and receive significant attention from researchers as drug delivery carriers. They find applications in developing various immediate and sustained-release oral formulations, such as medicated gums. Bitter drugs combine with ion exchange resins and remain intact at salivary pH 6.8, thus making the drug unattainable for taste perception. These resins release the drug only at acidic pH, which is present in gastric conditions. The ion exchange resins extensively used for taste masking are Amberlite IRP69, Amberlite IRP64, Indion 214, Indion 204, Kyron T-104, and Kyron T-114. The formulation and in vivo release of ion-exchange resins are shown in Figure 2 [20]. Marzouk et al. made an effort to formulate taste-masked Levocetirizine (LCZ) chewing gum employing Kyron T-114 (Ion-Exchange Resin). This taste-masked composite was then developed into medicated chewing gum by using directly compressible gum base Health in gum® along with PEG-400 as a plasticizer. Secondly, it was also taste masked by using Cyclodextrin-complexation method, using Kleptose to overcome its poor taste and release. Then, chewing gums were prepared to employ the taste-masked drug, directly compressible gum base, and a plasticizer, such as glycerol or soy lecithin. The formulated gums were evaluated for content uniformity, physicochemical properties, and drug release [21]. Muthukaumar et al. developed dextromethorphan hydrobromide and guaifenesin chewing gum with Kyron T-114 (ion-exchange resin) in order to mask its bitter taste and enhance its release [22].

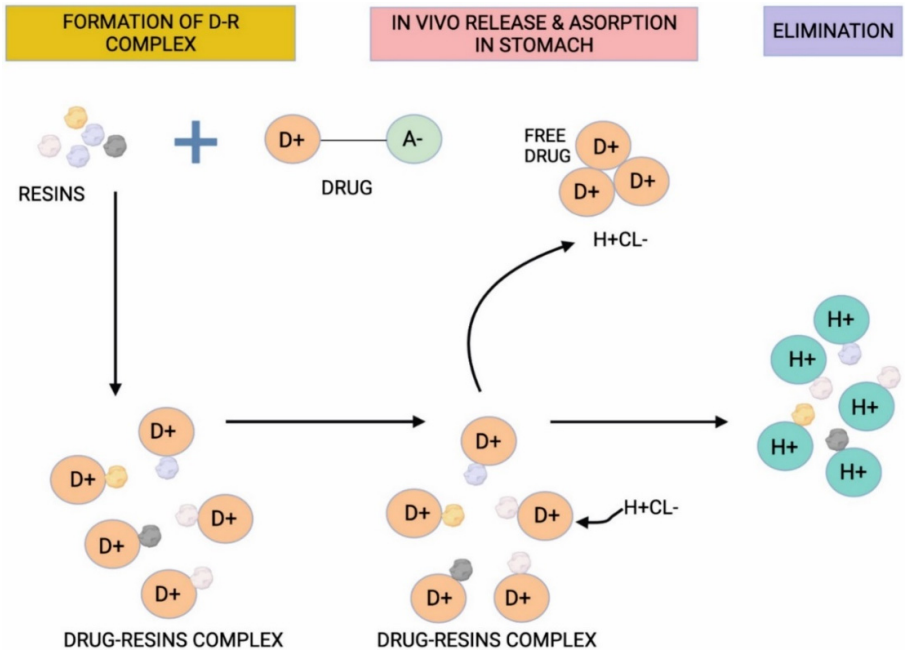

Figure 2. Formation and in vivo release mechanism of ion-exchange resins.

2.3. Inclusion Complexation

Inclusion complexation involves enclosing the guest molecule inside the void of a host or complexing agent. This technique masks the bitter taste of drugs by preventing their contact with taste buds thereby decreasing the bitter taste sensitivity [23]. The most commonly used complexing agent is cyclodextrin, which is a sweetened, non-toxic, cyclic oligosaccharide obtained from starch. The cyclodextrin molecules have a unique structure with a hydrophobic cavity and a hydrophilic surface in which a guest molecule can be entrapped [24]. Cyclodextrin can form an inclusion complex with a wide variety of solid, liquid and gaseous compounds. α-cyclodextrin, β-cyclodextrin, and γ-cyclodextrin are three important types of cyclodextrins, which are composed of six, seven, and eight glucose units, respectively. β-cyclodextrin (β-CD) is the most commonly used type of cyclodextrins due to its lower price and economical production [25]. Andersan et al., [26] developed chewing gums employing beta-cyclodextrin–inclusion complexes with Cetirizine to mask its bitter taste. Therefore, attempts were made to mask the unpleasant taste, recognize the reason for the loss of its stability and discover approaches for countering the problem. Various formulations were prepared by varying the drug-complexing agent ratio and studied for taste abatement potential. Stojanov et al., studied the efficient effect of cyclodextrins on taste and release of the drug. Various complexes were prepared from α-, β- and γ-CD using different molar ratios. It was observed that the presence of cyclcodextrin enhances the cetirizine release from chewing gum (up to 75% after 8 min of chewing) [27].

2.4. Effervescent Agents

Effervescent agents have been used for a long as taste-masking agents for oral formulations, such as powders, granules, gums, lozenges, etc. They contain active ingredient(s) and a combination of sodium bicarbonate and acids, which release carbon dioxide when dissolved in water [28]. Lombardy et al. [29] patented a novel effervescent chewing gum that polishes teeth and freshens breath. The inventive chewing gum comprised a sodium bicarbonate gum base encapsulated with a citric acid coating, which upon chewing releases CO_2. The coating may also contain TiO_2 as a product whitener. The medicated chewing gum patented by Niazi et al., [30] was developed containing phenylpropanolamine hydrochloride and chlorpheniramine maleate, which includes a chewing gum base, a taste masking effervescent agent, and willingly a taste bud numbing agent, such as benzocaine,

spilanthol, etc. Some of the examples of the medicated chewing gums taste masked by various technologies are discussed in Table 1.

Table 1. Taste masking of Medicated Chewing gums by different techniques.

Drug	Taste-Masking Techniques	Excipients	References
Levocetirizine dihydrochloride	Cyclodextrin-complexation and ion exchange resins	Kleptose, Captisol, Kyron T-314, Kyron T-154	[21]
Nicotine	Spray-dried microparticles using bioadhesive polymer	Nicotine bitartarate, Hypromellose, alginate, mannitol	[31]
Caffeine	Co-encapsulation of caffeine with sweeteners and coating with water-insoluble or water-soluble polymers	Zein, shellac, HPMC, gelatin, Gum Arabic, Corn syrup, dextrose, thaumatin, alitame	[32]
Magnolia bark	Use of flavors	Peppermint oil	[33]
Cetirizine	Inclusion- complexes with sweeteners & flavors	β-cyclodextrin, aspartame, menthol, peppermint flavor, and vanilla flavor.	[34]
Oral hygiene gum	Effervescent agents	The core contains bicarbonate and the coating contains encapsulated edible acid (citric acid)	[29]
Phenylpropanolamine HCl	Effervescent agents, taste bud desensitizing agents, sweeteners, and flavors	Benzocaine, spilanthol, corn syrup, mannitol, spearmint flavor, sodium bicarbonate, tartaric acid NutraSweet	[30]
Nystatin	Solid dispersion	PEG 4000, liquid sorbitol, xylitol, aspartame, oily flavors	[35]
Metformin	Drug mixed with sweeteners mixture followed by spray drying or freeze-drying (Microencapsulation)	Glycerin, aspartame, sodium saccharin, potassium -acesulfame, spearmint essence	[36]
Aloe vera	Sweeteners & flavors	Aspartame, maltitol, xylitol, eucalyptus, peppermint, banana	[37]
Scletium tortuosum	Sweeteners & flavors	Xylitol, mannitol, sorbitol, cherry flavor	[38]
Salvia divinorum	Alkaline buffer, sweetening agent, encapsulating buffer	-	[39]
Nicorandil	Sweeteners & flavors	Sucralose, aerosil, sorbitol, vanillin	[40]
Dextromethorphan HBr	Spray-dried microparticles (Microencapsulation)	Dextromethorphan, sucralose, aerosil dispersed in ethanol	[41]

3. Potential of Microencapsulation in Chewing Gum-Types, Aspects and Prospects of Flavor Microencapsulation

The bitter taste of a drug in the formulation of a chewing gum is the biggest hurdle in chewing gums. Flavor microencapsulation technology is the most economical and commonly employed method in a chewing gum's bitter taste. It is currently an active field of research and it has numerous applications in drug formulation and confectionery so as to deliver the colorants, flavoring agents, or vitamins at the right time, in the right quantity, and at the right rate. The most important aspect for research and development of flavor microencapsulation is to understand how industrial constrain and requirement to make microencapsulation technology viable; and transition of laboratory scale to pilot scale production and marketing of finished product. There are several problems related to the

microencapsulation of flavor and sensitive ingredients; therefore, flavor formulators and microencapsulation processors must make use of appropriate encapsulation materials and techniques. Sometimes different release profiles— chewing style differences, drug dilution, bad aftertaste, uneven release, interaction of drug and other ingredients—pose a problem. Certain flavoring agents are volatile in nature so their stability and interaction with other gum components need to be taken care of. At that point of time, microencapsulation of ingredients plays a pivotal role [42]. Microencapsulation involves the coating of tiny dews of solid or liquid material with a layer of polymer. Micro-coating is a really useful technique for the fabrication of constant-release gastro-intestinal dosage forms, disguising the unpleasant taste of drugs, and encapsulating flavors and sweeteners for sustained palatability. Various encapsulation methods involve spray drying, spray cooling, fluidized bed drying, lyophilization, etc. The mechanism of microencapsulation is shown in Figure 3 [43]. Taste masking can be done by decreasing the solubility of the drug in saliva by coating it with an appropriate polymer as only the soluble fraction of the drug can generate taste sensation. Mehta et al., [44] formulated and evaluated Diphenhydramine Hydrochloride medicated chewing gum via an eco-friendly gum base Corn -Zein for treatment of motion sickness. Taste disguising of bitter drugs can be done by using various combinations of polymers such as cellulosic polymers, polyvinyl acetate, and water-soluble polymers such as hydroxyethylcellulose, polyvinylpyrrolidone by using various techniques, such as coacervation—phase separation, spray drying, etc. In a study by Sander et al., [31] the possibility of the spray drying technique in the formulation of Nicotine Bitartrate chewing gum was explored. The drug was coated with polymers, such as hypromellose or alginate, and then compressed into gum tablets. Swami et al. [41] formulated Dextromethorphan hydrobromide chewing gums by using a directly compressible gum base. It was then renewed into spray-dried form and mixed with Pharmagum M, a directly compressible base, to enhance solubility and to mask the bitter taste of the drug. One such Metformin gum was formulated by Mostafavi et al. to overcome its side effects counting abdomen discomfort, vomiting, diarrhea, etc. [36]. The drug was mixed with suitable sweeteners and the mixture was freeze-dried and spray-dried using diverse polymers or excipients. Then, the gums were evaluated for taste masking effects by employing human volunteers. Mohammadi et al., microencapsulated caffeine by the emulsion technique in order to control its release from the medicated chewing gum. The coating material used was alginate derived polymers. The prepared microcapsules showed a great potential for controlling the release and the bitter taste of caffeine [45].

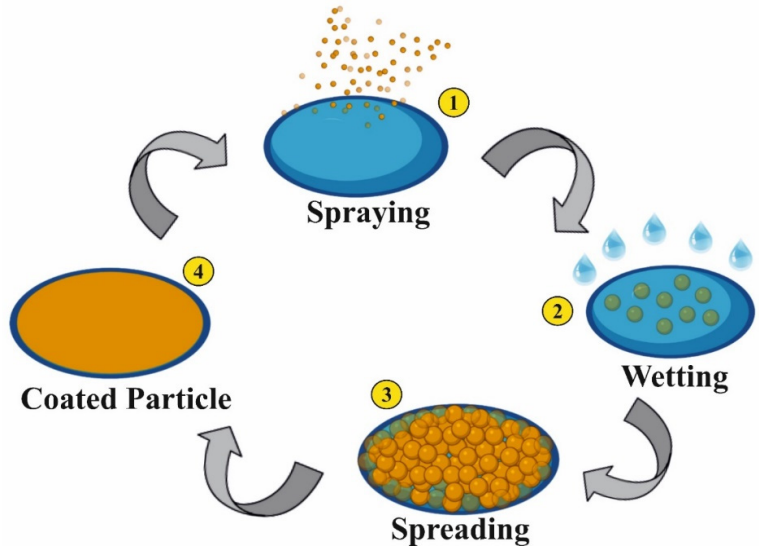

Figure 3. Mechanism of microencapsulation.

The flavor industry uses various microencapsulation technologies in the preparation of chewing gums and other confectionery products. The distinctive features of the gums are provided by selecting the suitable microencapsulation technique and particle size distribution of the flavors used. The larger particles and irregular distribution of flavor in mastication gum provide increased essence perception. In addition, the use of liquid flavor in chewing gum delivers a continuous level of flavor sensitivity. From a perception viewpoint, the flavor is constantly released with less flavor perception as the chewing time is increased [46]. The microencapsulated flavor is localized over a confined space in the gum and released during mastication to provide a "flavor gust" effect, thus providing a high sensory perception over a long chew time. Optimized combinations of liquid flavor with microencapsulated flavors deliver distinctive sensory performance over chew time. Liquid flavor provides a blunt flavor release whereas constant or successive release is provided with many microencapsulated forms. The flavor loading concentration has to be controlled to provide a robust flavor perception without flavor charring. The major attributes of flavor microencapsulation obtained from various methods are described in Figure 4 and the majorly used methods, i.e., spray drying and cyclodextrin-complexation has been briefly discussed [47]. The amount of coating in microencapsulated flavors provides the anticipated release and protection needed. Many flavors being non-polar, employ a polar coating material, such as proteins, gums, solid fats, etc. [48]. The drug coated with an emulsifier is released in saliva due to various mechanisms, including heat or chewing. Various coating polymers ratified for chewing gum applications are cellulose, lactose polymers, polyvinyl-pyrrolidine (PVP), modified starches, etc. [49]. The flavors are encapsulated into a carrier matrix for their effective and first-line treatment [50].

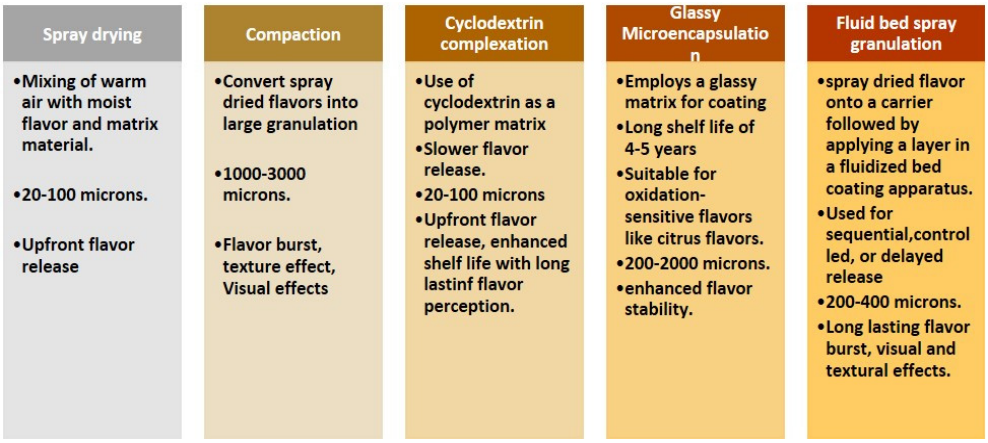

Figure 4. Properties of Flavor Microencapsulates from different techniques.

When compared to other encapsulation methods, spray drying is a simple and economical method. Spray drying is an extensively used technique for the conversion of emulsions, solutions, suspensions, and dispersions into a dry powdered form. Notably, thermo-sensitive and volatile flavors and fragrances could be spray-dried without loss of activity [51]. A variety of polymer matrices or their combination can be chosen for the encapsulation process taking into account the preconditions of the formulation. The common polymers used are discussed in Figure 5 [52]. The choice of encapsulating materials is usually determined by various objectives, such as flavor masking, controlled release, or ingredient protection. Various flavors and essential oils have been microencapsulated, such as peppermint oil, caraway oil, limonene, coconut oil, chia seed oil, etc., to enhance the stability and utility of flavors [53]. The ideal properties of a good polymer are inert, compatible with excipients, economical, bland taste, stable, GRAS status (generally recognized as safe), film-forming ability, and solubility in a suitable solvent. The encapsulation efficiency of the microparticle or microsphere or microcapsule depends upon different factors, such

as concentration of the polymer, solubility of polymer in solvent, rate of solvent removal, solubility of organic solvent in water, etc.

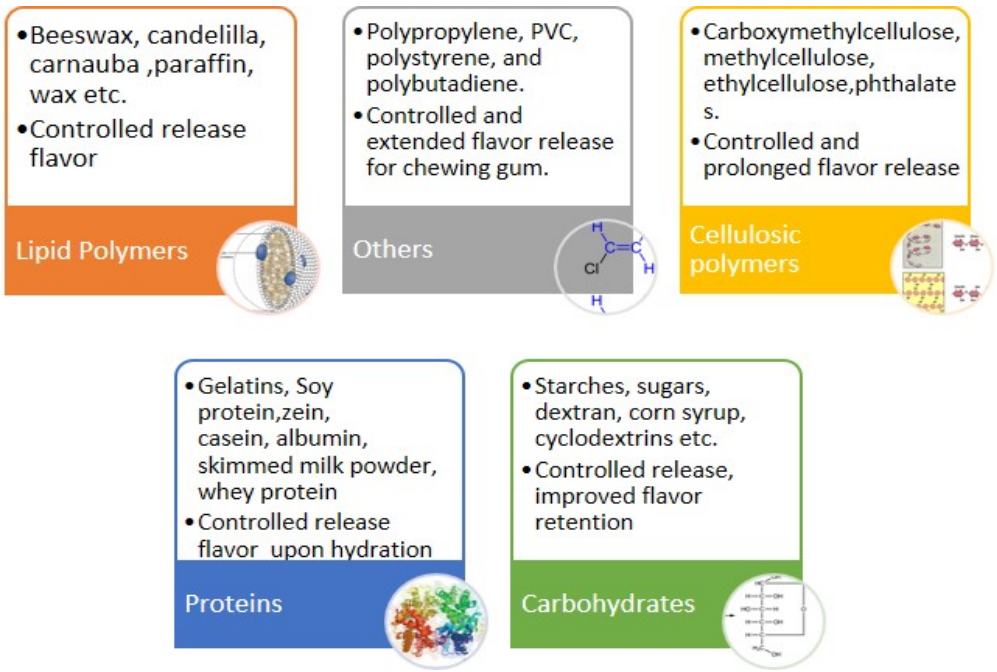

Figure 5. Polymers used for flavor microencapsulation in Medicated Chewing Gums.

Cyclodextrins are oligosaccharides that are used to improve the stability of flavors and active ingredients through molecular encapsulation. Cyclodextrins form inclusion complexes by trapping the molecule in a cavity, thus protecting the wide variety of volatile flavors from environmental hazards [47]. Furthermore, they are being exploited as carriers for controlled release, timed release, and target release of active compounds [54]. The performance of these controlled-release inclusion complexes can be estimated by their release profile at various parameters of interest. Furuta et al., [55] confirmed that the alcohols of extreme polarity and short alkyl chain length improved the inclusion of *d*-limonene.

4. Taste Modification by Ingredient Encapsulation- Merits and Applications in Chewing Gums

There is abundant evidence that bioactive compounds, pharmaceuticals, flavors, sweeteners, salts and acids can be encapsulated within chewing gum (Figure 6). Chranioti et al. used Arabic gum, maltodextrin, and various modified versions of gum Arabic gum for the microencapsulation of saffron and beetroot extracts by encapsulation techniques such as freeze-drying. The microencapsulated powder was evaluated for color change during stowage at 40 °C for 10 weeks and water content. Then, this powder was fused into chewing gum. Gum Arabic and maltodextrin displayed maximum protection with water activities of 0.82 and 0.66, respectively. Furthermore, the chewing gum having gum Arabic-modified starch showed the greatest color stability [56]. Disguising undesirable taste and odor is the main objective in developing diverse formulations. To diminish the undesirable physicochemical attributes, the flavor components play a vital role [57]. Though, in certain cases, the use of flavor to achieve the desired sensory effect, cannot façade the offending constituents. So, encapsulation techniques have been employed to make a barrier around the bitter actives to lessen the initial perception of the undesirable characteristics.

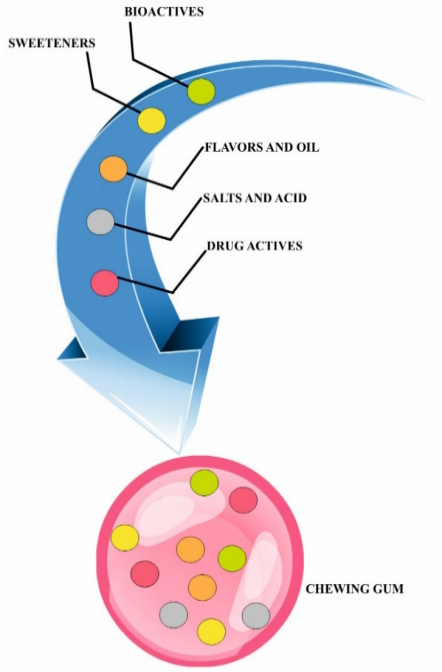

Figure 6. Graphic representation showing major ingredients employed in the formulation of encapsulated chewing gums.

Boghani et al. provided taste enhancement to the bitter active ingredient by using various taste potentiators. The active ingredient and/or taste enhancer was encapsulated using water-soluble sweeteners, 2, 4 -dihydroxybenzoic acid, and 3-hydroxybenzoic acid to alter the release rate and taste of the composition upon chewing. Flavoring and scenting agents are classified either as natural or artificial and are available as essential or volatile oils, fruit juices, distilled fractions, concentrated extracts, syrups, alcoholic solutions, etc. The bitter taste of extract comprising Pogostemi Herba is masked by using Xanthan gum and glycyrrhiza [58]. Flavors, along with Monosodium glycyrrhizinate, have been employed to disguise the harsh taste of guaifenesin. Al-melh et al., patented an anesthetic gum to alleviate pain from orthodontic surgeries, containing Prilocaine HCl and Lidocaine HCl as the anesthetic components. The anesthetic chewing gum also included sweeteners, anti-adherents, lubricants, opacifiers, glidants, and flavoring agents. The flavoring agents include peppermint oil and a flavor enhancer, such as menthol [17]. Various applications of microencapsulation are discussed below.

4.1. Bioactive Encapsulation

They are the extra-nutritional constituents, which provide beneficial health effects even at a low concentration [59]. To maintain the stability and release of the bioactive components in chewing gum formulations, the selection of the encapsulation matrix and method should be done accordingly [60]. Chewing gum can also be a suitable delivery system for a bioactive, as it provides persistent and controlled release patterns. In a study, Palabiyik et al., [61] used encapsulated pomegranate peel extracts in chewing gums (both sugar and sugar-free) and assessed the release kinetics of phenolic compounds after chewing. Both chewing gums, sugared and non-sugared, showed a greater release rate of phenolic compounds. They exhibited a 75.6 and 38.3% release of ellagic acid, 94.8%, and 82.5%, and release of punicalagin, for non-sugared and sugared gum, respectively. The greater release rate in non-sugared gum was ascribed to the interaction of phenolic compounds and sorbitol, which upsurged the release of phenolics. Potineni et al., reported that the release profile of cinnamaldehyde from a sugar-free chewing gum was correlated to the release of the sugar alcohol phase [62].

4.2. Sweetener Encapsulation

This microencapsulation of sweetener can disguise the disagreeable savor, and prolong the sweet sensation through a steady and controlled release [63]. To mend the stability, Pegg and Shahidi [64] encapsulated aspartame within a matrix composed of plasticizer and polyvinyl alcohol (PVA) and then employed it in chewing gum. Additionally, neotame was spray-dried with gum Arabic and maltodextrin, and the microcapsules obtained were combined to form chewing gums. Rocha-Selmi et al. [65] encapsulated aspartame using gelatin and gum Arabic (matrix formers) through binary emulsions, followed by complex coacervation. The obtained microcapsules were utilized in chewing gum. In a parallel study, Santos et al. used complex coacervation and dual emulsion techniques for co-encapsulation of menthol and xylitol to prepare microcapsules for chewing gum. It was stated that the microcapsules obtained were circular and a great encapsulation efficacy was accomplished. Time-intensity (TI) sensory analysis indicated a controlled release of xylitol and menthol, which provides a longer duration of cooling perception [66].

4.3. Flavor Microencapsulation

Flavor or essence is one of the most significant organoleptic aspects of chewing gum as it provides an immediate and long duration of taste perception during the whole chewing process [67]. In common, (PTR)-MS, APCI-MS, TI, IGC, and HS-SPME-GC/MS methods have been exploited to assess the controlled-release pattern of volatile components in chewing gums. The release of hydrophobic or hydrophilic flavor from chewing gum has been explored by scientists where they can be present as either droplets or in the dissolved form [68]. Upon mastication, initial burst release was created by the flavor droplets embedded in the hydrophilic matrix, whereas those dissolved in the hydrophobic regions caused a subsequent release. It was recommended that a flavor can provide either slow release or blunt release by distributing itself in hydrophobic or hydrophilic parts of the chewing gum.

In another study, Yoshii et al., [69] explored the menthol/γ-cyclodextrin (CD) complex release kinetics from chewing gum. The release mechanism from menthol followed Avrami's equation. The gum containing menthol/γ-cyclodextrin (CD) powder showed more efficiency in retaining menthol and a high activation energy as compared to its β-CD counterpart. It was proved that flavor in liquid form shows a better release rate as compared with the encapsulated. Flavor microencapsulation enables chewing gum formulators to control the palatability and performance of the formulation. Chewing gums with a unique flavor-changing attribute is necessary for longer-lasting perception and masking the bitter taste of the drugs. Flavor encapsulation slows down the interactions between chewing gum excipients and various environmental radicles. A stable dry powder is much easier to handle as compared to a volatile liquid flavor [48]. Chewing gum is a multidimensional delivery approach that has distinctive physicochemical properties characterized by a hydrophobic gum base core. The hydrophobic gum base binds with many lipophilic flavors, resulting in the slower release of flavor and thus poor palatability [70]. Chewing gums can contain flavor microcapsules; the core of which contains liquid flavor and the outer shell is composed of cross-linked proteins which strengthen the core material. The shell segregates the core from the gum base and will disrupt during chewing to release the flavor [71]. To sustain the release of the flavor, the gum is embossed with microcapsules filled with various flavoring oils. The flavor is released on chewing the gum and disrupts the shells of the microcapsules to release the flavoring oils as shown in Figure 7 [72]. Various advantages of flavor microencapsulation are described in Figure 8.

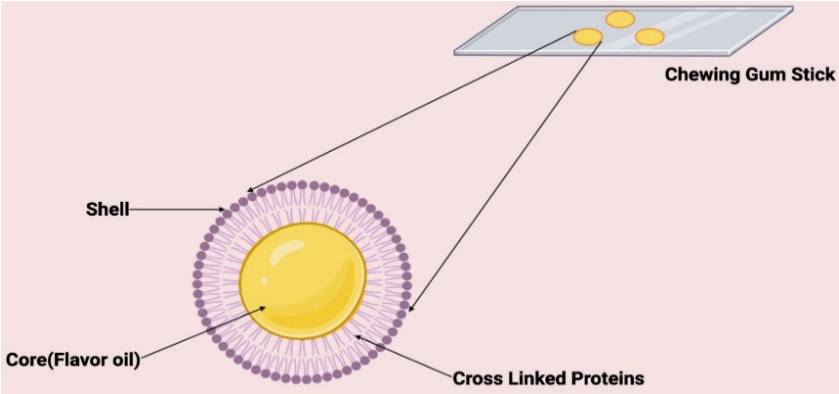

Figure 7. Flavor Microcapsule in chewing gums.

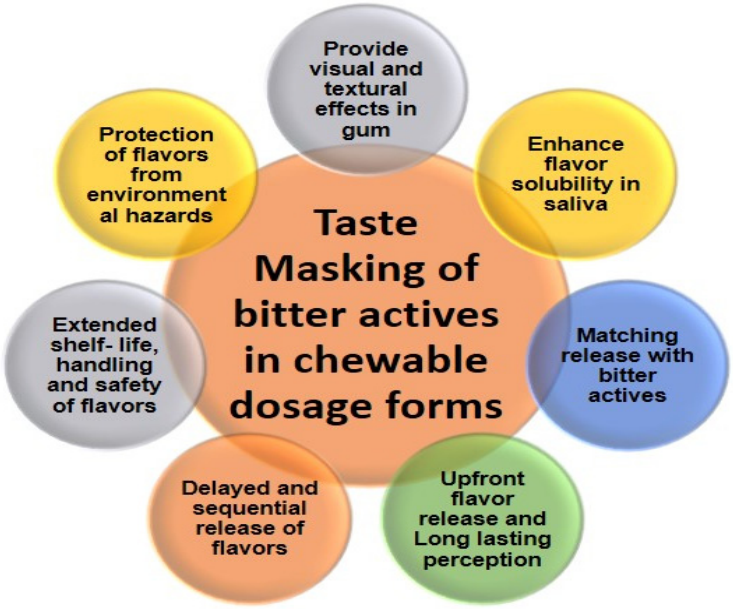

Figure 8. Advantages of Flavor microencapsulation in chewing gums.

4.3.1. Controlled-Release or Modified Release

The slow, fast, concurrent release of flavor in chewing gum determines the overall perceived palatability of the formulation. Chewing gum with a lipophilic gum base portion, a thermoplastic polyolefin polymer, and a coated flavor component was prepared. This polymer contributed to the chewing gum's brilliant texture, long shelf-life, and controlled release flavor quality. The polyolefin thermoplastic elastomer was selected from ethylene-octane copolymer, propylene-ethylene, ethylene-butane, or combinations [73]. The use of flavor in large concentrations may result in undesirable textural characteristics and unstable organoleptic features [74]. The encapsulated spray-dried flavoring minimizes these negative interactions between flavor and lipophilic gum base [75]. The controlled-release chewing gum of caffeine was formulated by Tyrpin et al., tangibly modifying caffeine's characters by spray-drying microencapsulation. The caffeine was treated by multiple steps, such as microencapsulation, agglomeration, absorption, etc. The treated caffeine was then co-dried and granulated to produce a modified-release active for use in chewing gum [32].

4.3.2. Multiple Flavors

A method of preparing a flavor-changing chewing gum was disclosed using multiple flavors out of which one is present in liquid form and the other is in encapsulated form. The

enclosed flavor may be formulated by using hydrophilic polymers, such as vinyl polymers, gums, polyesters, proteins, waxes, or their byproducts. As chewing gum is masticated, the flavor distributes within the saliva, giving the primary flavor perception. Then, the secondary flavor was released from the water-insoluble encapsulated polymer providing a slower release rate [76]. A chewing gum composition was developed by Lenzi et al., which included three flavors, providing enduring flavor perceptions and different release timings. The primary flavor starts to release when the gum is masticated, the second flavor was released after the release of the first flavor has ceased, and so on. The flavor includes various fruity and mint flavors. The chewing gum composition also comprised at least one crosslinked hydrocolloid, which encapsulates multiple flavors. The hydrocolloid was nominated from the group comprising alginates, hydroxypropyl methylcellulose, propylene glycol alginate, xanthan gum, konjac, carrageenan, gum Arabic, guar gum, pectin, gellan gum, pullulan, agar, carboxymethyl cellulose, gelatin, etc. [77].

4.3.3. Upfront or Blunt Flavor Release

Prompt and constant flavor release in chewing gum can be achieved by employing encapsulated flavor systems using hydrophilic carbohydrates that release the flavor instantly upon dissolution [75]. Other hydrophilic polymers comprising polyols, hydrocolloids, polysaccharides, and blends have also been revealed in several patents related to chewing gums [48]. The upfront release of flavors and sweeteners in Cetrizine chewing gum was done using inclusion complexation with β-cyclodextrin, aspartame, menthol, peppermint flavor, and vanilla flavor [33].

4.3.4. Sustained or Continual Flavor Release

The hydrophilic encapsulated flavors are relatively preferred for prompt release, as they are released in close coordination with the sweeteners. The discharge of flavor from chewing gum is also affected by the hydrophobicity of the flavor itself. The encapsulation materials having high hydrophobicity may retard the flavor release [78] and the flavor with hydrophilic material will be released from chewing gum more promptly.

4.4. Salts and Acids

The salts and acids can easily be incorporated into chewing gum for therapeutic action. To improve the enamel remineralization of hydroxyapatite crystals, fluoride can be added to calcium-containing chewing gum [57]. Kitasako et al., [79] evaluated the influence of fluoride and calcium salts containing chewing gums on crystallization and remineralization of enamel lesions and found a positive response. Abbasi et al., [80] examined the application of citric acid microencapsulation in chewing gum formulation by microwave technique. The microwave processing method was used to enclose the gum core with various materials, such as inulin and casein. The results revealed that various organoleptic features of chewing gums were amended by using inulin-microencapsulated citric acid as compared to free citric acid in the formulation.

4.5. Prophylactic Agents

Barry and Trogolo [81] efficaciously formulated a novel chewing gum preparation containing an antibacterial agent and an inorganic porcelain carrier for the treatment of various periodontal conditions, such as dental plaque, oral malodor, gingivitis, etc. An encouraging methodology was developed to formulate chlorhexidine digluconate chewing gum with a controlled release pattern [82]. The antibacterial bioactive was treated via numerous steps of agglomeration, encapsulation, and absorption. The co-dried bioactive fused into the gum provided a fast/delayed release mechanism during chewing. Similarly, Faraj et al., [83] established a peptide chewing gum containing an antiplaque antibacterial vehicle for sustained release. The formulation was stable in acidic conditions but suffered quick hydrolysis in the basic environment. It was discovered that the chewing gum system could be a promising approach for the delivery of prophylactic agents by providing a

suitable absorption mechanism, good stability, and constant release behavior. The examples of some of the ingredients encapsulated by various methodologies have been discussed in Table 2.

Table 2. Application of ingredients encapsulated in chewing gums.

Encapsulated Ingredients	Examples	Excipients Used	Encapsulation Techniques	Reference
Bioactives	Catechins	Polyvinyl acetate (PVAc)	Hot melt fluid bed coating and dispersion	[84]
	Pomegranate peels	Maltodextrin	Spray drying	[61]
Sweeteners	Aspartame	Polyvinyl alcohol	Freeze drying	[64]
	Aspartame	Gum Arabic and Gelatin	Double emulsions followed by complex coacervation	[65]
Flavors	Xylitol and Menthol	Gum Arabic	Combination of complex coacervation and double-emulsion technique	[66]
Salts & acids	Calcium and fluoride	Oligosaccharides	Spray drying	[79]
	Decapeptide	Hydroxyapatite	Inclusion- complexation	[83]

5. Flavor Microencapsulation in Chewing Gums—Patent Review

The solvents or diluents act as a vital part of the formulation of flavor systems. Water is a frequently used solvent to deliver a hydrophobic flavor system for the formulation of spray-dried microencapsulated flavors. The solvents must avert the flavor portion from segregating into the vehicle phase to avoid flavor loss in the careful vaporization of the solvent [46]. The flavor to matrix ratio is also an imperative factor affecting particle size and encapsulation efficacy. In common, the proportion of flavor to polymer material is approximately 1:4 [85,86]. The entire chewing gum and confection industry have been led by a few market troupes such as Warner-Lambert, Wrigley, Kraft Foods Global, Cadbury Adams, Hershey companies, etc. Some of these patents on applications of microencapsulated flavors and other confections in the chewing gum industry are discussed below and are given in Table 3.

Castro and Johnson, [78] made flavored chewing gums that have improved flavor retention using flavor encapsulation. The invention was useful for all types of flavors but was preferred for volatile flavors. The invention was a method of encapsulating flavor comprising various encapsulating ingredients, such as acacia gum, corn syrup, gelatin, etc. Song et al., [87] patented a composition for enhancing the duration of flavor in chewing gum. The invention utilizes a cellulosic matrix conjoined with a multi-factorial carboxylate to yield a low water-soluble polymer matrix. This polymeric matrix was ground and mixed with a flavor to be used in chewing gum compositions to assist a sustained release of the flavor. Cherukuri et al., [74] invented chewing gum using microencapsulated flavoring agents prepared by complex coacervation. The invention pertained to the formulation of spheroidal microcapsules comprising a flavor emulsion in the core with a resin and a coating film of hydrocolloid materials (a mixture of gelatin and gum Arabic) over the core. The microencapsulated flavor used was peppermint oil and the resins used were glycerol ester of partially hydrogenated wood rosin. Caroll et al., [76] patented a masticatory gum formulation with multiple flavors having an incessant release, containing a lipophilic gum base portion and at least one encapsulated flavor constituent (0.1 to 2.0% by weight). The encapsulated flavor constituent contained a water-insoluble coating and the chewing gum portion contained another liquid flavor (0.15 to about 3.0% by weight). The water-insoluble polymer was nominated from the collection containing polyolefins, vinyl polymers, gums, waxes, etc. The encapsulated flavor and liquid flavors were selected from various combinations, such as lime/lemon-grapefruit, orange-cream, pineapple-banana, pineapple-coconut, etc.

Table 3. Patents on taste masking of medicated chewing gum using microencapsulation.

Patent No.	Title	Method Used
US7022352	Encapsulated flavors and chewing gum using the same	Improved flavor retention using flavor encapsulation by spray drying using various polymers, such as gum Arabic or maltodextrins etc.
US6428827	Long flavor duration releasing structures for chewing gum and method of making	Modified flavor release interval in chewing gum comprising a hydroxypropyl cellulose matrix cross-linked with a multi-factorial carboxylate
US7851000B2	Taste-potentiator compositions and edible confectionery and chewing gum products containing the same	Taste enhancers modify the taste perception of active ingredients contained in the formulation
US0064783A1	Flavor impregnation of nicotine chewing gum core	Impregnating the chewing gum core by adding one dose of liquid flavor mixture
US5266335A	Microencapsulated flavoring agents and methods for preparing the same	Microencapsulated flavoring agents prepared by complex-coacervation
US4485118A	Gum composition with plural time releasing flavors and method of preparation	Sequentially releasable multiple flavor systems. One of the savors is encapsulated within a hydrophobic coating and another one is available for immediate release
US4724151A	Chewing gum compositions having prolonged breath-freshening	Improved mouth-freshening effects by utilizing a lipophilic gum base, a sweetening agent, and a blend of spray-dried flavors
WO 012009A1	Chewing gum comprising nicotine	Multilayer chewing gum for sustained and extended release
US1123445	Microencapsulation	Encapsulated flavors for flavor retention and taste masking
US0105485	Flavor encapsulation using electrostatic atomization.	Electrostatic spray drying process for encapsulation of volatile flavor oil

Lenzi et al. [77] developed a chewing gum formulation containing various flavor compositions to provide a distinctive and enduring flavor sensation to the consumer. The first flavor composition (fruit flavor) begins to release after mastication; the second flavor (mint flavor and a fruit flavor) starts to release afterward, and so on. The formulation also contained a third flavor composition (mint flavor) encapsulated with a polymer. The encapsulating hydrocolloid polymers nominated from the group comprising of various alginates, guar gum, carrageenan, pullulan, konjac, xanthan gum, pectin, hydroxypropyl methylcellulose, gum Arabic, agar, carboxymethyl cellulose, gelatin, etc. A mint gum with a unique flavor blend to provide a considerably improved perception of breath-freshening was patented by Mansukhani. The chewing gum compositions contained a combination of mint oil flavor with a specific quantity of menthol, a spray-dried mint oil flavor, and spray-dried menthol flavor. The carrier solution used to prepare spray-dried mint flavors for sugar-containing chewing gum is usually a sucrose solution [88].

Witteveen et al. prepared an encapsulated flavor, which contains a core material and a combination of finely-divided xanthan gum, native starch, and konjac (4–16% by weight of the encapsulated flavor). The encapsulated flavors may be completely free from gelatin, while retaining the desirable qualities of gelatin and may be used for any confections in order to preserve its perception until the desired release time. The microencapsulates were prepared by using the spray drying method. Xanthan gum is a well-known rheology modifier and a stabilizer in food stuffs and confection. Konjac is the root of an Asian plant *Amorphophallus konjac*, which is widely used as a nutritional supplement [89]. Sobel et al. disclosed an electrostatic spray drying process for encapsulation of volatile flavor oil by employing a carrier or wall material. The use of electrostatixc charge is done in order to

reduce the process temperature in particular, inlet temperatures in the range of 25 °C to 110 °C, and outlet temperatures in the range of 25 to 80 °C. The low drying temperature provided various benefits, such as better retention of volatile flavor components, better hydration and dissolution in water-based applications [90]. Most recently in 2019, Carinsa group obtained a new patent with a "dual chewing gum" that changes its taste. The vardenafil chewing gum (Levitra®) worked by sequentially releasing one flavor after another. They combined different liquid aromas with other microencapsulated components so that saliva dissolves them completely. Due to this the consumer perceives the change in flavor [91]. In 2020, Kristina et al., developed a nicotine bitartrate chewing gum containing two layers in which one layer provides immediate release and another layer provides extended release. Various sugar alcohols, such as maltitol, xylitol and at least one buffer solution, were used as core materials. The buffer solution provided a suitable pH for nicotine to be available in free form and able to penetrate oral mucosa. The aim of the invention was to provide the taste making as well as regulate the release of nicotine [92]. Various microencapsulated bioactives, excipients and medicaments were employed to formulate medicated chewing gums [93].

6. Recent Technology Platforms for Flavor Microencapsulation

Platform Technology is a basic tool to implement the principle in applications. Gum flavor technology has been mounting gradually thus plentiful drug delivery and confectionary syndicates are now engaged in providing flavor microencapsulation patented technologies [5]. One such established key player is Tastech® encapsulation solutions in the UK, which specialized in developing innovative controlled release flavorings and free-flowing powders used in food and other confections. The use of these products in chewing gums can upsurge shelf life, mend taste and texture, protect vital ingredients from moisture, enhance flavor perception, and reduce cost in use. Their front-line technologies include Flavor8®, CoreShell®, Matrix Encapsulation®, Spray drying® and Powder stabilisation® techniques to attain amplified shelf life and amended flavor release and perception [94]. The bitter taste of caffeine has been masked and its release has been delayed by the use of these patented platforms. The release of the amino acid, leucine, has been delayed to provide an extended effect. The various patented technology platforms for encapsulated flavors used in formulating taste-masked medicated chewing gums are hereby discussed. The flavor encapsulation technology encompasses the inclusion of active ingredients inside a carrier material. The carrier material must be adequately robust and biodegradable to provide stability and strength. Taste-Tech typically uses vegetable fats. The various technologies are shown in Figure 9 [94].

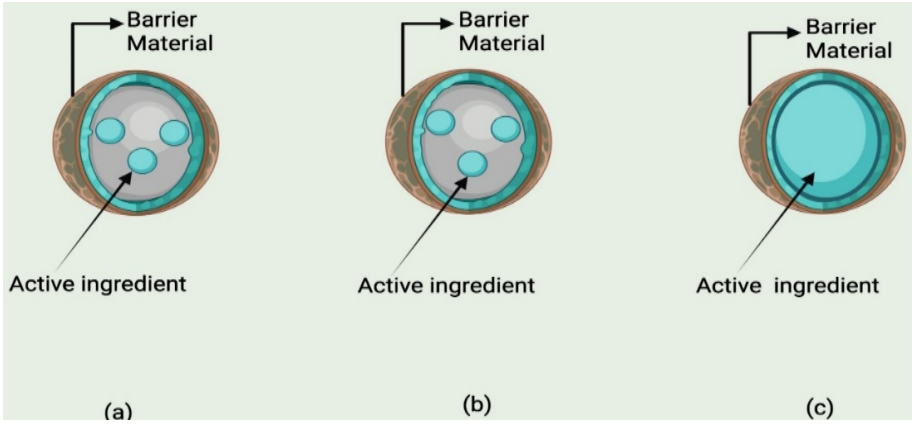

Figure 9. (**a**) Spray-dried flavor technology (**b**) Matrix encapsulated flavors (**c**) Core-shell encapsulation.

6.1. Flavor8®

This proprietary encapsulation-based flavor technology provides benefits in highly lipophilic and low water-activity systems. The full impact of the flavoring is provided in the mouth during the chewing of the gum. This technology guards the volatile flavor, leading to a reduced strain on the packaging. Various patented flavorings are almond, aniseed, banana, cherry cola, lemon, lime, mango, menthol, mint, strawberry, etc. [95]. Liquid flavorings are the most cost-effective and economical approach used in chewing gum formulation. Yet, there is a limitation of liquid flavors as they bind to the lipophilic gum base and a part of it will go unused. Thus, TasteTech's flavour8 technology bolts the volatile flavor up, till it is activated with high impact during mastication. It is a powder-based technology, which is obtained by converting volatile flavor oils into encapsulated powders, thus preventing the volatiles from early release [96].

6.2. Spray Dried Flavoring®

This is one of the ancient and frequently used techniques, employed to convert liquid volatile components into fine powder. The technique is highly economical, ideal for high-impact, quick-release flavors, easy to handle, and is used mainly in nutritional supplements and confectionary sectors. The product's shelf life can be extended. Various spray-dried products are Acesulfame K, Acesulfame -K with Sucralose, Ascorbic Acid, Aspartame, Menthol, peppermint oil, etc. [97]. Taste-Tech is a commercial manufacturer of controlled-release microencapsulated ingredients and flavorings. They have patented a sugar-free chewing gum formulation, with high-intense sweeteners and encapsulated flavors. It provided an improved delivery of overall flavor and sweetness perception for over 20 min [98]. Furthermore, AXIM Biotechnologies has confirmed commercializing chewing gum comprising microencapsulated cannabinoids for future use. It validated that it can provide more bioavailability as compared to other formulations [99].

6.3. Matrix Encapsulation®

Matrix encapsulation means dispersing small globules of the active ingredients or more than one active ingredient inside an insoluble polymer. The particles, which measure 100–250 µm, are suited for this type of encapsulation procedure. This technology is used to encapsulate high-intensity sweeteners as well as flavor. TasteTech® matrix encapsulation procedure entraps liquid flavors into lipid microspheres, creating purposeful powders that are easy to process and cost lucrative. Matrix encapsulation can enfold more than one active ingredient within one particle, giving improved flexibility and control [100].

6.4. Coreshell®

The Core-shell encapsulation technique confines the active ingredient inside a thin cover, to generate a coarse particle of 500–1800 µm. This technique provides higher protection against moisture and creates a barrier between two or more incompatible substances. This encapsulation technique converts liquid flavors into free-flowing powders that provide increased flavor perception. This technique also retains the quality and stability of the product by lowering the deliquescent nature of core materials [101].

6.5. Powder Stabilisation®

Intense flavor impact with a high powder stabilization can provide easy processing. Their stabilized powders, such as Stabilized Menthol Plus®, is up to five times more effective than their spray-dried counterparts, making them up to 50% cheaper [102]. This technology enables high loading of the active ingredient (up to 93%) and provides a free-flowing powder for easy dosage. Typically, a fine powder with an average size of 50 microns is produced, which is compatible with standard powder dosing equipment. Stevia, sucralose, sugar, tartaric acid, L-menthol, and menthol are some of the examples [103].

7. Challenges and Future Perspectives—Conclusions

The use of simple flavors and sweeteners cannot provide a good perception up to a long chew time. Thus, microencapsulation of flavors and sweeteners has unlocked a new realm in the field of food and confections, such as chewing gum [104]. Flavor modification in chewing gum can provide taste masking, flavor enhancement, sequential, delayed, or controlled release [105]. Flavor encapsulation slows down the interactions between the chewing gum excipients, the presence of oxygen radicles, and various environmental changes. The controlled-release chewing gum of caffeine was formulated by tangibly modifying caffeine's characters by spray-drying microencapsulation [106]. Some of the patents on applications of microencapsulated flavors include spray-dried flavors for flavor retention, modifying flavor release by use of hydroxypropyl cellulose matrix, taste potentiators, multiple flavors, etc. [107]. One such established key player is Tastech® encapsulation solutions in the UK, which provides its front-line technologies such as Flavor8®, CoreShell®, Matrix Encapsulation®, Spray drying®, and Powder stabilization® to attain amplified shelf life and amended flavor release and perception [108].

However, besides these merits, flavor encapsulation also suffers from certain demerits. Flavor microencapsulation technology involves increased production cost that results in an economic limitation of the process. In addition, chewing gum is a complex delivery system containing a lipophilic matrix, which makes it difficult to understand the release pattern of the flavors. While encapsulating ingredients, there are numerous limitations in choosing the wall materials, as they need to be food grade or generally recognized as safe (GRAS). When a core material is encapsulated, its interaction and stability with other components, such as active material, gum, sweeteners, glidants, texturizers etc., needs to be properly understood. For example, cinnamaldehyde and menthol flavors in chewing gum have reported to cause certain allergic reactions, such as oral contact dermatitis, lichenoid reactions, stomatitis etc. [109]. Anthocyanins are very sensitive to pH and temperature changes, and hence its bioavailability and antimicrobial and antioxidant potential are diminished by the gastrointestinal environment. Thus, stability and their biological activity can be improved by encapsulating them into colloidal particles. Another major challenge is the release of core material at the appropriate time and site during release. So, while choosing a coating material for encapsulation, the ratio of core to coating material, and the method of encapsulation should be given critical consideration. Moreover, the analytical and sensory evaluation, such as human panel sensory testing, time-intensity method, entrapment efficiency etc., needs to be carried out before incorporation into any gum matrix [110]. However, as its advantages overpower the limitations, it can provide multi-factorial benefits in the future.

Microencapsulation of flavor with spray drying is the most economical and commonly employed method. It is currently an active field of research and it has numerous applications in confectionery so as to deliver the colorants, flavoring agents, or vitamins at the right time, in the right quantity, and at the right rate. The most important aspect for research and development of flavor microencapsulation is to understand the industrial constraints and requirements to make microencapsulation technology viable and transition of laboratory scale to pilot scale production and marketing of finished product. There are several problems related to the microencapsulation of flavor and sensitive ingredients; therefore, flavor formulators and microencapsulation processors must make use of appropriate encapsulation materials and techniques.

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