A review on formulation of nutraceutical products in the form of Oro dispersible film.

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ABSTRACT:

Nutraceutical can be simply defined as the product derived from food sources with health benefits and also this product provides protection against chronic diseases and also boosts the immunity. These products have both nutritional and medicinal value and hence are also called as medical foods. Nutrients in form of powders, small solids or droplets have found to improve bioavailability. Nutraceuticals will play an important role in future in the medical field and therapeutic development. This study mainly aims to formulate nutraceutical products in form of Oro dispersible film to increase the bioavailability and reduce the disadvantages like chocking while swallowing mainly in case of tablets and capsules and avoiding the need of water as in swallowing tablet, capsules. Oral films are single or multilayered, mucoadhesive thin polymeric films. Oro dispersible films are a novel preparation with a huge scope in pharma and nutraceutical industries in future. The oral films are formulated using various Active pharmaceutical ingredients, film forming polymers, flavors, colors and sweeteners.

1) INTRODUCTION

Over the past few years, an increasing number of dietary supplements have become available in supermarkets and health food shops and they are also available for purchase in pharmacies.

The term "nutraceutical" is used to describe these medicinally or nutritionally functional foods. Nutraceuticals, which have also been called medical foods, designer foods, phytochemicals, functional foods and nutritional supplements, include such everyday products as "bio" yoghurts and fortified breakfast cereals, as well as vitamins, herbal remedies and even genetically modified foods and supplements **.[1].**

The term "nutraceutical" was coined in 1989 by Stephen De Felice, founder and chairman of the Foundation for Innovation in Medicine, an American organization which encourages medical health research. He defined a nutraceutical as a "food, or parts of a food, that provide medical or health benefits, including the prevention and treatment of disease". [2, 3, 4].

Nutraceutical is the hybrid of 'nutrition' and 'pharmaceutical'. Nutraceuticals, in broad, are food or part of food playing a significant role in modifying and maintaining normal physiological function that maintains healthy human beings. The food products used as nutraceuticals can be categorized as dietary fibre, prebiotics, probiotics, polyunsaturated fatty acids, antioxidants and other different types of herbal/ natural foods. These nutraceuticals help in combating some of the major health problems of the century such as obesity, cardiovascular diseases, cancer, osteoporosis, arthritis, diabetes, cholesterol etc. In whole, 'nutraceutical' has lead to the new era of medicine and health, in which the food industry has become a research oriented sector. [5].

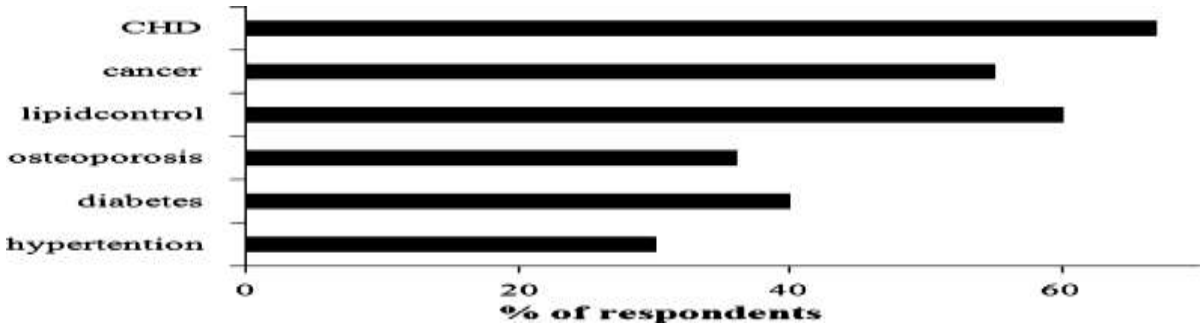


Fig 1: Therapeutic areas covered by nutraceutical products. [6]

Oral route of drug administration is a most preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability. Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for paediatrics, geriatrics, nauseous and non-compliance patients. Orally disintegrating films or oro-dispersible films (ODFs), when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form.

ODFs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug delivery systems. These systems were developed in late 1970 to serve as an alternative to conventional dosage forms, for instance, fast disintegrating tablets and capsules for geriatrics and paediatric patients having difficulty in swallowing conventional dosage forms.

A typical ODF is usually equal to the size of a postage stamp. In market place, the introduction of ODT was strongly associated with counselling of patients about the appropriate administration by giving instruction like ‘‘do not chew/do not swallow’’. However, in spite of these instructions, incidents regarding chewing and swallowing were often reported. But, ODFs untied the masses from these adverse events.

The administration of ODFs has numerous advantages and some of them are as follows:

i. Easy transportation.
ii. Ease of swallowing for geriatrics and paediatrics.
iii. Convenient and accurate dosing.
iv. No need of water for administration.
v. Convenient for dysphasic patients having difficulty in swallowing tablets and capsules.
vi. Rapid onset of action with increased bioavailability due to bypassing hepatic first pass effect and stability.

No expensive lyophilization, high mechanical strength, rapid disintegration, and reduced choking risks are the quality attributes of ODFs. ODFs have attained remarkable significance in pharmaceutical industry for the reason of possessing unique properties and fast disintegration time ranging from seconds to one minute. ODFs design permits to incorporate a variety of drugs for their pharmacological effects e.g., anti-tussive, anti-epileptic, anti-asthmatic, expectorant, etc.

High temperature and moisture sensitivity necessitating expensive packaging and inability of high dose loading are some disadvantages of ODFs. [7, 8, 9]

2) MATERIALS AND FORMULATION METHODS REQUIRED FOR DEVELOPMENT OF ODFs.

2.1) MATERIALS REQUIRED:

ODFs are fast disintegrating thin films having an area ranging from 5 to 20 cm2 in which drug is incorporated in the form of matrix using hydrophilic polymer. Active pharmaceutical ingredient can be incorporated up to 15 mg along with other excipients i.e., plasticizers, colorants, sweeteners, taste masking agents, etc. The general composition of an ODF is shown in Table 1. [10]

Table 1: Composition of typical oro-dispersible film.

COMPONENTS	CONCENTRATION (%)
API	1-25
Hydrophilic polymer	40-50
Plasticizer	0-20
Color,filler,flavour	0-40

2.1.1) Active pharmaceutical ingredient:

Various classes of vitamins, minerals, salts, antioxidants, dietary supplements, fortified dairy products and herbals can be incorporated into ODFs as nutaceuticals.

2.1.2) Hydrophilic polymers

The successful development of an ODF is a function of justified selection and concentration of polymers as the mechanical strength of films is strongly associated with these factors. They can be used either alone or in combination with other polymers to modify film properties. The concentration of used polymers is also important factor while developing an ODF. The integrity of fast dissolving oral films is dependent upon careful selection of polymer nature and concentration. Generally, polymer concentration used in preparing ODFs is around 45% w/w of total weight of dry thin strip, however, it can be increased up to 60–65% w/w in order to attain the film of desired attributes and characteristics. Polymer used as a film forming agent in formulation of thin strips should possess certain properties (Table 2).

Table 2: Ideal properties of a hydrophilic polymer
Non irritant.
Should not hinder with the disintegration time of ODF.
Affordable.
Should possess adequate shelf-life.
Should possess good spread ability.
Should exhibit sufficient tensile strength.
Should have good mechanical properties.
Non-toxic.

In recent era, both natural and artificial polymers are used for developing ODF formulation. (Table 3)[11]

Table 3: Most commonly used natural and synthetic polymers in ODFs.

Type of polymer	Examples
Natural	Starch, polymerized rosin, pullulan, sodium alginate, Pectin, gelatin, and maltodextrins
Synthetic	Polyvinyl alcohol, hydroxy propyl methyl cellulose, sodium carboxy methyl cellulose, polyvinyl pyrrolidone, and hydroxy propyl cellulose

2.1.3) Plasticizers

In general, mechanical properties such as tensile strength and percent elongation are improved by adding plasticizer to the formulations (Arya et al., 2010). The concentration of plasticizer usually ranges from 0% to 20% w/w. Common examples of plasticizers are PEG, glycerol, diethyl phthalate, triethyl citrate, tributyl citrate, etc.[12]

2.1.4) Surfactants

Surfactants play a vital role as dispersing, wetting and solubilizing agent thus enabling films to disintegrate within seconds releasing the incorporated drug, speedily. Commonly used surfactants are benzalkonium chloride, tweens, and sodium lauryl sulfate. Often, polaxamer 407 is used due to its many advantages [13].

2.1.5) Flavours

Flavours are needed to mask the bitter or nauseating taste of incorporated drug. Amount of flavor depends upon its nature and strength. Any US-FDA approved flavor can be used such as sweet, sour or mint flavor (Siddiqui et al., 2011). One of the research work verified that mint, licorice and sucralose mixture flavors appropriately mask the bitter taste of diclofenac sodium. Electronic tongues are used to discriminate the effect of various taste masking agents (TMAs). [14]

2.1.6) Sweetening agents

Sweetening agents are designed to disintegrate or dissolve in oral cavity. Both artificial and natural sweeteners are used in preparing ODFs (Table 4). Neotame and Alitame are 2000–8000 times sweeter than sucrose (Siddiqui et al., 2011).

Sucralose was found to be 600–1000 times sweeter than sucrose when oral disintegrating films of donepezil were evaluated for taste, after taste mouth feel. Aspartame and saccharin sodium are likely to be 200 and 300–500 times sweeter compared to sucrose, respectively. It was also reported that sweeteners and flavors have minor effect on flexibility of film [15].

Table 4: Examples of some commonly used sweetening agents used in ODFs.

Type of polymer	Examples
Natural	Glucose, fructose, dextrose, sucrose, and isomaltose.
Synthetic	Acesulfame-K, sucralose, and neotame

2.1.7) Saliva stimulating agent

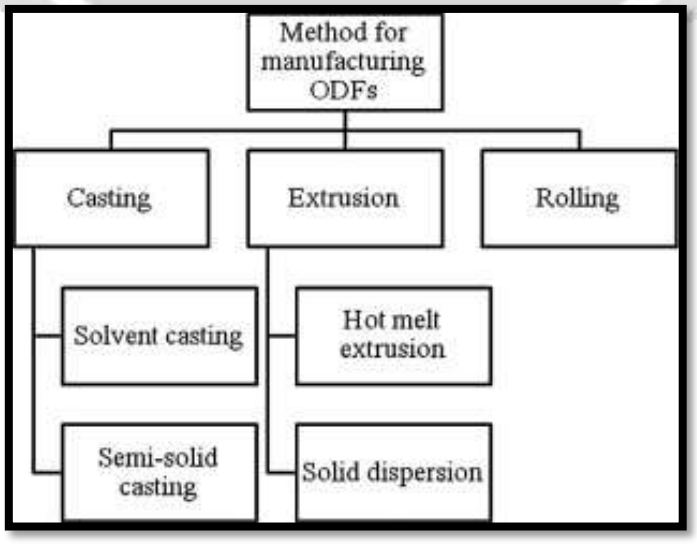
Salivary stimulants are generally acidic in nature stimulating the production of saliva in buccal cavity, consequently, promoting the disintegrating of ODFs. Some commonly used saliva stimulating agents are citric acid, malic acid, tartaric acid, ascorbic acid and lactic acid (Siddiqui et al., 2011).

2.1.8) Coloring agents

Pigments are used as coloring agents. Titanium dioxide is most widely used colorant in ODFs and various other pharmaceutical preparations. Apart from titanium dioxide, a full range of colors are available including FD and C, natural and custom pantone-matched colors (Siddiqui et al., 2011).

2.2) APPROACHES FOR MANUFACTURING OF ORODISPERSIBLE FILMS / FORMULATION METHODS:

Methods mainly employed for manufacturing ODFs are shown in Fig. 2 (Siddiqui et al., 2011).



2.2.1) Solvent Casting Method

Water soluble polymers are dissolved to form homogenous solution. Drug and other water soluble components are allowed to dissolve in small amount of water. Both solutions are mixed with each other with continuous stirring. Entrapped air bubbles are removed by applying vacuum. Solution formed is casted on non treated surface. Subjected for drying and cut in pieces. [16]

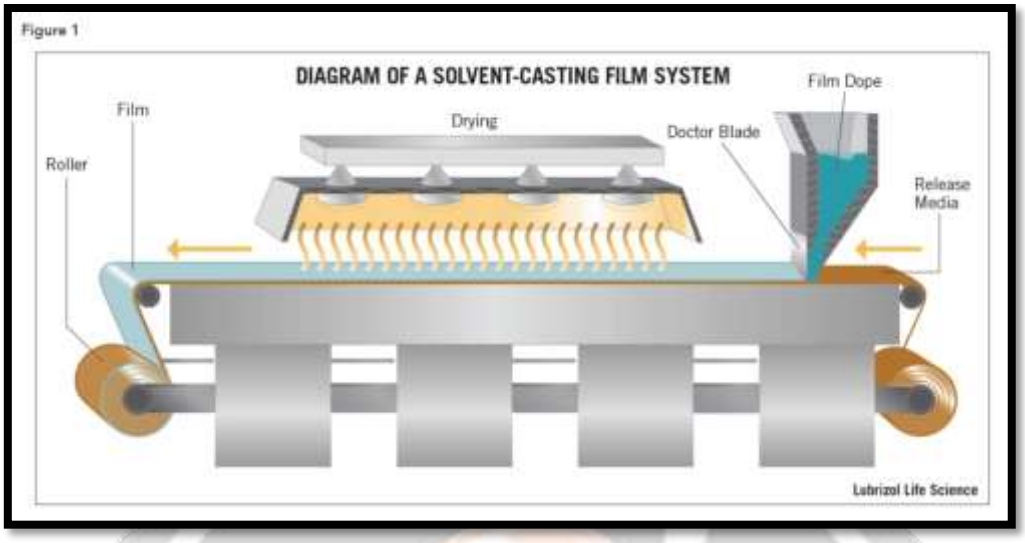


Figure 2: Solvent Casting Film system.

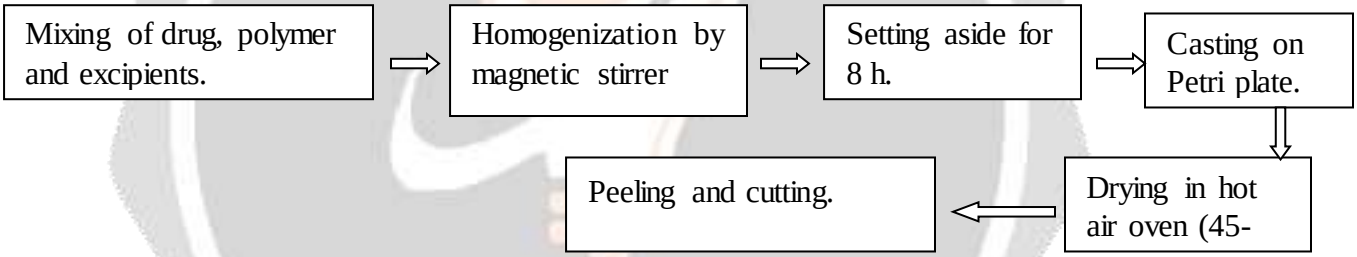


Figure 3: Flow chart of solvent casting method.

2.2.2) Hot Melt Extrusion

In hot-melt extrusion, the dry ingredients for the film are heated and homogenized by the action of an extruder screw until they are molten and mixed. The melted material is forced through a flat extrusion die that presses the extrudate into the desired film shape. The thickness and strength of the film can further be affected by elongation rollers while the material is still hot and pliable. The extruded film is then cooled, cut and packaged. [17].

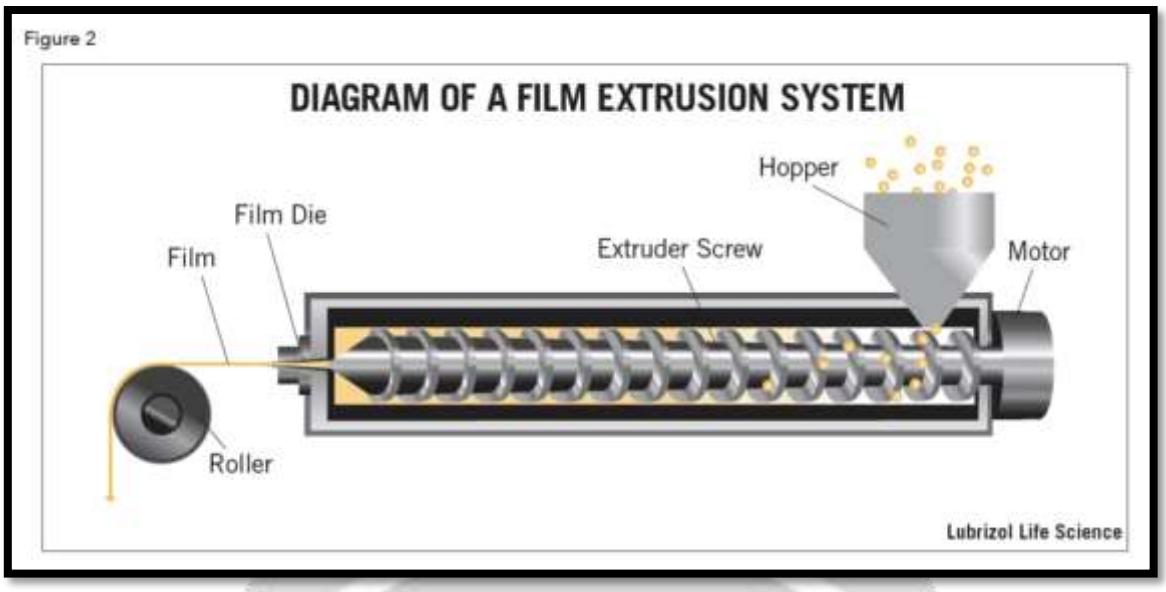


Figure 4: Hot melt extrusion technique.

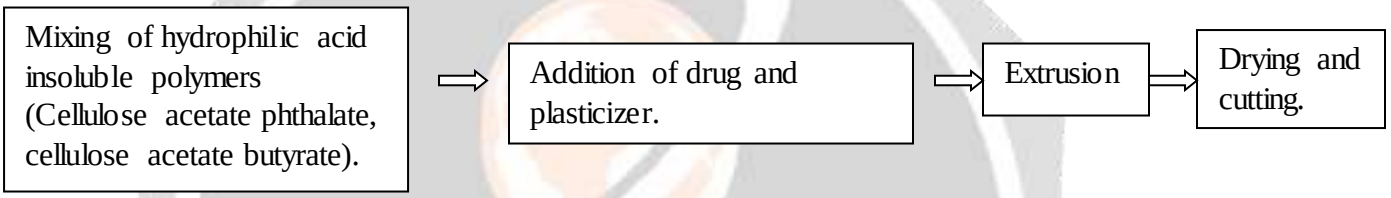


Figure 5: Flow chart of hot melt extrusion method.

Semisolid Casting Method

Solution of water soluble film forming polymer is prepared. Resulting solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate). Appropriate amount of plasticizer is added so that gels mass is obtained. Finally the gel mass is casted in to the films or ribbons using heat controlled drums. The thickness of the film should be about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4[18]

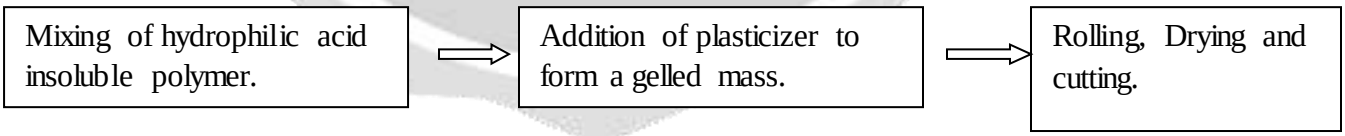


Figure 6: Flow chart of semi-solid casting method.

2.2.3) Rolling Method

In this method the film is prepared by preparation of a pre-mix, addition of an active and subsequent formation of a film. Prepare pre-mix with film forming polymer, polar solvent and other additives except a drug, add pre mix to master batch feed tank. Feed it via a 1st metering pump and control valve to either or both of the 1st and 2nd mixers. Add required amount of drug to the desired mixer. Blend the drug with master batch pre mix to give a uniform matrix. Then a specific amount of uniform matrix is then fed to the pan through 2nd metering pumps.

The film is finally formed on the substrate and carried away via the support roller. The wet film is then dried using controlled bottom drying. Solvent used is mainly water and mixture of water and alcohol [19].

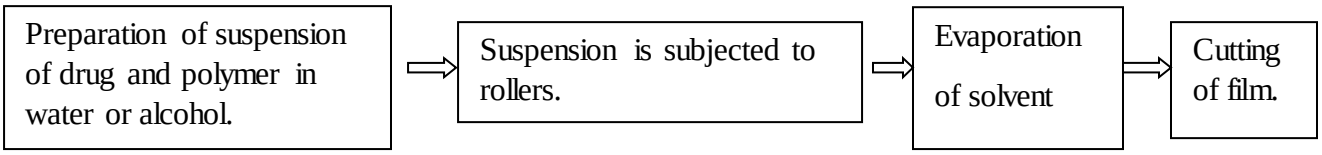


Figure 7: Plot of rolling method.

3) EVALUATION OF ODFS

After the films are produced by one of the above manufacturing method, they are subjected to evaluation. Evaluation is very important and crucial step required to maintain inter and intra batch uniformity between films. Various parameters are studied which can be divided depending upon physical and chemical properties.

3.1)Physical Parameters

Physical parameters are important as they are performed on final dosage form which gives idea about the uniformity between batches and also to maintain aesthetic appeal of the final formulation. As the USP

describes only a tensile strength test for surgical sutures and patches, technical regulations from other industries such as the plastic industry can be used as templates. Tensile tests according to the ASTM International Test Method for Thin Plastic Sheeting (D 882-02) or tests described in the DIN EN ISO 527-1 and 527-3 regulations can be utilized [20].

Mechanical Parameters

a) Dryness / Tack test Dryness can be described as the property to measure the solvent or water content present in the film whereas tack is the tenacity with which the film adheres to any piece of paper which is pressed into contact with the strip. Eight stages of film drying process have been recognized i.e. set-to-touch, dust-free, tack-free, dry-to-touch, dryhard, dry-through; dry-to-recoat and dry print free. Various instruments are now available to measure these properties. At lab scale this can be done by using thumb and pressing it against the film.

b) Tensile strength can also be defined as the maximum stress applied to a point at which the film specimen breaks and can be computed from the applied load at rupture as a mean of three measurements and cross-sectional area of fractured film from the following equation.[21]

Tensile strength (N/mm^2) = [Breaking force (N) /Cross sectional area of sample (mm^2)]

c) Percentage elongation

Elongation is a kind of deformation. It is a simple change in shape that anything undergoes when under stress, which can be measured using a texture analyzer. In other words, when a sample is put under tensile stress, the sample deforms, becomes longer or gets elongated. It can be calculated by measuring the increase in length of the film after tensile measurement by using the following formulae. [20]

Percent Elongation = [L-L0] X 100 / L0

Where L is the final length and L0 is initial length.

d) Young's Modulus

Young's modulus or elastic modulus is the measure of stiffness of film. The methods used for the measurement of tensile strength could be utilized here as well. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows.[20]

Young's Modulus= Slope x 100/ Film thickness x cross head speed.

Hard and brittle film demonstrates a high tensile strength and Young's modulus with small elongation.

e) Tear Resistance

Tear resistance of plastic film or sheeting is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51 mm (2 in.) /min is employed and is designed to measure the force to initiate tearing. The maximum stress or force (that is generally found near the onset of tearing) required tearing the specimen is recorded as the tear resistance value in Newtons (or pounds-force). [20]

f) Folding endurance

The flexibility of film is an important physical character needed for easy application on the site of administration. The flexibility of the film can be measured quantitatively in terms of folding endurance and is determined by repeatedly folding the film at 180° angle of the plane at the same plane until it breaks or folded to 300 times without breaking. The number of times the film is folded without breaking is computed as the folding endurance value. [20]

Other physical parameters

a) Appearance

All prepared films can be checked for their appearances either they are transparent or opaque. Visual inspection is normally performed but instruments like microscope can also be used for determining surface properties.

b) Thickness

Thickness of the prepared film can be measured by micrometer screw gauge at different strategic locations. Film thickness should be measured at five points i.e. from the centre and from all the four corners and then mean thickness is calculated. This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip[20].

c) Weight variation

Individual film should be weighed and the average weights are calculated. Then the average weight of the films is subtracted from the individual weight of the film. A large variation in weight indicates the inefficiency of the method employed and is likely to have nonuniform drug content [20].

d) Contact angle

Contact angle can be measured by Goniometer (AB Lorentz and wettre, Germny) at room temperature. This can be done by taking a dry film and placing a drop of distilled water on the surface of the dry film. Images of water droplet are recorded within 10 seconds of deposition by means of digital camera. The contact angle can be measured on both side of drop and average is taken [22]

e) Transparency

The transparency of the films can be determined using a simple UV spectrophotometer. Cut the film in the rectangular shape and placed inside the spectrophotometer cell. Determine the transparency of the film at 600nm.The transparency of the film can be calculated as follows.[21]

$$\textbf{Transparency} = (\log T600)/b = -\epsilon C$$

Where, T600= transmittance at 600nm b= film thickness (mm) C= concentration

f) Moisture content:

The amount of moisture affects the brittleness and friability of films. Basically, the contents in the product regulate the degree of moisture in a particular film. The amount of moisture present in the film can generally be determined using moisture content testing equipment, Karl fisher titration method or by weighing method. Typically, a specific size of pre-weighed film is heated to 100–120 °C until it attains constant weight and the difference in weight gives the amount or degree of moisture present in the film. Moisture content can be calculated as.[20]

$$\textbf{\% Moisture content} = [(\text{Initial weight} - \text{Final weight}) \times 100/\text{Initial weight}].$$

The moisture content in an ideal film should be <5%.

3.2) Chemical Parameters

a) Surface pH test

Surface pH of the film can be determined by placing the film on the surface of 1.5% w/v agar gel followed by placing pH paper (pH range 1-11) on films. The change in the colour of pH paper is observed and reported.[23]

b) Disintegration time

Disintegration time provides an indication about the disintegration characteristics and dissolution characteristics of the film. The required size of film (2×2 cm^2) is placed in a stainless steel wire mesh containing 25 ml of pH 6.8 simulated salivary fluid. Time taken by film to break and dissolve is measured as in-vitro disintegration time.[23]

c) In vitro dissolution test

Dissolution testing can be performed using the standard basket or paddle apparatus described in any of the pharmacopoeia. The dissolution medium will essentially be selected as per the sink conditions and highest dose of the API. Many times the dissolution test can be difficult due to tendency of the strip to float onto the dissolution medium when the paddle apparatus is employed.[17]

d) Thermal analysis

Thermo-grams of the samples can be recorded using a differential scanning calorimeter, which provides insight into the state of the drug molecules inside the film. Any shift in the endothermic or exothermic peak or widening of peak area directly represents phase transition, recrystallization or molecular interaction of the drug molecule entrapped inside the film. This can be assessed by heating the sample in an aluminum pan from room temperature to elevated temperature (~500 °C) at a specified heating rate (~10 °C/min)16. e) Crystallinity The physical form (crystalline or amorphous) of the drug molecule inside the film can be easily determined by X-ray crystallographic analyses using X-ray diffractometer. The films can be placed in the sample holder and the XRD transmission diffractograms can be acquired with a specific X-ray source over a start to end diffraction angle, scan range and scan speed. [19]

f) Assay / Content uniformity

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%. [23]

4) In Vivo test

Efforts have been made to simulate the in vivo disintegration, such as contact angle measurements and thermo-mechanical analysis of the swelling behaviour of the films. In vivo testing mainly involves tasting of the films and their in-vivo disintegration time with help of the tasting panel and human volunteers. Electronic tongue tester is also used to evaluate taste of the films.[23]

5) CONCLUSION

In today's fast running modern world, people are not much focusing on their basic diet due to which lots of macro and micro nutrient deficiencies are gaining popularity day by day. To counteract these problems nutraceutical products such as multivitamins, immunity boosters, antioxidants etc. play vital role. As modern drugs, nutraceuticals also need to be formulated by novel approaches. The study **"A review on formulation of nutraceutical products in the form of oro-dispersible film"** focuses on possibilities of development of nutraceutical products in the form of oro-dispersible films. Delivery of nutraceuticals through oral thin film provides several advantages. ODFs are a very suitable dosage form for children and the elderly, because they are easy to swallow and involve no risk of choking. Though the use of MDT(Mouth Dissolving Tablets)is popular but then also it has to its credit disadvantages like hygroscopic dosage which may lead to stability issues, grittiness in mouth if not formulated properly, fear of choking, which can be overcomes by ODFs.This drug delivery have tendency to replace the over the counter products from market because of consumer preference

also in US, Japan and Europe, the prescription ODFs have now been approved which have potential to dominate over other oral dosage form of same drug. The ODF technology is just in the beginning stage and has bright future because of both patient compliance and pharmaceutical acceptability. Hence this promising drug delivery system needs to be explored more for the benefit of researchers and human being at large.

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