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Oral Edible Films: Recent Trends on Edible films

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ABSTRACT

Oral route is still the preferred route of drug administration for majority of the population as it is non invasive and convenient but has some inherited flaws as certain patients like young children and geriatric patients have difficulty in swallowing. Recent trends are shifting toward design and development of a novel carrier system for existing drugs. Oral disintegrating films (ODF) play an eminent role, as it dissolves rapidly in the mouth and reaches directly into systemic circulation. Various methods have been used for formulating ODF, among which solvent casting is frequently used. The film consists of generally both hydrophilic and hydrophobic polymers and other suitable excipients which either dissolves or disperses rapidly in the oral cavity and releases the active ingredient. The present review is mainly focused on the formulation approaches, their evaluation and therapeutic benefits of ODF.

Keywords: Oral strips, Mucosal Delivery, Polymer films, Fast dissolving film, ODFs

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INTRODUCTION

Oral disintegrating films (ODF) have received significant attention over the past few decades. These delivery systems are known by many names including fast dissolving films, rapid dissolving films, oral dispersible strips, versa film, quicksol and simply oral films. While small differences do exist under these terminologies, they all include essentially the same concepts. Typically, ODF do not need to be taken with water or another liquid which contributes to their ease of use An ODF is a thin strip that readily and rapidly dissolves or disperses in the limited volume of fluid available in the oral cavity, primarily saliva. From technology standpoint, the films are relatively easy to make and can be based on many well-known hydrophilic and hydrophobic polymers and excipients. Solvent casting remains the most popular method for their formulation, various other methods such as spray, rolling and extrusion methods have also been reported. Their primary advantage lies in their use in selective patient population such as geriatric and pediatric patients. In addition, these are also useful where rapid action is desired or a convenient method of dosing is needed. However, recently a number of ODF have been introduced as marketing strategy. Irrespective of the intended motivation, ODF have become a popular new drug delivery system on the market. These are now mentioned in regulatory documents in Europe and United States [1, 2].

Advantages of ODF

The most significant advantage of ODF is improved end user compliance in geriatric and pediatric patient population. Since ODF is easy to administer and does not require administration of a drink, it forms a convenient mode of oral administration. There is also a possibility of tailoring the formulation for select patient populations. For example ODF for pediatric patients can be suitably flavored and colored for better acceptability. ODF also offer the advantage of ease of carrying the product by a patient when they are on the go away from home, reducing the likelihood of missing a dose.

When compared with other oral dosage forms, ODF provide several advantages. For example, orally disintegrating tablets (ODT) are hard to formulate and require heavy equipment for manufacturing. ODT are also subject to issues like friability and moisture uptake because they are formulated to be soft tablets. ODT also require special packaging to eliminate handling related stability problems. Liquid dosage forms have to be measured and swallowed by the patients. This involves the possibility of dose variation and may involve help of a caregiver.

ODF provide unit dosing in a convenient form. ODF offer advantage in marketing of the products. As a relatively new drug delivery technology, it can extend the life cycle of patented drugs. ODF

allow companies to file an approval application under 505(b) [2] process which does not required clinical data. This makes the approval process faster and cheaper where market exclusivity is not needed. Regulatory requirements in this regard vary from region to region.

ODF may offer therapeutic or clinical advantages as well. The most common advantage in this regard is the improved compliance due to ease of dosing. They can also provide faster drug delivery to the body due to rapid dissolution of drug. Another advantage often mentioned is the possibility of significant dose being absorbed from oral mucosa. This results in by passing the first pass effect from oral absorption [3].

Disadvantages of ODF

In addition to many advantages, ODF also have certain disadvantages. The most common disadvantage is the poor stability of many ODF. The reason for this is the fact that ODF are designed to dissolve rapidly. Therefore, many ingredients used in their formulation are hydrophilic. These ingredients are likely to attract moisture during storage and use. Another major disadvantage of this system is the dose limitation. In general, ODF contain less than 50mg of active although several newer systems like GAS-X strips claim to have higher capacity. However, dose limitation remains a major disadvantage of these systems. Taste masking is yet another challenge for ODF. These systems will expose the oral cavity to the taste of all ingredients in the formulation. Taste making can be a formidable challenge to overcome for actives with strong taste.

Formulation of ODF

From formulations standpoint, essential ingredients of ODF include an active ingredient, matrix forming agents, plasticizers and stabilizers. Additional ingredients include pH modulating agents, saliva stimulating agents and ingredients for aesthetic and palatable reasons such as color, flavor, etc. Table 1 lists the categories and examples of these ingredients.

Table 1: Commonly used excipients

Ingredient Category	Example	Purpose	Reference
Matrix former	HPMC, HPC, PVP, Gelatin	Matrix forming agents	[4, 33]
Plasticizer	Glycerin, Propylene glycol	Tensile strength	[4, 33]
Stabilizer	Tween, SDS	Dispersing, wetting	[4, 33]
pH modulation/saliva stimulation	Citric/Ascorbic acid	buffer ingredients	[4, 33]
Aesthetic	Neotame, colors, Menthol	Flavor, sweetener, color	[4, 33]

FOLLOWING ARE THE MATERIALS COMMONLY USED IN THE FORMATION OF ODFs

Polymers

The primary polymer used is almost always a hydrophilic polymer in order to achieve rapid fluid uptake and dissolution. Examples of such polymers include modified cellulose materials such as hydroxypropylmethylcellulose and other similar polymers. Synthetic polymers such as polyvinyl pyrrolidone and polyvinyl acetate are also used. The purpose of the polymer is to hold the active and excipients together in a thin strip with enough strength to withstand the processing shipping and use. The polymer also serves to quickly absorb aqueous fluid from the oral cavity and dissolve to release the active. Therefore, selection of the polymer is a critical factor. In fact the commercial viability and patent protection of ODF are based on a unique combination of polymers[4].

The concentration of polymer in the film ranges from 40-50% by weight [5]. This level of polymer is required for several reasons. The polymer solution is used to dissolve or suspend the active ingredient. Therefore, the primary solution or suspension has to have significant viscosity. Another reason is that the polymer provides strength to the film. It also serves to attract fluid from the oral cavity to cause dissolution or dispersion of the film.

Polymers for ODF must possess several attributes in order to serve the above purposes. These include high solubility, tensile strength and mechanical properties, inertness, lack of toxicity, stability and compatibility with other ingredients in the formulation, and acceptable taste. If a particular design or formulation does not allow a single polymer to achieve all of the above attributes, a mixture of polymers can be used. Among the above properties, tensile strength and high solubility are the primary and most critical properties.

HPMC is the most commonly used polymer in ODF. It is a modified cellulose polymer that provides most if not all the desired properties. It is available in several grades of molecular weight and viscosity and is sold under the trade name of methocel. It also accommodates other ingredients easily to form flexible films. Plasticizers such as glycerin and propylene glycol can be readily added to HPMC films. Several studies have shown that this polymer is suitable for water soluble as well as water insoluble active ingredients [6-8]. HPMC is available in several molecular weight grades ranging from 5000 to over 150,000 [9-15]. It is also available in high and low viscosity grades for various applications [16]. Typical concentration reported for ODF use are in the range of 20 to 40% by weight.

Other cellulose based polymers in ODF include hydroxypropyl cellulose (HPC) and carboxymethyl cellulose (CMC). Both of these are also available in several molecular weight grades. These polymers allow high drug loading and typically have high swelling and solubility properties which are critical attributes for a film [17, 18]. In addition, these polymers also show some degree of bioadhesion due to rapid uptake of moisture [19, 20]. They can be used in conjunction with HPMC and other polymers to enhance their properties.

Polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP) and polyethylene oxide (PEO) are examples of synthetic polymers used in ODF. Among these, PVA can be used in hydrolyzed form or partially hydrolyzed form [21-23]. Degree of hydrolysis of PVA dictates its water solubility. Fully hydrolyzed grades are not soluble in water and are therefore not suitable for fast dissolving films. Partially hydrolyzed grades have higher water solubility and can be used in fast dissolving films. PVA can be combined with other polymers of similar nature to achieve the required blend of properties. PVP comes in several molecular weight grades which allow a wide range of water solubility. It forms very flexible films and can dissolve relatively high amounts of actives [24-26]. PVP is easy to process and lends itself to several formulation processes. It has been shown to be useful for controlled or slow release of active from films [27]. PEO has a unique property of being a flexible polymer which eliminates the need to add a plasticizer. It forms films with high resistance to shear stress and still affords fast dissolution [28-32].

Other polymers reported for ODF are pectin, starch and pullulan. Pullulan is an expensive polymer and is not easily available, hence is not preferred by itself. It is commonly combined with other polymers such as starch to reduce cost [33-35]. It does offer the advantage of forming transparent films. Pectin has swelling properties and provide high viscosity. This polymer is suitable for actives that have to be dispersed instead of being dissolved in the films. It has high capacity for actives and can slow down the release of actives [36, 37]. Although starch is listed as one of the choices of polymers for ODF, it is generally not preferred due to its low resistance to shear stress and high temperature [38-40].

Selection of Polymer

Polymer selection is an important decision in early design of the product. Several factors have to be considered in this decision. For example, if fast dissolution is desired, maltodextrin based matrices can be highly desirable. It has been shown that maltodextrin based ODF with glycerin as the plasticizer for piroxicam had a fast dissolution time [41]. The films in this study were prepared by solvent casting method as well as hot-melt extrusion method.

For poorly water soluble actives, a HPMC/HPC based film has been reported [42] In this study, a fast dissolving oral film containing dexamethasone as active was prepared. HPMC/HPC combination allowed the use of PEG as plasticizer to obtain the desired release rate of poorly soluble active.

Use of HPMC with glycerin as plasticizer has been reported for poorly soluble drugs. In this ODF, nanoparticles of several drugs including griseofulvin, naproxen and phenylbutazone were suspended in HPMC/glycerin system and cast into films [43]. The resulting films were able to deliver the nanoparticles without the use of a surfactant in the formulation. The study showed that the particle size of the actives did not change after their release from ODF. Similar films were reported for loperamide and ibuprofen as well [44]. ODF have also been prepared for delivery of peptides. In these studies, films based on gelatin and chitosan were proposed for delivery of peptides [45].

Plasticizers

Plasticizers are formulation excipients to impart good mechanical properties to the film. These properties include tensile strength and resistance to shear stress. Examples of commonly used plasticizers are butyl citrates, glycerin, diethyl phthalate, PEG and PG [46, 47]. Plasticizers can range in concentration from 1-20% on final weight basis. Their choice and content depends on the desired properties and the polymer used.

Stabilizers

Stabilizers in ODF are generally added to improve performance characteristics and stability of the film. They play a role in dissolution, dispersion, wetting and fast release. Sodium lauryl sulfate is the most commonly used surfactant in this regard. Other surfactants used as stabilizers are poloxamer and tweens [48].

Additional Ingredients

In addition to the polymer, plasticizer and stabilizers, several other ingredients such as flavor, sweetener, and saliva stimulating agents can be added to ODF. Saliva stimulating agents serve the purpose of increasing fluid available for film dissolution. These ingredients are usually organic acids such as citric and tartaric acid [48]. To some degree sweeteners can also serve the function of saliva stimulation. These ingredients are useful for films intended to be place on the tongue or in buccal cavity for rapid dissolution. For films intended for sublingual administration, saliva stimulation can reduce the residence time of the film under the tongue thereby compromising its performance. Coloring and flavoring agents are added for appearance and taste, respectively. These are usually selected from the GRAS listed ingredients based on the properties of the active

ingredient. Sweeteners can be natural carbohydrates or artificial sweeteners such as acesulfame and neotame. For ODF where a strong sweetener is desired to mask the taste of the active, artificial sweeteners are preferred.

Methods of preparation

Method of preparation depends on the properties of the active and the polymer. The choice also depends on the scale of manufacture. In general, the following methods are used to prepare ODF

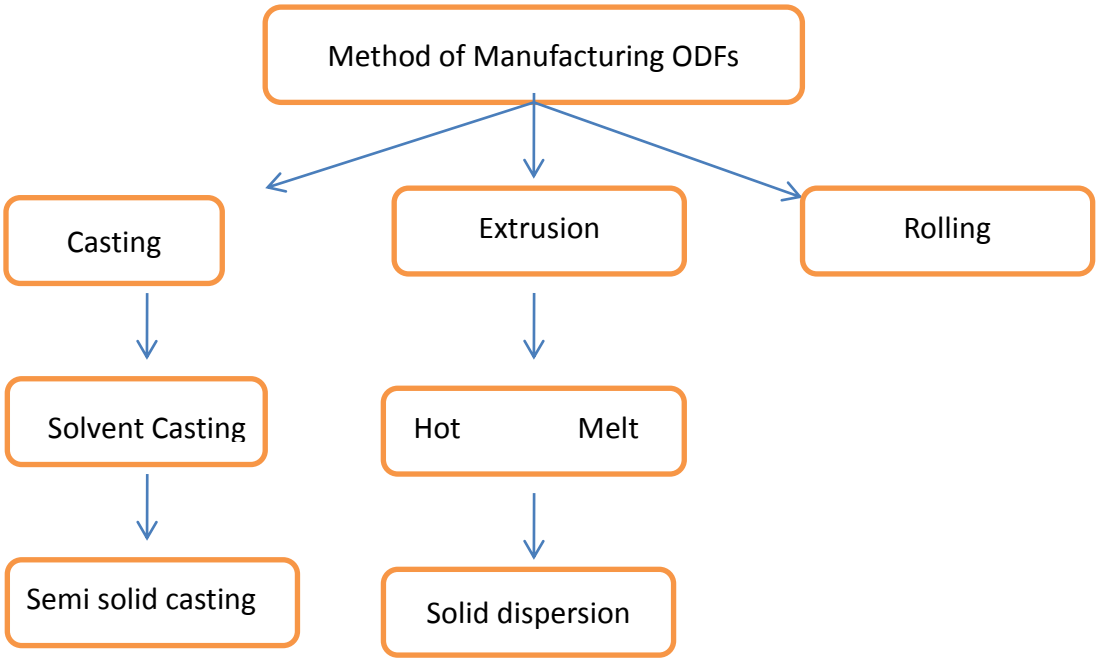

Figure 1 - Methods of preparation of Oral disintegrating films

Solvent Casting

This is the most commonly used method to prepare ODF. It can be used with water insoluble ingredients, however it lends itself better for water soluble ingredients. The process involves dissolving or dispersing the ingredients in water, followed by spreading of the solution as a thin layer. The final step is the removal of enough water to obtain a flexible film. Residual moisture needed in the film depends on the polymer and active properties. This method has been reported by several authors [49]. In certain cases where the polymer or active is slow dissolving, the process may take several hours to obtain the solution. Removal of solvent generally requires high temperature and air flow, rendering the process unsuitable for thermolabile materials.

However, in certain cases, it may be possible to remove solvent at room temperature. One of the drawbacks of this method is the long processing time. Another drawback is the need for high viscosity for uniform suspension where all ingredients are not soluble in the matrix. High

viscosity also increases the likelihood of air entrapment in the film. This method can be used with a variety of polymers including pullulan, HPMC, and PVA.

An extension of the solvent casting method is the semi-solid casting method. In this method a solution or suspension of the final formulation is subject to either temperature or pH change to convert the contents into a gel. The gel is set into films and allowed to dry [50]. The gelled mass can be cast into films by shear based spreading or rolling.

Flow diagram:

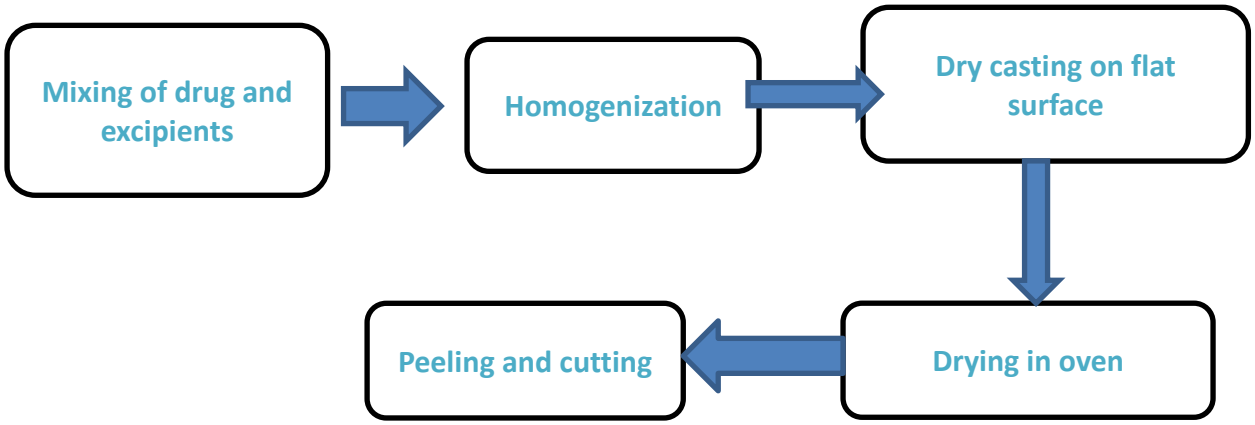

Figure 2 – Flow diagram for Solvent casting

Hot Melt Extrusion

Hot melt extrusion involves the application of heat and high pressure to the matrix. The process involves mixing of ingredients in solid state, followed by forcing the ingredients through a high shear opening while simultaneously applying heat in order to melt or soften the mass. This method does not involve the addition of a solvent. However, since significant application of heat is involved in this method, it is not suitable for thermolabile materials [51, 52].

A variation of this method is the solid dispersion extrusion. This method involves mixing the drug with a suitable solvent followed by addition of melted polymer to the solution. The mass is extruded to obtain a uniform matrix which is cast into films and cut into shape. This method involves the use of some solvent. Another variation of the method of extrusion is the rolling extrusion method. In this method the formulation ingredients are dissolved in an organic solvent such as alcohol or alcohol-water mixture. The mass is extruded, cast into films and dried.

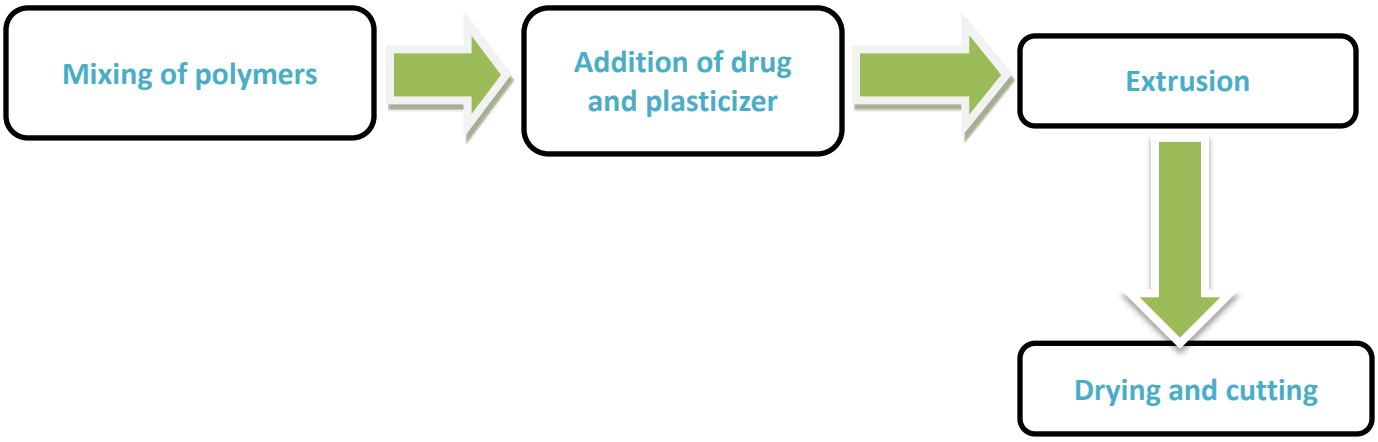

Figure 3 - Flow diagram for hot melt extrusion

PROPERTIES of ODF PRODUCT

There are several critical properties of ODF that need to be achieved and characterized for a viable product. In addition to the conventional tests like disintegration test, Thickness, In-vitro dissolution and content uniformity, several other tests are also performed. Some of the critical ones are mentioned below.

Tensile strength and stability

Physical strength is the most important attribute of ODF. The product must be able to withstand formulation related stress, manufacturing process related stress, and storage and handling conditions. There are no specific requirements for this attribute the properties of each ODF are evaluated on individual basis. Tensile strength is one of the parameters that is measure and reported for all ODF [53, 54]. There are no defined values across the ODF range, the values have to be established for each product based on the need and its properties. A balance has to be achieved between tensile strength and mechanical strength. The film should not resist deformation to a point of becoming brittle, but must resist deformation in order to maintain its integrity [55.]

Physical and chemical stability for ODF is as important as for any other system. ODF are prone to more stability issues than solid dosage forms due to the fact that they contain higher amount of residual solvent. In addition, stability affecting factors such as exposure to high temperature and high moisture level are also typically involved during the manufacturing process. For this reason it is important to have tests in place to monitor stability during entire process of manufacturing, storage and use. Appearance of ODF is a critical quality criteria. The size and shape of the product must remain unchanged during its shelf life. Drug release profile is another critical criteria that must be monitored throughout the shelf life of the product. If fast dissolution/disintegration time is claimed, it is important to meet the FDA guidelines at all time of the product life cycle [56, 57].

Residual solvent

Since ODF are designed to be flexible, they can contain significantly higher moisture than regular solid dosage forms. Moisture contents in excess of 5% are not uncommon in ODF. Additionally, the ingredients used in ODF are hydrophilic in nature and therefore prone to absorb moisture during storage. This makes packaging configuration an important decision. Change in moisture content during storage is likely to have an effect on both physical and chemical stability. For example, excess moisture may turn the product sticky and hard to use, while excessive loss of moisture makes them brittle. Dissolution profile is closely related to the moisture content of the product.

Dryness test/Tack test

As the film should be dried to the extent where it is tack free. This test is usually carried out to evaluate the ability of a film to stick to a piece of paper pressed between strips. This test is also done using equipments. [31, 32]

Folding endurance

It also measures the mechanical strength of film. Folding endurance value is number of times the film is folded without breaking at the same point. It is indirectly proportional to the plasticizer concentration [32.]

Swelling Capability

Initial weight of the film is noted and is placed on a pre weighed wire mesh. This mesh containing the film is dipped in a simulated saliva and increase in weight of the film is noted at regular intervals until no more weight gain is observed.[32]

$$Degree\ of\ swelling = \frac{final\ weight - initial\ weight}{initial\ weight} \qquad \textbf{(1)}$$

Contact angle

It is usually measured by goniometer. On the film surface, a drop of distilled water is placed and water droplets images are taken using digital camera and these images are analyzed by using software for determining contact angle.

Table 2: Commercially Available ODFs

Brand	Manufacturer	Active Pharmaceutical ingredient
Triaminic	Novartis	Dextromethorphan HBr
Theraflu	Novartis	Dextromethorphan HBr
Gas-X	Novartis	Simethicone
Suppress	InnoZen	Menthol
Orajel	Del	Menthol/Pectin

Listerine	Pfizer	Cool mint
Rapidfilm	Labtec GmbH	Ondansetron
Breakyl	Biodelivery Sciences	Fentanyl
Pharmfilm	MonoSol Rx LLC/ Reckitt Benckiser Pharmaceuticals	Buprenorphine Hcl + Naloxone Hcl
Pharmfilm	MonoSol Rx LLC	Ondansetron Hcl
Rapid dissolving film	Kyukyu pharmaceutical Co. ltd	Amlodipine besilate
Rapid film	APR applied Pharma Research/ MonoSol Rx LLC	Zolmitriptan
Schelzfilm	Hexal Sandoz	Risperidon
Schelzfilm	Hexal pharmaceuticals	Olanzapine
Smartfilm	Pfizer Inc	Sildenafil citrate

Packaging of ODF

Packaging considerations are important parameter for storage, protection and stability of dosage form. Packaging of ODF includes foil paper/plastic pouches, single pouch, aluminum pouch, blister packaging with multiple units and barrier film. Barriers films are primarily used with drugs which are moisture sensitive.

CONCLUSION

Oral dispersible film (ODF) has been explored to deliver drugs effectively. The main catalysts of the drug delivery market are end user compliance, awareness of consumer and the patents. It takes enormous efforts and money to discover and develop new chemical entities, hence the primary focus in the next coming years will be on new drug delivery systems like ODF, for already approved drugs in order to extend their patent duration and also file under 505(b)2. On the other hand this market has not been explored to its potential. In addition to this even animals are also encountering the same compliance issue, hence it is clear that veterinary health care market has a huge market potential in addition to the human beings. In forth coming years ODF delivery system will become popular drug delivery as it has all the pre-requisites to satisfy consumer, regulatory requirements and is scalable.

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