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ORAL MEDICATED JELLIES – A REVIEW

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ABSTRACT

Oral medicated jellies developed dated back to 20th century, remain popular among the consumer and hence it has continued commercial production. Oral medicated jellies are palatable solid dosage forms administered in the oral cavity, meant to be dissolved in mouth or pharynx for its local or systemic effect. Oral medicated jellies provide several advantages as pharmaceutical formulations however with some disadvantages. Oral medicated jellies as a dosage form can be adopted for drug delivery across buccal route, labial route, gingival route and sublingual route. Multiple drugs can also be incorporated in them for chronic illness treatments. Oral medicated jellies are available as over the counter medications in different flavor based of mango, pineapple, strawberry, chocolate etc., containing drugs for anaesthetics, erectile dysfunction, arthritis, antihypertensive, sore throat. Once weekly oral medicated jellies was approved in 2012 by the ministry of Health Labour and Welfare of japan as the world's first drug for osteoporosis in a jelly formulation. The rationale behind the use of oral medicated jellies in International market as one of the most favored dosage form for both male and female sexual dysfunction. This review focuses various aspects oral medicated jellies formulation providing an insight to the formulation scientist on novel application of this drug delivery system.

KEYWORDS: Oral medicated jelly, chronic illness, aneasthetic, hypertension, oesteophoresis.

INTRODUCTION

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desired therapeutic concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. Drugs are more frequently taken by oral administration.[1] It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost, convenience of self administration, compactness and easy manufacturing. The most evident drawback of the commonly used oral dosage forms like tablets is difficulty in swallowing, leading to patient's incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.

To fulfill these medical needs, pharmaceutical technologists have developed a novel oral dosage form known as Oral medicated jellies (OMJs) which disintegrate rapidly in saliva, usually in a matter of seconds, without the need of water. Drug dissolution and absorption as well as onset of clinical effect and drug bioavailability may be significantly greater than those observed from conventional dosage forms.

Over a decade, the demand for development of oral medicated jellies (OMJs) has enormously increased as it has significant impact on the patient compliance. Oral medicated jellies are appreciated by a significant segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications. Common among all age groups, dysphasia is observed in about 35% of the general population, as well as up to 60% of the elderly institutionalized population and 18-22% of all patients in long-term care facilities. OMJs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

"Jelly can be defined as transparent or translucent non-greasy, semisolid preparations meant for external as well as internal application". The medicated jelly has through years gained increasing acceptance as a drug delivery system. Several ingredients are now incorporated in medicated jelly. I.e. drug which required fast onset of action, drug which have major absorption site is stomach and small intestine. They may be prepared form natural gums, such as tragacanth, pectin, sodium alginates or +from synthetic derivatives of natural substance

such as methyl cellulose and sodium carboxymethyl cellulose. Children may consider jelly as more preferred method of drug administration compared with oral liquid or tablets. The use of medicated jelly is feasible as local treatment of disease of the oral cavity as well as treatment of systemic condition.

Types of Jelly

There are three types of jellies.[2,3]

1. Medicated jelly: These are chiefly used on mucous membrane and skin for their spermicidal, local anesthetics and antiseptic properties. These jellies contain sufficient water. After evaporation of water, jellies provide a local cooling effect and residual film gives protection. For example, ephedrine sulphate jelly is used as a vasoconstrictor to arrest the bleeding of nose.

2. Lubricating jelly: These jellies are used for lubrication of diagnostic equipment such as surgical gloves, cystoscopes, catheters.

3. Miscellaneous jelly: These are meant for various applications like patch testing, electro cardiography.

Oral Medicated Jellies

Oral Medicated Jellies have been found to be the choice for Psychiatric and patients suffering from stroke, thyroid disorder, Parkinson's diseases and multiple sclerosis, nausea, vomiting and motion sickness. At present, OMJs are the only quick-dissolving dosage form recognized by FDA and listed in Approved Drug Products with Therapeutic Equivalence Evaluations (also called the Orange Book). Although chewable tablets have been on the market for some time, they are not the same as the new OMJs. Patients for whom chewing is difficult or painful can use these new tablets easily. OMJs can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth. OMJs release drug in the mouth and for absorption passed through local oromucosal tissues and through pregastric (e.g., oral cavity, pharynx, and esophagus), gastric (i.e., stomach) and postgastric e.g., small and large intestines) segments of the gastrointestinal tract (GIT).

History of Omjs[4]

Recent market studies indicate that more than half of the patient population prefers OMJTs to other dosage forms and most consumers would ask their doctors for OMJs (70%), purchase

OMJs (70%), or prefer OMJs to regular tablets or liquids (>80%). These responses may, in part, be attributed to known OMJ advantages such as ease of administration, ease of swallowing, pleasant taste and the availability of several flavors. OMJs also offer clinical advantages such as improved safety and, in some cases, improved efficacy and other broader indications. In addition, several business needs are driving OMJ technology development and the commercialization of new products such as the need for expanded product lines, improved life-cycle management, extended patent life and marketing advantages.

Ideal Characteristics of Omjs

OMJs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.

1. ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
2. Be compatible with taste masking.
3. Effective taste masking technologies should be adopted for bitter taste drugs.
4. Be portable without fragility concern.
5. Leave negligible or no residue in the mouth after oral administration.
6. Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.
7. Allow high drug loading.
8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.
9. The drug and excipients property should not affect the orally disintegrating tablet.

Advantages of Omjs

The performance of OMJs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable OMJ to perform this unique function.

1. OMJ can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients

who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance.

2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
3. OMJ is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.
4. Good mouth feel property of OMJ helps to change the perception of medication.
5. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
6. OMJ opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
7. Suitable during traveling where water may not be available.
8. Conventional manufacturing equipment.
9. Cost effective.
10. Good chemical stability as conventional oral solid dosage form.
11. Allow high drug loading.
12. Provides rapid drug delivery from dosage forms.
13. Adaptable and amenable to existing processing and packaging Machinery.
14. Rapid onset of action.
15. It is convenient to administer – anywhere, anytime, doesn't require water.
16. The treatment can, if required, be terminated at any time.
17. It may prove to be particularly suitable for the systemic delivery of drugs, which are susceptible to metabolism in the gut wall or liver.

In addition, the drugs that are released from jelly and swallowed, will be introduced in the gastrointestinal tract either dissolved or suspended in saliva and thus will be present in alreadily bioavailability form.

Limitations of Omjs

1. Cost-intensive production process;
2. Lack of physical resistance in standard blister packs;
3. OMJ requires special packaging for properly stabilization &safety of stable product.
4. It is also shows the fragile, effervescence granules property

5. Limited ability to incorporate higher concentrations of active drug.
6. ODT is hygroscopic in nature so must be keep in dry place.

The Need for Development of Omjs

The need for non-invasive delivery systems persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

Patient factors

Orally disintegrating dosage forms are particularly suitable for patients, who for one reason or the other, find it inconvenient to swallow traditional tablets and capsules with an 8-oz glass of water. These include the following

- Pediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

Challenges in Formulating Omjs[5]

Palatability

It is a formidable challenge for formulation scientists to mask the taste of bitter tasting drugsselected for Oral medicated jellies. As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste masked form. Hence, taste masking of the drugs becomes critical to patient compliance.

Hygroscopicity / Moisture sensitivity[6]

Several oral jelly dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging.

Dose /Amount of drug

The application of technologies used for OMJs is limited by the amount of drug that can be incorporated into each unit dose. Molecules requiring high doses present mainly three challenges to the development of fast dissolve dosage forms; a) taste masking of the active ingredient, b) mouth feel or grittiness and c) Jelly size. These challenges are not unrelated because most drugs will require taste masking, the amount of taste masking materials used in different dosage forms will depend on the drugs degree of bitterness relative to its dose, which will in turn affect the final tablet size.

Aqueous solubility[7]

Water soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various jelly forming excipients such as almond gum that can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of jelly

The degree of ease in taking a jelly depends on its size. It has been reported that the easiest size of jelly to swallow is 78mm while the easiest size to handle was one larger than 8 mm. Therefore, the jelly size that is both easy to take and easy to handle is difficult to achieve.

The Drug Property

Many drug properties could potentially affect the performance of jellies For example, the solubility, crystal morphology, particle size and bulk density of a drug can affect the final jelly characteristics, such as jelly strength and dissolve.

Mouth feel

The OMJs should not disintegrate into larger particles in the oral cavity. The particles generated after disintegration of the OMJ should be as small as possible. OMJ should leave minimal or no residue in mouth after oral administration. Moreover addition of flavors and cooling agents like menthol improve the mouth feel.

Sensitivity to environmental conditions

OMJ"s generally should exhibit low sensitivity to environment conditions such as humidity and temperature as most of the materials used in an OMJ are meant to dissolve with minimum quantity of water.

Drug Selection Criteria for formulation[8]

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for OMJ.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for OMJ.
- partially non ionized at the oral cavity's pH;
- Ability to diffuse and partition into the epithelium of the upper GIT (log P >1, or preferably >2);
- ability to permeate oral mucosal tissue. Drugs having ability to diffuse and partition into the epithelium of the upper GIT (log P > 1, or preferable > 2);
- those able to permeate oral mucosal tissue are considered ideal for OMJ formulations.

Several factors must be considered when selecting drug candidates for delivery as OMJ dosage forms. In general, an OMJ is formulated as a bioequivalent line extension of an existing oral dosage form. Under this circumstance, it is assumed that the absorption of a drug molecule from the OMJ occurs in the post gastric GIT segments, similar to the conventional oral dosage form. But this scenario may not always be the case. An OMJ may have varying degrees of pre-gastric absorption and thus, the pharmacokinetic profile (including the maximum plasma concentration, time to achieve maximal plasma concentration and area under the plasma concentration time curve of an equal dose of an OMJ and a conventional oral dosage form) will vary. Therefore, the OMJ will not be bioequivalent to the conventional oral dosage form. Examples are cited in the literature in which the pharmacokinetic profiles and bioavailabilities of the same dose of drug in an OMJ are not bioequivalent to the conventional oral dosage form. For example, OMJ formulations

of selegiline, apomorphine and buspirone have significantly different pharmacokinetic profiles compared with the same dose administered in a conventional dosage form.

It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an OMJ. For example, safety profiles may be improved for drugs that produce a significant amount of toxic metabolites mediated by firstpass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pregastric GIT.

In contrast, the following characteristics may render a drug unsuitable for delivery as an OMJs.

PatiSSSents who concurrently take anticholinergic medications may not be the best candidates for these drugs. Similarly, patients with Sjögren's syndrome or dryness of the mouth due to decreased saliva production may not be good candidates for these tablet formulations. Drugs with a short half-life and frequent dosing, drugs which are very bitter or otherwise unacceptable taste because taste masking cannot be achieved or those which require controlled or sustained release are unsuitable candidates of rapidly dissolving oral dosage forms.

Researchers have formulated OMJ for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction.

Drugs Suitable for Jelly

- **Analgesics & Anti-inflammatory Agents;** Diflunisal, Fenbufen, Fenoprofen, Ibuprofen.
- **Anti-Arrhythmic Agents;** Amiodarone Hcl, Disopyramide, Flecainide Acetate.
- **Anti-coagulants;** Dicoumarol, Dipyridamole.
- **Anti-fungal Agents;** Butoconazolenitrate, Clotrimazole, Econazolenitrate.

- **Anti-bacterial Agents;** Benethamine Penicillin, Cinoxacin, Ciprofloxacin Hcl, Clarithromycin.
- **Anti-gout Agents;** Allopurinol, Probenecid, Sulphinpyrazone.
- **Anti-hypertensive Agents;** Amlodipine, Carvedilol, Benidipine, Darodipine, Dilitazem Hcl.
- **Anti-migraine Agents;** Dihydroergotamine Mesylate, Succinate.
- **Anti-muscarinic Agents;** Atropine, Benzhexol Hcl, Biperiden, Ethopropazine Hcl.
- **Anti-neoplastic Agents**; and Immunosuppressants Aminoglutethimide, Amsacrine Chlorambucil, Cyclosporin, Dacarbazine, Estramustine.
- **Anti-protazoal Agents;** Metronidazole, Nimorazole, Nitrofurazone, Omidazole, Tinidazole.
- **Anti-thyroid Agents;** Carbimazole and Propylthiouracil.
- **Anxiolytic, Sedatives, Hypnotics and Neuroleptics;** Alprazolam, Amylobarbitone, Barbitone
- **Cardiac Inotropic Agents;** Amrinone, Digitoxin, Digoxin. Corticosteroids Beclomethasone, Betamethasone, Budesonide, Cortisone Acetate.
- **Diuretics;** Acetazolamideamiloride, bendrofluazide, bumetanide, chlorothiazide, chlorthalidone.
- Enzymes All Enzymes.
- **Anti-sparkinsonianAgents**; Bromocriptinemesylate, lysuride maleate.
- **Gastro-intestinal Agents;** Bisacodyl, cimetidine, cisapride, diphenoxylate Hcl, famotidine.
- **Histamine H,-Receptor Antagonist;** Acrivastine, astemizole, cinnarizine, cyclizine.
- Lipid Regulating Agents; Bezafibrate, Clofibrate, Fenofibrate, Gemfibrozil, Probucol.
- **Local Anaesthetics;** Lidocaine.
- **Neuro-muscular Agents;** Pyridostigmine.
- **Nitrates and other Anti-anginal Agents;** Amyl Nitrate, Glyceryltrinitrate, Isosorbide Dinitrate.

2. Gelling Agents

These are usually hydrocolloids, which have been found appropriate for the formulation of gel like matrix. Some examples of them are as follows:

i. Sodium Alginate: It is used in a variety of oral and topical pharmaceutical formulations. In topical formulation, it is widely used as thickening agent and suspending agent in a variety of pastes, creams and gels, also used in cosmetics and food products.

ii. Pectin: Pectin has been used as an adsorbent and bulk forming agent, experimentally it has been used in gel formulation for oral sustained delivery of drugs.

iii. Tragacanth: Tragacanth gum is used is used as an emulsifying and suspending agent in a variety of pharmaceutical formulations. It is used in creams, gels, and emulsion formulations.

iv. Gelatin: Gelatin is widely used in a variety of pharmaceutical formulations, including its use as a biodegradable matrix material in an implantable delivery system. Gelatin is also widely used in food products and photographic emulsions.

v. Xanthan Gum: It is widely used in oral and topical pharmaceutical formulations, cosmetics and food as suspending agent and stabilizing agent. It is also used as a thickening and emulsifying agent. It is also used as a hydrocolloid in the food in industry, and in cosmetics it has been used as thickening agent in shampoo.

vi. Cellulose Derivatives: E.g. Methyl cellulose sodium carboxy methyl cellulose.

3. Preservatives

Since jellies are aqueous preparations which may allow the microbes to grow. Preservation must be selected to avoid any incompatibilities with the gelling agents, which may retard the shelf life of the product. Cellulose derivatives and clay resist the microbial attack. Some examples of them are as follows:

- Methyl Paraben
- Propyl Paraben
- Benzoic Acid
- Benzalkonium Chloride
- Chlorhexidine acetate

4. Stabilizers

There are some additives that are added as stabilizers in the formulations to prevent the drying of jellies. Some examples of them are as follows:

- Propylene glycol

 Sorbitol

 Chelating Agent, e.g. EDTA is added to prevent the sensitivity of bases and the medicaments towards heavy metals.[9]

Preparation Method of Jelly[10]

- Jellies were prepared by heating and congealing method.
- Prepared using freshly boiled and cooled distilled water as per composition listed.
- Sucrose syrup prepared in water on heating and stirring at 80^0c for about 90 minutes.
- Weighed polymer powder was dispersed in 10 ml of water maintained at 90^0c throughout the preparation.
- The dispersion was stirred using a magnetic stirrer for 20 mins to facilitate hydration of gelling agent.
- Drug taken in to another beaker and solubilized using alchol.
- Simple syrup was add to it under continuoues stiring.
- The citric acid and preservatives were added under continuous at 60^0.
- The final weight was adjusted with purified water, mixed, transfer to suitable moulds, sealed and allow to cool that room temperature($25^0 \pm 5^0$c) to form a jelly like texture.
- Finally, when jelly set it is wrapped in gelatin paper and stored in dry place.

Evaluation Parameters[11,12]

1. Physical appearance: The medicated jelly was examined for physical appearance in terms of clarity, texture and consistency.

2. Stickiness and grittiness: Texture of the medicated jelly in terms of stickiness and grittiness had been evaluated by visual inspection of the product after mildly rubbing the jelly sample between two fingers.

3. Spreadability: For the determination of spreadability sample of jelly was applied between two glass slide and compressed to uniform thickness by placing 1000gm weight. The time required to separate the two slide moves over the lower slide was taken measure of spredability.

i. $S = m * L/T$.

Where m = weight tide to upper slide,

L = length moved on glass slide,

T = time taken.

4. Viscosity: Viscosity had been measured using Brookfield Viscometer. As the system is non-Newtonian spindle no.4 was used.

5. pH: The pH of all the jelly was determined using digital pH meter. 0.5 gm of the weighed formulation was dispersed in 50 ml of distilled water and the pH was noted.

6. Content Uniformity: The content uniformity test is to ensure the every dosage form contains equal amount of drug substance. Jelly from the each formulation were taken, crushed and mixed. From the mixture drug equivalent of mixture was extracted thoroughly with suitable media. The amount of drug present in each extract was determined using suitable analytical method.

7. *In-vitro* Dissolution Study: An in –vitro dissolution study will performed with USP basket apparatus using suitable dissolution medium. Dissolution medium was kept at 37^0 C± 0.5^0 Cand 50 rpm. The sample are withdrawn after10, 20, 30, 40, 50, 60 minute and replaced with fresh media. The Sample ware determined for drug release using suitable analytical method.

8. Syneresis: Syneresis is the contraction of the gel upon storage and separation of water from the gel. It is more pronounced in the gels, where lower concentration of gelling agent is employed. It is one of the major problems associated with low acylated guar gum gels.

9. Stability Studies: The stability study was evaluated as per ICH guidelines.

CONCLUSION

To be concluded that prepared medicated jelly is more organoleptically accepted particularly by patients with disability in ingestion of food and drink, in other words, those having difficulty in mastication and swallowing. The present study concludes that oral medicated jellies can be very promising for effective doses to systemic circulation. These may also provide an added advantage of circumventing the hepatic first pass metabolism. Prepared medicated jelly is cost wise cheap and acceptable and have gained relevance in pharmaceutical industry as a novel, patient friendly, convenient products.

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