Oral Jellies for Improving Oral Drug Delivery in Dysphagia

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Abstract:

For many years, oral solid dosage forms were the most preferred dosage forms for a wide range of population due to their safety, efficacy, stability, cheapness and ease of administration. Swallowing difficulties and bioavailability problems are the main disadvantages for this rout.

For this reason, researchers try to develop easier rout of administration such as orodispersible tablet, mucoadhesive, sublingual and oral jelly was developed in an attempt to overcome this restriction. The ultimate purpose for this research is to introduce opportunities of providing the oral jelly as a suitable alternative to the readily available solid dosage forms of the same medicament, representing by that easily swallowed dosage form with improved bioavailability.
Key words: Bioavailability, Dysphagia, Gel forming polymers, Preservatives.

الجل الفموي كتطورللايصال الدوائي في حالة صعوبة البلع

زينب حسن مهدي

*** فرع الصيدلانيات/ كلية الصيدلة/ الجامعة المستنصرية/ بغداد/ العراق**

الخلاصة:

كانت الصيغ الفموية الدوائية الصلبة ولعدة سنوات من أكثر الصيغ الدوائية تفضيلاً وإنتشاراً نظراً لكونها آمنة وفعالة ، فضلاً عن ثباتيتها وتوفرها وسهولة إستخامها. وبالرغم من ذلك، كان هناك العديد من المعوقات لإستخدام هذه الصيغ منها صعوبة البلع فضلاً عن مشاكل التوافر الحيوي، لهذا السبب قام الباحثين بتطوير أشكال صيدلانية سهلة البلع كالحبوب الفموية القابلة للتشتت والحبوب الملتصقة، فضلاً عن الجل الفموي من أجل تجاوز هذه المشكلة. يتمثل الهدف الأساسي من هذا البحث إستعراض وتقديم الجل الفموي كبديل مناسب للصيغ الفموية الصلبة المتوفرة وموفراً بذلك شكلاً دوائيا جديداً سهل البلع ذو توافر حيوي محسن.

لكلمات المفتاحية: التوافر الحيوي، صعوبة البلع، البوليمر المكون للجل، المواد الحافظة.

Introduction

Jelly can be defined as transparent or translucent non-greasy, semisolid preparations meant for external as well as internal application [1]. Oral jellies history was developed in the 20th century. They are formulated by combining the medicinal agent with a certain gelling agent consisting from natural gums, such as tragacanth, pectin, sodium alginates or from synthetic derivatives of natural substance such as methyl cellulose and sodium carboxy-methyl cellulose. They are designed to deliver the active ingredient for local or systemic effects [2,3].

Regardless of the remarkable progression in drug delivery, oral route remains the most preferred route for the administration of active ingredients. The main disadvantage of solid dosage forms is swallowing difficulty especially for pediatrics, geriatrics, and other population suffering from nausea, vomiting. For this reason, other solid preparation was developed to

overcome swallowing difficulties such as orodispersible, buccal, sublingual and the recently developed oroslippery tablets. Unfortunately, certain limitation was accompanied with these formulations including drug/dose limitations, taste masking problems and other formulation problems such as friability and hygroscopicity [4].

On the other hand, oral liquids like syrups, suspensions were considered as a suitable alternative in such cases, however certain formulation problems for the liquid preparations including stability, dispersibility, taste masking problems, dosage wastage and dumping problems [5].

Accordingly, oral jellies were developed as a novel easily swallowed oral dosage form which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Furthermore, it enhances a dissolution and absorption as well as onset of clinical effect and drug bioavailability. In addition, patient preference who enjoying the taste and the chewing property of the flavored jellies [6, 7].

Generally, the digestive system consisted from digestive organs (oral cavity, pharynx, esophagus, stomach, small intestine and large intestine) and accessory organs which assists in food digestion (tongue, teeth, salivary glands, liver, gallbladder and pancreas) [8].

Furthermore, the GIT composed from four layers arranged from outermost to innermost layer:

Mucosa, submucosa, muscularis and serosa [9]. These are illustrated together in Figure 1.

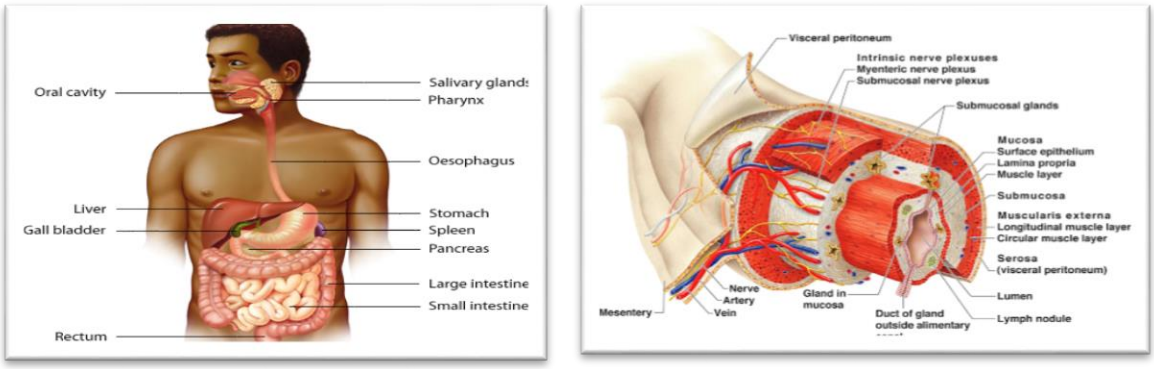

Figure (1): Anatomy and physiology of the digestive system [10]

Swallowing or is "the process of moving the ingested material from the oral cavity to the stomach without forcing it into nasopharynx or trachea" [8,11]. It is considered as a combination of reflexive and voluntary activities that is controlled by the medulla oblongata, which is considered as the swallowing center that controls the activity of the trigeminal, glossopharyngeal and vagus nerves which is responsible for swallowing process [12,13].

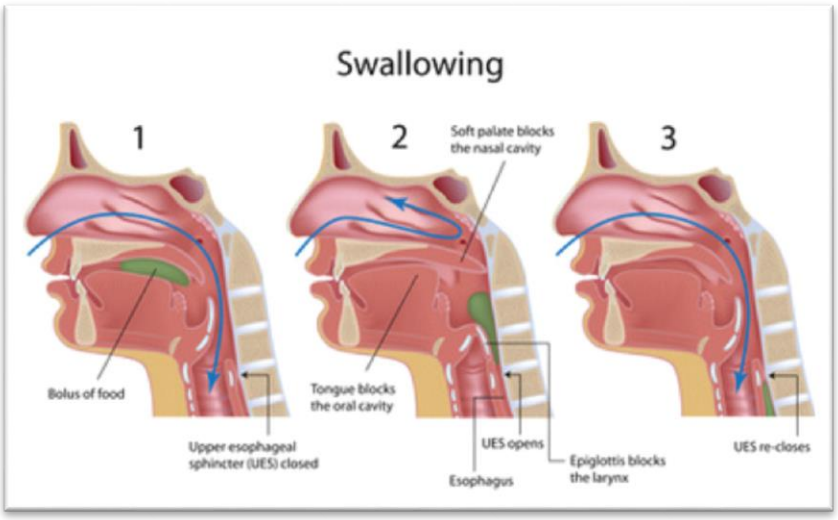

Figure (2): Swallowing process mechanism [14]

Dysphagia

Dysphagia is a medical term originated from the Greek words dys, meaning "difficulty", and phagia, meaning "to eat", it indicates the difficulty in moving foods and liquids from the mouth to the stomach [15]. Dysphagia is classified anatomically as either oropharyngeal (related to the difficulties in the passage of food from the oropharynx to the esophagus) or esophageal dysphagia (problems in passing food to the stomach resulting from abnormalities in esophageal peristalsis or in the lower esophageal sphincter). These are caused either due to mechanical obstruction resulting from malignancy (dysphagia for solids) or neuromuscular or motor disorder (dysphagia for both solid and liquid) [16]. Dysphagia causes several complications like poor medication adherence, dehydration, malnutrition, bronchospasm and airway obstruction, as well as aspiration pneumonia and chronic chest infection [11]. In order to overcome this problem five aspects can be performed. Surgery, dilation, and endoscopy can be used for management of mechanical dysphagia. On the other hand, medications can be used to reduce the symptoms associated with swallowing difficulties like hyperacidity in addition to the replacement of the medications that exacerbate this problem like drugs for insomnia and epilepsy. The final approach for the management of dysphagia involves swallowing rehabilitation via swallowing therapy and dietary changes which could be performed by different exercises in addition to the administration of thickened liquids or soften foods to make them easier to swallow [15,17].

It is estimated that dysphagia is a common problem in about 35% of the population specially pediatrics, geriatrics and patients suffering from significant illness like cerebrovascular accidents, neurodegenerative disorders, head and neck cancer, or head injury. For this reason, oral jellies were developed to reduce swallowing problem and suffocation associated with tablets and capsules due to its rheological properties which facilitates the swallowing process [18,19].

Basic Criteria for the Drug to Be Formulated as Oral Jellies [20, 21]:

Many factors must be considered when selecting drug candidates to be incorporated in oral jellies. In general, these newly developed dosage form has a different pharmacokinetic profile than the equal dose of the available dosage forms due to the possibility of pre-gastric absorption before the expected post-gastric pathway. Consequently, certain requirements should be available in the drug to be formulated as oral jellies like:

- Having small to moderate molecular weight.

- ❖ Possessing good stability in saliva and water.
- ❖ Its capability to permeate, diffuse or partition to the oral mucosa and into the epithelium of the upper GIT (log P >1, or preferably >2).
- ❖ It should be partially non-ionized at the pH of the oral cavity.
- ❖ Having a moderate or long half-life to avoid frequent dosing.
- ❖ The low dose drugs are preferred more (less than 50 mg).
- ❖ Drugs with a very bitter or unacceptable taste and odour drugs are unsuitable for oral medicated jellies.
- ❖ Not suitable for anticholinergic drugs or patient suffering from Sjögren's syndrome (dryness of the mouth) due to decreased saliva production.

Challenges in the Formulation of the Oral Jellies:

Several challenges present upon the formulation of the oral jellies, these may include:

1. **The amount of drug:** The technology of oral jelly is limited to the dose of the drug which could be incorporated in a unit dose formulation, since molecules requiring high doses present mainly three challenges including taste masking of the active ingredient, jelly size and mouth feel or grittiness [22].
2. **Palatability:** Taste masking of bitter drug presents a basic challenge for the formulators during preparation of the oral jellies since most active ingredients are unpalatable which might affect the patient acceptance and compliance [23].
3. **Aqueous solubility:** The water-soluble drugs have various formulation challenges as they form eutectic mixtures, which result in freezing point depression and the formation of a glassy solid that may cause a loss of supporting structure upon drying that eventually causing a collapse of the dosage form. This collapse could be prevented by the addition of certain gelling agent that induce crystallinity and provide rigidity like the almond gum [24].
4. **The drug property:** Certain properties such as crystal morphology, particle size, solubility and bulk density could affect the jelly performance [25].
5. **Hygroscopicity and environmental sensitivity:** Oral jellies are generally hygroscopic in its nature, for this reason special packaging should be applied to protect them from humidity and temperature [26].

The main advantages in oral jellies possess certain advantages such as improving the bioavailability by reducing first pass effect since it is introduced to the GIT as dissolved or suspended form in the saliva, in addition to its higher patient acceptance and compliance due to its rheological behavior and its suitability of administration at any time and place without the requirement of water. Furthermore, oral jellies can be easily produced with low cost giving an elegant dosage form [27]. On the other hand, the, main constrains of oral jellies are represented by the possibility of unpleasant mouth feel in case of improper formulation, the requirement of special packaging due to its high moisture content, in addition to flatulence and diarrhea which might result from the presence of sucrose and sorbitol [28].

Main Constituents of Oral Jellies:

Commonly, the oral jellies formulated using *active ingredient* **several** groups of medicaments could be incorporated to the oral jellies as illustrated in table 1:

Table (1): Active ingredients in oral jellies [6, 29]

Medication group	Example
Anti-helminthic	albendazole and mebendazole.
Anti-histamine	citrizine and cinnarizine.
Analgesic	ibuprofen, paracetamol and diclofenac.
Anti-emetic	domperidone and ondansetron.
Anti-diabetic	metformin and glibenclamide.
Leukotriene antagonist	zafirlukast and montelukast.

In addition, *gel forming polymers*, can be used different hydrophilic polymers can be used in the preparation of the oral jellies which might be used alone or in combination in order to give the desired gelling effect. The hydrophilic nature of these polymers promotes a faster disintegration and release from the prepared jellies due to the high-water intake comparing to insoluble polymers. However, the release of the active ingredients could be reduced by increasing the polymer molecular weight [30]. The various types of natural and synthetic polymers which could be incorporated in the oral jellies include pectin, gelatin, xanthan gum, tragacanth, cellulose derivatives and sodium alginate [31].

Furthermore, *stabilizers* such as sorbitol and propylene glycol are added to the jelly formulation to prevent the drying and maintain the required properties to the pharmaceutical product until it is consumed by the patient. Furthermore, EDTA is an example of chelating agent that is used to avoid any interaction between the drug and the jelly base [32].

Preservatives is another constituent that can be added in oral jellies are usually susceptible for microbial contamination as a result of its hydrophilic nature, for this reason preservative is essential component to retain the required shelf life of the preparation. Different preservatives are available for example methyl and propyl paraben, sorbic acid, sodium benzoate, and benzoic acid [33]. The pH modifiers, flavoring agents, coloring agent and sweeting agent [34-37] as shown in Table 2 and 3.

Table (2): Different flavoring agents with their specific taste masking effect [36]

Flavouring agent	Taste
Acidic	Orange, lemon, cherry, grape fruit
Alkaline	Vanilla, chocolate, mint
Bitter	Orange, anise, lemon
Metallic	Grape, berry
Sweet	Honey, chocolate, raspberry, bubble gum, mint

Table (3): Sweetening agent and their degree of sweetens comparing to sucrose [37]

Sweetener	Degree of sweetens compared to sucrose (X)
Sucralose	1000X
Dextrose	0.75X
Saccharin	500X
Aspartame	250X
Xylitol	1X
Sorbitol	0.5X

Preparation Method of the Oral Jellies:

All components should be accurately weighed then dissolve the gelling agent in a certain volume of distilled water usually at 95 ºC with stirring for 30 minutes. This was followed by adding of the sugar syrup to the polymer dispersion that is commonly performed at 80-85 ºC with continuous stirring. The active ingredient should be dissolved in suitable solvent like ethanol, glycerin or propylene glycol. Afterward, the drug solution is added to the polymer and glucose mixture after settling at 50-65ºC with continuous mixing.

The next step is the addition of stabilizers such as propylene glycol, citric acid and preservatives including methyl and propyl paraben with continuous stirring for several minutes in order to obtain a soft jelly with suitable pH and to prevent any microbial contamination. Finally, a coloring and flavoring agent should be added to the previous mixture that is followed by adjusting the pH with a certain amount of sodium citrate solution with a stirring for further few minutes. The resultant mixture should be poured in polyethylene mould and allowed to be cooled at room temperature with an air tight seal [31,39]. Figure 3 shows the appearance of different oral jellies formulated by different researchers. Oral jelly then evaluated for physical appearance viscosity, pH determination, syneresis, spreadibility, content uniformity, *in-Vitro* drug release, taste masking effect and stability test [41-50].

Figure (3): Example of some formulated oral jellies [28]

Recent studies on oral jelly formulations:

Different studies on oral jellies were implemented in the past few years. In 2009 Gohel M. C. et.al formulate paracetamol oral gel for oral administration, they prepare different formulas using different concentration of gellan gum as gelling agent (0.1, 0.3 and 0.5%) with two different concentration of sodium citrate as stabilizer (0.3 and 0.5%), polyethylene glycol 400 was used as solubilizer for the drug and sucrose/sucralose was used as co-solute. They found that the gel consistency depends on the concentration of gellan gum and sodium citrate in addition to the amount of the co-solute. Furthermore, the formulas with (0.3%) gellan gum and (0.3%) sodium citrate was selected as the optimal giving the best consistency with a complete release within 30 minutes [50].

Another study on paracetamol was performed by Hassen Bennasir A. H. and Shanmugam S., their study involves the measurement of drug content, stability and in-vivo screening effect on rabbit. The gel was prepared using (2%) carbapol as gelling agent which is neutralized by certain amount of sodium hydroxide. This research revealed the proper formulation and effectiveness of the prepared paracetamol oral gel as antipyretic agent to reduce the temperature of the animal under study [51].

Another study was performed by Katakam P. et.al. in 2014 to formulate carbamazepine oral jelly using different concentrations of pectin, guar gum, gellan gum and pectin-guar gum combination as gelling agent. It was found that oral jelly formulas with (1.2%) pectin, (1.5%) gellan gum and (1:0.4%) pectin-guar gum were the optimum formulas in masking the bitter taste of the anti-convalescent carbamazepine with acceptable mouth feel and flavour that could be successfully applied to paediatric and geriatric patient with swallowing difficulties [52].

Additionally, Natarajan R. et.al. formulated tadalafil oral jelly in 2014 for the treatment of erectile dysfunction. Different formulas were prepared using different concentrations of carbapol 940 as gelling agent that is neutralized with triethanolamine. Tadalafil oral jelly with (0.3%) carbapol was the selected formula giving the best release characteristics that is comparable to the marketed product, in addition to its better stability among the prepared formulas [53]. In the next year, Mahendrakumar D. and Zankhana S. formulated an oral jelly of palonosetron hydrochloride the antiemetic used in chemotherapy and radiation treatment. The researchers prepared different formulas of the oral jelly using different concentrations of different gelling agents including (2, 3%) of sodium alginate, carbapol 940, gelatin and carrageenan, (1, 1.5%) tragacanth gum and (4, 4.5%) xanthan gum. The research revealed that all the formulated oral jelly was acceptable with the formula contain 3% gelatin was the most preferred one giving the higher percentage of drug release with 60 minutes [54].

In 2016, Javalgikar A. and Shinde V. B. formulated a clotrimazole oro-retentive jelly by using xanthan gum in different concentration (0.5, 1, and 1.5%). The study showed that clotrimazole oral jelly was effectively prepared using xanthan gum with no syneresis and acceptable pH, physical properties and stability with the formula containing 1.5% xanthan gum gives the best in-vitro release effect (93%) within 30 minutes. The net result of this research confirmed the successful preparation of clotimazole as oral jelly which could be retained in the oral cavity for long time giving a local effect to treat oral candidiasis and increasing the bioavailability of the drug by-passing the first pass effect [55]. Furthermore, during 2017, Jadhav S. B. et.al. prepared an oral jelly of ondansetron hydrochloride for the treatment of nausea and vomiting.

Different oral jellies were prepared using different gelling agent in different concentrations including gelatin, tragacanth, xanthan gum and sodium alginate. They found that all the prepared

formulas showed an acceptable physico-chemical property with the maximum in-vitro release in 60 minutes observed in oral jelly containing (1.5%) xanthan gum [56]. Another study was performed by Ruheena T. and Sirisha M. they used xanthan gum and gelatin at different concentration in order to prepare domperidone oral jelly to give a faster relief from nausea and vomiting comparing to other dosage forms. They selected medicated jelly with 10% gelatin as the optimum formula which gives about (98%) drug release with 35 minutes [57].

Recently, in 2019, Prasanthi N. L. et.al. formulated anthelmintic pediatric oral edible jelly from the extract of tree Moringa oleifera, which is known as "miracle tree" due to the beneficial effect of all its parts. The nutritive part of the plant (leaves, seeds, roots) was reported to have an anthelmintic effect. The extraction was performed by Soxhlet extractor using four different solvents (aqueous, ethanol, methanol and chloroform), which was followed by formulation of the edible jelly using (2%) agar and (4%) gelatin as gelling agents. The researchers found that the herbal jelly prepared from the methanolic extract and gelatin had higher % release in 30 minutes, with an effective anthelminthic activity that is proved to be better than the commonly used piperazine citrate [58]. Table 4 illustrates some of the medicated oral jelly that is available in the market with their main application.

Table (4): Examples of the marketed medicated oral jellies [59]

Active ingredient	Application
Sildenafil	Erectile dysfunction
Tadalafil	Erectile dysfunction
Calcium polystyrene sulfonate	Hyperkalaemia
Isosorbide	Hydrocephalus
Donepezil hydrochloride	Alzheimer's dementia
Amlodipine besilate	Hypertension
Lactulose	Hyperammonemia
Aciclovir	Viral infection
Cilostazol	Chronic arterial obstruction
Alendronate	Osteoporosis

Conclusion:

The development of an oral jelly opens a new era for a drug delivery of different active ingredients. It provides an easily swallowed dosage form which can be given without the need of water, making it a good substitute over the readily available solid dosage forms for administration to dysphagic populations including pediatrics, geriatrics, or in case of nausea, vomiting in addition to travelling patient. Furthermore, it introduces the drug in a readily soluble form which might enhances the bioavailability of many poorly soluble drugs. Further studies are required to discover the various applications of this dosage form and to determine the possible ways to improve its stability.

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