

Formulation, Development and Characterization of Oral Jelly to Improve Therapeutic Effectiveness

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ABSTRACT

The oral route is the most convenient and has great effectiveness in taking new chemical entities; hence it has improved patient acceptance. However, the main limitations associated with such formulations involve unpleasant or bitter taste as well as problems related to swallowing and reduced bioavailability of chemical entities. When it comes to children, the main limitation is they cannot safely swallow the medications in the form of tablets and capsules. But kids, even those without teeth, can swallow the jelly easily. As in the development of new dosage forms for every child, taste, color, smell, texture, and appearance are important factors in improving patient compliance. Children refuse to tolerate the same medication again, which becomes a big problem for parents trying to take the medication. An effective way to solve such types of problems involves the production of children's friendly dosage formulations with attractive and eye catching taste, smell, color as well as texture. The most identical characteristic of oral jelly as dosage form is that it are easy to chew and dissolves rapidly in saliva so no water is required. Moreover, the good texture and appearance make it easy to attract patients as well as to improve patient compliance. Above all, it provides a soft and beautiful texture, causing no discomfort to patients.

Keywords: Jelly, Gelling agents, First-pass metabolism, Improvement of bioavailability.

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INTRODUCTION:

An ideal active chemical entity to cure from any disease is the one that reaches the optimum concentration at the absorption window as early as possible i.e. at the site of action within specified time at predetermined rate and maintain steady state concentration for the overall duration of the treatment. Most widely preferred routes for the administration of newly discovered API and recent forms of already existing drugs is nothing but the oral route. Recently, some rate retarding oral drug delivery systems are developed that retard the rate of release of active chemical entity for several hr (by combining the active chemical entity with rate retarding materials like polymers or by forming the film coat on the surface of core material containing pharmaceutical ingredient. Such type of modified drug delivery systems offer reduced dosing frequencies, reduced adverse effects and improved bioavailability. Since oral medicated formulation is non invasive hence it offers low cost, additionally its safety, efficacy, effectiveness, convenience of self administration, ease of production as well as administrations results in improved patient's compliance.¹

Most proffered oral solid dosage forms involve tablets, capsules, granules, powder and pills. The most evident limitations of such type of oral dosage form involves swallowing problems, resulting in patient's discomfort specially in the case of pediatric and geriatric patients, as well as it is observed in case of patients who ill in bed as well as who actively doing work or travelling or busy and having no access to water. Hence to avoid such inconveniences and to fulfill all the medical needs, the pharmaceutical researches developed a new novel drug delivery system known as Oral Medicated Jellies (OMJ's). The OMJ's require less time in terms of seconds to disintegrate in saliva and those are taken without need of water. Also it takes less time to dissolve, absorb and show clinical effects as related to that of other oral dosage forms; hence it shows better patient compliance.²

Oral jelly candies are becoming very common in pediatrics because as they enjoy to chew, therefore they may be used as a most effective method of administration of active chemical entity as an another preferable route to that of other unit and liquid dosage forms. Oral administration of medicinal jelly is

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beneficial not only for local treatment related to oral cavity but to treat the systemic conditions.³

Dysphagia

Dysphagia is none of the problem related to swallowing. It has potential to cause severe complications including malnutrition as well as risk of aspiration, it can carries limited social as well as psychological burden on patient. Patients having dysphagia will complaint about sensation related to food or drink sticks, holds up or stop in the throat or chest, but uncommonly they can have other discomfort such as regurgitation, vomiting or retrosternal disturbance. Most common signs include swallowing related to coughing as well as regurgitation of previously swallowed foods. Such discomforts related to swallowing are arises from problems related to control of neural system, coordination of muscles, inflammation and neoplasia.^{3,4}

Oral medicated Jellies

Orally administered drug containing jellies are palatable solid dosage form and are prepared to dissolve in saliva or oral cavity or pharynx to produce local as well as systemic effect. Japanese pharmacopeia defines jelly as the non flowable glutinous orally administrating formulation with definite size as well as shape. Jelly can be identified as semisolid formulations having no greasy or transparent or translucent characteristics, produced with the purpose of use internally as well as externally. The formulation components of medicated jelly includes active pharmaceutical moiety, For example, a medicine that has to start working quickly has a major absorption location in the stomach and small intestine. They also includes gums mainly naturally isolated gums or its synthetic derivatives. As jellies have eye catching appearance, pleasant taste as well as they are easy to handle, hence everyone can prefer jelly as a medication over other oral typical conventional formulations.^{4,6}

Need For Jelly Development

The basic purpose for non invasive delivery of active chemical moiety is patient's poor acceptance and compliance with, already approved conventional forms, limited market size of active pharmaceutical ingredient companies and active chemical entity usage can be related to the more cost of management of disease. The development of oral medicated jelly as an novelty in effective delivery of active chemical entity, aims to improve the safety as well as effectiveness of administered chemical moiety as well as patient compliance and convenience.^{5,6}

Ideal Characteristics of Jellies

- Jelly is compatible with pleasing feel of mouth and after sometime it does not leave any residue in oral cavity.
- It has capable of loading high amount of drug.
- Jellies are compatible with bitter drug and they are able to mask its taste.
- In altered environmental conditions they have low sensitivity for example in case of change in temperature as well as humidity.

- Jellies are hygroscopic in nature.
- Jellies are adaptable as well as they have minimal expense for conventional processing and also for packaging equipment.
- Jellies can be portable without fragility concerns.
- The excipients as well as drug characteristics has no or minimal effect on the oral disintegration of jellies.⁵

Advantages of Medicated Jelly

- It is simple to handle and no water required, that's way it is straight forward for the administration at any time and at any location.
- With the help of jellies it is possible to deliver the drugs that are likely to be metabolized in the liver or gut wall.
- The medications that are disintegrated and ingested from the jelly formulation have capability to reach quickly in the gastrointestinal tract in terms of seconds because they can be in dissolved or suspended from in saliva.
- Pharmaceutical medicated jellies are ideal to administered within the patients (pediatrics, adults, psychiatrics) who are unable to swallow other conventional solid products for improvement of patient compliance. Hence it serves as an most effective method for patients having dysphasia as it results in lowers aspiration risk.
- It has smooth mouth feel and it alters how people perceive medications.
- Economical as compared to other oral dosage forms. Jellies can enable heavy drug loading.
- Jellies can enable heavy drug loading. Fast medication delivery from the dose forms is offered as compared to other solid dosage forms.
- Those are flexible and compatible with current processing and packaging equipments.
- Jellies have capability to give local and systemic effect.
- Jellies are also capable to overcome dental caries as well as candidiasis like problems.
- It is possible to avoid the common limitation of choking and suffocation during oral administration of other conventional products due to physical obstruction which results as providing improved safety.⁵

Disadvantages of Jelly

- As the jelly formulation is aqueous one there is need to do proper packaging for improvement of stabilization as well as safety of drugs.
- As jelly contains sweetening agents like sorbitol or sucrose it can cause flatulence as well as diarrhea like disorders.
- They have store in dry place as they are hygroscopic in nature.
- The production process of jelly is cost intensive.⁵

Types of Jellies

Figure 1 highlights the different types of jellies.

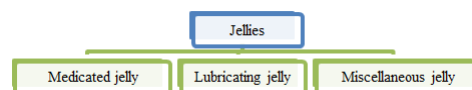


Figure 1: Types of jelly

Medicated jelly

Medicated jellies are generally used on the mucosal layer as well as on the skin also they have spermicidal, local anesthetics and antiseptic properties. They are capable of holding adequate amount water and on the evaporation it gives a quite cooling effect and they form residual film over skin which provides protection from foreign materials. Example: Domperidone oral medicated jellies for faster relief from nausea as well as vomiting as compared to that of other products.⁶

Lubricating jelly

The main purpose behind the development of such type jelly is to lubricate equipments such as diagnosis like surgical gloves, catheters, cystoscopes.⁶

Miscellaneous jellies

Miscellaneous jellies are developed with various purposes such as for patch testing, electro cardiography.

• Patch testing

In this test jellies are act as vehicle of allergens, to be attached to the outermost membrane of skin for sensitivity detection, as well as they can help to separate the particles.⁶

• Electro-cardiography

In this test electrode jelly may be applied for the reduction of electrical resistance within the skin of patient and electrodes of cardiograph. For the production of good conductivity NaCl is applied and after that pumice powder is applied on the surface of skin for the removal of horny layer of skin which act as the barrier for electrical resistance.⁶

Formulation Composition of Jellies

Drug selection criteria

- The drugs having capacity to pierce the oral mucosa are good candidates.
- The drugs which are in its unionized form at the salivary pH of oral cavity.
- Jellies possess the capacity to get diffuse and partitionate ($\log P > 1$, or preferred > 2) from the epithelium of upper GIT track.
- Drugs having molecular weights between small and medium are good candidates for jelly formulations.
- Preferably less than 50 mg of dose medications are good candidates.
- Active pharmaceutical ingredients with which require frequent dosing because of its short half life are inappropriate to use in oral medicated jelly formulations.
- The drug those are stable in both water as well as saliva.
- The drugs have capability to penetrate through oral mucosal tissue membrane.⁷

Gelling Agents

Gelifying agents are usually hydrocolloids, used to form gel like matrix. Colloid based dissolving gelling agents create a internal structure mainly weakly cohesive in nature to dissolve in the liquid phase.

Examples of gelling agents included in Figure 2.

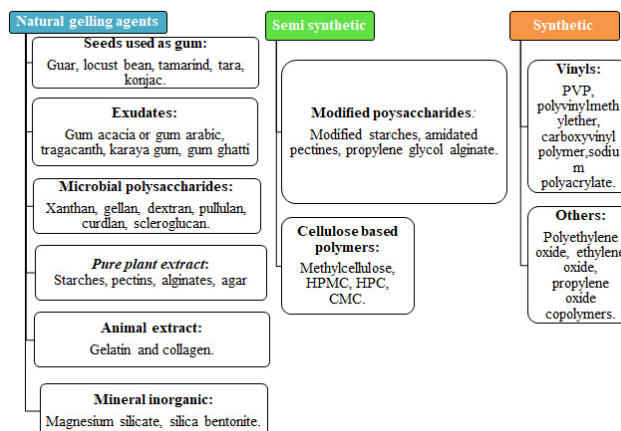


Figure 2: Classification of gelling agents

Natural

• Guar gum

It is extracted from *Cyamopsis tetragonoloba* plants seed which is a member of *Leguminosae* family. Hydrophilic gum is present in the endosperm region and it is used to stabilize, emulsify and thicken the various products. It has an ability to get swell or dissolve in polar solvents and it can form strong H^+ bonds with solvent but in the solvents, specially non-polar it can form weak H^+ bonds as compared to polar solvent.⁸

• Locust bean gum

It is also identified as carob bean gum, and it can be formulated with the help of endosperm of carob seeds (*Ceratonia siliqua*). The isolation process of carob gum involves the two steps i.e hull removal from the seeds with thermo-mechanical or chemical treatment. When separation of hull is done, seeds are then split according to its length and then the portion of germ is isolated from the endosperm. Afterwards endosperm is subjected through the process of grinding, sifting, grading and packaging then finally it will be marketed for various use.⁹

• Tamarind gum

Tamarind gum is isolated from the seeds of *tamarindus indica* L. Seeds of mature pods are milled and grounded through a mesh. Then with continuous stirring add the milled tamarind seeds into bidistilled water. After boiling of mixture upto 80°C kept the mixture aside for the separation of mucilage. Centrifuge the resulting solution, after centrifugation the supernatant represents the mucilage content, filtrate the solution and store the mucilage at cool and dry place.¹⁰

• Tara gum

It is a cheapest alternative of gum guar and locust. It is isolated with the help of mechanical separation process from endosperm of Tara seeds (*Caesalpinia spinosa*).¹¹

• Konjac

Konjac glucomannan is a polysaccharide having hydrophilic property and it is isolated from the tubers of konjac. α -mannase can be responsible for the hydrolyzation at the last part of small

intestine as well as colon in the human body. The formulation methods of konjac as a gelling agent mainly includes processing of alkaline, cross linking of borate, compounding of polymer, electric field preparation at high voltage and after modification metal ion cross linking.¹²

Extrudates

- *Gum arabic*

Producers of marketable gum arabic include *Acacia senegal* (Hashab gum), and *Acacia seyal* (tall gum). *Acacia seyal* var. *seyal* (tall) is found in the Savanna belt of Sudan.¹³

- *Tragacanth*

Astragalus genus species used to produce gum tragacanth. *A. gummifer*, *A. parvianus*, *A. flucosus*, *A. rahensis*, *A. gossypinus* and *A. microcephalus* are commonly used tragacanth producing species. Types of gum tragacanth on the basis of shape are ribbon and flakes. The incisions mainly horizontal and diagonal results in production of ribbon shaped gum and the vertical produce flake shaped gum exudates like granules.¹⁴

- *Gum Karaya*

Karaya (*Sterculia Urens*) is a plant belonging to the Malvaceae family. Due to its acid stability, karaya gum is the most difficult gum to dissolve. Colloidal particles are not hydrophilic, but they absorb water and expand up to 60 times their original volume, allowing the liquid to freeze. It can exhibit swelling properties due to the presence of acetyl groups in its structure.¹⁵

- *Gum ghatti*

Gum ghatti was isolated from the tree *Anogeissus latifolia* (Combretaceae). It contains calcium salts of high molecular weight complex polysaccharides consisting of sugars and uronic acids. It has stabilization, binding, thickening, emulsifying and suspending type of actions. It can produce stable o/w emulsion that's way it can be used in the development of oil soluble vitamin containing formulations.¹⁶

Microbial polysaccharides

- *Xanthan gum*

Microbial polysaccharide developed from glucose fermentation of *Xanthomonas campestris* is nothing but the xanthan gum. Also known as gum corn, keltrol, polysaccharide B-1459, rhodigel, and vazan NF. Beside its gelling property it is also used as stabilizer in emulsion and suspension formulations.¹⁶

- *Gellan gum*

It is isolated from the *Pseudomonas elodea* in the form of Anionic deacetylated exo-polysaccharide having tetra saccharide repeating units of one α -L-rhamnose, one β -D-glucuronic acid as well as two units of β -D- glucose.¹⁶

- *Dextran gum*

Dextran is isolated from sucrose with the help of dextranase as a bacterial enzyme. *Leuconostoc mesenteroides*, *Saccharomyces cerevisiae*, *Lactobacillus plantarum* and *Lactobacillus sanfrancisco* are type of microorganisms useful for the preparation.¹⁷

- *Pullulan*

Pullulan gum is a complex polysaccharide, it can be produced extracellularly with the help of *Aureobasidium pullulans* fungus. Structurally it is a complex linear polysaccharide with maltotriose and maltotetraose units linked together with the help of α -D-(1 \rightarrow 6) bonds on its terminal portion.¹⁸

- *Curdlan*

Curdlan is isolated from *Alcaligenes faecalis var myxogenes*. Soil bacteria is responsible for the microbial synthesis of curdlan. Non pathogenic rod shaped bacterium *Agrobacterium sepcies*. is a gram (-)ve, used for the development of curdlan. Also the *Agrobacterium fabrum* was used for the production it is separated from the leguminous plants nodules of mainly groundnut and pea plant.¹⁹

- *Scleroglucan*

Scleroglucan is secreted by *Sclerotium fungi*. Only D glucose is released upon complete hydrolysis, from this hydrophilic homo polysaccharide. Due to its weak triple helix cross-linking mechanism, sclerodextran tends to form thermoreversible gels at low temperatures (around 70°C).²⁰

Pure plant extracts

- *Starch*

It is isolated with the help of Seeds, maize, waxy maize, high amylose maize, wheat, rice, tubers, roots, especially potatoes, sweet potatoes and cassava. Starch is a natural water soluble polymer, having swelling or gelling ability. It has multiple roles depending on structure and its arrangements including binding, compaction, disintegration and film forming property. It is nothing but an polysaccharide that can be produced from plants or it can be present in fruits, roots, tubers, legumes as well as cereals. Starch granules synthesized from plants through the process of polymerization of glucose including carbon dioxide photosynthesis.²¹

- *Pectins*

Pectin, a polysaccharide and polygalacturonic acids methylated ester occurring naturally. It commercially isolated from peels of citrus and pomace of apple under mild acidic conditions. Its gel forming ability is depends upon the molecular size and degree of esterification, that's way the gelling ability of pectin is different for its varying sources. Powdered dry form of pectin, when mixed with water, then it have tendency to hydrate very rapidly and it result in its clump form. Such clumps are consist of semidry packets of pectin, with highly hydrated outer layer coating.²²

- *Alginates*

Alginate is a polysaccharide isolated naturally with the help of brown algae, It is used in the food industry to change food properties such as rheology (thickening), water binding capacity, emulsion stability and film forming properties. Like other polysaccharides such as gelatin or agar, alginate can thermally form a gel. There are two ways to prepare alginate gels: ionic cross-linking with cations (ionic gels) or acid precipitation (acidic gels).²³

- *Agar:*

Is an polysaccharide and hydrocolloid seaweed with significant gelling ability. Red algae for example *Gelidiella acerasa*, *Gracilaria lemaneiformis*, *G. crassa*, *G. falkenbergii* as well as *G. vecosa* are used for the development of agar. *Agarophytes* and *G. acerosa* formulate agar with bacteriological action and *Gracilaria* species produces agar having food like quality. For the isolation of agar, refined seaweeds are boiled by adding water at more than 100°C temperature and for the purpose of proper separation 0.02% of sulphuric acid or 0.05% of acetic acid is mixed in the resulting solution.²⁴

Animal extract

- *Gelatin*

Gelatin is a polymer produced naturally from hydrolytic degradation of proteins as well as collagen. It has two types of gelatin i.e type A, it is an acidic gelatin having isoelectrical point at 6-9 and another type B is an alkaline gelatin having isoelectrical point 5 and are made up from degradation of collagen. Gelatin is extracted from porcine and bovine.^{25,26}

- *Collagen*

All collagen different from each other in terms of sequence, structure as well as function and are found in vertebrates and invertebrates Therefore, each product is distributed differently in the skin, bones, tendons, vessels or intramuscular connective tissue to ensure the stability and properties of the tissue and body.²⁶

- *Mineral inorganic*

Magnesium silicate and silica betonies

Silicate gel has a certain limitations such as it has fire extinguishing effect, synthesize harmful gas, reduced compressive strength, undefined time of gelation, easy dry cracking and powder after water loss, hence it limits its application. Bentonite is composed from montmorillonite and it also has layered silica like structure. It has been reported that bentonite has been added to the polymer for the formation of good matrices for preparation of hybrid gels.^{27,28}

Semi-synthetic gelling agents

- *Modified polysaccharides*

The gelation properties of gels is influenced by propylene glycol esterification, it form electrostatic association combined with hydrogen bonding leads to rapid formation of weak gels. Unlike other polysaccharides such as gelatin or agar, alginate can form temperature-independent gels. Alginate gels can be formed by two methods: ionic cross-linking with cations (ionic gels) or acid precipitation (acidic gels).²⁹

- *Cellulose based polymers*

It is widely used natural biopolymer. Plants, natural fibers, cotton, hardwoods or softwoods, linen, jute, hemp contain large amount of such type of polymers it can be synthesized with the help of fungi and it also found in animals. Plants derived cellulose a derivative found as fibers from macromolecules

with hundreds of glucose molecules. They are classified according to the separation of electrolytes or charges, such as non-ionic (non-ionic) polymers (e.g. MC, EC, HEC, HPC, HEMC, HPMC) and charged ionic (anionic and cationic) polymers.³⁰

Synthetic gelling agents

- *Vinyls*

Polymethyl vinyl ether is a synthetic copolymer of methyl vinyl ether and maleic anhydride. The most commonly used plasticizer in the production of polymethyl vinyl ether hydrogels is polyethylene glycol. Carboxyvinyl polymers (Carbopol grades) are used as gelifying agents in the ophthalmic delivery of various active chemical moieties.^{31,32}

- *Others*

Poly(ethylene oxide) is nothing but synthetic polymer having same chemical structure as that of polyethylene glycol having higher molecular weights. Polyethylene oxide is produced with the help of catalytic polymerization of ethylene oxide in the presence of metallic systems as a catalyst. Depending on molecular weight of Polyethylene oxide it has varying rates of dissolution and swelling, viscoelastic behavior, extent and duration of bioadhesion can be achieved. Hence, it is popular among the bioadhesive dosage forms.³³

Sweetening Agents

Sucrose

It is the most preferred sweetening agent because its hydrophilic as well as economical property in its highest purified form. Its physical properties and chemical properties are stable in various ranges of pH.³⁴

Saccharin

It has excellent solubility and water stability. But in increased amount it gives bitter or metallic after taste.³⁴

Dextrose

It is chemically in its anhydrous as well as monohydrate form, among those hygroscopic nature is seen in its anhydrous forms. Dextrose has 70 % more sweetening property as compared to sucrose in the various formulations.³⁴

Sucralose

It is produced by replacement of 3 -OH⁻ groups (hydroxyl) with -Cl⁻ (chlorine) atoms in the structure of sucrose molecule and used as an artificial sweetener. It is about 320-1,000 times sweet as compared to that of sucrose, twice sweet as compared to that of saccharin, and thrice sweet as compared to that of aspartame. As compared to sucrose it has reduced onset of sweetness but it can be remain for longer time.³⁴

Mannitol

When fructose is hydrogenated it results in the production of mannitol, it is a white, crystalline polyol. It has a similar sweetness as to sucrose of about 50%. Due to the negative heat of mixture, it has freely hydrophilic property. When chewed it gives quite chill feeling or completely dissolves in the oral cavity after administration.³⁴

Sorbitol

Is an alcoholic sweetener form as well as is an isomeric form of mannitol. It is about 60% sweet as compared to that of sucrose. It has thickening property and it is used as humectant in cosmetics. It is used in the development of soft gel capsules. It is available in the form of Sorb Tab and crystalline type in the direct compression procedures.³⁴

Coloring Agents

Uses of coloring agents;

- Help recognition and differentiation of pharmaceutical formulations.
- It can help to match the illusion of formulation with flavors used.
- It gives information about aesthetic illusion of the product as well as to increase patient acceptance.
- To give pleasing illusion to products.
- Helps to improve patient acquiescence.
- To keep the dosage form's color uniform to differentiate from other.

Types of coloring agents

- *Natural colors*

Such types of colorants are isolated from natural sources as well as it can be chemically produced as β -carotene and Lycopene.

- *Mineral colors*

Mineral colors such as blend of ferric oxides mainly red and yellow and results into flesh color.

- *Dyes*

Such types of colorants are synthetic chemical compounds used to give color after complete dissolution in a suitable solvent such as glycerin as well as propylene glycol. It is composed of 80 to 93% of pure colors. For example, Crystal violet, safranin, methylene blue, etc.

- *Lakes*

Aluminium salt of FD and C hydrophilic dyes when extended on a substratum of alumina then it is known as lakes. When it is produced with the help of calcium salt of FD and C dyes then such types are permitted.³⁵

Flavoring Agents

With the help of flavoring agents it is possible to mask bitter taste of products. Due to that it is possible to improve patient compliance. There are five types of flavoring agents such as Acidic (orange, lemon, cherry), alkaline (vanilla, chocolate, mint), bitter (orange, fennel, lemon), metallic (grape, berry) and sweet (honey, chocolate, raspberry, mastic, mint).³⁶

Preservatives

Mainly jellies are in the aqueous forms that's way they commonly prone to the microbial growth. Although cellulose derivatives and clay resist the growth of microorganism but preservation is must important in the limitation of all incompatibilities within chemical moiety and other excipients

such as gelling agents which are affects on product shelf life. Some commonly used preservatives in the jelly formulations includes: Methylparaben, propylparaben, benzoic acid, benzalkonium chloride thiaz chlorhexidine acetate.³⁷

Stabilizers

Generally those are added to retain important characteristics of formulations as well as to avoid incompatibilities during shelf life of product. Generally Propylene glycol and Sorbitol are used. Chelating agents can be used to avoid the incompatibilities of drug and other components of formulation e.g. EDTA.³⁸

Method of Preparation of Jellies

Generally, jelly is prepared by using heating and congealing method

For the development of jellies weigh each and every required ingredients accurately using calibrated weighing balance. In organic phase add weighed amount of drug and stirrer the solution until drug get dissolved completely. The aqueous phase consists of sugar solution with required amount of gelling agent, stirrer it with the help of mechanical stirrer and heat the solution until it results in desired stiffness. After complete dissolution of gelling agent add stabilizers and citric acid for pH adjustment and boil the resulting solution for few minutes to get homogeneous mixture. In this solution preservatives are added with continuous stirring to form uniform mixture. In this resulting solution add organic phase containing drug with stirring on mechanical stirrer. Pour the prepared solution into moulds and allow it for cooling.³⁹

Molds and Packaging Material of Jelly

There are so many categories of molds for the development of jelly like plastic, silicon, flower, copper, chocolate etc. Moulds for jelly formulations are shown in Figure 3 and packaging materials for jelly are shown in Figure 4.

To avoid any incompatibilities there is need to store jelly within glass containers or in plastic containers and pouches as well as to prevent spoilage of product only paraffin seal is not adequate. Hot jelly is able to sterilize the container itself hence there is no need to pasteurize it.^{39,40}



Figure 3: Moulds for jelly formulations

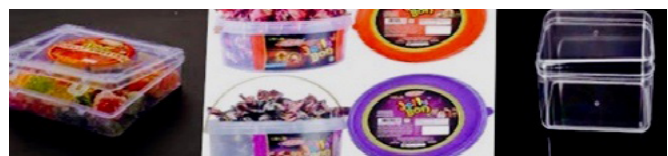


Figure 4: Packaging of jelly formulation

Formulation Challenges of Oral Medicated Jellies

Moisture content

Jelly products are unable to retain physical properties under normal ranges of temperature as well as humidity because they are hygroscopic in nature, that's why they require specialized product packaging for more protection from humidity.³⁹

Palatability

To mask the bitter taste of oral medicated jelly product is an most important challenge for scientist to develop novel dosage forms. Majorly, pharmaceutical drugs are unpalatable in nature therefore most of the time orally administered product contain taste masked form of the medicament because it can directly affect the compliance of patient.³⁹

Aqueous solubility

Hydrophilic drugs are more prone to challenges of formulation because they have ability to produce eutectic mixtures that's results in depression of freezing point as well as it is able to form glassy solid that has limitation to collapse on drying during the sublimation process due to the loss of supporting structure. But those are having collapsible structure and it is possible to prevent such type of problems with the help of jelly forming components for example almond gum which is able to induce crystallinity as well as induce rigid formulation.³⁹

Dose or amount of drug

Chemical entities that require high doses are gone through three challenges for the development of instantly dissolving pharmaceutical products;

Taste masking of the active chemical entity or medicament.

Mouth feel as well as grittiness after the administration of dosage form and size of jelly formulation.

Required amount of active chemical entity in various products will be depends on the bitterness degree of drug and dose which can ultimately affect the size of formulations.³⁹

Size of jelly

Easy administration of a jelly by the patient is relied on its size. Till now researchers have reported that the most compatible size for swallowing is of about 78mm while for the purpose of handling easiest size will be larger than 8 mm, but it is difficult to achieve both parameters simultaneously.³⁹

Mouth feel

For the better mouth feel it is important that after the oral administration the process the disintegration of particles released from jelly could be smaller as possible and they are able to produce minimal residue in mouth. For the improvement of mouth feel flavors and cooling agents such as menthol are added to formulation beside that it can also results in improvement of patient compliance.³⁹

Sensitivity

All the ingredients involved in the development of jelly are able to dissolve in minimum quantity of water, the formulated jelly can posses less sensitivity for change in environmental conditions.³⁹

Drug property

Solubilization, morphology of crystal, size of particle as well as drugs bulk density has ability to change end characteristics of jellies formulation including its strength and dissolution properties of jelly.³⁹

Evaluation Parameters of Jelly Formulation

Physical appearance

Physical examinations are important part in each and every formulation because it can gives the information about patient acceptance as well as their compliance. We have to evaluate prepared jellies visually for color, size, shape, texture, clarity and their consistency.^{40,41}

Weight variation

Weight variation of jellies is calculated from the weight of 10 jellies and its average after removed from the mold, taken into the beaker for weighing individually.^{40,41}

Stickiness and grittiness

Stickiness as well as grittiness property has been examined simply by rubbing it slowly between two glass slides or fingers.^{40,41}

pH

This can be simply examined at room temperature with the help of digital pH meter. To evaluate it simply 1% solution was prepared by taking 0.5g of sample of jelly and further it is added into the 50ml distilled water and pH of resulting solution is calculated on digital pH meter because its affect on not only the stability but also on the taste of final product.^{40,41}

Pourability of the mixture

Salts of buffers (retarders) such as trisodium citrate acts as an important material in the process of pourability, during the hot phase it can be able to approach pectin molecules it can also interfere sterically and results in raising the pH prior to mixing of an acid, and prevent pregelation process. As the concentration of buffer salts increases the setting temperature will be reduces and thus it require longer time for the setting of molecules, that's way it can provides appropriate time for pouring as well as settling of the jellies.^{40,41}

Water activity

The amount of water available in the product is termed as water activity. It is considered as an most important factor in process of control of spoilage. Water activities below 0.91 most of the

Table 1: Components of artificial saliva

Ingredients	Quantity
NaHCO ₃	5.208g
K ₂ HPO ₄ ·3H ₂ O	1.369g
NaCL	0.877g
KCL	0.477g
CaCl ₂ ·2H ₂ O	0.441g
Water	Qs 1 litre.

Table 2 : Literature survey for jelly formulations

<i>S. No.</i>	<i>Drug</i>	<i>Excipients</i>	<i>Outcomes</i>	<i>References</i>
1	Oral jellies of carbamazepine	Gellan gum, polyethylene glycol-400, sodium lauryl sulfate, citric acid, sucrose, methyl paraben, propyl paraben with Cremophor RH 40	The pH levels of formulations was shown in the range of pH 6.37 ± 0.03 and 6.83 ± 0.04 . Each of the formulations exhibited a drug release rate exceeding 50% within a 15 minute timeframe, with the exception of those comprised solely of gellan gum.	42
2	Formulation and evaluation of domperidone oral jelly	Sucrose, Xanthan gum, Gelatin, Citric acid, Sodium citrate and Sodium benzoate were used.	The F5 formulation has the greatest drug concentration, $99.300 \pm 51\%$. Using the simulation approach, the drug release of soft chew and jelly formulations is 95.8% and 98.39% in 25 minutes, respectively.	43
3	Oral jelly of trazadone hydrochloride	Xanthan gum, gelatin, sugar, citric acid, sucrose, methyl paraben and propyl paraben were used for the development of jelly.	Drug content of F1 to F8 formulations was found in between 88.42 to 98.95%. F7 batch consist of gelatin with xanthan gum showed 98.95 % release of drug.	44
4	Oral soft chewable jelly containing flurbiprofen	HPMC K100, Pectin, sodcmc, Tween 80, Polyethylene glycol (PEG400), Citric acid, methylparaben, propylparaben	(FP2) formula composed of pectin(4.5%) and sucrose (40% w/v) was choosen as optimum as it showed high percent DE (78.95%) as well as better consistency characteristics.	45
5	Ketoconazole jelly	Carboxy Methyl cellulose sodium salt, Xanthan gum, Sucrose, Citric acid was used for the development of jelly.	Among the seven formulations, formulation K3 with 5% Sodium carboxy methyl cellulose was found to be promising.	46
6	Etilefrine hydrochloride jelly	Gum such as (Guar, xanthan, tragacanth), sodium alginate, Pectin, methylparaben, propylparaben, Sucrose, calcium chloride potassium dihydrogen sulphate, disodium hydrogen phosphate, Citric acid, rosuvastatin are the other constituents.	More than 96% of etilefrine dissolved within 10 min while only 22.35 was dissolved as compared to marketed tablet.	47
7	Oral soft jelly containing glibenclamide	Gum guar, pectin, methyl paraben, stevia , mannitol, citric acid, sodium citrate, are all ingredients.	The amount of glibenclamide in all the batches was in between 98.3 ± 1.0 which is substantially within acceptable limits.	48
8	Oral Medicated Jelly of Palonosetron Hydrochloride	Tragacanth gum, sodium alginate, gelatin, Carbopol 940, Xanthan gum, Carrageenan, propylene glycol, Citric acid, Methyl paraben and Propyl paraben are all ingredients.	According to the observations of various parameters of formulation F8 with 3% gelatin as gelling agent has been shown acceptable values as compared to that of others.	49
9	Sildenafil Citrate Oral Jelly	HPLC-grade ammonium acetate and acetonitrile, potassium bromide reagent, Sodium carboxymethylcellulose, glycerin,talc, sodium benzoate, saccharin sodium, 0.01N hcl,	The percentage of drug content in all of the formulations between 98.25–99.35%, showing that the drug has uniform distribution as it is present within the acceptable level of 90%–110%	50
10	Tadalafil oral jelly	Triethanolamine, Propylene glycol, Carbopal 940, Sucrulose, Acetonitrile, glacial acetic acid, sorbitol	The drug content f1 to F6 ranges from 70.25 to 98.80%. When compared with marketed product the similarity factor (f2) values of all the (f1 to f6) formulation were 50.64, 56.72, 61.80, 70.93, 93.58 and 86.30.	51
11	Medicated jelly of vitamin C	Starch, sorbitol, gelatin, Hydroxyl naphthol blue disodium salt, octanol and Liquid glucose sugar.	All the preped solutions showed greater than 50% release of drug in 15 minutes and 93% release of drug in 30 minutes.	52
12	Oral Soft Jellies of Salbutamol Sulphate	Sorbitaol, Polyethylene glycol 400, Glycerin, Sodium citrate, Gelatin, Sucrose, Propyl paraben, Methyl cellulose, Sodium carboxy methyl cellulose, Methyl paraben and Aspartame.	The ph of all the formulations was found between 6.54 ± 0.06 to 6.74 ± 0.02 . In all produced jelly formulations the weight variation = $0.99\% \pm 1.24$ to $1.01\% \pm 0.74$. The content of drug from $98.23\% \pm 0.58$ to $99.25\% \pm 0.35$.	53
13	Granisetron Chewable Pediatric Oral Jelly using natural jelling agents.	Citric acid, sucrose, methylparaben, propylparaben, amaranth, strawberry	F1 consist of 4.5% gelatin had shown optimum results, with maximum drug release 99.4% in 15 min as well as acceptable results of all evaluation tests.	54
14	Taste Masked Doxycycline hcl Medicated Jelly	Glucose, 2- hydroxypropyl β -cyclodextrin, Starch, Citric acid,	In vitro dissolution test on formulation in artificial saliva revealed maximum 99.3% drug release within 20 min. The medicated jelly showed the 1st order release kinetics. The chewing has shown drug release of greater than 90%.	55

15	Jelly candy containing carrageenan and konjac	K –Carrageenan, Konjac, kcl, Dextrose, Potassium citrate, High Fructose Syrup, Sugar, Sodium benzoate.	The jelly candy texture produced by A batch with k-carrageenan : konjac ratio (40: 25) was found similar to that of commercial one. Hardness = 470.7 g, elasticity = 4.5 mm , stickiness = 36.15 g.	56
16	Albendazole Jelly using Heating Method for Anthelmintic Activity	Gum acacia, tragacanth, Gelatin, Methyl paraben, Propyl paraben, Sucrose, Citric acid, Glycerin.	Drug content (%) 91.45±0.65. According to evaluation study, as the polymer concentration was increased, stickiness of jelly was reduced and as the concentration of polymer was reduced, stickiness and grittiness of jelly was improved with maximum drug content (%) 91.45±0.65.	57
17	Jelly for supplement of calcium	Pectin, gelatin, agar, tragacanth, sodium alginate, citric acid, sugar syrup, propylene glycol, sodium bemzoate, calcium gluconate are all ingredients.	When compared to the others, formulation containing 3% gelatin as gelling agent showed satisfactory results.	58
18	Ondansetron medicated jelly	Gelatin, Carbapol 934, Dextrose, Citric acid, Methyl paraben, Sucrose are all ingredients.	The drug content of F3 formulation was in the range of 87.67% indicating that formulation have homogeneous of content and bioavailability has improved.	59

bacteria are unable to grow and water activities less than 0.80 most of the molds cease to grow.^{40,41}

In-vitro taste analysis

Foe the analysis of taste competency of jelly formulations 5 ml of simulated salivary pH was used. At least single jelly of individual batch is introduced in 5 ml solution for 60 -120sec and the resulting solution is filtered. Drug contents are examined by checking the absorbance of the filtrates.^{40,41}

In-vivo taste evaluation

Taste evaluation can be done by *In-vivo* i.e with the help of human volunteers. At taste panel experts keep 5g of optimized formulation for 5 sec, in their mouth. Report the comment of volunteers after administration of product.^{40,41}

Viscosity study

Determination of viscosity of jelly can be done by using Brookfield Viscometer having spindle no. 4 in which non Newtonian system is present and measure the results for fix time (2 min) with 1.5 rpm at 25 ± 5°C.^{40,41,3}

Formula for the viscosity was given as,

$$\text{Viscosity in centipose} = \text{Dial reading} \times \text{Factor}$$

Texture analysis

It involves pressing of jelly with two fingers and hemispherical probe with a diameter of about 12 mm is useful in the replication of geometry of a finger pressed on the sample.^{40,41,8}

Content uniformity

Crush jelly formulation from every batch and prepare its homogeneous mixture. Isolate average amount of drug from the mixture with the help of suitable media. Examine the quality of drug by using suitable analytical techniques. The main purpose behind this test is to assure that each final product contains similar amount of active chemical entity within each batch of formulation.^{40,41,2}

Drug content

To perform drug content studies randomly select jellies and then crush it with the help of mortar, then take equivalent amount of

mixture as to that of drug then dissolve it in 100ml phosphate buffer having pH 6.8. Then analyze the resulting solution spectrophotometrically by using UV spectrophotometer.^{40,41,9}

In-vitro dissolution study

To check dissolution behavior of drug, generally paddle type USP apparatus is used. Take 900ml dissolution medium (Artificial Saliva) and optimize the conditions such as temperature 37⁰C ± 0.5⁰C and 50 rpm speed. We have to withdraw upto 5 ml of sample at 10, 20, 30, 40, 50, 60, 90 and 120 min and at that time we have to maintain sink condition by replacing it with fresh media. Then dilute the resulting solution up to 10 ml with same solvent. The drug content of sample is determined with the help of absorbance by using UV spectrophotometers or by using suitable analytical method.^{40,41,48}

Components of artificial saliva

Formulation builders of artificial saliva are described in Table 1.

Spreadability

For the determination of spreadability we have to place approximately 2.5g of jelly in between 2 glass slides by keeping 1000 gm weight for 5 minute and compress it to get proper thickness. Spreadability is determined in terms of time in second required for the separation of 2 slides. Lesser the time interval required to cover the distance it results effective spreadability.^{40,41}

Syneresis

Upon storage separation of water from resulted product then is known as syneresis. We have to observe all the jelly at (25 ± 5°C) and 8 ± 1°C.^{40,41}

Stability studies

As per ICH guidelines for the stability studies we have to place all the samples for about 3 months at various temperature conditions (0-8⁰C) as well as at room temperature. Then we have to observe at interval for about 1 month for viscosity, appearance and pH conditions.^{40,41}

25°C or 60%RH ($\pm 2^\circ\text{C}$ or $\pm 5\%\text{RH}$)
 30°C or 65%RH ($\pm 2^\circ\text{C}$ or $\pm 5\%\text{RH}$)

Literature Survey for Jelly Formulations

The Table 2 highlights the current scenario about the characteristics, Drug selection criteria, properties for selection of excipients and evaluation parameters on the mouth dissolving jellies.

Applications

- Children's and adult patients who have dysphagia or any another problem related to difficulty in chewing or swallowing jellies are considered as effective ideal dosage form.
- For the patients having risk of choking.
- For the patients who has unavailability of water for consuming oral dosage forms.

CONCLUSION

As jelly formulations have quick onset of action in the event where water is unavailable, ease of use and enhanced patient compliance, they are most effective and preferable to other traditional dose forms. Patients with dysphagia and pediatrics can use the jelly formulation more efficiently and conveniently. It is possible to regulate the drug release rate as well as level of drug plasma concentration by adjusting the viscosity of jelly with the help of a gelling agent. Both solid and liquid dosage forms of oral jelly can benefit greatly since it stays solid in storage, maintaining the dosage form's stability and it turns into a liquid within a few seconds to minutes of after being administered. They could also have the benefit of avoiding the hepatic first pass metabolism. It is the innovative strategy that seeks to increase patient compliance while simultaneously enhancing safety and efficacy. The pharmaceutical business has recognized the novelty, patient friendliness and convenience of medicated jelly preparation as a cost effective and acceptable product. As a result, oral jelly has a great chance of being the preferred drug delivery method for the majority of medications in the near future.

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