




# Gummies and gel tablets: New approaches to oral drug delivery

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**ABSTRACT:** Oral drug intake is accepted as the most preferred route of administration to reveal therapeutic effects in local and systemic diseases. The most important advantages of the oral route are that it is the most preferred route of administration in terms of not requiring specific sterility conditions, cost-effectiveness, ease of production of the dosage form, high patient compliance, and being non-invasively applicable. However, pediatric, geriatric and bedridden patients and disadvantaged patients who are dysphagic or mentally unable to adapt have difficulties using conventional oral dosage forms such as tablets or capsules. Alternative formulations, such as liquid dosage forms or orally dispersible tablets, have facilitated the administration of orally administered drugs and can relatively reduce problems related to dysphagia (difficulty swallowing). However, liquid dosage forms have the disadvantage of low stability in the long term. It is known that orodispersible tablets reduce patient compliance due to the taste of the active ingredient that cannot be suppressed and the drying sensation they leave in the mouth in the geriatric population with reduced saliva production. All these shortcomings increase the search for a new generation dosage form. Gummies and gel tablets are among the new-generation dosage forms introduced to the market as an alternative to conventional oral dosage forms and whose market share is expected to increase. Gummies and gel tablets do not require water or pleasant chewiness. Thanks to their advantages, such as exciting colour, odour and taste, an increase in patient acceptability has been observed compared to other oral dosage forms. This review mentions the advantages and disadvantages of oral administration, conventional oral dosage forms, detailed information about gummies and gel tablets, preparation methods, excipients used, current research and the place and future of these innovative dosage forms in the pharmaceutical industry.

**KEYWORDS:** Gummy; gel tablet; oral drug delivery; pediatric; geriatric

## 1. INTRODUCTION

There are many ways of taking the drug into the body, such as oral, sub-mucosal (buccal and sublingual mucosal route), parenteral, transdermal and pulmonary applications [1]. Oral drug intake is accepted as the most preferred route of administration to reveal therapeutic effects in local and systemic diseases, and many drugs, from small molecules to biomacromolecules, can be used this way [2]. They can also be used in local treatments such as gastrointestinal system (GIS) disorders (reflux, cancer, infection, inflammation and ulcer) [3,4]. The oral route has versatile physiological conditions and is essential for selective absorption of the drug to achieve the desired level of therapeutic effect [5]. The aim is to see the therapeutic effect of the drugs taken through this application by dissolving them in the appropriate region throughout the GI tract and then absorbing them [6, 7].

Most pharmaceutical products are designed to be taken orally. In particular, most of the current dosage forms in the pharmaceutical market are solid dosage forms developed for oral use [8,9]. The market share of these drugs is estimated to be approximately 90% [10]. It has been reported that the production cost advantage of these orally used drugs also increases the market share rates [11].

While conventional oral drug delivery systems require the drug to be administered more than once a day because it cannot be kept within the therapeutic range, continuous drug intake is significantly eliminated with gastroretentive controlled drug delivery systems [5]. With oral drug intake, the oral cavity, oesophagus, stomach, small intestine and colon play an active role in absorption. However, physicochemical challenges exist in developing orally administered drug formulations, such as poor water solubility and membrane permeability limitations. After oral administration, the degree of absorption of the drug may vary depending on the residence time in the GI tract, its adhesiveness, the accompanying nutrients and the pH of the GI fluid [3].

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When taking oral medication, the patient's ability to self-administer medication without the need for medical personnel and being a painless alternative to non-invasive and parenteral applications increases the patient's rate of acceptance of treatment [12]. Among the reasons for increasing patient compliance with oral drug administration are the typical tissue damage observed in parenteral administration, regional pain, and the need to keep the patient under surveillance [13]. In cases of sudden side effects that develop in the patient with parenteral administration, it is not possible to terminate the treatment because the drug is administered directly into the bloodstream. Due to this disadvantage compared to the advantage of rapid therapeutic effect obtained with injectable applications, oral therapy is thought to be a more reliable treatment for the patient [14]. These advantages are essential for the sustainability of treatment, especially for chronic patients [15].

To avoid injectable formulations, oral drug delivery is a more popular and convenient method [16]. However, dysphagic, pediatric and geriatric patients have various limitations in taking oral drugs, making compliance with treatment difficult. Especially in the geriatric patient group using multiple medications, oral medications are shown to cause the patient to drift away from treatment psychologically. However, oral drug intake causes local irritation and nausea at a higher rate compared to other drug delivery systems. This reduces the continuity of treatment in the geriatric population [8,17]. At the same time, the inability of infants and most children to use solid dosage forms limits the options in drug formulations that can be taken orally [15,18].

Reasons such as poor stability in the GI tract, low solubility and low permeability, among the difficulties encountered in oral drug intake, cause low bioavailability [19]. Another limitation is that the therapeutic effectiveness of drugs that are expected to be effective in emergencies is taken late [6,12]. Many dosage forms have been and continue to be examined for oral drug delivery to improve bioavailability, therapeutic effectiveness and patient compliance [20].

This review aims to comprehensively analyse gummy and gel tablet formulations, which have emerged as innovative oral dosage forms aimed at overcoming the limitations associated with conventional oral delivery systems. This study focuses on the potential advantages of these formulations in improving bioavailability, therapeutic efficacy, and patient compliance, particularly in pediatric, geriatric, and dysphagic populations. Additionally, it seeks to explore the evolving trends, technological advancements, and future prospects of gummy and gel tablets in the pharmaceutical industry, addressing their impact on patient-centered drug delivery and the market landscape.

## 2. ORAL ROUTE

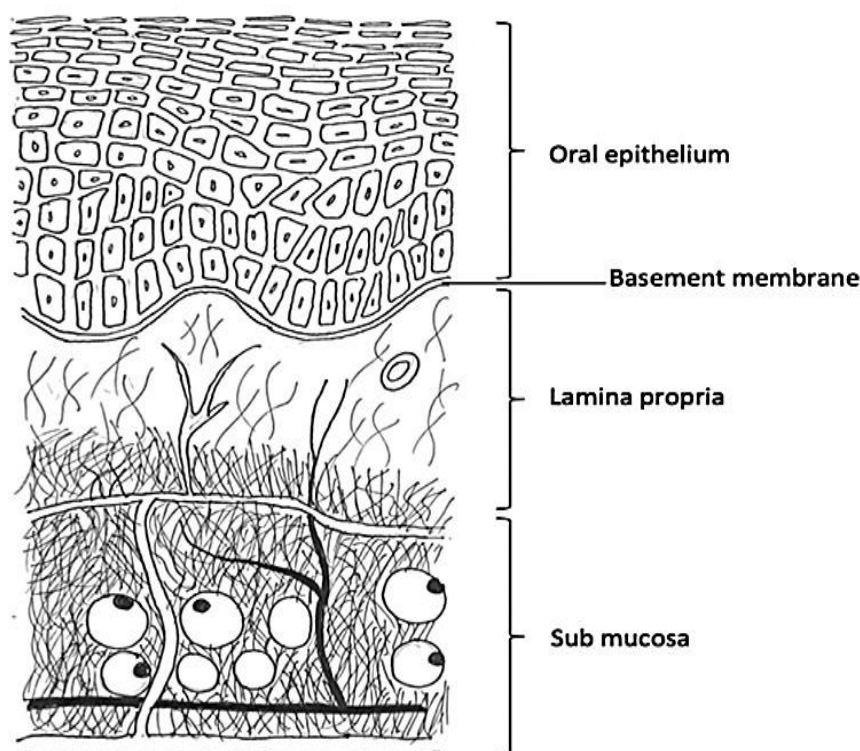
The oral cavity constitutes the first part of the digestive system, and its anatomical structure includes different structures such as the tongue, cheek, teeth, gums, hard and soft palate and the mucosa covering the inner surface of the cheek [21]. The oral cavity, which is highly preferred due to its easy accessibility to systemic circulation, is covered with oral mucosa. The highly vascularized oral mucosa allows the drugs absorbed therein to pass through the liver into the systemic circulation without suffering first-pass effects and restrictions through the GI tract [22]. However, it is known that the oral mucosa also contains restrictive conditions for oral drug delivery due to enzymatic components and limited surface area [23].

The mucosa, which continues throughout the GI tract, is connected by four concentric layers: the submucosa, muscularis propria mucosa, connective tissue and neurovascular networks [24]. The mucus, which has a strong and sticky gel structure, is negatively charged at the pH of the oral mucosa and binds to the epithelial cell surface. The complex formed by the functional groups of polymers or other excipients and mucus glycoproteins prolongs the residence time of the drug in the area. The mucus layer, which spreads into the oral cavity as a thin film, binds tightly to the particles and reduces the permeability rate of the drug [25,26]. As shown in Figure 1, bioavailability decreases with proteolytic degradation in mucosal barriers [26]. In chewable dosage forms, since the taste of the active ingredient is masked with sweeteners and flavourings, it helps to forget nausea along with the chewing reflex and increases its absorption due to the excess blood flow in the oral cavity. Prolonging the time it stays in the mouth also contributes to increased absorption [27].

For the drug administered orally to be released and have the targeted effect, it must dissolve, diffuse and then be absorbed in the parts of the GI tract, including the oral cavity, oesophagus, stomach, and small and large intestine [28].

Transcellular and intercellular pathways are the two main pathways of drug permeation. The transcellular pathway occurs by transcytosis by cells, while the intercellular pathway occurs by diffusion through the gaps between epithelial cells [29]. Poor permeability is an important parameter determining the

pharmacokinetics for most hydrophilic and some high molecular weight hydrophobic drugs [30]. Various physiological barriers, such as poor intestinal permeability and poor diffusion, seen in many oral pharmaceutical preparations, cause drug degradation, low permeability in the GI tract, and low bioavailability [31]. The GI tract, which has poor permeability to the bloodstream and foreign substances, also restricts the absorption and, thus, the bioavailability of drugs. The double layer of the GIT, consisting of phospholipids, is a restrictive step for hydrophilic macromolecules while allowing the permeability of lipophilic macromolecules [29].



**Figure 1.** Structure of the oral mucosa [26].

To ensure absorption of the drug, it is expected to be soluble in gastric fluid [29]. The presence of enzymes such as pepsin and gelatinase in the stomach are essential barriers for orally administered drugs, as they cause the denaturation of many medications [32]. The flow rate of gastric juice in the lumen reduces the contact time between the epithelial layer and drug molecules. However, mechanical degradation within the lumen caused by osmotic stresses occurring throughout the GI tract is also among the factors that reduce drug effectiveness [33]. While the stomach has a strongly acidic pH (1.0-2.5), the pH gradually increases in the duodenum and ileum. For drugs whose solubility changes sensitively to pH, regionally varying pH values are essential in the absorption of the drug [29].

To increase the rate of drug absorption, molecules must remain in the area of effect for a long time, and the absorption area must be large. Drugs generally remain in the oral cavity and oesophagus for a short time. Therefore, the absorption period is short. However, for drugs that pass into the small intestine, the length of the intestine prolongs the absorption period of drugs. In this way, the small intestine is known as the place where drugs show higher absorption and have different digestive enzymes and various receptors and carriers [24, 29]. Among the three parts of the small intestine, the ileum and jejunum have a higher absorption area than the duodenum [29]. However, the absorption of some drugs from this region is restricted due to digestive enzymes, mucosal layer, bile salts, and tight connections between cells [34].

The large intestine, which contains bacterial enzymes that can break down drugs, is a limiting condition for the desired effective drug concentration [34]. In addition, irregular absorption may be observed depending on the patient's intestinal structure and gastrointestinal content when taking the drug. Figure 2 summarizes the obstacles and passageways encountered during absorption [35]. As the drug enters the systemic circulation, a first-pass effect is observed in the lungs, especially the liver and other metabolically active tissues. It is metabolized in these tissues before reaching the area of effect of the drug, causing



undesirable situations such as decreasing the concentration of the active substance and increasing the dose [36].

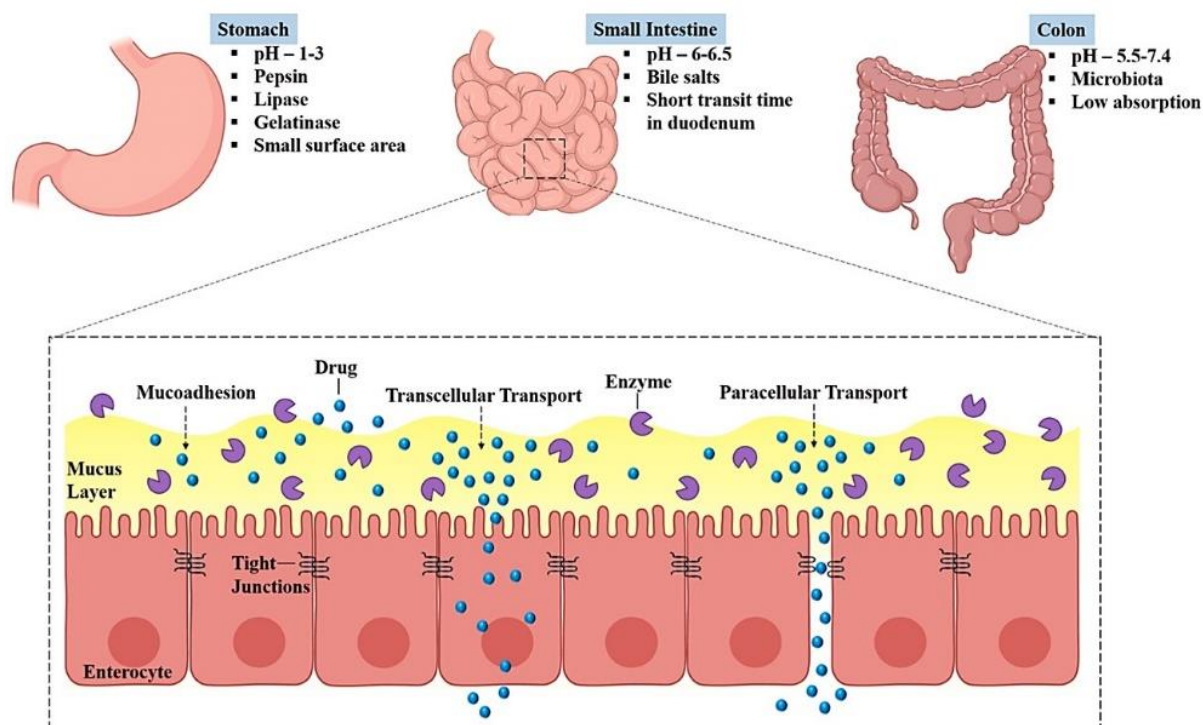


Figure 2. GI mucosa and absorption pathways [35].

### 3. CONVENTIONAL ORAL DOSAGE FORMS

Liquid dosage forms, which can be administered as emulsion, suspension or solution, are preferred, especially in geriatric and pediatric patient groups and in patients experiencing swallowing problems. Emulsions are dispersions consisting of a liquid carrier phase that is immiscible with the internal phase and can be prepared in forms such as oil in water or water in oil. Suspension dosage forms can be found in the pharmaceutical market as ready-to-use (diluted) or dry powders to be reconstituted later. Since the pKa of the active substance and stomach pH affect the absorption rate of the drug, the possibility of precipitation of the drug creates a restrictive obstacle in delaying absorption [6].

Tablets and capsules are known as the most common commercial dosage forms. The use of tablets and capsules poses difficulties in patient compliance in diseases requiring combined treatment, such as geriatric patients with more than one disease [34]. Capsules and tablets have been widely used since the early days of modern pharmacy. Modifications are continued by developing technologies according to the pharmaceutical industry's and patient groups' needs during the process [37].

Capsules, which account for over 10% of the market share and 20% of prescription drugs, enable oral delivery of powders, granules, liquids and semi-solids in a film shell. Some water is required to take this oral dosage form. Situations such as the patient's inability to swallow or sticking to the oesophagus are limiting for this dosage form. In addition to challenging and soft gelatin capsules, gelatin-free capsules can also be obtained with the help of cellulose derivatives, starch and carrageenan [38].

Among the new-generation tablet dosage forms, buccal tablets are applied to the mucosal layer between the lips and gums, while sublingual tablets are used under the tongue. Although these tablets are generally considered advantageous, coordination of keeping them under the tongue or in the cheek may be complex in pediatric, geriatric and bedridden patients. This process can be carried out more quickly in chewable formulations for every patient with developed chewing reflexes. Tablets are also included in these formulations, eliminating the need for the patient to swallow the entire medicine [26].

Solid dosage forms are expected to dissolve and disintegrate more slowly in the mouth. Although they may contain more than one active ingredient, increasing the lozenge size in cases where a high amount of active ingredient needs to be loaded creates a disadvantage in patient compliance. However, adding taste masking agents equivalent to the increased active ingredient ratio is also necessary. The inability to use active substances that do not dissolve in the oral mucosa in both buccal and sublingual tablets and lozenges

is among the disadvantages of these drugs [39]. The patient controls the disintegration time of these tablets, which contain a soluble sugar-based matrix. In conventional sublingual and buccal tablet formulations, the drug is expected to disperse and enter the systemic circulation within a maximum of 30 minutes, depending on oral intake, while it is also likely to remain stable against the forces that may be applied during transportation and storage. In sublingual and buccal dosage forms, the drug must be masked with sweeteners and aromatizers, if necessary, for the acceptability and sustainability of the treatment [26].

Chewable tablets, which show ease of production, correct dose adjustability, long-term stability and ease of transportation, offer ease of swallowing by breaking into pieces in the oral cavity. This is one of the reasons for the preference for the disadvantaged group. Its use without the need for water makes accurate dosing possible. It is intended to be taken into the body without any deterioration in its structure during chewing, and it is expected not to leave an unpleasant taste in the mouth. Chewable tablets are generally preferred in preparing high-dose active ingredient groups such as multivitamins and transporting supplements to the body. Therefore, it cannot be applied to every active substance [40]. Although they are considered advantageous in-patient groups with swallowing difficulties, there is a warning on the product label that it should not be swallowed without chewing. Despite this warning, typical side effects include swallowing chewable tablets without chewing, causing intestinal ischemia. Chewable tablets must be resistant to breaking or cracking during packaging and transport. However, they should not be so hard that they will crack teeth or prosthesis teeth while being chewed. This is seen as a handicap for chewable tablets [41].

#### 4. NEW GENERATION ORAL DOSAGE FORMS

The oral route, which is the most preferred route for delivering drugs into the body, exhibits a low bioavailability profile for many active substances. These active substances include large molecular peptides, recombinant therapeutic agents and proteins. Low permeability through the mucosa, low absorption zones in some regions of the GIT, and low concentration of solutes cause low bioavailability and stability problems for large and hydrophilic molecules. Studies on new-generation oral dosage forms continue to increase daily to overcome these limitations [42].

Orodispersible tablets (ODTs), one of the new dosage forms, turn into suspension or solution form within a maximum of 3 minutes and act quickly with minimum water requirement [43]. According to FDA data, oral films must be light (up to 500 mg) and disintegrate within 30 seconds [44]. The direct compression method is widely used in preparing ODTs in terms of cost and ease of production. However, the size, hardness and disintegration capacity of ODTs produced with this method are limited. Excipients that provide optimum binding are needed to ensure these tablets' rapid disintegration and not affect their hardness [45]. To increase the patient acceptability of ODTs, studying them in petite sizes is necessary. For this reason, there are limitations regarding the amount of active substance. At the same time, while aiming for high bioavailability with rapid effect, care should be taken to avoid leaving a bad feeling and taste in the mouth. Due to their size, high amounts of active substances cannot be loaded, and there are limitations to using active substances that do not dissolve in the oral mucosa [43].

Oral thin films/strips are flake-like dosage forms with 1-3 cm<sup>2</sup> dimensions and an ideal thickness of less than 1 mm. It aims to increase its applicability to the mucosal region by determining its dimensions. They are an excellent alternative to conventional dosage forms with their ultra-thin, flexible and less irritating feel. They dissolve more quickly than conventional dosage forms such as buccal or sublingual tablets. However, their small size limits the amount of dose that can be loaded [26]. Insufficient elasticity of the films may cause breakage, irritation in the application area and even undesirable effects. Furthermore, an overly elastic film is likely to cause problems in handling and application due to its excessive stickiness and flexibility [26,46].

Orodispersible wafers or orodispersible lyophilizes, examples of mucoadhesive dosage forms, are obtained by determining different casting molds of solutions and suspensions, adding them to blister packs and drying them. Wafers, which can be produced in various sizes depending on the casting molds, have a porous and fragile structure, and therefore, special peelable blister packaging is needed in packaging selection [47]. Wafers, defined as flexible polymeric fibres with an average size of 2-10 cm<sup>2</sup> and a homogeneous surface of 20-500 µm thickness, can show absorption through the oral mucosa. Thus, rapid drug absorption and rapid onset of the desired therapeutic effect can be achieved. However, this rapid onset of action also poses the risk of unwanted side effects [42]. Their significant disadvantages include high temperatures and humidity stability problems and the need for special packaging [47].

#### 4.1. Gel Tablets

Gel tablets are among the chewable tablet group's new dosage forms. Although chewable tablets exist in large numbers in the pharmaceutical industry, gel tablets remain a relatively new and underdeveloped topic [48]. This dosage form is soft, flexible and elastic gel-based tablets in a form similar to gummy formulations. These tablets cannot be prepared with tablet machine punches; they are ready using silicone or metal molds [49].

Gel tablets, which do not require water for oral administration, appear to be an excellent alternative to conventional solid dosage forms [48,50]. The oral mucosa moistens the tablet mass during chewing, allowing it to be swallowed easily. In this way, it is deemed suitable for disadvantaged groups [48]. In addition, the possibility of maskable taste, pleasant odours and tastes, variety of shapes and versatility in sizes make this dosage form enjoyable. The lack of limitation in sizing also allows the loading of high doses of medication [51].

The water contained in the gel tablets provides a suitable environment for the growth of microorganisms. Therefore, it is necessary to add preservatives and sweeteners to the formulation. Added sweeteners can replace water, but they are not sufficient as preservatives. Preservatives contribute to extending the shelf life of formulations. However, it should also be considered that preservatives such as citric acid can lower the pH and provide an environment for the growth of microorganisms [48].

#### 4.2. Gummies

These chewable gum-like formulations are among the innovative drug carrier systems that have attracted attention since they were introduced to the pharmaceutical market, as they increase patient compliance, especially in pediatric patient groups and patients with swallowing problems. Due to their advantages, these formulations stand out as “paediatrics-specific” or “tailored” drugs [52]. Gummy formulations stand out as an alternative to other dosage forms with unique benefits, such as ease of application, ability to be used in all patient groups with advanced chewing ability, non-invasiveness, and attractive colour and shape [53-55].

Gummy formulations containing pharmaceutical or nutraceutical ingredients used by chewing are prepared from a gum base consisting of natural or synthetic elastomers, waxes, lipids, emulsifiers and plasticizers. In addition, sweeteners, flavourings, colourants, and softeners are added to the formulation to increase patient compliance with taste and appearance [56].

Gummy formulations loaded with the active ingredient can be soft, sticky, and in different colours and shapes, as shown in Figure 3 [52]. The main components of gummies are sweeteners combined with gelling agents such as gelatin, gum or pectin [57]. This dosage form attracts even more consumer attention since sorbitol and xylitol can be used instead of sugar [54]. Gelatin is widely used in gummy formulations as it is a biocompatible and biodegradable material with a melting temperature similar to human physiological temperatures [58].



**Figure 3.** Gummies containing active pharmaceutical ingredient [52].

The active ingredient(s) in gummy formulations begin to be released during chewing and absorbed through the oral mucosa after mixing with saliva. Then, they must be swallowed and delivered to the stomach for primary absorption. Gummies allow the transportation and controlled release of a wide variety of active substances, both water-soluble and water-insoluble, into the body. At the same time, their long-term stay in the oral cavity due to how they are applied allows them to be used in treating mouth and throat diseases. Among the reasons for its preference is that it does not require water during use and can be applied whenever and wherever desired [56].

The production of gummy dosage forms has become widespread to provide easier swallowing, an attractive appearance, and delicious tastes for active substances (such as Vitamin C) that cannot maintain their stability when exposed to oxygen, moisture, pH changes, heat, and light during production and shelf life and that need to be dosed in high amounts [53]. It is also possible that the semisolid nature of gummy bases may produce changes in the rate of dissolution and absorption of the drug under long-term storage conditions or during chewing. Although the ICH recommends room temperature and accelerated conditions for the stability of gummy formulations, stability conditions at room temperature are preferred over accelerated test conditions [56]. Gummy formulations also have significant disadvantages, such as high sugar content, the need for chewing, and taste masking issues. [52,56].

It is thought that increasing and enriching the contents of gummy formulations will effectively use active ingredients for patient groups of all ages. Also, it is predicted that the solid matrix of this innovative drug carrier system will prevent the size instability of nano-liposomes in the dispersion medium, too [59].

Gummy formulations are mostly prepared by conventional methods. The gum base is softened in a mixer at temperatures between 50 °C and 70 °C, and other formulation ingredients are added. Afterwards, the desired shapes can be given by lowering the temperature [56].

## 5. PREFERRED EXCIPIENTS IN THE PREPARATION OF GUMMY AND GEL TABLETS

To ensure the physical, chemical and microbiological stability of gummy and gel formulations, sweeteners, flavourings, preservatives, stabilizers, solvents, pH regulators, and colouring agents must be added along with gelling agents [60].

Most gelling agents are known as polysaccharides and gel-forming polymers. Gelatin, a natural product obtained from cow and pig skin or bones, contains many amino acids. It is used in formulations as an emulsifier, microencapsulating agent, stabilizer and gelling agent [48]. Gelatin creates a stable gel texture and is used as an emulsifier, making it preferred in gummy formulations. The amount of gelatin affects the viscosity and texture of the formulations. In addition, the gelling concentration also affects the gummies' hardness, stickiness, chewiness and solubility [57].

Compared to other gelling agents (such as starch and pectin), gelatin as a gelling agent offers advantages such as ease of use, cost-effectiveness, dissolution profile and transition temperature. The widespread use of gelatin prevents reactions, especially in pediatric groups, to unfamiliar tissues and provides ease of use [17,61].

Contact with taste receptors on the tongue due to partial or complete dissolution of the active substances in the oral mucosa may create a sour taste that may reduce patient compliance. Sweeteners and flavourings are essential to prevent or minimise this effect. Sucrose is the most preferred sweetener due to its high purity and economical properties. Additionally, sweeteners can improve viscosity, which helps achieve controlled release. Another factor affecting the taste and stability of formulations is known as pH. Studies have reported that sucrose precipitates in the presence of citric acid. To prevent this, it is recommended that citric acid, widely used among pH regulators, be added in minimum amounts [62,63].

Preservatives are added to ensure the microbiological stability of gummy and gel tablet formulations in aqueous form, and stabilizers are added to keep the product stable throughout its shelf life [63]. Table 1 lists the gel-forming agents, sweeteners, aromatizers, preservatives, stabilizers, and other excipients commonly used in gummy and gel tablet formulations.

**Table 1.** Most preferable excipients in gummies and gel tablets

Gelling agents [64]	Sweetening agents [65]	Flavoring agents [66]	Preservatives [62]	Stabilizers [67]	Solubilizing agents [68]	pH regulating agents [50]	Coloring agents [69]
Tragacanth gum	Sucrose	Peppermint	Methyl paraben	Propylene glycol	Cremophor RH40	Citric acid	Tartrazine
Sodium alginate	Aspartame	Mango	Propyl paraben	Sorbitol	PEG 400	Fumaric acid	Sunset yellow
Pectin	Dextrose	Lemon	Benzoic acid	EDTA		Malic acid	Carmosine
Gelatine	Thaumatococ	Strawberry	Benzalkonium chloride			Phosphoric acid	Amaranth
Hydroxypropyl methylcellulose	Saccharin	Pineapple	Chlorhexidine acetate			Succinic acid	Ponceau 4R
Gellan gum	Acesulfame	Raspberry				Tartaric acid	Brilliant black
Carrageenan	Stevia					Maleic acid	
Xanthan gum	Cyclamate					Acetic acid	
Other cellulose derivatives	Maltose					Hydrochloric acid	
	Ribose					Lactic acid	
	Trehalose					Propionic acid	
	Xylose						
	Sorbitol						
	Maltitol						



## 6. PREPARATION METHODS OF GUMMY AND GEL TABLETS

### 6.1. Heating, Molding and Cooling Method

Heating and cooling methods are frequently used to prepare gummy and gel tablets. In this method, gel-forming agent(s) are first added to the dispersion medium of the formulation (usually ultrapure water) and allowed to swell by stirring at room temperature. This mixture is then mixed in a water bath set at a specific temperature until it becomes homogeneous and dense. Then, sweeteners, pH regulators, aromatizers, colourants, stabilizers, and finally, active ingredient(s) are added to this hot mixture, and mixing continues. After the mixture becomes homogeneous, it is poured into molds. Afterwards, the molds are kept at room temperature for a suitable period and then removed from the molds [60]. After the homogeneous mixture is left at room temperature for a while, it is cooled by keeping it in the refrigerator for 24 hours. Finally, the resulting gummies are taken out from the molds [70].

### 6.2. 3D Printing Method

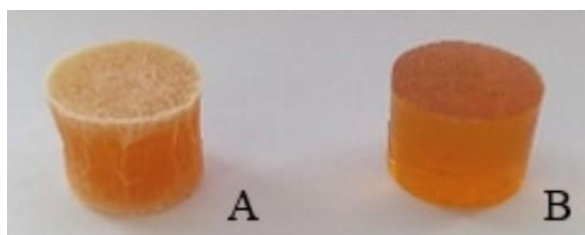
Offered as an alternative to the traditional pharmaceutical industry, 3D printing is obtained by creating 3D objects layer by layer with a personalized treatment approach. This technique, which improves the release and absorption profile of the active substance thanks to production technologies, is also used in the production of gummy and gel tablet formulations. To improve the organoleptic properties and taste of the formulations, sweeteners and other excipients need to be added. Gel-forming agents in pure water are dissolved in a water bath set at a certain temperature. By continuing to mix slowly, a homogeneous mixture is created. Afterwards, sweeteners and aromatizers are added. If necessary, active substance(s), viscosity-increasing agents and stabilizers are added to this mixture. The mixing must be done manually to prevent the ink from mixing with air. The formulation is left in a water bath set at a specific temperature until the bubbles disappear. Prepared inks are frozen at room temperature and stored in the refrigerator until use. Before printing, the inks are kept in a water bath set at a specific temperature for a while so that the ink can come out of the nozzle, the desired shape is drawn smoothly, and 3D structure is formed [71].

## 7. GUMMY AND GEL TABLETS IN THE GLOBAL PHARMACEUTICAL MARKET

Gummy and gel tablets, among the new-generation pharmaceutical dosage forms, appear to have a wide demand and usage area among medical products, including drug delivery systems and nutraceuticals [54]. According to 2023 data, the market share value of gummy formulations is 23.93 billion US dollars, and this number is expected to show an annual growth rate of 11.8% in 2024-2030. In North America, gummy formulations will account for 37.42% of global revenues in 2023. However, from 2024 to 2030, the Asia Pacific gummy market is expected to grow by 12.9% and the European gummy market by 11.5%. The increasing need and interest in probiotics, vitamin, and mineral supplements, as well as the advantages of carrying these formulations to the body in gummies and gels, support the market share of gummies and gel tablets [72].

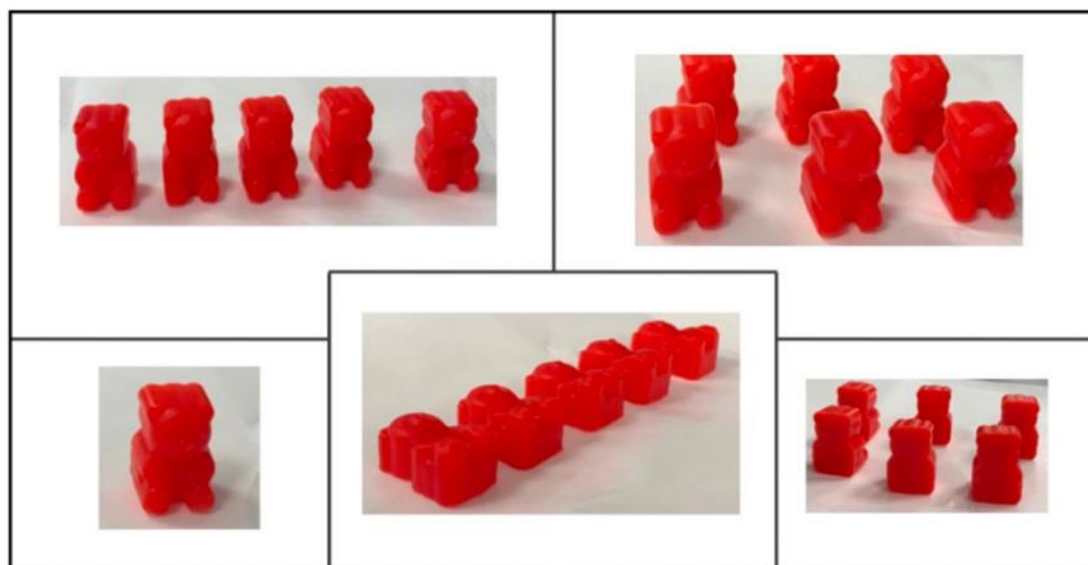
## 8. CURRENT STUDIES WITH GUMMY AND GEL TABLETS

Matulyte et al. have developed innovative chewable gel tablets containing coconut essential oil microcapsules with natural ingredients for taste and flavour. They also explained the differences in the gel tablet appearance and analysis of the addition of glycerin in these formulations. Figure 4 shows the developed gel tablets. It has been reported that sugar crystallisation is prevented, and the hardness rate decreases in tablets containing glycerin [49].



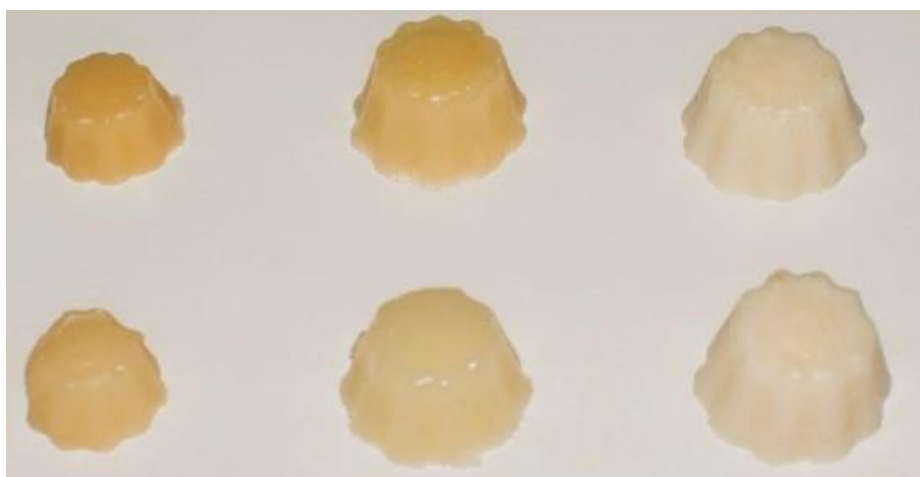
**Figure 4.** Gel tablet without glycerin (A), gel tablet with glycerin (B) [49].

Kean et al. developed polymeric-based gummy formulations containing isoniazid for treating tuberculosis in pediatric patients. These polymeric-based gummies, also called FlexiChew, are given in Figure 5. This study reported that they were visually attractive, uniform in size, lightweight, mechanically robust, had high chewability, and provided more effective taste masking than placebo [58].



**Figure 5.** FlexiChew gummy formulations containing active pharmaceutical ingredient [58].

Gonzalez et al., developed gel tablet formulations containing praziquantel that treat and prevent parasitic infections. Six different formulations were developed and characterized by varying factors, such as the amount of gelatin and the way praziquantel was added (Figure 6). Praziquantel is included in formulations in nanoparticulate size. In this way, they showed that substances with low water solubility can be loaded in nanosize. No complex equipment or procedures were required to develop gel tablet formulations. Preparing drugs in this way has been reported to be a simple and cost-effective manufacturing procedure [51].



**Figure 6.** Gel tablet formulations containing active pharmaceutical ingredient [51].

Rani et al. developed different gummy formulations using *Moringa olifera* leaf powder, which contains high antioxidants and nutrients and varying concentrations of pectin and gelatin. The developed gummy formulations were evaluated regarding viscosity, weight, size, swelling ratio, dispersion time, and chewability. As a result, it has been reported that the type and concentration of the gelling agent significantly affect the dispersion time, integrity, hardness, flexibility and chewability. Among the prepared formulations, it has been reported that gummies developed using 10% gelatin and 1.5% pectin have optimum properties. Figure 7 shows visuals of this developed gummy formulation [57].

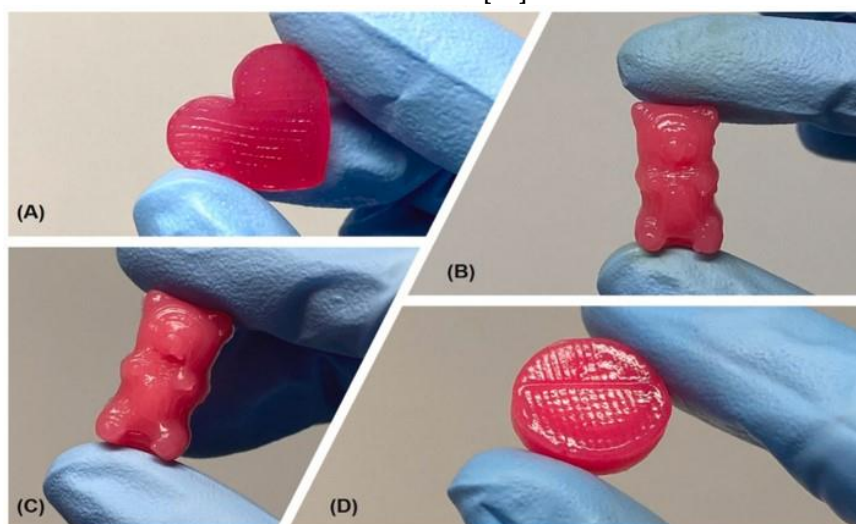


**Figure 7.** Gelatin and pectin based herbal gummy formulations [57].

Baydin et al. conducted a study in which they compared gels prepared using gelatin with plant-based polysaccharide gels prepared using agar and pectin in terms of rheology, organoleptic and functional aspects. Compared to gels containing agar and pectin, gels prepared with gelatin have been reported to have a lower gelation/melting temperature. Gels prepared with agar had the highest hardness and brittleness. It has also been reported that gels prepared with pectin have the lowest hardness and brittleness [73].

Helena et al. developed ranitidine-containing gummies by extrusion 3D printing method. They obtained gummy formulations in various shapes and sizes by using gelatin, corn starch, liquid sweetener, carrageenan, xanthan gum, and strawberry extract in different concentrations as excipients (Figure 8). As a result of the in vitro characterization of the developed formulations, it was reported that the 3D printing method is a sensitive, controlled and easy-to-use technique and can be printed successfully. The results of rheological tests confirmed the suitability of the inks used for 3D printing technology, and it was reported that the best results were obtained with inks containing starch [71].

Kadhim et al. conducted a study to formulate the active ingredient granisetron, used to prevent nausea and vomiting before radiotherapy and chemotherapy, in a new dosage form with natural ingredients and to facilitate its use in the pediatric patient group. They developed gel tablets containing the active ingredient granisetron by using gelatin and carrageenan as gelling agents. The prepared formulations were evaluated on pH, content uniformity, drug-polymer compatibility, chewability, physical stability, organoleptic controls and yields. As a result, it was reported that formulations prepared with 4.5% gelatin released granisetron in the shortest time at a rate of 99.4% [74].



**Figure 8.** Gummy formulations prepared with 3D technology [71].

Elena et al. developed antimicrobial gummy formulations with bovine colostrum (colostrum), essential oils, lactic acid bacteria strains, and combinations. Agar was used as a gelling agent to prepare the formulations. The prepared formulations were tested against pathogenic bacteria. The highest antimicrobial activity was observed in formulations containing *L. paracasei* LUHS244 and bovine colostrum in combination with *Thymus vulgaris* and *Eugenia caryophyllata*. Thus, it has been observed that gummies, which offer easy use with natural ingredients, increase patient compliance and ease of use both as nutraceutical and pharmaceutical [75].

Considering that rugged tablets and capsules for oral drug intake cause problems in people experiencing dysphagia, Dille et al. prepared chewable gel tablets and conventional challenging chewable tablet formulations containing ibuprofen, acetaminophen and meloxicam and compared them with each other. As a result of this comparison, they reported that the chewable gel tablets exhibited good stability (up to 24 months) for all three active ingredients. It has been emphasized that soft chewable gel tablet formulations with high chewability, easy-to-swallow, well-masked taste and extended shelf life are helpful for various active pharmaceutical ingredients compared to conventional dosage forms [17].

Prakash et al. prepared gel tablets containing carbamazepine using pectin, gellan gum and pectin-guar gum as gelling agents. They obtained acceptable physicochemical properties and stability in the gel tablets they prepared. It has been reported that these gel tablets may be an effective alternative to the oral use of carbamazepine, whose absorption from the gastrointestinal tract is slow and irregular [68].

Sabri et al. prepared flurbiprofen gel tablets using the heating and freezing method (Figure 9). Three different gelling polymers were used in the preparation: pectin, sodium carboxymethyl cellulose and hydroxypropyl methylcellulose. It has been reported that acceptable consistency was achieved in gel tablets prepared with pectin and sodium carboxymethyl cellulose. They noted that pectin and sucrose concentration significantly affected gel tablets' viscosity [76].

Niam et al. have prepared gummy formulations containing bastard cedar leaves, senna leaves, and lemon juice using gelatin, xanthan gum, and simple syrup as gel-forming agents. They have reported an acceptable taste and aroma, are effective against obesity, and increase patient compliance [70].



**Figure 9.** Gel tablets containing flurbiprofen [76].

## 9. FUTURE PROSPECTS OF GUMMY AND CHEWABLE GEL TABLETS

The future of gummy and gel tablet formulations is anticipated to be highly promising, driven by significant growth potential in response to rising consumer demand for user-friendly, palatable dosage forms. These formulations are expected to appeal to a broad range of demographics, including pediatric, geriatric, and dysphagic patients [72]. Advances in manufacturing technologies, such as 3D printing, are projected to enable the precise customization of dosage forms with complex multi-layered structures, allowing the incorporation of multiple active ingredients within a single matrix. These technological developments will likely facilitate personalized dosing and pave the way for innovative controlled-release formulations, thereby significantly enhancing therapeutic outcomes. As the market continues to evolve, these advancements are expected to address unmet needs in oral drug delivery, ensuring that future formulations provide improved patient compliance and superior clinical benefits [71].

## 10. CURRENT COMMERCIAL PRODUCTS ON GUMMY AND GEL TABLETS

A current variety of commercial gums and gelatin tablets, classified by brand, product type, and purpose, is given in Table 2. This table highlights the variety of options available and the functional applications these formulations serve in the market.



**Table 2.** Example of commercially available products of gummies and gel tablets

Companies	Product	Purpose of Use
L'il Critters [77]	Multi + Digestive Support, Gummy Bear Vitamin	Health and Development
	Gummy Vites Multivitamin	
	Paw Patrol Multi Gummy Vitamin	
	Immune C™ Plus Zinc and Vitamin D Gummy Bear Vitamin	Immune Support
	Vitamin D3 Supplement Gummy	
	Fiber Gummy Bear Supplement	Digestive Health Support
	Probiotic Gummy Bear Supplement Dihydrochalcone	
Centrum [78]	Kids MultiGummies in Tropical Punch Flavors	Multivitamins
	Women MultiGummies in Tropical Fruit Flavors	
	Men MultiGummies in Tropical Fruit Flavors	
	Adults Multivitamins	
	MultiGummies Men Vitamins	
	MultiGummies Women	
	MultiGummies Multi + Mental Focus	Maternal Health
	MultiGummies Multi + Beauty	
	PreNatal Multivitamin Gummies	
Vitafusion [79]	Morning Sickness Relief Gummies	Sleep Support
	PostNatal Multivitamin Gummies	
	SleepWell Supplement Gummy	Stress Support
	Max Strength Melatonin Gummy	
	Extra Strength Melatonin Supplement Gummy	Beauty
	Melatonin-Free SLEEP Gummy	
	Ashwagandha Gummy	
	Multi + Beauty Gummy Vitamin	Immune Support
	Gorgeous Hair, Skin and Nails Supplement Gummy	
	Extra Strength Biotin Supplement Gummy	
	Extra Strength Biotin Supplement Gummy	
	Multi + Immune Support Gummy Vitamin	
One A Day® [80]	Super Immune Support Gummy	Multivitamins
	Triple Immune Power Gummy	
	Prebiotic Immune Support, Supplement Gummy	Immune Support
	Multi+ Hair, Skin & Nails Support	
	Multi + Immunity Defense	
	Multi + Brain Support	
	Elderberry Gummies with Immunity Support from Vitamin C and Zinc	
SmartyPants [81]	Women's 50+ Advanced Multivitamin with Immunity + Brain Support	Health and Development
	Men's 50+ Advanced Multivitamin with Immunity + Brain Support	
	Prenatal Multi & Omegas	Digestive Health Support
	Masters Women 50+ Formula	
	Organic Toddler Multi & Omegas	
	Adult Formula and Fiber	
	Kids Mineral Formula	Food Supplement
	Toddler Multi & Omegas	
Nordic Naturals [82]	Adult Prebiotic and Probiotic Immunity Formula - Strawberry Crème	Food Supplement
	Kids Prebiotic and Probiotic Immunity Formula - Strawberry Crème	
	Ultimate Omega in Fish Gelatin	Food Supplement
Queisser Pharma [83]	Focus Support	
	Blood Sugar Support	Food Supplement
	Coenzyme Q10	
	Aktiv-Memory	Food Supplement
	Lacterna	

According to the data obtained from this review, some similarities exist between gel tablets and gummy formulations. The fact that both dosage forms are user-friendly and chewable is due to the ease of use, especially in children, the elderly or individuals with swallowing difficulties. However, there are some fundamental differences. The main point where they differ here is the carrier pure formulation base used. Gummy formulations are generally prepared with high molecular weight gelling polymers such as gelatin, pectin or agar. These polymers provide a more complex and denser consistency by trapping water in the matrix. The degree of cross-linking of the polymers and the concentration of the gelling agents used can directly affect the hardness and elasticity of the product. In this way, gummy formulations have a more complex elastic texture and create a more intense feeling during chewing. Gel tablet formulations are

formulated with low viscosity gelling polymers such as hydroxypropyl methyl cellulose or carbopol. In this way, they have a softer and more flexible structure. These types of products generally have a higher water content, creating a more homogeneous gel matrix. As a result, the differences in consistency between these two dosage forms are due to the chemical structure of the base materials used, water content and manufacturing processes, resulting in each formulation offering a unique user experience.

## 11. CONCLUSION

Although the oral route is the most preferred route of administration to deliver drugs to the body, the disadvantages of conventional dosage forms have led to the need for new-generation dosage forms. Gummies and gel tablet formulations are among the new-generation dosage forms studied based on this need. These formulations increase patient compliance, especially in pediatric, geriatric patient groups and dysphagic patients, with their ease of use and different colours, odours and shapes. Due to their applicability to all patient groups with developed chewing ability, they have a place in veterinary practices and humans. At the same time, the increasing need and demand for supplements such as probiotics, minerals, and vitamins, as well as the advantages offered by producing these supplements in the form of gummy and gel tablets, have increased the market share of these formulations. Their rapid increase in market share supports the high level of patient compliance. Producing new, improved dosage forms for oral drug intake is essential for patients and the pharmaceutical industry. The studies conducted, and the data presented to shed light on new studies on gummy and gel tablet formulations.

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