



## OVERVIEW ON FAST DISSOLVING FILMS

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### ABSTRACT

The objective of our review is to compile the recent advancements and literatures regarding the fast dissolving film i.e. Oral dissolving film Technology (ODFTs) that can be administered in the buccal cavity for a shorter period of time in Secs and gives better therapeutic action. The methodologies used in the development of ODFTs for pediatric and geriatric patient's population, who are difficulty in swallowing larger dosage forms. This technology has been used for local action, rapid release products. ODFT offers an alternate platform for molecules that undergoes first pass metabolism. Our review article suggests that (ODFT) can be the possible way to improve patient compliance and robustness. Various pharma companies adopted advance technologies to make ODFT commercialized in large scale despite of several limitations.

**Keywords:** ODFT, Buccal Cavity, Pediatric Patients, Geriatric Patients

### INTRODUCTION

Among the various routes, the oral route is the most acceptable for the patients. Many pharmaceutical companies have directed their research activity in reformulating existing drugs into new dosage forms. One such relatively new dosage form is the oral strip, a thin film that is prepared using hydrophilic polymers that rapidly dissolves on the tongue or buccal cavity. Developing formulations for children has been a challenging task. Amongst other factors, palatability of formulations of pediatric oral medications is one of the most significant factors influencing compliance to therapeutic regimens<sup>1,2</sup>. Although solid dosage forms are widely accepted by elders and adolescents, younger children tend to prefer liquid formulations that are easier to swallow<sup>3</sup>. Keeping the ease of administration and swallowing in mind, pharmaceutical research has led to the development of Oral Disintegrating Tablets (ODTs). ODTs have been defined as "A solid dosage form containing medicinal substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue". United States Food and Drug Administration further defines ODTs as solid oral preparations that disintegrate rapidly in the oral cavity, with an *in-vitro* disintegration time of approximately 30 s or less, when based on the United States Pharmacopeia (USP) disintegration test method or alternative<sup>4</sup>.

Research and development in the oral drug delivery segment has led to transition of dosage forms from simple conventional tablets/capsules to modified release tablets/capsules to oral disintegrating tablet (ODT) to wafer to the recent development of oral films (ODF). Basically the (ODF) can be considered as an ultra-thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other excipients. The advantages of convenience of dosing and portability of ODF have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

The ODT in market was accompanied by educating the mass about the proper way to administer the product like giving instructions "do not swallow" or "do not chew". The process of manipulating the ODT in oral or buccal cavity was also important. However since the ODT derived products were readily popular in the market in the form of breath-freshening strips, no further efforts were needed to re-instruct the populace about the technique of administration of this dosage form. (ODFT) was already popular amongst the people in the early 2000 year with the introduction and widespread use of listerine pocket strips, a new launch in the mouthwash range.

Technology Catalysts forecasts the market for drug products in oral thin film formulations to be valued at \$500 million in 2007 and could reach \$2 billion by 2010<sup>5</sup>. However only a few products

consisting bitter molecules have been able to be commercialized because of the complexity associated with the ODT.

### The advantages and disadvantages of oral formulations such as:

1. Availability of larger surface area that leads to rapid disintegrating and dissolution in the oral cavity.
2. The disadvantage of most ODT is that they are fragile and brittle, which warrants special package for protection during storage and transportation. Since the films are flexible they are not as fragile as most of the ODTs. Hence, there is ease of transportation and during consumer handling and storage.
3. As compared to drops or syrup formulations, precision in the administered dose is ensured from each of the strips.
4. No need of water has led to better acceptability amongst the dysphagic patients. The difficulty encountered in swallowing tablets or capsules is circumvented. The large surface area available in the strip dosage form allows rapid wetting in the moist buccal environment. The dosage form can be consumed at anyplace and anytime as per convenience of the individual.
5. The oral or buccal mucosa being highly vascularized, drugs can be absorbed directly and can enter the systemic circulation without undergoing first-pass hepatic metabolism. This advantage can be exploited in preparing products with improved oral bioavailability of molecules that undergo first pass effect<sup>6</sup>.
6. Since the first pass effect can be avoided, there can be reduction in the dose which can lead to reduction in side effects associated with the molecule.
7. Patients suffering from dysphagia, repeated emesis, motion sickness, and mental disorders prefer this dosage form as they are unable to swallow large quantity of water.

A number of molecules can be incorporated into this delivery system. They may include cough/cold remedies (antitussives, expectorants), sore throat, erectile dysfunction drugs, antihistaminics, antiasthmatics, gastrointestinal disorders, nausea, pain and CNS (e.g. anti-parkinsons disease). Other applications comprise caffeine strips, snoring aid, multivitamins, sleeping aid etc.

The ODFT technology continues to be viewed as an alternative for ODT products that would afford a superior barrier to generic entry and product differentiation to over-the-counter brands. From the marketing perspective, a patented ODF technology would be beneficial. The grant of marketing exclusivity to the new dosage form would help to gain more revenue. As compared to the other ODTs such as tablets; the product is robust. From the patient point

of view OS offers ease of administration and improved compliance. The manufacturing of this dosage form is cost-effective with affordable end-products. From clinical aspect, the improved bioavailability can be advantageous in reducing the dose of the formulation. This would lead to product with minimized side effects. The product can be a substitute with more clinical advantage. However, not all drugs can be incorporated into this dosage form. The disadvantage of ODFT is that high dose cannot be incorporated into the strip. Hence researchers has proven that the concentration level of active can be improved up to 50 percent; per dose weight. Novartis Consumer Health's Gas-X® thin strip has a loading of 62.5 mg of simethicone per strip <sup>7</sup>.

#### Formulation considerations

Formulation of oral Strip (OS) involves the intricate application of aesthetic and performance characteristics such as taste masking, fast dissolving, physical appearance, mouth-feel etc. The excipients used in formulation of OS are given below as per their categories. From the regulatory perspectives, all excipients used in the formulation of OS should be generally regarded as Safe (i.e. GRAS-listed) and should be approved for use in oral pharmaceutical dosage forms.

#### Strip forming polymers

A variety of polymers are available for preparation of OS. The polymers can be used alone or in combination to obtain the desired strip properties. The film obtained should be tough enough so that there won't be any damage while handling or during transportation. The robustness of the strip depends on the type of polymer and the amount in the formulation <sup>8</sup>. The various polymers available, pullulan, gelatin and hypromellose are most commonly used for preparation of OS. Pullulan is a natural polymer obtained from non-animal origin and does not require chemical modification. Modified starches are also used for preparation of OS. Due to low cost of this excipient it is used in combination of pullulan to decrease the overall cost of the product. About 50 to 80 percent;w/w of pullulan can be replaced by starch in the production of OS without loss of required properties of Pullulan. Combination of microcrystalline cellulose and maltodextrin has been used to formulate OS.

#### Plasticizers

Plasticizer is a vital ingredient of the OS formulation. It helps to improve the flexibility of the strip and reduces the brittleness of the strip. Plasticizer significantly improves the strip properties by reducing the glass transition temperature of the polymer. The selection of plasticizer will depend upon its compatibility with the polymer and also the type of solvent employed in the casting of strip. The flow of polymer will get better with the use of plasticizer and enhances the strength of the polymer <sup>9,10</sup> Glycerol, Propylene glycol, low molecular weight polyethylene glycols, phthalate derivatives like dimethyl, diethyl and dibutyl phthalate, citrate derivatives such as tributyl, triethyl, acetyl citrate, triacetin and castor oil are some of the commonly used plasticizer excipients. Typically the plasticizers are used in the concentration of 0-20 percent; w/w of dry polymer weight <sup>11</sup>. However, inappropriate use of plasticizer may lead to film cracking, splitting and peeling of the strip. It is also reported that the use of certain plasticizers may also affect the absorption rate of the drug.

#### Sweetening agents

Sweeteners have become the important part of the food products as well as pharmaceutical products intended to be disintegrated or dissolved in the oral cavity. The classical source of sweetener is sucrose (derived from cane or beet in the form of liquid or dry state), dextrose, fructose, glucose, liquid glucose and maltose. The sweetness of fructose is perceived rapidly in the mouth as compared to sucrose and dextrose. Fructose is sweeter than sorbitol and mannitol and thus used widely as a sweetener. Polyhydric alcohols such as sorbitol, mannitol, and isomalt can be used in combination as they additionally provide good mouth-feel and cooling sensation. Polyhydric alcohols are less carcinogenic and do not have bitter after taste which is a vital aspect in formulating oral preparations. The artificial sweeteners have gained more popularity in food and

pharmaceutical preparations. Saccharin, cyclamate and aspartame are the first generation of the artificial sweeteners followed by acesulfame-K, sucralose, alitame and neotame which fall under the second generation artificial sweeteners. Acesulfame-K and sucralose have more than 200 and 600 time sweetness. Neotame and alitame have more than 2000 and 8000 time sweetening power as compared to sucrose. Rebiana which is a herbal sweetener, derived from plant *Stevia rebaudiana* (South American plant) has more than 200 - 300 time sweetness <sup>12</sup>.

#### Saliva stimulating agent

The purpose of using saliva stimulating agents is to increase the rate of production of saliva that would aid in the faster disintegration of the rapid dissolving strip formulations. Generally acids which are used in the preparation of food can be utilized as salivary stimulants. Citric acid, malic acid, lactic acid, ascorbic acid and tartaric acid are the few examples of salivary stimulants, citric acid being the most preferred amongst them.

#### Flavoring agents

It was observed that age plays a significant role in the taste fondness. Flavoring agents can be selected from synthetic flavor oils, oleo resins, extract derived from various parts of the plants like leaves, fruits and flowers. Flavors can be used alone or in the combination. Peppermint oil, cinnamon oil, oil of nutmeg are examples of flavor oils while vanilla, cocoa, coffee, chocolate and citrus are fruity flavors. Apple, raspberry, cherry, pineapple are few examples of fruit essence type. The amount of flavor needed to mask the taste depends on the flavor type and its strength.

#### Coloring agents

Pigments such as titanium dioxide or FD & C approved coloring agents are incorporated (not exceeding concentration levels of 1 percent; w/w) in OS when some of the formulation ingredients or drugs are present in insoluble or suspension form.

#### Quality control tests

##### Thickness

It can be measured by micrometer screw gauge at different strategic locations. 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.

##### Dryness test/tack tests

About eight stages of film drying process have been identified and they are 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. Although these tests are primarily used for paint films most of the studies can be adapted intricately to evaluate pharmaceutical OS as well <sup>13</sup>. The details of evaluation of these parameters can be checked elsewhere and are beyond the scope of this review. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip. Instruments are also available for this study.

##### Tensile strength

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks <sup>14</sup>. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip as given in the equation below:

$$\text{Tensile strength} = \frac{\text{Load at Failure} \times 100}{\text{Strip thickness} \times \text{Strip Width}}$$

##### Percent elongation

When stress is applied, a strip sample stretches and this is referred to as strain. Strain is basically the deformation of strip divided by original dimension of the sample. Generally elongation of strip increases as the plasticizer content increases. <sup>15</sup>

$$\% \text{Elongation} = \frac{\text{Increase in length of strip} \times 100}{\text{Original length of strip}}$$

Initial length of strip

### 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 to tear the specimen is recorded as the tear resistance value in Newtons (or pounds-force) <sup>16</sup>.

### Young's modulus

Young's modulus or elastic modulus is the measure of stiffness of strip. It is represented as the ratio of applied stress over strain in the region of elastic deformation as follows:

$$\text{Young's modulus} = \frac{\text{Slope} \times 100}{\text{Strip thickness} \times \text{Cross-head speed}}$$

Hard and brittle strips demonstrate a high tensile strength and Young's modulus with small elongation.

### Folding endurance

Folding endurance is determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film is folded without breaking is computed as the folding endurance value <sup>17</sup>.

### Disintegration time

The disintegration time limit of 30 s or less for orally disintegrating tablets described in CDER guidance can be applied to fast dissolving

oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30 s <sup>18</sup>.

### 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 <sup>19</sup>. 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.

### Assay/drug content and 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 percent.

### Organoleptic evaluation

For evaluation of psychophysical evaluation of the product, special controlled human taste panels are used. *In-vitro* methods of utilizing taste sensors, specially designed apparatus and drug release by modified pharmacopoeial methods are being used for this purpose. These *in-vitro* taste assessment apparatus and methodologies are well suited for high-throughput taste screening of oral pharmaceutical formulations <sup>20</sup>.

### Marketed products of oral films <sup>20</sup>

Product category	Ingredients	Indication/applications
Biofilm		
Energy boosters	Caffeine, green tea extract and guarana	The product maintains the energy levels.
Detoxification strip	Green tea extract which is high in polyphenols and rich in anti-oxidants.	Wound healing, regulating body temperature, blood sugar and promoting a healthy digestion
Male vitality strip	Maca root extract and Siberian ginseng extract, herbs which enhance libido, Cinnamint flavor.	Aphrodisiac
Appetite suppressant	fucus vesiculous and guarana extract, garcinia cambogia	Cambogia helps to reduce the food intake by suppressing appetite.
Vitamins and food supplements	Various vitamins, minerals and supplements	It is useful for the people who do not like to pop up the tablets or soluble supplements
Breath freshener strip, (Antibacterial strip)	Contain mint flavor and antibacterial agent, cetylpyridinium chloride	Mouth freshener
Saliva promoting strips	Fruit acid extracts, range of flavors	It is used in the dry mouth as a side effect of the other medications.
Labtec GmbH		
Ondansetron	Ondansetron 4 mg and 8 mg.	It is used in the prevention of chemotherapy and radiation-induced nausea and vomiting and prevention of postoperative nausea and vomiting.
Rapidfilm®		
Donepezil Rapidfilm®	Donepezil Hydrochloride 5 mg and 10 mg.	Treatment of mild to moderately severe dementia of the Alzheimer's type.
Paladin Labs (Bioenvelop)		
Smoking cessation	Nicotine	To reduce the smoking habit
Multivitamin for kids and adults	B6, B12, C, D3 for kids, D3 for adults	Multi vitamin supplement,
Teeth whitening	-	Lifestyle improvement product
Food supplements	Benzocaine, Caffeine, Melatonin, MentholOmega, Hoodia, Protein, Vinpocetine	Nutraceuticals
Minerals	Chromium	Mineral supplements
Natural products	Ginseng, Guarana	Aphrodisiac, Appetite reducer.
Innozen Inc		
Chloraseptic® Relief Strips™	Benzocaine 3 mg, BHT, corn starch, erythritol, FD&C Red 40, hydroxypropyl methylcellulose, malic acid, menthol, monoammonium glycyrrhizinate, cherry flavors, polyethylene oxide, sucralose	Occasional minor irritation, pain, sore throat and sore mouth
Chloraseptic® Kids Sore Throat Relief Strips	Benzocaine 2 mg & menthol, grape flavor, BHT, corn starch, erythritol, FD & C Blue 1, FD & C Red 40, hydroxypropyl methylcellulose, malic acid, menthol, monoammonium glycyrrhizinate, polyethylene oxide, sucralose	Occasional minor irritation, pain, sore throat and sore mouth
Suppress™ Cough strips with	Dextromethorphan hydrobromide 2.5 mg, Asulfame potassium, FD&C Blue 1, glycerin, menthol, natural and artificial flavors, pectin,	Temporarily suppresses coughs due to minor throat and bronchial irritation

Dextromethorphan Suppress™ Cough strips with menthol	peppermint oil, sucralose, sugar, water Artificial flavors, ascorbic acid, aspartame, asulfame potassium, carrageenan, diglycerides, fatty acid ester, FD&C yellow 5 (tartrazine), glycerin, menthol, mono glycerides, pectin, sodium alginate, sorbitan monolaurate, sorbitol, spices, starch, water	associated with cold or inhaled irritants. Temporarily suppresses coughs due to minor throat and bronchial irritation associated with cold or inhaled irritants.
Hughes Medical Corporation		
Methylcobalamin	1 mg	Peripheral neuropathy, Diabetic neuropathy
Dextromethorphan	2.5 mg - 5.5 mg -15 mg	Anti-tussive agent used to prevent cough.
Folic Acid	1 mg - 5 mg	Required for formation of healthy red blood cells and used in anemia.
Loratidine	10 mg- 20 mg	Allergy
Caffeine	2.5 mg	CNS stimulant
Diphenhydramine HCl	2.5 mg - 5 mg	Antihistaminic
Novartis Pharmaceuticals		
Night Time Triaminic Thin Strips® Cold & Cough	Diphenhydramine HCl 12.5 mg, Phenylephrine HCl 5 mg, acetone, FD&C blue #1, FD&C red #40, flavors, hypromellose, maltodextrin, mannitol, polyethylene glycol, polypropylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide.	Antihistamine/cough suppressant, Nasal decongestant. It temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold.
Triaminic Thin Strips® Long Acting Cough	Dextromethorphan 5.5 mg (equivalent to 7.5 mg Dextromethorphan HBr), acetone, alcohol, dibasic sodium phosphate, FD&C red #40, flavors, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polacrillin, polyethylene glycol, pregelatinized starch, propylene glycol, purified water, sodium phosphate, sorbitol, sucralose, titanium dioxide.	It temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold.
Triaminic Thin Strips® Cough & Runny Nose	Diphenhydramine HCl 12.5 mg, acetone, alcohol, FD&C blue #1, FD&C red #40, flavors, hydroxypropyl cellulose, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, propylene glycol, purified water, sodium polystyrene sulfonate, sorbitol, sucralose, titanium dioxide	It reduces cough due to minor throat and bronchial irritation as may occur with a cold. It relieves itchy, watery eyes due to hay fever.
Day Time Triaminic Thin Strips® Cold & Cough	Dextromethorphan 3.67 mg (equivalent to 5 mg Dextromethorphan HBr), Phenylephrine HCl 2.5 mg, acetone, alcohol, FD&C blue #1, FD&C red #40, flavors, hypromellose, isopropyl alcohol, microcrystalline cellulose, polacrillin, polyethylene glycol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose, titanium dioxide	It is used as nasal decongestant.
Triaminic Thin Strips® Cold with Stuffy Nose	Phenylephrine HCl 2.5 mg, acetone, alcohol, FD&C blue #1, FD&C red #40, flavors, hypromellose, isopropyl alcohol, maltodextrin, microcrystalline cellulose, polyethylene glycol, propylene glycol, purified water, sodium polystyrene sulfonate, sucralose and titanium dioxide	It temporarily relieves nasal and sinus congestion as may occur with a cold.
Theraflu® Daytime Thin Strips	Dextromethorphan 14.8 mg (equivalent to 20 mg Dextromethorphan HBr), Phenylephrine HCl 10 mg, acetone, alcohol, FD&C red #40, flavors, Hypromellose, mannitol, polyethylene glycol, polystyrene sulfonate, polacrillin and sucralose	It reduces cough due to minor throat and bronchial irritation as may occur with a cold.
Theraflu® Nighttime Thin Strips	Diphenhydramine HCl 25 mg, Phenylephrine HCl 10 mg, acetone, alcohol, FD&C blue #1, flavors, Hypromellose, mannitol, polyethylene glycol, polystyrene sulfonate, polacrillin and sucralose	It is used for nasal congestion, runny nose, sneezing, itchy nose and throat etc.
Theraflu® Thin Strips®-Multi Symptom	Diphenhydramine HCl 25 mg, acetone, alcohol, FD&C red #40, flavors, Hypromellose, hydroxyl propyl cellulose, maltodextrin, microcrystalline cellulose, polyethylene glycol, pregelatinized starch, polystyrene sulfonate, sorbitol and sucralose. Titanium dioxide.	It temporarily relieves nasal and sinus congestion as may occur with a cold.
Pfizer Inc		
Listerine® pocketpaks®	Available in cool mint®, Fresh Citrus, Cinnamon, and fresh burst®. Pullulan is used as a film forming polymer.	These strips dissolve instantly and kill 99 percent; of bad breath germs.
Prestige Brands		
Little cold sore throat strip	Ascorbic acid, pectin	Cold/allergy
Chloraseptic relief strip	Benzocaine, menthol	Sore throat
Bio Delivery Sciences International		
Onsolis™	Fentanyl buccal soluble film	Pain in opioid-tolerant patients
BEMA™	Buprenorphine	Therapeutic alternative for patients with incomplete pain relief or those unable to tolerate

## CONCLUSION

Our review concludes that, many of the pharmaceutical companies are switching their product franchise from ODTs to ODFTs. This technology option can also provide a good platform for patent non-infringing product development. ODFT allows brand extension for products. The ODFT is a good tool for product life cycle management for increasing the patent life of existing molecules or products. Compared to some of the complicated and expensive process (like

lyophilization) used to manufacture ODTs, the ODFT is relatively easy to fabricate; thus reducing the overall cost of the therapy.

## REFERENCES

1. Crama A, Breikreutz J, Desset-Brèthes S, Nunnd T and Tuleuf C, Challenges of developing palatable oral pediatric formulations, Int J Pharm 2009; 365: 1-3.
2. Florence A.T, Neglected diseases, neglected technologies, neglected patients? Int J Pharm. 2008; 350: 1-2.

3. Committee for Medicinal Products for Human Use, European Medicines Agency EMEA, Reflection paper: formulation of choice for the pediatric population, Sep. 2006.
4. Guidance for Industry: Orally Disintegrating Tablets, Center for Drug Evaluation and Research (Centre for Drug Evaluation and Research, CDER) US FDA, Dec. 2008.
5. Technology catalysts International Corporation, accessed on 2010 feb 28<sup>th</sup> Available from <http://www.technology-catalysts.com>.
6. Zhang H, Zhang J and Streisand J.B, oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications, Clin. Pharmacokinet. 2002; 41: 661-680.
7. accessed on 2010 mar 3<sup>th</sup> Available on <http://www.gas-x.com/>.
8. Corniello C, Quick dissolving strips: from concept to commercialization, Drug Del. Technol. 2006; 6: 68 -71.
9. Sakellariou P and Rowe R.C, Interactions in cellulose derivative films for oral drug delivery, Prog. Polym. Sci. 1995; 20: 889 - 942.
10. Banker G.S, Film coating theory and practice, J. Pharm. Sci. 1966 ; 55: 81- 89.
11. McIndoe L.M.E, Castor oil. In: Rowe R.C, Sheskey P.J and Owen S.C, editors, Handbook of Pharmaceutical Excipients, Pharmaceutical press, London 2006.p. 128 - 130.
12. Prakash, G.E. DuBois, J.F. Clos, K.L. Wilkens and Fosdick L.E, Development of rebiana, a natural, non-caloric sweetener, Food Chem. Toxicol. 2008; 46: S75 - S82.
13. Sward G, Drying time, in: Sward G. (Ed.), Paint Testing Manual - physical and chemical examination of paints varnishes lacquers, and colors, 13th Ed., American Society for Testing and Materials. p. 268.
14. Felton L, Donnell P. O, McGinity J, Mechanical properties of polymeric films prepared from aqueous dispersions, in: Aqueous polymeric coatings for pharmaceutical dosage forms, 3rd edition, McGinity J, Felton L Drugs and the pharmaceutical sciences, p. 108.
15. Fulzele S.V, Sattuwar P.M and Dorle A.K, Polymerized rosin: novel film forming polymer for drug delivery, Int J Pharm. 2002; 249: 175 -184.
16. American Standard of Testing and Materials, ASTM D1004 - 08 Standard Test Method for Tear Resistance (Graves Tear) of Plastic film and Sheeting.
17. Shinde A.J, Garala K.C and More H.N, Development and characterization of transdermal therapeutics system of tramadol hydrochloride, Asian J. Pharm. 2008;4: 265 - 269.
18. Barnhart S, Thin film oral dosage forms, in: Modified release drug delivery technology, Rathborne M, Hadgraft J, Roberts M, Lane M, 2nd edition, Drugs and the pharmaceutical sciences, p. 209 - 216.
19. Nishimura M, Matsuura K, Tsukioka T, Yamashita H, Inagaki N, Sugiyama T and Itoh Y, In vitro and *in vivo* characteristics of prochlorperazine oral disintegrating film Int J Pharm. **368** ;2009 ;368: 98 - 102.
20. Anand V, Kataria M, Kukkar V, Saharan V and Choudhury P.K, The latest trends in the taste assessment of pharmaceuticals, Drug Discovery Today ;2007; 12: 257 - 265.