***Original Research Article***

# Formulation Development and Evaluation of Fast Dissolving Oral Films of Alprazolam


## ABSTRACT

Fast dissolving oral films provide convenient, safe and simple way of drug administration. Moreover they offer improved patient compliance due to straightforward and non-invasive nature. The aim of current research was to develop fast dissolving oral films of alprazolam for treatment of anxiety disorders. Films were developed by solvent casting method using HPMC (Hydroxypropyl Methyl Cellulose) as film former and PEG (Polyethylene Glycol) as plasticizer. All formulation (F1-F12) were assessed for various parameters including thickness, tackiness, percent elongation, folding endurance, tensile strength, contact angle, transparency, content uniformity, disintegration and dissolution times. The thickness of optimized formulation was found to be 65µm and the Tensile strength, Percent elongation, Folding Endurance, Transparency, Contact angle, Assay/ content uniformity, Disintegration Time and Dissolution for optimized formulation were found to be 5.38%, 45%, 290 times, 100.1%, 180$^{o}$, 98.65%, 20seconds and 106.6% respectively. Drug release studies displayed 106.60% release of total drug content after time duration of 1.813 minutes. The results of the study concluded that newly developed fast dissolving film of alprazolam have potential to provide fast delivery of the drug and thereby enhanced patient compliance.



## Key Words:

Fast Dissolving Oral Films, Alprazolam, film formers.


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# 1 INRODUCTION

Therapeutic agents can be administered through different routes including oral, parenteral etc. (Dixit *et al.*, 2009) however, dysphagia and fear of choking are commonly found in all age groups (Saini *et al.*, 2011). Fast dissolution of oral dosage forms is a wide field and comprises of three types of formulation and dosage development. **Lyophilized technology, Fast Dissolving Oral Dispersible Tablets, Fast Dissolving Oral Thin Films (FDOTF)** (Bhyan *et al.*, 2011), (Saini *et al*., 2011). Fast dissolving oral tablets are the innovation in oral route of drug administration as they overcome limitations of others. This innovation was introduced in $19^{th}$ century that leads to Fast Dissolving Oral Films (FDOF) (Arya *et al.*, 2010).

They quickly disintegrate and dissolve hence this technique is important for the drugs that have poor aquous phase solubulity (NIMBAL *et al.*, 2013). These are innovations in oral route with no fear of choking or injection, also no need of fluid intake. (Patel *et al.*, 2010), (Damle *et al.*, 2013). This dosage form also augments safety and effectiveness of therapeutic agents by evaluation of a dosage form that is easy in administration and compatible to patient use (Shirsand *et al.*, 2008), (Arya *et al*., 2010). Various over the counter and potent medicines are under era of development. Because of advantages of fast dissolving oral films will be the most demanding dosage in the near future (Pandya, 2013). Thickness of these oral films vary from 50-200nm (Mandeep *et al.*, 2013). Depending upon method of manufacturing and release mechanism fast dissolving oral films are divided into three different types. **Flash Release, Mucoadhesive melt-away wafers, Mucoadhesive sustained release wafers** (Bala *et al.*, 2013). Fast dissolving films of Granisetron Hydrochloride were developed that showed better results than its other oral dosage forms (Rathore *et al.*, 2019)

## 1.1. Oral Route of Administration

Oral route includes buccal, sublingual and sublabial administration. It is the most accepting route (Gandhi *et al.*, 1994).

Bioavailability of therapeutic drug substance experiences great variation via this route. As the pH of enteral tract varies greatly so oral route of administration is effective for drugs with varying $pK_a$ values and moderate to high oral bioavailability and acid stable products (Rowland, 1972). Also this route is applicable only for the

drugs with no data of G.I irritations. Other factors are: Emptying of Gastric tract, Intestinal motility, Nature of food, Intestinal metabolism and transport, Hepatic metabolism (Gwee *et al.*, 1999).

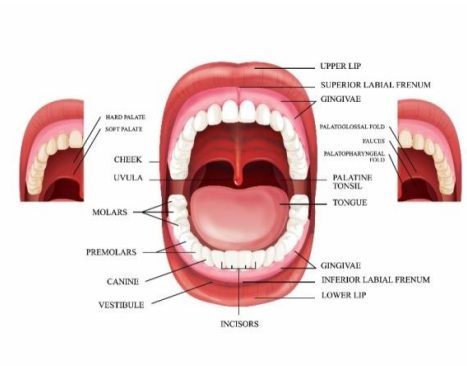


**Figure: 1:** Anatomy and physiology of oral cavity

## 1.2 Drug Profile& Pharmacokinetics

Alprazolam is a potent therapeutic ingredient. It is a short acting benzodiazepine with benzene group at 1 and 4 positions of compound and also a minor tranquillizer. It is prescribed for the treatment of specialized anxiety disorders e.g mania & pania and also in generalized anxiety disorders e.g agoraphobia. When we are concerned with mechanism of action of Alprazolam, it immediately binds to GABA receptors and causes potentiation. Pharmacokinetics of Alprazolam when administered orally shows absorption i.e eighty to ninety percent with peak plasma concentration of about 12-22 µg/L. Volume of distribution $V_d$ for Alprazolam is 1-1.3L/kg. $T_{1/2}$ is 9-16hrs and about 0.8-1.5ml of drug can be cleared from the body per kilogram of body weight. Orally Alprazolam is 80-100% bioavailable and show its therapeutic effects (Damle *et al*., 2013).

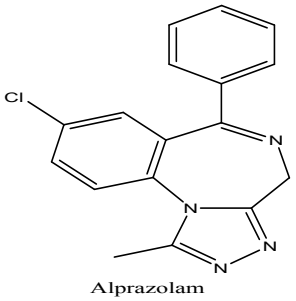


**Figure 2:** Structure of Alprazolam

## 1.3 Candidate Drugs for Fast Dissolving Oral Films

Many drugs which are more potent and have low therapeutic dose like antitussives, expectorants, antiasthamatics, antiepileptic can be formulated in film form for the patients suffering from Gastrointestinal disorders, Nausea, Pain or Central Nervous System (CNS) disorders.

**Table 1:** Commercially available brands of FDOF (Bhyan *et al*., 2011)

| Sr. # | Product | Manufacturer | API |
|---|---|---|---|
| 1. | Cough Suppressant | Monosol Rx | Dextromethorphan HBr |
| 2. | Cough/cold Suppressant | Monosol Rx | Diethylhydramiane Citrate |
| 3. | Breath Strips | Monosol Rx | Cool Mint |
| 4. | Rapid Dissolving Films | Labtec Pharma | Ondansatron |
| 5. | Rotavirus Vaccine | John Hopkin Undergraduate biomedical engineering students | Rotavirus Vaccine for infants |
| 6. | Fast dissolving films | Hughes Medical Cooperation | Methycobalamine |
| 7. | Fast dissolving films | Hughes Medical Cooperation | Diphenhydramine HCl |
| 8. | Fast dissolving films | Hughes Medical Cooperation | Folic Acid |
| 9. | Fast dissolving films | Dow Chemical Company | Bezocain |
| 10. | Fast dissolving films | Dow Chemical Company | Caffeine |

## 1.4 Alprazolam Dosage Forms

Lots of research work is available on oral tablet, parenteral and aerosol dosage from of alprazolam (Mahaguna *et al.*, 2003), (Evans, 1993). Sublingual tablets of alprazolam were formulated and efficacy was compared with that of conventional tablets (Márquez *et al.*, 2011). Commercially available formulations of alprazolam and diazepam injections comprise one or more solvents to solubilize. These components tend to precipitate while injected in aqueous media (Yalkowsky *et al.*, 1983). Aerosol systems of Alprazolam comprises of about 5% w/w of active pharmaceutical ingredient delivered to a mammal through inhalation route (Rabinowitz *et al.*, 2004).

### 1.4.1 Advantages

As in case of panic disorders and other anxiety abnormalities dose of alprazolam is three to four times per day. After introduction of sustained, controlled and extended released tablets patient non-compliance of taking unit dose repeatedly has been overcome.

### 1.4.2 Limitations

Dysphagia is commonly found in all age groups. Because of this effect more than half of patient population does not feel convenient in taking oral solid dosage forms like tablets. While taking oral tablets patients especially pediatric and geriatrics experience a fear of chocking. Due to these reasons there is patient non-compliance for the dosage form. Furthermore fluid intake is required for the administration of tablets of alprazolam while in case of fast dissolving oral films there would be no need of water as film disintegrate through saliva and dissolve API contents. Tablets take 15minutes to disintegrate as per official standards while on the other hand disintegration time for oral films is only within 5-30 seconds. Hence there is rapid dissolution of alprazolam.

In case of parental formulations as they are contain one or more co-solvents in their formulations; there is a chance of precipitation while they are administered in aqueous media. Patient non-compliance with respect to pain of injection. For inhalations of alprazolam there is need to educate patient for use of inhaler. As alprazolam is controlled drug there could be a chance of mishandling of aerosol sprays of alprazolam that result in difficulties (O'Sullivan *et al.*, 1994).

## 1.5 Problem Statement

The conventional dosage forms of alprazolam such as tablets are administered 3-4 times by patients suffering from anxiety disorders. There are problems associated with parenteral dosage forms like precipitation in aqueous media and patient education is mandatory for inhalation therapy. Oral films are considered as patient friendly alternatives of conventional dosage forms and thus gained tremendous attention in the recent years. Oral films are regarded as a customized or personalized dosage form for patients like pediatrics, geriatrics, bed-ridden and patient with different diseases. Going through literature, we found limited information for evaluation of alprazolam in the form of oral films. Therefore, to address the issues posed by the conventional

dosage forms of alprazolam, we made an attempt to develop oral films of alprazolam with different polymers and evaluated their physicochemical characteristics.

# 2 Formulation Development

### 2.1.1 Formulation Considerations

Typical Fast Dissolving Oral Films contain following major components Active Pharmaceutical Ingredient (API), Film Forming Polymers, Plasticizers, Sweetening Agents, Saliva stimulating agent, Flavoring agent and Coloring agent (if required).

These ingredients could vary in concentration as per compatibility of API with excipient or excipient with other excipient. Usually concentration limits of these ingredients used for film formation are: Active Pharmceutical Ingredient…1-30% w/w, Film Forming Polymers…40-45% w/w, Plastisizers…0-20% w/w, sweetening agents…quantity sufficient, Saliva Stimulating Agents…3-6% w/w, Flavoring Agents… quantity sufficient, Coloring Agent… quantity sufficient (Siddiqui *et al*., 2011). Drugs with small molecular weight and potent drugs are very good candidates for development of formulation of fast dissolving oral films (Bhyan *et al*., 2011).

### 2.1.2 Film Forming Polymers

Wide variety of polymers is available and used in the development of films. Synthetic, semisynthetic, hydrophilic polymers are used. Normally a film contains about 45% of film forming polymer by weight (Nagar *et al*., 2011).

### 2.1.3 Overview of Polymers

The polymers used in the formulation of fast dissolving strips should be devoid of leachable impurities, non-toxic and non-irritant. Some of them are discussed below together with their film forming abilities and physichochemical properties.

### 2.1.4 Plullan

Aureobasidium pullulans is fungus-like yeast which produces the polymer plullan. The composition of plullan includes glucan which in turn made of three glucose molecules and maltotriose units (Cheng *et al*., 2010).

Plullan is available as white amorphous, tasteless powder with no descriptive odor. It chars at 280°C and starts to decompose at 250°C. Regarding solubility it forms a clear

solution in water and alkaline solutions and insoluble in organic solvents (Graham, 1993).

### 2.1.5 Gelatin

Gelatin is composed of proteins fractions. It is soluble in water above 40 $^{0}$C. Its physical properties are closed to the amino acid composition as well as molecular weight distribution (Killekar et al., 2012). Gelatin film produce a smooth mouth feel, excellent carriers for flavors and was found to dissolve rapidly (Yougyata *et al*., 2013).

### 2.1.6 Chitosan

It is also an important polymer for better characterization of film. It contains glycopyranose rings in its structure. It forms a viscous polymer material that is porous in appearance but films developed by it are uniform n thickness, compact and cohesive (Yogyata *et al*., 2013).

### 2.1.7 Hydroxypropyl Methyl Cellulose (HPMC)

Hydroxypropyl Methyl Cellulose is actually a cellulose derivative that is composed of methylated, hydropropyl cellulose. It has been divided into different grades depending upon solubility and temperature sensitivity. Lower grades of HPMC like Methocel E3, E5, and E15 have low viscosity and are particularly used for film formation. HPMC can also used for aqueous coating but it has poor water solubility (Priyank *et al*., 2011).

## 2.2 Plasticizer

Plasticizers are the ingredients that are used to improve and maintain the brittleness of oral films that concerned with the folding endurance of final unit dosage form. Concentration limit of plasticizers for this purpose is 0-20% w/w of dry polymer used alone or in combination (Bhyan *et al*., 2011). These includes Propylene Glycol (PG), Glycerol, Polyethylene Glycol (PEG) e.g. PEG-400, PEG-600, PEG-2000, PEG-4000, PEG-6000, Caster Oil etc. (Haff *et al*., 1985).

## 2.3 Sweeteners

Sweeteners are the agents that are used to mask the unpleasant taste of oral dosage forms and also in fast dissolving oral films. Usually they are used as per requirement

however within concentration limit of about 3-6% w/w. Classification of sweeteners includes natural and artificial sweeteners. Sorbitol, mannitol, Saccharin sodium, Aspartame, Cyclamate Sodium, Sucralose are some famous examples of sweetening agents.

## 2.4 Saliva Stimulating Agent

Saliva stimulating agents are used to enhance the production of saliva. Increased production of saliva is required for mucoadhesion of oral films that further helps in better penetration of oral film through oral cavity which latter results in better release and absorption of therapeutic ingredient. Citric acid is the most common and easily available example of saliva stimulating agents. Further such examples are lactic acid, malic acid etc. They are used within concentration limit of 2-6% w/w of unit formulation of film. Flavouring agents and colorants are alos used.

# 3 MATERIALS AND METHODS

## 3.1 Materials

Alprazolam was received as gift for research purpose from Arsons Pharmaceutical Industries Pvt. Ltd. HPMC E5 was purchased from Shandong Landu, China. HPMC E15 was obtained from Shandong Landu, China. PEG-400 was purchased from Hebei Shuangniu, China. PEG-6000 was purchased from India. Aspartame was purchased from Singapore. Citric Acid Monohydrate was purchased from Shandong Landu, China. Fresh distilled water was obtained from distillation plant of Arsons Pharmaceutical Industries Pvt. Ltd.

## 3.2 Methods

### 3.2.1 Compatibility Studies

Drug excipient compatibility studies were conducted using Fourier Transform Infrarad Technique (FTIR) and no interaction was observed between the active and the excipients (BEYATRICKS, 2019).

Fourier Transform Infrared spectrophotometer (FT-IR) spectral measurements were performed using Agilent Technologies, Model No. Cary 630 Fourier transforms infrared spectrophotometer. The pure drug and pure drug along with polymer mixture were mixed together for analysis of interaction between these mixtures. The scans were collected for Alprazolam and Alprazolam with other excipients and also

excipients with other excipients. The scans were collected in the range of 4000-400 $cm.^{-1}$

### 3.2.2 Formulation Development

#### 3.2.2.1 Preparation of Fast Dissolving Oral Films of Alprazolam

Casting of film forming solution was practiced for the development of fast dissolving oral films. In this method HPMC E5 and E15 were used as water soluble polymers. This film forming agent was dissolved in 10ml of water on continuous stirring by magnetic stirrer for about 10minutes until a clear solution had been formed on hot plate. Then PEG-400 was added as plasticizer in the same mixture of polymer. Hold this solution for cooling and defoaming. After this alprazolam was dissolved in 10ml water and mixed for 10 minutes by using magnetic stirrer. Then excipient phase and active phase were mixed together. At the end sweetening agent: aspartame, saliva stimulating agent: citric acid and menthol crystals were added in the solution. Then solution was casted on petridish and dried at 40-45$^{o}$C for 24hours. After complete drying the film was carefully removed from the petri dish and cutted into 2 x $3cm^2$and wrapped in aluminium foil and stored in desiccators below 30$^{o}$C for further evaluation.

## 3.3 Calculation of Dose

Dose of Alprazolam was calculated by the formula was calculated as 0.0039gm of Alprazolam per petri dish of 11cm of diameter (Akca *et al.*, 2018).

The Diameter of Petri dish is of 11 cm

Area of circle (Petridish) $= \pi r^2$

$= 3.14x (5.5)^2$

$= 94.985\ cm^2$

Size of strip 3cm x2 cm

Area of film of 3cm x2 cm = 6 $cm^2$

The Alprazolam concentration to be present in one strip = 0.25mg/strip

The drug Alprazolam calculated for the Area 94.985 $cm^2$ of Petri dish = 3.96mg

## 3.4 Characterization of Film

### 3.4.1 Assay Determination Of Alprazolam By HPLC

Special Apparatus, Reagents and Solution include Suitable high-pressure liquid chromatograph (Schimatzo) equipped with a UV detector at 231 nm and connected with computing system. Chromatographic column, 25cm x 4.6mm (i.d.) 5µ Hypersil BDS-C18 (Schimatzo). Glass fibber Filter (type GF/A available from Whatman, Ultrasonic bath, Distilled water. **Mobile phase** was formed by mixing filtered and degassed solutions of methanol, acetonitrile and water in ratio of 10%, 60% and 30% respectively.

Filter through 0.2-micron membrane & degas the solution in an Ultra sonic bath for 5 minutes.

#### 3.4.1.1 Chromatographic Conditions:

High-pressure liquid chromatograph was equipped with a UV detector at 231 nm and connected with computing system. Chromatographic column 25cm x 4.6mm (i.d.), 5µ Hypersil BDSC18.Glass fibber Filter (type GF/A available from Whatman. 20µL injection was inserted at a flow rate of 1.5ml/min at ambient temperature. **Standard Solution:**50 mg of Alprazolam was weighed and transferred into a 50 ml volumetric flask, then dissolved in 20ml of Mobile Phase and diluted to volume with the same. Solution was filtered through a Whatman 2 filters, discarding the first 10ml of filtered solution. Then 1 ml of the filtered solution was transferred into a 50 ml volumetric flask and diluted to the mark with Mobile Phase. Final solution was sonicated for 3 minutes filtered to use. **Sample solution:** Take film sampleof alprazolam equivalent to 1 mg Alprazolam into a 50ml volumetric flask, dissolve in 20 ml of Mobile Phase and dilute to volume with the same. Filtered through a Whatman filters, discarding the first 10 ml of filtered solution and collect the filtrate. Sonicate for 3 minutes filter and use. **Chromatographic Procedure:** Base line of chromatographic system was stabilized by running blank solution. Then standard solution run through the mobile phase and chromatograms were collected. After standardization of system procedure same dilutions of sample solution were injected one by one and chromatograms were recorded.**Limits:** The contents of Alprazolam should be 90-110% of the stated amount (U.S.P pharmacopoeia).

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279 **Table-2 : Composition of Formulations**

| Ingredients | Formulation Code | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 | F10 | F11 | F12 |
| Alprazolam (gm) | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 | 0.0039 |
| HPMC E5 (gm) | 0.350 | 0.400 | 0.370 | 0.350 | 0.200 | 0.400 | 0.450 | 0.300 | 0.500 | 0.500 | 0.500 | 0.200 |
| HPMC E15 (gm) | - | - | - | - | - | - | - | - | - | - | - | 0.300 |
| PEG 400 (gm) | - | - | 0.300 | 0.300 | 0.300 | 0.250 | 0.350 | 0.300 | 0.250 | 0.300 | 0.300 | 0.300 |
| Aspartame (gm) | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 | 0.0020 |
| Citric Acid Monohydrate (gm) | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 | 0.003 |
| Menthol Crystals (gm) | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 | 0.0010 |
| Distilled Water (ml) | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |

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# 4 RESULTS

## 4.1 Drug Excipient Compatibility

Fourier Transform Infrared spectrophotometer (FT-IR) spectral measurements were performed using fourier transform infrared spectrophotometer (Agilent Technologies, Canada). The therapeutic ingredient and the mixture of drug and excipient were analyzed for finding out any interaction between drug and polymer. The scans were recorded in the range of 4000-400 $cm^{-1}$.

The structure of alprazolam showed the aroamtic functional groups (C-C) of arene, azarene, benzene and hetroarene. CHN containing amine group, (N-N) imine group, iminyl group, halogen containing arylchloride and arylhalide and a leaving group. The peak area near 1400 to 1600$cm^{-1}$ represents aromatic functional groups. Peak area near 1330-1400$cm^{-1}$ represents C-H bonding in structure of alprazolam, peak area near 1420$cm^{-1}$ represents CHN bonding instructure. IR band of (N-N) imine group appeared around 3150-3300$cm^{-1}$. From these results it was concluded that all the functional groups of alprazolam showed peaks and there was no any incompatibility between alprazolam and any excipients used.

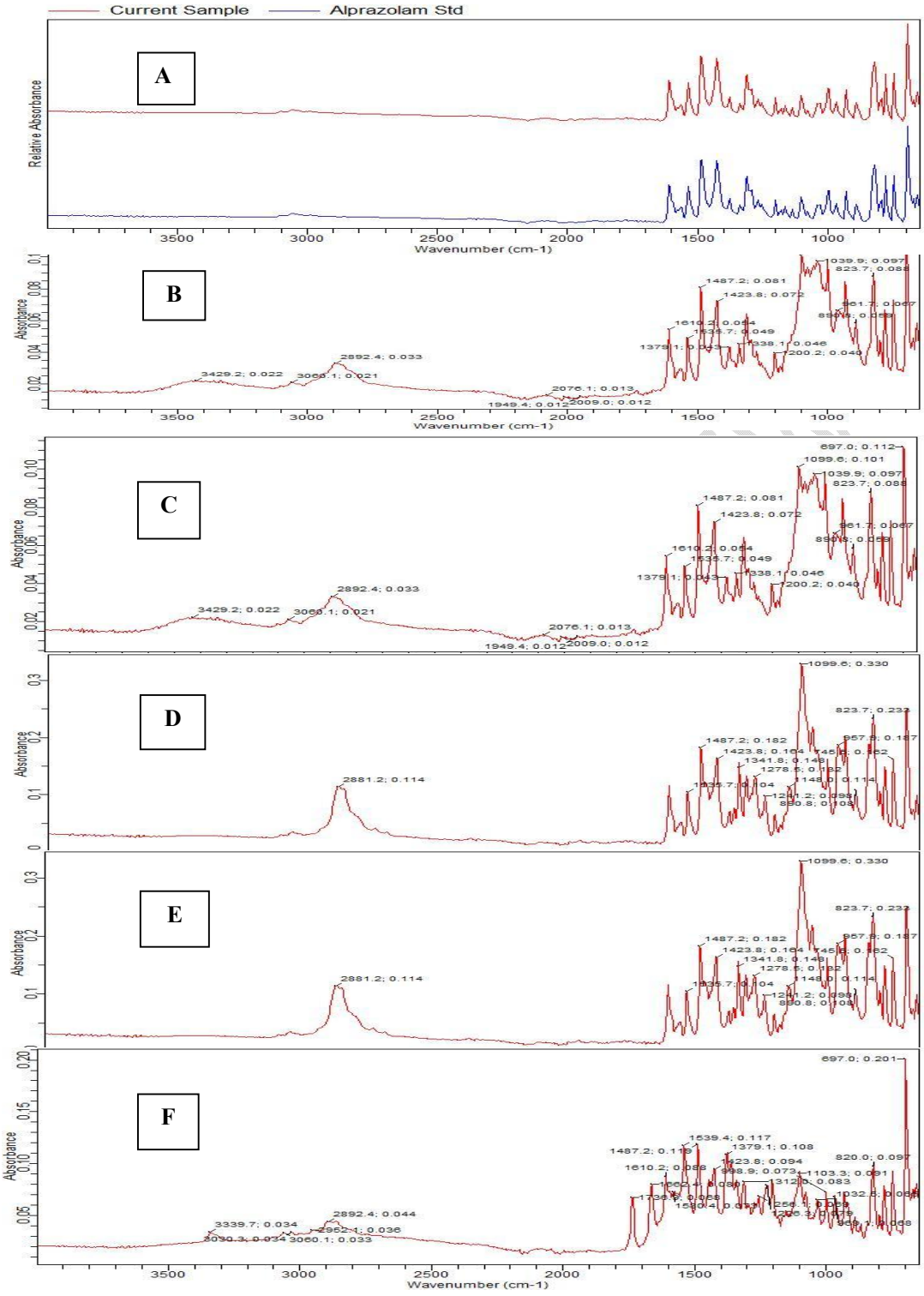


**Figure 3:** FTIR spectra of alprazolam standard v/s sample **(A)**, mixture of alprazolam and HPMC E5 **(B)**, mixture of alprazolam and HPMC E15 **(C),** mixture of alprazolam and PEG 400 **(D)**, mixture of alprazolam and menthol **(E)**, mixture of drug and all the used excipients **(F).**

## 4.2 Development of Fast Dissolving Oral Films

Fast Dissolving Oral Films of Alprazolam were developed by using water soluble film forming agents alone or in combination with other polymers and PEG400 was used as plasticizer by solvent casting method. Quantity of polymer and plasticizer was varied and results for different formulations were observed and reported. Furthermore quantities of sweetener and saliva stimulant were kept constant for better observation of results for polymer and plasticizer behavior.

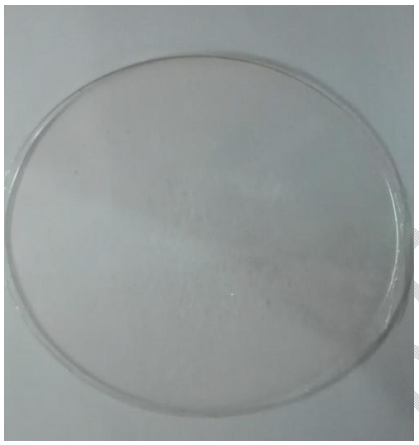

**Figure 4:** Fast dissolving oral film manufactured by casting method

## 4.3 Linearity

Testing method validation of alprazolam was carried out by evaluating and analyzing assay at different concentrations of alprazolam. The stock solution was gravimetrically diluted in mobile phase to concentrations of 0.005mg/ml, 0.01mg/ml, 0.02mg/ml,0.03mg/ml, 0.04mg/ml and 0.05mg/ml respectively and area of curve was tabulated in table 3.

A Linear straight line shows that the analytical method is validated.

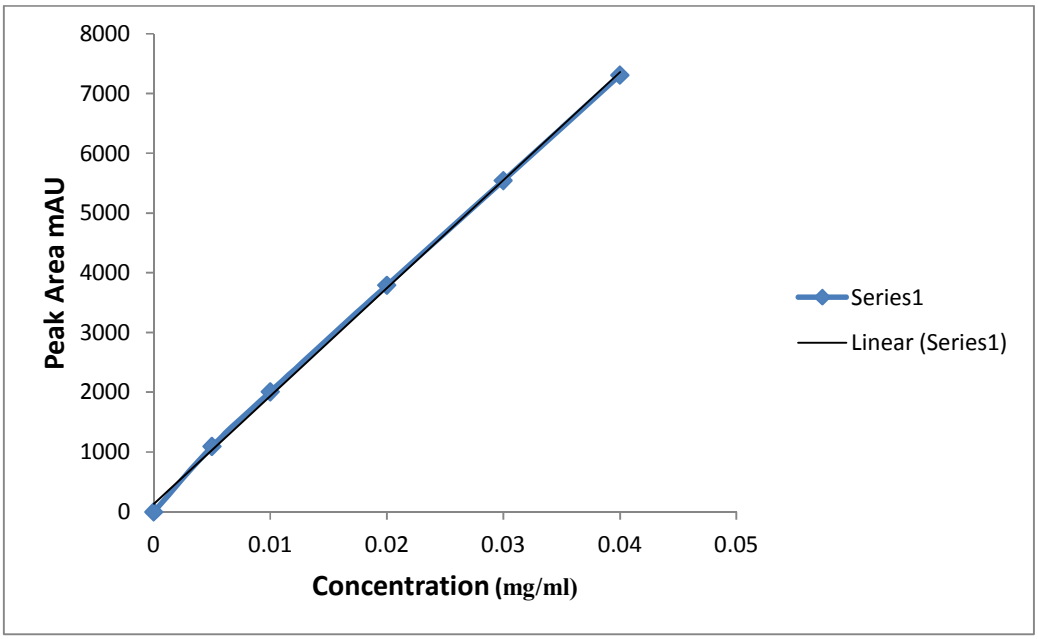


**Figure 5:** The calibration graph showing linear relationship between the concentration and peak area of anylate in solution. Six sample solutions of different concentrations were prepared i.e 0.005mg/ml, 0.01mg/ml, 0.02mg/ml, 0.03mg/ml, 0.04mg/ml and 0.05mg/ml and readings taken to observe peak areas for relationship between concentration and peak area. It was observed that as the concentration of anylate increses the peak area also increases.

**Table 3:** Quantitative assay of Alprazolam, an active pharmaceutical ingredient of film

| Sr. # | Concentration mg/ml | Injection # | Retention Time(min) | Peak Area | Avg. peak area |
|---|---|---|---|---|---|
| 1. | 0.005 | 1A | 1.808 | 1087.54 | 1095.81 |
| | | 1B | 1.807 | 1099.02 | |
| | | 1C | 1.810 | 1100.87 | |
| 2. | 0.01 | 2A | 1.807 | 2011.10 | 2010.55 |
| | | 2B | 1.810 | 2010.54 | |
| | | 2C | 1.809 | 2010.01 | |
| 3. | 0.02 | 3A | 1.808 | 3799.10 | 3793.06 |
| | | 3B | 1.812 | 3778.98 | |
| | | 3C | 1.811 | 3801.12 | |
| 4. | 0.03 | 4A | 1.809 | 5601.10 | 5544.79 |
| | | 4B | 1.814 | 5542.26 | |
| | | 4C | 1.809 | 5491.01 | |
| 5. | 0.04 | 5A | 1.809 | 7322.23 | 7308.90 |
| | | 5B | 1.809 | 7394.16 | |
| | | 5C | 1.812 | 7210.32 | |
| 6. | 0.05 | 6A | 1.812 | 9122.10 | 9136.99 |
| | | 6B | 1.812 | 9119.99 | |
| | | 6C | 1.812 | 9168.87 | |

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## 4.4 Thickness

Six samples were analyzed from each formulation for the purpose of measurement of thickness of fast dissolving oral film. The thickness of formulated film was observed from five different places (four corners and one center of film) by calibrated micrometer screw gauge and average was taken, results were in the range of 35µm to 66µm as shown in figure 6. Furthermore the average thickness of formulation $F_1$was 35 µm, $F_2$was 40µ, $F_3$was 54µm, $F_4$was 55µm , $F_6$was 63µm , $F_7$was 65µm , $F_8$was 64µm , $F_9$was 66µm , $F_{10}$was 65µm , $F_{11}$was 64µm, $F_{12}$was 70µm.

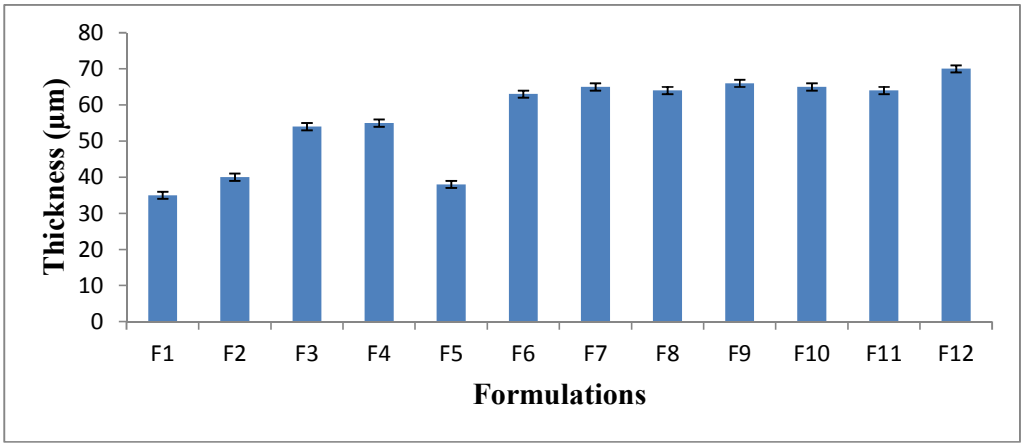


**Figure 6:** Graph showing average thickness of different formulations from $F_1$ - $F_{12}$. X-axis represents the formulations and y-axis represents the thickness in µm of film.

## 4.5 Dryness/ Tack Test

This is the physical test for films. Film must be dried enough that it could not be sticked to the surface of its packing material. There is no criterion for this characterization but it could be observed physically that either film showed any tackiness or not. For this characterization six films from each formulation were pressed in aluminium foil individually and their stickiness or adherence to foil was observed and adherence was checked. Films were observed physically that they are set to touch, dust free, tack free (with dry surface), dry to touch, dry hard, dry to handle, dry to re-coat and print free.

## 4.6 Tensile Strength

The stressing force applied outward to the film at its edges until it breaks is the tensile strength of film. To calculate the value of tensile strength the force required to rupture

or break the film was divided with cross sectional dimensions of film i.e thickness and the width of film.

Six fast dissolving oral films from each formulation were analyzed for tensile strength and load applied at breakage point was observed and tensile strength was calculated as shown in figure 7. Furthermore it was observed that average tensile strength for formulations $F_1$ to $F_{12}$ was 1.43, 2.50, 1.85, 1.82, 1.32, 3.17, 5.38, 3.12, 3.03, 3.85, 2.34, 2.85 $N/cm^2$respectively.

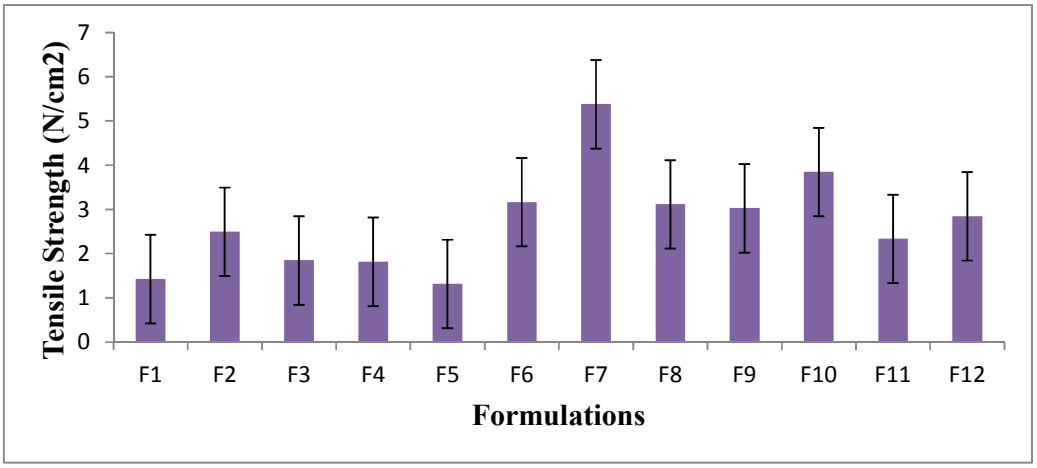


**Figure 7:** Graph showing average tensile strength of different formulations from $F_1$ - $F_{12}$.X-axis represents the formulations and y-axis represents the tensile strength of film.

## 4.7 Percent Elongation

The percent increase in length of film when a stretching force is applied to it is called the percent elongation. It is the change in shape or deformation of film divided by its cross sectional area. Percent elongation was performed for six samples from each formulation by using tensile strength tester. Generally elongation of film increases as the plasticizer content increases. It could also be calculated by subtracting the final length of film from its initial length i.e before applying stretching force and dividing with initial length of strip.

Generally elongation of strip increases as the plasticizer content increases.

This test was performed by tensile strength tester. Initially length of film was measured and then film was placed between the jaws of instrument and the point where film near to break was noted. At this point the increase in length of fast dissolving oral film was measured with the help of vernier calliper and percent

elongation was calculated by given formula. It was observed that the average percent elongation for formulations $F_1$ to $F_{12}$ was 10, 20, 10, 13.3, 10, 20.7, 45, 20, 16.7, 26.7, 16.7, 40 respectively.

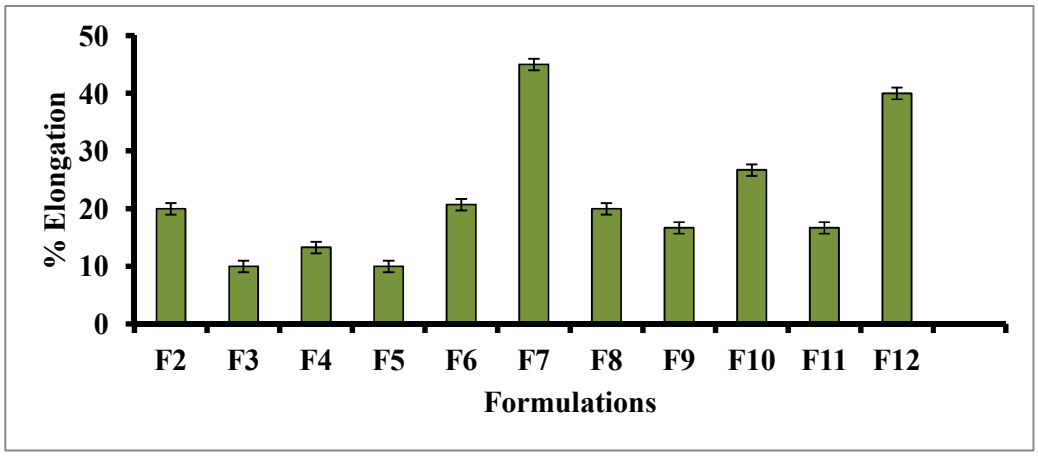


**Figure 8:** Graph showing % elongation of different formulations from $F_1$ - $F_{12}$X-axis represents the formulations and y-axis represents the percent elongation of film.

## 4.8 Folding Endurance

Folding endurance is the ability of film that how many times it could be folded without any crack or breakage. It was performed by repeated folding of the strip at the same place till the strip breaks. For each formulation six samples were analyzed for folding endurance and it was observed that folding endurance for formulations $F_1$ to $F_{12}$ was 120, 232, 230, 180, 208, 210, 290, 242, 200, 283, 150 and 123 respectively.

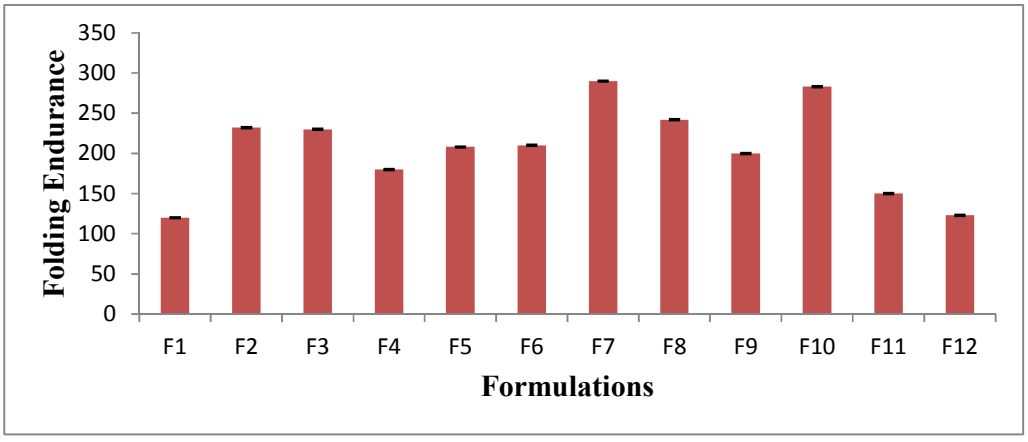


**Figure 9:** Graph showing folding endurance of different formulations from $F_1$ - $F_{12}$X-axis represents the formulations and y-axis represents the folding endurance of the film.

## 4.9 Transparency

Transparency shows that how much the film is free from any foreign particle or any haziness of casted solution as the transparency of film matters for its physical appearance. Six film samples were examined by putting their suitable size as per cell of U.V spectrophotometer. The transmittance of films was determined at 600 nm. The transparency of the films was calculated as follows:

Transparency = (logT600)/b = - €c

In this equation T represents the transmittance of film, b is the thickness of film and c is the concentration at which formulation was developed. The average transmittance observed for formulations $F_1$to $F_{12}$ was 87.7%, 99.8%, 99.9%, 99.9%, 87.7%, 100.00%, 100.1%, 87.2%, 100.1%, 99.9%, 100.6% and 82.2% respectively.

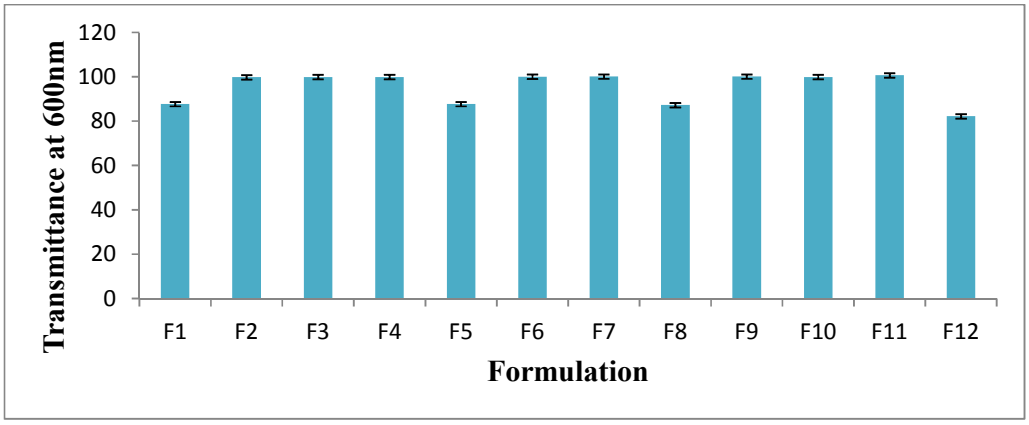


**Figure 10:** Graph showing transmittance of different formulations from $F_1$ - $F_{12}$.X-axis represents the formulations and y-axis represents the transmittance at 600nm. U.V Spectrophotometer was used for checking transmittance of film. Parameters of UV. Spectrophotometer were setted on transmittance. Wavelength setted at 600nm and reading was taken after calibration or autozeroing the instrument.

## 4.10 Contact Angel

Contact angle was measured to judge the wetting property of film that to how much extent water will adhere and swells the film. A drop of distilled water was dropped and readings were taken within ten seconds. The average contact angle observed for formulations $F_1$to $F_{12}$ was120°, 140°, 134°, 154°, 141°, 138°, 180°, 176°, 170°, 170°, 177° and 168° respectively.

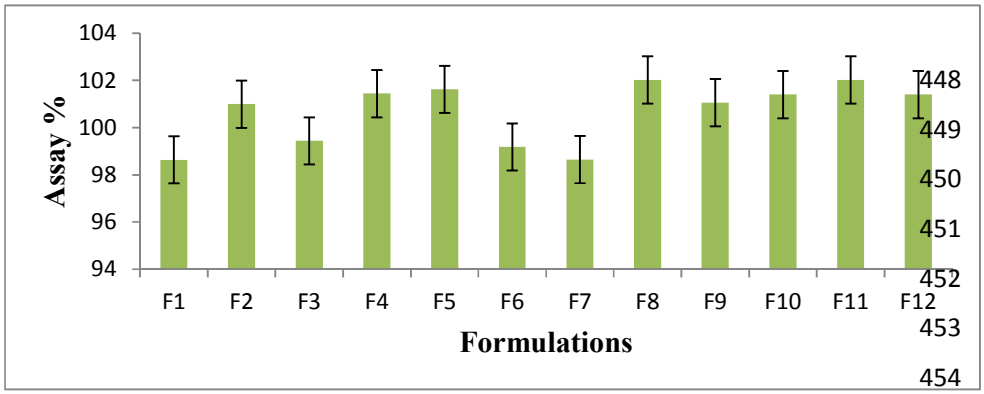


**Figure 11:** Graph showing contact angle of different formulations from $F_1$ - $F_{12}$. X-axis represents the formulations and y-axis represents the angle that the water formed at the surface of film.

## 4.11 Assay/ Content Uniformity

Assay/Content Uniformity on films of all the formulations ($F_1$-$F_{12}$)was measured by following method described earlier and results were recorded by using HPLC (Schimatzo) as shown in figure 12. The content uniformity observed for formulations $F_1$to $F_{12}$ was98.64%, 100.99%, 99.44%, 101.44%, 101.62%, 99.18%, 98.65%, 102.02%, 101.06%, 101.40%, 101.40%, 102.02%, 99.29% respectively.

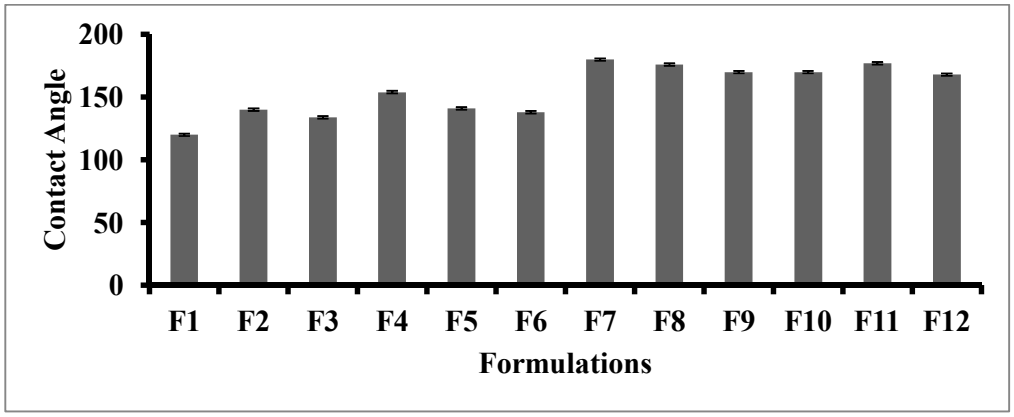


**Figure 12:** Graph showing % assay of different formulations from $F_1$ - $F_{12}$. X-axis represents the formulations and y-axis represents the assay results in percentage. Assay was performed using high-pressure liquid chromatograph that was equipped with a UV detector at 231 nm and connected with computing system. Chromatographic column 25cm x 4.6mm (i.d.), 5µ Hypersil BDSC18.Glass fibber Filter (type GF/A available from Whatman. 20µL injection was inserted at a flow rate of 1.5ml/min at ambient temperature.

## 4.12 Disintegration Time

Disintegration time is the time taken by the film to disintegrate in water. According to CDER guidelines the time taken by oral films must be less than 30 seconds, as this is the era of development for oral film technology these are considered to be standard

guidelines. Pharmacopoeia disintegrating test apparatus was used for this study. Typical disintegration time for strips was 5–30s. In this research the disintegration time observed for formulations $F_1$ to $F_{12}$ was 31, 30, 18, 19, 22, 19, 20, 20, 21, 20, 20, 32 respectively.

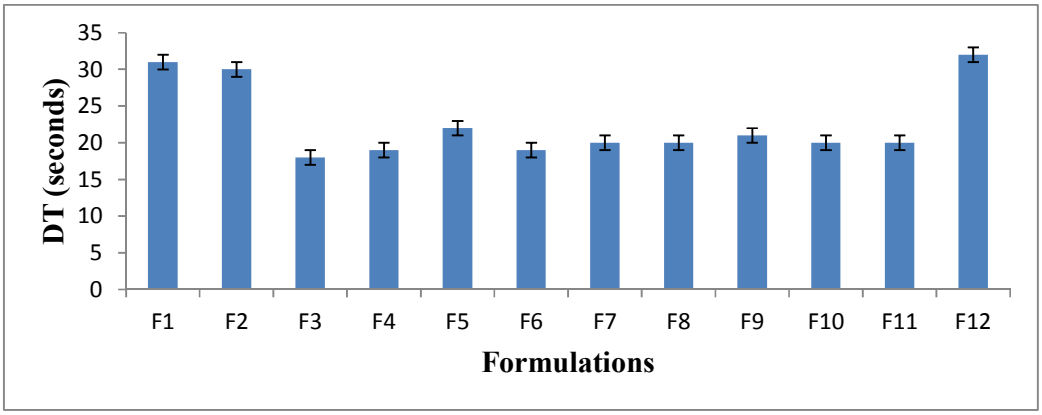


**Figure 13:** Graph showing disintegration time of different formulations from $F_1$ - $F_{12}$. X-axis represents the formulations and y-axis represents the disintegration time in seconds.

## 4.13 *In vitro* Dissolution Studies

Dissolution studies were performed in *in vitro* experimental system i.e USP Apparatus I (Setouhi *et al*., 2010).The dissolution observed for formulations $F_1$ to $F_{12}$ was 95.2%, 92.4%, 93.0%, 104.7%, 94.30%, 95.9%, 106.6%, 101.4%, 95.6%, 96.2%, 96.7%, 97.4% respectively.

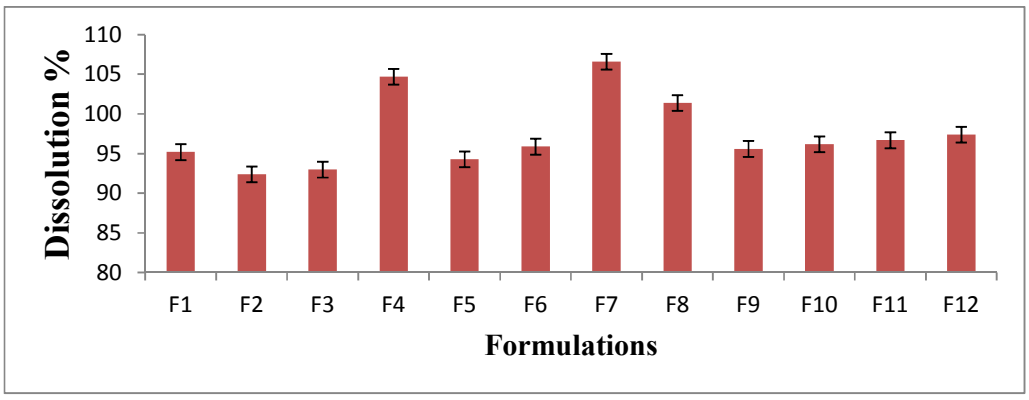


**Figure 14:** Graph showing Dissolution of different formulations from $F_1$ - $F_{12}$ in percentage values. X-axis represents the formulations and y-axis represents the dissolution results in percentage. Dissolution studies were performed using high-pressure liquid chromatograph that was equipped with a UV detector at 231 nm and connected with computing system. Chromatographic column 25cm x 4.6mm (i.d.), 5µ Hypersil BDSC18.Glass fibber Filter (type GF/A available from Whatman. 20µL injection was inserted at a flow rate of 1.5ml/min at ambient temperature.

## 4.14 HPLC Analysis

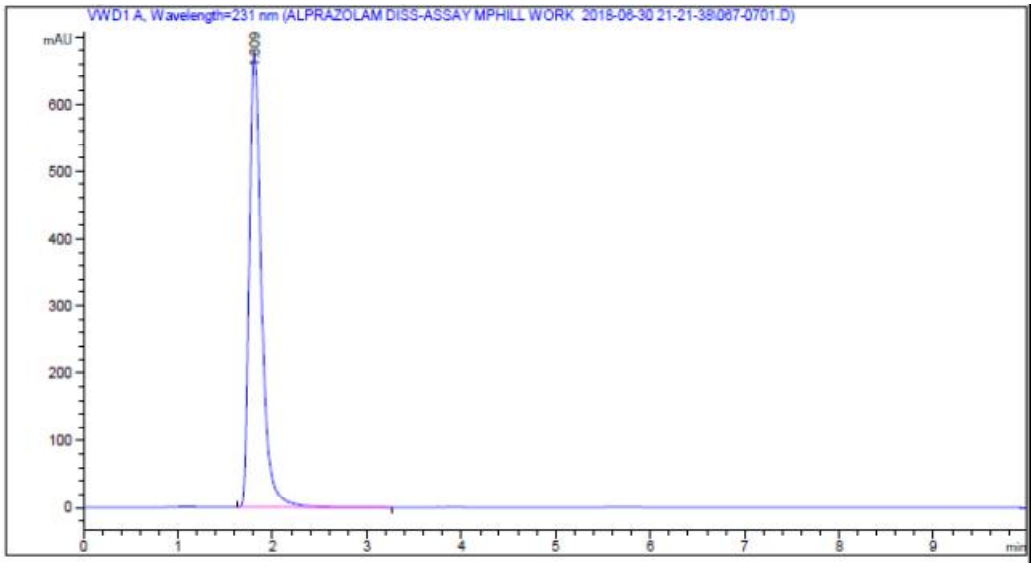


**Figure 15:** HPLC Chromatogram of Sample 05A (Assay). X-axis represents the time in minutes and y-axis represents the height of peak in mAU. The graph shows peak area of 6106.45020 mAU at retention time of 1.809 minutes. The height of peak is 674.00757 mAU. High-pressure liquid chromatograph was equipped with a UV detector at 231 nm and connected with computing system. Chromatographic column 25cm x 4.6mm (i.d.), 5µ Hypersil BDSC18.Glass fibber Filter (type GF/A available from Whatman.20µL injection was inserted at a flow rate of 1.5ml/min at ambient temperature.

# 5 DISCUSSION

All the fast dissolving oral films (Formulation $F_1$-$F_{12}$) containing alprazolam were prepared by using Hydroxypropyl methyl cellulose E5, Hydroxypropyl methyl cellulose (E15) (alone or in combination), PEG-400, aspartame and citric acid monohydrate using solvent casting method. Water was used to prepare solution. Solvent casting method has some advantages over other film forming methods i.e distribution of casted film in a better and uniform way with stable dimensions (Siemann, 2005). Films obtained are more clearly showing highest purity and lowest degree of haze. No technical expertise is required (Mahajan, 2012).

Fourier Transform Infrared spectrophotometer (FT-IR) spectral measurements were performed. The pure drug and physical mixture were mixed together for analysis of interaction between these mixtures. The structure of alprazolam showed the aroamtic functional groups (C-C) of arene, azarene, benzene and hetroarene. CHN containing amine group, (N-N) imine group, iminyl group, halogen containing arylchloride and arylhalide and a leaving group. The peak area near 1400 to 1600$cm^{-1}$ represents aromatic functional groups. Peak area near 1330-1400$cm^{-1}$ represents C-H bonding in structure of alprazolam, peak area near 1420$cm^{-1}$ represents CHN bonding in structure. IR band of (N-N) imine group appeared around 3150-3300$cm^{-1}$. From these results it was concluded that all the major functional groups of alprazolam showed their characteristic peaks and there was no any significant interaction between alprazolam and excipients used.

Linearity or standard calibration curve is the straight line curve that must show the linear response of API at increased concentrations. Standard calibration curve was developed for alprazolam by developing different concentrations of drug substance (Kunte, Tandale, 2010).

Linearity experiments were conducted to identify the range over which Alprazolam exhibit linear response. The stock solution of Alprazolam was prepared by dissolving 50 mg of finely powder homogeneous sample of Alprazolam into 100 mL of mobile phase and different concentrations of Alprazolam were prepared. The stock solution was gravimetrically diluted in mobile phase to concentrations of 0.005mg/ml, 0.01mg/ml, 0.02mg/ml, 0.03mg/ml,0.04mg/ml and 0.05 mg/ml respectively and readings were taken to observe peak areas for relationship between concentration in

550 percentage and peak area in mAU. It was observed that as the concentration of anylate
551 increses the peak area also increases. A Linear straight line shows that the analytical
552 method is validated.

553 Micrometer screw guage was used to moniter the uniformity in thickness of films
554 (Khatoon *et al*., 2014). Six samples from each formulation were examined and
555 thickness was checked from four corners and middle point of film and average was
556 taken. Thickness should be 5-200µm (Collins *et al.*, 1987). The thickness of film was
557 measured by micrometer screw gauge at different strategic locations i.e from four
558 corners and center of film. Similarly the variation of mass between different films
559 will also be measured by measuring 1cm$^2$ size of three films from each formulation.
560 Thickness and mass of films are closely co related with each other (MADDELA *et al.*,
561 2019).

562 (Sandeep *et al*., 2011) research showed the thickness of films measured by using
563 micrometer. Three readings from each formulation samples were noted and their
564 average was considered as final. Thickness of fast dissolving oral films of all
565 formulations must show uniform thickness. Films of formulations with more
566 concentration of film forming polymer must show more thickness and vice versa. It is
567 also clear that the thickness of fast dissolving oral films is directly proportional to the
568 concentration of polymer (Bais *et al*., 2016), (Rathore et al., 2019)

569 Different formulations were evaluated against different concentrations of film
570 formers and it was observed that as the concentration of PVA (Film Former) was
571 increased thickness of fast dissolving film is increased and such type of findings
572 were also observed previously (Rajni *et al*., 2014). Our results showed thickness
573 of film in between 35 to 70µm, furthermore it was observed that the thickness of
574 fast dissolving oral film was low i.e 35µm for formulation F1 which had lowest
575 concentration i.e350mg of film forming polymer HPMC E5 and highest i. e 70µm
576 for the formulation F12 which had highest quantity of carrier concentration i.e
577 300mg HPMC E 15 and 200mg HPMC E 5. Hence it is concluded from the results
578 observed that film forming polymers also endure the thickness of film as the films
579 containing more concentration of polymer have more thickness and vice versa. It
580 was noticed that films formed by HPMC E5 provided lower thickness compared to
581 films of HPMC E15.

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582 Films must be characterized for tackiness and dryness as the tackiness of film is the
583 ability with which film sticked to the surface of paper or foil (Khatoon *et al*., 2014).

584 Tackiness of film could be controlled by controlling environmental parameters i.e
585 temperature, relative humidity etc. It is reported in literature that higher relative
586 humidity gives high tackiness and vice versa (Bais *et al*., 2016).

587 In this research films were physically observed for tackiness and dryness and it was
588 observed that all the films were dust free and dry and no print was observed. It was
589 further cleared from transparency test of films. Where the transparency of all the
590 samples was within 82.2% to 100.6%.However it was observed that tackiness of
591 formulation $F_{11}$ was found maximum and for formulation F12, it was minimum.

592 The stressing force applied outward to the film at its edges until it breaks is the tensile
593 strength of film. To calculate the value of tensile strength the force required to rupture
594 or break the film was divided with cross sectional dimensions of film i.e thickness and
595 the width of film (Dahima *et al*., 2010). It was calculated by the applied load at
596 rupture divided by the cross-sectional area of the strip as given in the equation below:

597 $$\text{Tensile strength} = \text{Load at failure} \times 100 / \text{Strip thickness} \times \text{Strip width}$$

598 Tensile strength of film was found to be increased by increasing contents of
599 Plasticizer PEG-400 which may increase the elasticity of the final formulation. Also
600 contents of film former like PVA may increase the elasticity and hence the tensile
601 strength of film due to elastic nature of film forming polymer (Rajni *et al*., 2014).

602 Tensile strength of film is essential to ascertain the elasticity of the film as this is
603 directly related to the folding endurance and percent elongation in the strip (Khatoon
604 *et al*., 2014).

605 In current research, the tensile strength of fast dissolving film was lowest for
606 formulation $F_1$ which contained lowest concentration of film forming agent with no
607 plasticizer and it was highest for formulation $F_7$ which had highest concentration of
608 plasticizer.

609 Hence it can be concluded from the results observed that the films containing no
610 plasticizer and lowest amount of film former had less tensile strength compared to
611 films in which film forming polymer and plasticizer was used.

The percent increase in length of film when a stretching force is applied to it is called the percent elongation. It is the change in shape or deformation of film divided by its cross sectional area (Dahima *et al*., 2010). Percent elongation was performed for six samples from each formulation by using tensile strength tester. Generally elongation of film increases as the plasticizer content increases. It could also be calculated by subtracting the final length of film from its initial length i.e before applying stretching force and dividing with initial length of strip. Generally elongation of strip increases as the plasticizer content increases.

Percent Elongation of film was found to be increased by increasing contents of Plasticizer PEG-400 which may increase the elasticity of the final formulation. Also contents of film former like PVA may increase the elasticity and hence the Percent Elongation of film due to elastic nature of film forming polymer (Rajni *et al*., 2014).Percent elongation of film is also essential to ascertain the elasticity of the film as this is directly related to the folding endurance and tensile strength in the strip that effects the wettability and dissolution of film through salivary contents (Cilurzo *et al.*, 2008).

Here in this piece of work the percent elongation of fast dissolving film was also observed lowest for formulation F1 which had lowest concentration of film forming agent with no plasticizer and it was highest for formulation F7 which had highest concentration of plasticizer.

It is concluded from the results observed that the films containing no plasticizer and lowest amount of film former had less percent elongation as compared to films in which film forming polymer and plasticizer had been used.

Folding endurance is the ability of film that how many times it could be folded without any crack or breakage (Dahima *et al*., 2010).

Folding endurance of film was increased with increase in concentration of plasticizer PEG-400 which may increase the elasticity of the final formulation. Also contents of film former like PVA may increase the elasticity and hence the Folding Endurance of film due to elastic nature of film forming polymer (Rajni *et al*., 2014).

Here in this research the folding endurance of fast dissolving film was also observed lowest for formulation $F_1$ which had lowest concentration of film forming agent with

643 no plasticizer and it was highest for formulation $F_7$ which had highest concentration
644 of plasticizer.

645 Hence it is concluded from the results observed that the films containing no
646 plasticizer and lowest amount of film former had less folding endurance as compared
647 to films in which film forming polymer and plasticizer had been used.

648 Transparency is the test performed to evaluate the percent transmittance of transparent
649 films using U.V Spectrophotometer. Transmittance of films was determined at $\lambda_{max}$ of
650 600 nm. Transparency shows that how much the film is free from any foreign particle
651 or any haziness of casted solution as the transparency of film matters for its physical
652 appearance. Six film samples were examined by putting their suitable size as per cell
653 of U.V spectrophotometer. The transmittance of films was determined at 600 nm. The
654 transparency of the films was calculated as follows:

655 $$\text{Transparency} = (\log T600)/b = - €c$$

656 In this equation T represents the transmittance of film, b is the thickness of film and c
657 is the concentration at which formulation was developed.

658 Results discussed by (Rajni *et al*., 2014) in which transparency of film were tested
659 using rectangular piece of films by putting it in inner side of U.V cell and
660 transmittance was observed at 600nm. All the formulations showed transmittance of
661 above 90%.Transparencywasobserved for different samples of formulations using
662 U.V Spectrophotometer and results were observed (Sandeep *et al*., 2011).

663 Here in this research transparency was observed by U.V Spectrophotometer at
664 wavelength of 600nm and setting U.V parameters at transmittance. It was observed
665 that transparency of formulation F11 was maximum and for formulation F12, it was
666 minimum.

667 From the above observation it was concluded that transmittance of film was effected
668 by its extent of transparency that in turn affected by solubility and compatibility of
669 API and excipients.

670 Contact angle determines the extent to which film could be adhered to water and show
671 its wettability that in turn determines the disintegration and dissolution properties of
672 the film. It was determined by putting a drop of distilled water on film and image was
673 recorded within 10 seconds after placement of drop. Angle of film was measured from

both sides of drop and then average was calculated for each formulation. The contact angle must be within 0-180$^{o}$ (Pallavi *et al*., 2014), (Soorya Sankar, 2017).

In this research also contact angel was observed by placing a drop of distilled water over film and angle at which water drop had been spread over film was measured by measuring droplet height, width, volume and area. It was observed that contact angle was maximum for film under formulation F7 and was minimum for formulation F1.

Drug contents should be within the range designed by any standard official Pharmacopoeia. Drug contents for all the formulations were 106% for X1, 95.0% for X2, 97.0% for X3 and 99.0% for formulation X4 results discussed by (Nitesh Chauhan *et al*., 2012).

In this research work drug content by using HPLC were observed similar and within pharmacopoeia limits and was observed minimum for formulation F1 and was maximum for formulations F8 and F11.

Disintegration time is the time taken by the film to disintegrate in water. According to CDER guidelines the time taken by oral films must be less than 30 seconds, as this is the era of development for oral film technology these are considered to be standard guidelines. Pharmacopoeia disintegrating test apparatus was used for this study. According to most research data available the average disintegration time for oral film is from five to thirty seconds.

Disintegration time study was carried out and time of disintegration was measured in seconds. All the formulations were disintegrated within 40seconds and similar results were seen in a previous investigation (Sandeep *et al*., 2011). Different formulations were evaluated against different concentrations of film formers and it was noticed that as the concentration of PVA (Film Former) was increased, disintegration time of fast dissolving film was also increased. Our results were in line with results reported earlier (Rajni *et al*., 2014). A study aimed to design and evaluate new disintegration protocols as an attempt to select the best approach that would reflect the *in-vivo* disintegration time in comparison to formerly reported procedures. Novel methods were designed, namely; the frame, the cell, and the agar plate methods, and compared to the previously reported methods; clamp and modified USP disintegration methods. Different ODFs were formulated using various viscosity grades of hydroxypropylmethyl cellulose. The mechanical characteristics of the prepared films

were studied using texture analyzer and film folding endurance test. The resultant disintegration time of the films measured by the aforementioned methods were compared and correlated with its *in-vivo* time. Interestingly, the results obtained through the use of the cell method for the low viscosity polymers did not vary significantly from that of their *in-vivo* results ($p$>0.05). Moreover, the disintegration time of all polymeric films determined by the cell method revealed independently on their viscosity the highest correlation with *in-vivo* disintegration time ($R^2$ = 0.999). Such findings indicated the suitability of the cell method in predicting in-vivo disintegration time of low viscosity polymeric films. (Saab *et al.*, 2019)

Disintegration time was observed within 18 to 32 seconds and formulation $F_{12}$ was disintegrated in greater time i.e 32 seconds compared to $F_3$, which disintegrated too quickly i.e in 18seconds.

The disintegration time of the fast dissolving films depends upon the type and percentage of film forming polymers used in the film formulations. The increase in amount of polymer increased the disintegration which is correlated with hindrance offered by polymer (Garsuch *et al.*, 2010).

In-vitro dissolution study was carried out in USP Apparatus I and cumulative drug percentage was calculated using U.V Spectrophotometer. Formulations exhibited maximum dissolution at 5minutes (Sandeep *et al*., 2011). Studies showed that fast dissolving oral films of vitamin B12 for pregnant women present better dissolution and disintegration results than in the form of tablets (BEYATRICKS, 2019).

In present research dissolution test was performed using Appratus-1. The dissolution medium used was consisted of in potassium phosphate buffer media. Dissolution test for all the formulations was performed and relevant chromatograms for blank, standards and samples were evaluated. Dissolution was observed minimum for formulation F2 i.e 92.40% at 1.811minute and was maximum for formulations F7 i.e 106.6% at 1.813 minutes. Among the formulations $F_1$, $F_2$, $F_3$, $F_5$, $F_6$, $F_9$ showed the lowest drug release i.e near or below 95%. However for formulations $F_4$, $F_7$, $F_8$, $F_{10}$, $F_{11}$ showed highest drug release i. e near or above 100%. This is due to more concentration of HPMC E5 in these formulations and more wettability of HPMC E5 in dissolution medium. While comparing formulation $F_2$ containing 1.96% of HPMC

737 with that of $F_7$ containing 2.16% of HPMC $F_2$ shows lower drug release due to less
738 concentration of HPMC at retention times of 1.811 and 1.813 minutes respectively.

## 739 6 CONCLUSION

740 Fast dissolving oral films of alprazolam were successfully prepared using solvent
741 casting method. Two polymers (HPMC E5, HPMC E15) were analyzed for the
742 purpose as alone or combination with varied concentrations of plasticizers (PEG-
743 6000, PEG-400). Smooth texture and adequate mechanical strengths were achieved
744 for all formulations. The optimized formulation ($F_7$) offered almost 106.60% of total
745 drug release after 1.813 minutes, good tensile strength (5.38 $N/cm^2$) and distinct
746 morphology. The overall results of the study concluded that alprazolam fast
747 dissolving oral films have potential to act as fast dissolving drug delivery system for
748 fast action of the drug.
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