

NOVEL DRUG DELIVERY TECHNOLOGIES-A CHANGING AND CHALLENGING GLOBAL SCENARIO

ABSTRACT

The development of novel drug delivery techniques has got its own specific challenges. The selection of the route of administration and the dosage form has to integrate therapeutic considerations, drug substance properties, selection of excipients technical formulation feasibility and, above all, patient needs. The change in lifestyle and changes in patient population in the emerging and developing countries, the needle free, painless, simple cost effective transdermal delivery system is expected to have a bright future. The article discusses about the different techniques explored by the pharmaceutical industries for the formulation of transdermal patches and Oro dispersible films and their merits and demerits along with the changing patient needs and importance of advanced drug delivery techniques like transdermal drug delivery systems and Oro dispersible films to fulfill the growing patient requirements. This advanced technologies has not been properly explored by pharmaceutical industries may be due to the limited manufacturing feasibilities and market requirements. However the studies and publications reveal that the developing and emerging countries are shifting to the advanced delivery techniques which has got potential patient and therapeutic benefits too. Transdermal systems are inexpensive when compared with other therapies. The patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs. The oral thin-film technology is still in the beginning stages and has bright future ahead.

Keywords: Formulation development, Novel drug delivery system, Transdermal drug delivery, Oro-dispersible film, Patches, Oral Wafers and Fast dissolving oral film.

INTRODUCTION

The pharmaceutical industry is changing day to day based on the changing patient requirements and global developments. The industries have diverted their research focuses from conventional dosage forms to novel drug delivery technologies which has got significantly improved market requirements. In recent years the pharmaceutical companies are struggling to maintain a balance between the downward pressure on prices and significantly raised innovation cost. It is going to be always a green zone for companies developing novel delivery technologies to maintain their market presence and share.

Developing platform technologies promises to be an area of exciting technological innovation which gives a new life to the molecule with patent protection and good market share. The introduction of novel delivery systems to an existing molecule should significantly improve its safety, efficacy and improved patient compliance. Most of the innovator companies have a parallel research pipeline for biopharmaceuticals and concentrates on protein-peptide base drug portfolio. The global market for “advanced drug delivery systems” is predicted to grow from US\$139 billion in 2009 to US\$197 billion in 2014*.(**Shahani, Shalini. Advanced Drug Delivery Systems: New Developments, New Technologies. Wellesley, MA, USA : BCC Research, August 2009. PHM006G*).Through this article we made an attempt to compile some of the majorly used advanced drug delivery technologies in the recent years like transdermal patches and oral dispersible films. The data has been collected from various sources including published literatures, peer articles, journals, patents etc.

TRANSDERMAL DRUG DELIVERY SYSTEM

Transdermal patches are the most widely used advanced drug delivery technology and are being developed for everything from contraception to Parkinson's disease. The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness.

The transdermal medications have proven to be less harsh on the effects of the liver and effective in transmission and treatment. In general, Transdermal patches are available to help quit smoking, to ease motion sickness, to provide oral contraception or to infuse hormones into the blood stream to alleviate symptoms of menopause.

There are three generations of transdermal drug delivery systems (TTDS) as published by Prausnitz and Langer

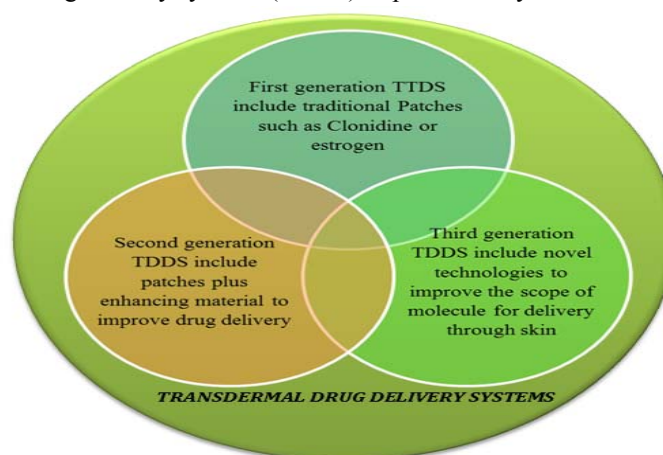


Figure-1: Three generations of Transdermal Drug Delivery Systems

All the drug delivery systems have got its own merits and demerits. The following charts shall be discussing in detail the Advantages and Disadvantages of Transdermal Drug Delivery Systems.





Figure-2: Advantages and disadvantages of transdermal drug delivery systems

Components of Transdermal Patch

- (1) Liner - Protects the patch during storage. The liner is removed prior to use.
- (2) Drug - Drug solution in direct contact with release liner.
- (3) Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.
- (4) Membrane - Controls the release of the drug from the reservoir and multi-layer patches.
- (5) Backing - Protects the patch from the outer environment.

Component name	Usage
Liner	Protects the patch during storage
Adhesive	Adhere the components of the patch and with the skin
Membrane	Controls the release of the drug
Backing	Protects the patch from the outer environment

Table-1: Components of a Transdermal Patch

Mechanism of Action of Transdermal Patch

The application of the transdermal patch and the flow of the active drug constituent from the patch to the circulatory system via skin occur through various methods.

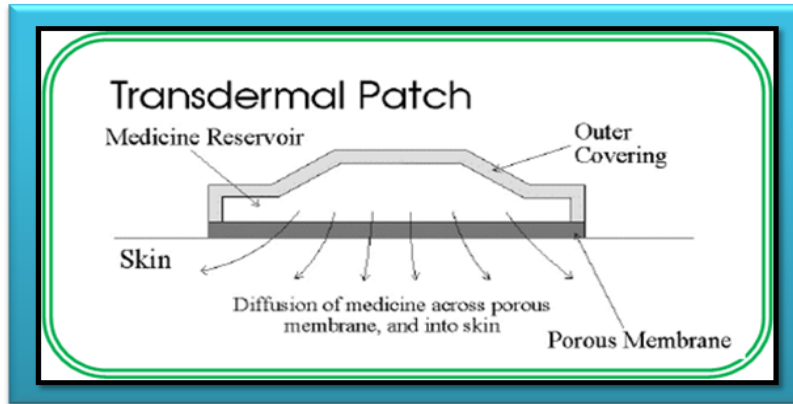


Figure-3: Mechanism of transdermal drug delivery systems

Currently there are two different types of simple patch design

1. Liquid reservoir system
2. Adhesive matrix system

Recently adhesive matrix system is widely used with three different layers, backing layer, drug+adhesive layer and protective layer which will be removed before applying the patch to the skin.

TDDSs have different drug release mechanisms

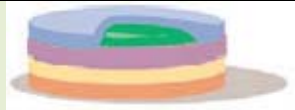
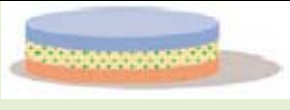
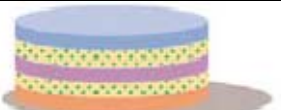













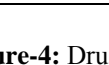

Reservoir system		Matrix system without rate controlling membrane		Matrix system with rate controlling membrane	
					
	Backing		Backing		Backing
	Drug		Drug in Adhesive		Drug in Adhesive
	Membrane		Membrane		Membrane
	Adhesive		Adhesive		Adhesive
	Liner		Liner		Liner

Figure-4: Drug release mechanisms of TDDS

Reservoir system

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Matrix system

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it.

Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Transdermal Enhancement Techniques

2nd Generation TDDS attempt to enhance the delivery of organic molecules through the stratum corneum by disrupting its barrier function and/or by providing some sort of driving force for the movement of molecules through the epidermis. In addition, these 2nd generation enhancement techniques are limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules. 2nd generation enhancement methods include chemical penetration enhancers, gentle heating, and iontophoresis.

Iontophoresis

Iontophoresis is the process of using small amounts of electrical current to move drugs across the skin and can also be used to enhance penetration of drug molecules through the stratum corneum. In an iontophoretic system, the anode will attract negative charged ions and repel positively charged drug molecules. Because most drugs are formulated as a salt, for instance fentanyl hydrochloride, the drug molecule becomes protonated and takes on a positive charge to the negative charge of the chloride anion. This results in the drug being repelled away from the anode and through the stratum corneum toward the dermis.

Chemical Penetration Enhancers

Small solvent molecules like ethanol and menthol will increase the solubility of drug molecules in the lipid bilayer and thereby enhance the intercellular route of drug movement. Dimethylsulfoxide will increase movement of drug molecules through the keratinocytes and enhance the trans cellular route of delivery

Molecules whose structures mimic that of phospholipids, those with a small, polar head and a long, hydrocarbon tail, will insert into the lipid bilayer and increase the fluidity within that layer.

If the bilayer is more fluid, it will be easier for drug molecules to move through it, also enhancing intercellular movement

Heat as a penetration enhancer

Heat can also be used as a penetration enhancer. In a CHADD(Controlled Heat-Assisted Drug Delivery) system, a mix of proprietary powders reacts with the air to generate heat that then warms the skin and increases the delivery of the drug. This heat device can be placed on top of an existing patch or other medication or it can be manufactured in combination with a drug of choice.

Thermal ablation as a penetration enhancer

Thermal ablation is another example of a 3rd generation technique improves the penetration, severely disrupts the stratum corneum. Thermal ablation heats the skin to 100s of degrees for very short periods of time (micro- to milliseconds) and forms painless, reversible microchannels in the stratum corneum without damaging the underlying tissue (Prausnitz 2008).

One way to create these thermal ablation microchannels in the skin is by using radio frequency (RF) waves (Galit 2008). These waves cause ions in the surrounding cells to vibrate, the vibrations cause heat, the heat causes evaporation, and the evaporation of water from the cells causes ablation.

Ultrasound as a penetration enhancer

Another 3rd generation technology that can be used to increase delivery of drugs across the skin is the use of ultrasound waves (Prausnitz 2008). Using ultrasound to deliver drugs across the skin is also referred to as phonophoresis or sonophoresis. This is the same type of ultrasound technology that is used in lithotripsy to break up kidney stones and gallstones.

Microneedles as a penetration enhancer

Microneedles are designed to penetrate the stratum corneum and deliver drug without reaching the nerves in the underlying tissues. Microneedles can be 200-750 microns in length (Cleary 2010) and are fabricated in groups called arrays that can contain 150-650 microneedles/cm². Some of the materials that have been used to make microneedles include silicon, metal, sugar, and plastics. Microneedles can be hollow and deliver drug through the pores of the needles or they can be coated with active ingredients that deliver the drug as the microneedles dissolve in the skin (Peterson 2006).

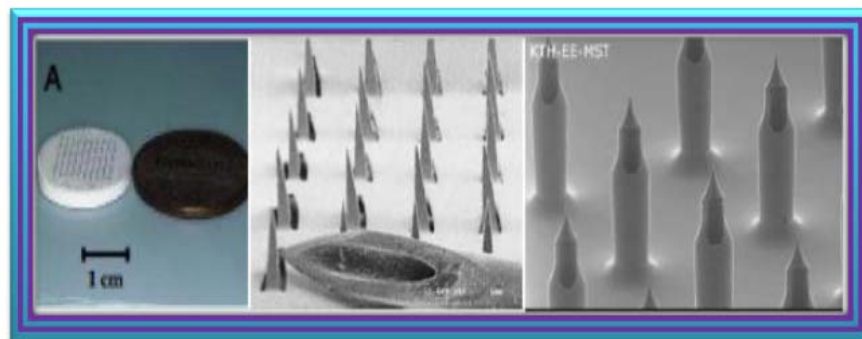


Figure-5: Dissolving microneedle array (Fukushima 2011); Solid microneedle array with hypodermic needle for comparison (Martanto 2004); Hollow microneedle array (Nordquist 2007)

Microneedles have been proven to be pain-free and they deliver the vaccine intradermally which has been shown to improve vaccine response rates, especially in the elderly, while using lower doses of the vaccine .

FACTORS IMPACTING BIOAVAILABILITY OF TRANSDERMAL DRUG DELIVERY SYSTEM

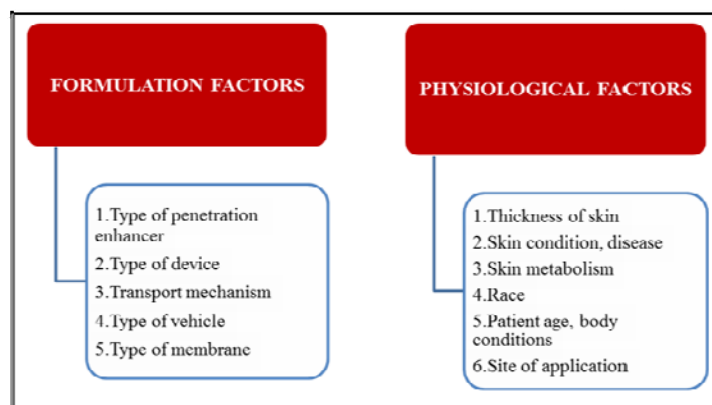


Figure-6: Factors impacting bioavailability of transdermal drug delivery system

Climara	Estradiol	3M Pharmaceuticals	Postmenstrual syndrome
Estraderm	Estradiol	Alza/Norvatis	Postmenstrual problems
Neupro [®]	Rigotine	UCB and Schwarz Pharma	Parkinson's disease
Nitro-dur	Nitroglycerin	Key Pharmaceuticals	Angina pectoris
NuPatch 100	Diclofenac diethylamine	Cadila Healthcare Ltd	Anti-Inflammatory
Matrifen [®]	Fentanyl	Nycomed	Pain relief patch
Nitrodisc	Nitroglycerin	Roberts Pharmaceuticals	Angina pectoris
Nicotinell [®]	Nicotine	Novartis	smoking cessation
Catapres TTS [®]	Clonidine	Alza/Boehinger Ingelheim	Hypertension
FemPatch	Estradiol	Parke-Davis	Postmenstrual syndrome
Nicoderm [®]	Nicotine	Alza/GlaxoSmithKline	Smoking cessation
Androderm	Testosterone	TheraTech/GlaxoSmithKline	Hypogonadism
Transderm-Scop [®]	Scopolamine	Alza/Novartis	Motion sickness
Nuvelle TS	Estrogen/Progestosterone	Ethical Holdings/Schering	Hormone replacement therapy
Deponit	Nitroglycerin	Schwarz-Pharma	Angina pectoris
Testoderm TTS [®]	Testosterone	Alza	Hypogonadism
Oxytrol [®]	oxybutynin	Watson Pharma	Overactive bladder
Prostep	Nicotine	Elan Corp./Lederle Labs	Smoking cessation
Duragesic [®]	Fentanyl	Alza/Janssen Pharmaceutical	Pain

Table-2: Some of the commercially available transdermal patches are listed below

ORO DISPERSIBLE FILM

Orodispersible films for oral delivery are gaining popularity. Whereas breath-fresheners and over-the-counter products have already become quite common in the US, the first prescription drug films were introduced into the EU and US markets only very recently. They enable an easy application, as there is no need to drink high amounts of liquids or swallow large solid dosage forms. Already considered as a unique Rx (prescription drug) dosage form by the FDA (oral soluble film), such products are not substitutable by conventional oral dosage forms. The official term defined by the European Medicines Agency is orodispersible film (ODF).

Oral wafers, or oro dispersible strips, are thin films of typically 2-8cm² area and 20-500 µm thickness, containing typically less than 50mg of API. They are administered directly on the tongue. Wafers can dissolve or disintegrate in the mouth within a few seconds without water. Spitting out is very unlikely due to the immediate disintegration and the adherence to the mucosa. To date few OTC products are commercially available for pre-school children, eg. in USA as Triaminic® Thin Strips™ Cough & Runny Nose (Novartis Consumer Health). The products, intended for children above 4 years, contain several excipients, such as film forming agents derived from cellulose and starch, as well as sweeteners, flavours, colouring agents and traces of class 3 residual solvents used as processing aids.

Fast dissolving oral films (FDOFs) are the most advanced form of oral solid dosage form due to more flexibility and comfort. Orodispersible formulations are beneficial especially for the paediatric but also for the geriatric population as swallowing high volumes of liquids can be omitted. Furthermore, risk of choking on this new dosage form is minimized due to its possible adhesion to the oral mucosa and its fast disintegration. It improves the efficacy of APIs by dissolving within minute in oral cavity after the contact with less saliva as compared to fast dissolving tablets, without chewing and no need of water for administration. The FDOFs place as an alternative in the market due to the consumer's preference for a fast dissolving product over conventional tablets / capsules.

ADVANTAGES AND DISADVANTAGES OF ORO DISPERSIBLE FILMS

Similar to most of the other dosage forms Oro dispersible films also got its own advantages and limitations. Few of them are listed below.

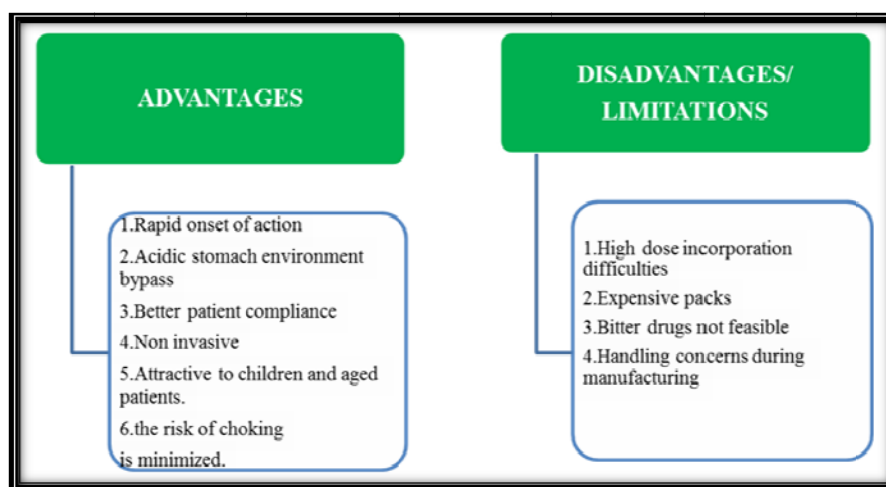


Figure-7: Advantages and disadvantages of oro dispersible films

MECHANISM OF ACTION

The mechanism of action for Orodispersible films are simple wetting, hydration, disintegration, dissolution and absorption. Once the film is placed on the tongue immediately it gets hydrated by saliva followed by rapid release of drug and absorption into the oral mucosa.

COMPOSITION OF A ORODISPERSIBLE FILM

In general the excipients used for the formulation of ODF's are similar to other solid oral dosage form except the addition of penetration enhancers, which is used case by case. The commonly used excipient categories include

1. Film forming agents
2. Surfactants
3. Sweetening agents
4. Plasticizers
5. Penetration enhancers
6. Fillers
7. Colorants

Film forming agents

Generally water soluble polymers are used as film forming agents like HPMC, HPC, Povidone, Cellulose polymers like CMC, SCMC, alginates etc. These polymers give mechanical characteristics to the film along with disintegration properties as well as mouthfeel.

Surfactants

These are majorly used to improve the wettability of drug substance and enhances the solubility. Some of the most commonly used surfactants in the industry are sodium lauryl sulphate, Polysorbates, poloxamer etc.

Sweetening agents

To improve the patient acceptance, sweeteners are unavoidable part of the Oral dispersible films. The widely used sweetening agents include natural sugars like fructose, sorbitol, mannitol etc. Artificial sweetening agents like acesulfame potassium, saccharines, neotame, alitame etc also are being commonly added to improve the acceptability and palatability of the formulations.

Plasticizers

The film mechanical properties like tensile strength shall be improved by the addition of plasticizers. Generally water soluble plasticizers like poly ethylene glycols are preferred. Water insoluble plasticizers like phthalates, glycerols etc can also be used case by case.

Penetration enhancers

For the improved absorption of drug in the oral region permeability enhancers are used. The permeability of buccal mucosa is 4-4000 times higher than skin. Some of the commonly used permeability enhancers include Cyclodextrin, Aprotinin, dextran sulphate, menthol, sodium tauro deoxycholate.

Fillers

The water soluble fillers like mannitol or other sugar alcohols, microcrystalline cellulose etc shall be used in the formulation as inert carriers

Colorants

Pigments such as titanium dioxide or a full range of colors are available, including FDandC colors, Natural Colours can be used as coloring agents in the formulation

FORMULATION TECHNIQUES

Generally the Oro dispersible film can be manufactured using the following methods

- ❖ Solvent Casting
- ❖ Hot Melt extrusion
- ❖ Solid dispersion extrusion
- ❖ Semisolid casting
- ❖ Rolling

Among these techniques Hot melt extrusion and Solvent casting are majorly adopted by pharmaceutical companies.

Solvent Casting

The oldest technology in plastic films manufacturing, the continuous solvent cast process, was developed more than hundred years ago. This is one of the major techniques adopted by the industry. In this method the water soluble excipients are dissolved to form a bulk solution. API and other materials were dissolved in small quantity of solution and added to bulk solution. Then the Solutions shall be poured onto a release liner that was fixed by vacuum suction on the film applicator. Afterwards they shall be casted by the help of a coating knife at the calculated thickness to achieve desired drug amounts per film.

Hot Melt extrusion

The drug substance along with polymers, plasticizers and other excipients shall be melted under controlled temperature. The melted mass shall be passed through a die which shapes the molten mass to the film and followed by pass through a drying tunnel and in the last step the films are punched, pouched and sealed.

EVALUATION OF ORO DISPERSIBLE FILMS

The major quality control checks are performed by evaluating the following parameters

1	Film Thickness and Weight	Determined by a Micrometer screw
2	Uniformity of Drug Content	Acceptance value not more than 15
3	Disintegration time	limit of 30 s or less for orally disintegrating tablets can be applied to fast dissolving oral film
4	Tack test /Dryness test	Film drying process steps- set-to- touch, dust-free, tack-free (surface dry), Dry-to-touch, dry-hard, dry-through (dry-to-handle), dry-to-recoat and dry print free.
5	Tensile Strength	Load at failure \times 100 $\frac{\text{-----}}{\text{Film thickness} \times \text{film width}}$
6	Folding Endurance	Folding endurance is determined by repeated folding of the film at the same place till the film breaks.
7	Percent Elongation	$\frac{L \times 100}{\text{-----}}$ Lo
8	Tear Resistance	The maximum stress or force (that is generally found near the onset of tearing) required to tear the film
9	Young's Modulus	Slope \times 100 $\frac{\text{-----}}{\text{Film thickness} \times \text{cross-head speed}}$
10	Electronic Taste Sensing	Electronic tongue measurements to distinguish between the sweetness levels
11	Morphology	Scanning electron microscopy (SEM) study refers the differences between upper and lower side of the films. It also helps in determination of the distribution of API.
12	Assay, Dissolution profile, Related Substance	Chemical analysis with regulatory acceptable limits

Table 3: Evaluation tools for Oro dispersible films

CONCLUSION

It can be concluded that in future patients are going to be much more involved in their own treatments to reduce costs and hence smart drug delivery technologies are part of what is going to enable this change safely. Transdermal systems are generally inexpensive when compared with other therapies on a monthly cost basis, as patches are designed to deliver drugs from 1 to 7 days. The other advantage of transdermal delivery is that multiple dosing, on-demand or variable-rate delivery of drugs, is possible with the latest programmable systems, adding more benefits to the conventional patch dosage forms. The general acceptability of transdermal products by patients is very high, which is also evident from the increasing market for transdermal products. The transdermal drug delivery market, worth

\$12.7 billion dollars in 2005, is expected to reach \$32 billion in n 2015. The change in lifestyle and changes in patient population in the emerging and developing countries, the needle free, painless, simple cost effective transdermal delivery system is expected to have a bright future.

The above presented details reveal the advantages of Oro dispersible films over other dosage forms and its industrial applicability. Orodispersible film (ODF) technology offers new possibilities for drug delivery by providing the advantages of oral delivery coupled with the enhanced onset of action and convenience to special patient categories such as pediatrics and geriatrics. The oral thin-film technology is still in the beginning stages and has bright future ahead because it fulfills all the need of patients. Eventually, film formulations having drug/s will be commercially launched using the oral film technology. However, for future growth point of view the oral thin film sector is well-positioned. In US market the OTC films of pain management and motion sickness are commercialized. More importantly, prescription ODFs have now been approved in US, EU and Japan which are the three major regions. These approved Rx films, have potential to dominate over other oral dosage forms of the same drugs. It seems that the value of the overall oral thin film market will grow significantly.

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