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# Characterization and Optimization of Mouth Dissolving Film of an Anticoagulant Drug: Apixaban

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**ABSTRACT:** Oral route is the most convenient route of drug administration among all other routes, but still it is challenging for paediatrics and geriatrics due to swallowing issue. Thus, to overcome this problem MDFs are used. This novel and safer approach; gives rapid systemic action by avoiding first pass metabolism. There are more several advantages like rapid disintegration, no need of water for administration, prevent degradation from acidic environment of stomach. The present research work aimed to prepare mouth dissolving films of an anticoagulant drug apixaban reduces the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Using Solvent casting method, the films were prepared and optimized using $3^2$ Factorial design considering two independent variables film forming polymer (HPMC E5) and Plasticizer (PEG 400). Dependent variables were taken as disintegration time, drug release and folding endurance. The prepared optimized formulation showed minimum disintegration time, highest dissolution rate (99.8 %) and satisfactory physicochemical properties. From the research, satisfactory results were obtained.

**KEY WORDS:** Mouth dissolving film, Apixaban, Stroke.

## I. INRODUCTION

Among, all the routes of drug administration, the most preferred one is oral route because of its convenient, cost effective and ease of administration that is highly convenient for both paediatrics and geriatrics. Although, it is still a challenging route for swallowing in both paediatrics and geriatrics. So to overcome it, the novel and safer drug delivery such as buccal film, oral strips have been developed. These systems were developed in1970,s as a novel dosage form to overcome the problem of swallowing for both paediatrics and geriatrics and for the systemic drug delivery the film was launched in 2004 [1,25].The ideal characteristics of that it should be Easy to handle and transport. It should have high stability and ease of administration. It should be easily ionized at oral cavity pH and pleasant in taste. Upto 40% of dose was incorporated in the formulation. It should have high tensile strength and does not stick to packaging material [3].The advantages of it such as, there is no need of water for administration, accurate dose can be delivered, easy to swallow for both geriatrics and paediatrics, acidic environment of stomach should be avoided. It also gives site specific and local action and provides rapid disintegration and dissolution in oral cavity, due to large surface area. [4, 5].The disadvantages are that it is not suitable for high dose, the packaging required is expensive, the dose uniformity is a technical challenge and the drugs which are unstable and irritate at buccal pH are not suitable. In addition, restriction of drinking and eating after consumption of oral film for required period of time. [2, 5, 6]

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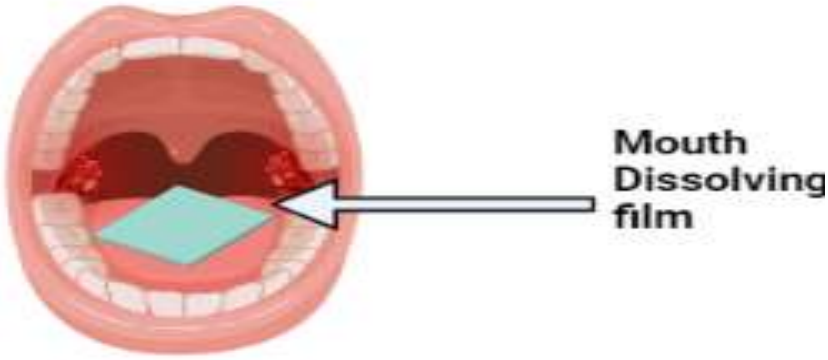


**Fig.1 Mouth dissolving film.**

**Classification of oral film:**
Three types of oral films are there:
A. Flash release
B. Mucoadhesive melt away wafer
C. Mucoadhesive sustained release
Types of oral films with their different properties are summarized in the below table.1

**Table 1.Types of film and their properties:** [7]

| **Property** | **A. Flash Release** | **B. Mucoadhesive melt away wafers** | **C. Mucoadhesive sustained release** |
|---|---|---|---|
| Area($cm^2$) | 2-8 | 2-7 | 2-4 |
| Thickness(µm) | 20-70 | 50-500 | 50-250 |
| Structure | Film; single layer | Single or multilayer system | Multilayer system |
| Excipients | Soluble, highly hydrophilic polymers | Soluble, Hydrophilic polymers | Low/Non soluble polymers |
| Drug phase | Solid solution | Solid solution or suspended drug particles | Suspension and/or solid solution |
| Site of action | Systemic or local | Systemic or local | Systemic or local |
| Dissolution | Maximum 60 seconds | Disintegration in few minutes, forming gel. | Maximum 8-10 hours. |
| Application | Tongue(upper plate) | Gingival or buccal region | Gingival |

## II. FORMULATION OF MOUTH DISSOLVING FILM

➢ **Active pharmaceutical ingredient:**

MDFs can be suitable for various APIs can be for mouth dissolving films. For improving dissolution and uniformity of MDFs; micronized drug can be effective(less than 20mg/day).For drug that is water soluble, there will be no issue of uniformity of distribution. But in water insoluble drug the uniformity may variate, thus to overcome it and for homogeneous distribution for better drug content uniformity, the water insoluble drug is added in milled, micronized form or nanocrystal or microcapsule to get smooth texture of the film. The examples of APIs includes antiasthmatics(e.g., salbutamol), antiulcer(e.g.,omeprazole),NSAIDS(e.g.,paracetamol,meloxican,valdecoxib),cough(e.g,dextromethorphan),menstrualpain(ketoprofen), smoking cessation (e.g., nicotine), allergic reaction(e.g., cetrizine, azatadine maleate). [2,8, 9, 10]

➢ **Film forming polymer:**

For the formation of the film, the polymers play an important role. Hydrophilic polymers can be used for the preparation of various

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 190-210 www.ijprajournal.com ISSN: 2456-4494

films. The amount of polymer added should affect the robustness of the film. Minimum 45% w/w of polymer should be present based on total weight of dry film. [60].Alone as well as in combination the polymer is used, to obtain desired properties of film.

The polymers used must be non irritant, non toxic, and should be inexpensive. It must have good spreadibility and wetting property. Polymer must have adequate tensile strength. The polymer must have good half life and it does not cause any secondary infection in oral mucosa or in dental site. Both natural and synthetic polymers are used for the preparation [2, 11, and 28].List of such polymers given below in table.2

**Table 2.Examples of Natural and synthetic polymers:** [3]

| **Natural polymers:** | **Synthetic polymers:** |
|---|---|
| Pectin | Polyvinyl alcohol |
| Starch | Hydroxy propyl cellulose |
| Guar gum | Polyvinyl pyrrolidone |
| Gelatine | Hydroxy propyl methyl cellulose |
| Pullulan gum | Sodium carboxy methyl cellulose |
| Carrageenan gum | Polyethylene oxide |
| Xanthan gum | Pyroli vinyl pyrollidine |

Examples of various polymers with their various properties are described in below table.3

**Table 3. List of properties of various films forming polymer: [**28]

| **Name of Polymer** | **Molecular weight (g/mol)** | **Solubility** | **Film forming ability** | **pH** | **Melting point** |
|---|---|---|---|---|---|
| Hydroxy propyl methyl cellulose | 10,000-1,500,000 | Soluble-cold water, Insoluble-chloroform and ethanol | It has film forming ability | 5-8 | 190-200ºc |
| Pullulan | 8000-2,000,000 | It is soluble in both hot and cold water | Having high adhesion and film forming capacity | 5-7 | 107ºC |
| Gelatin | 15000-250,000 | It is soluble in acid, glycerine and alkali-swell in water | Very good film forming capacity | 3.8-6.0 | - |
| Starch and modified starch | 50,000-1,60,000 | Insoluble in cold water and ethanol. At 37ºC swells in water about 5-10% | Modified starch is having property to form a fast dissolving film | - | 250ºC |
| Kollicoat | About 45000 | ≥50% in water | Good film forming property | 6-7 | - |

- **Plasticizer:**

Plasticizers should be used to improve the flexibility as well as the mechanical properties of film like tensile strength and elongation and reduce the breakability of the film. A plasticizer selected should be compatible with APIs as well as with the other ingredients. For improving the strip property of plasticizers, the glass transition temperature of polymer for non-aqeous solvent system reduced in the range of 40-60 and for aqeous system the glass transition temperature of polymer is reduced below 75. Examples of some plasticizer are castor oil, polyethylene glycol, citrate derivatives. Etc [2, 12].Various examples of APIs along with the plasticizers used is described in below table.4

International Journal of Pharmaceutical Research and Applications
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**Table.4 Examples of API with plasticizer used:** [2, 26, 27, and 28]

| API | Name of Plasticizer |
|---|---|
| Triclozan | PEG |
| Montelukast sodium | Glycerine |
| Sertraline | PEG |
| Loperamide | PEG |
| Famotidine | PEG |
| Ropinirole hydrochloride | PEG |
| Cetrizine | PEG |
| Telmisartan | PEG |
| Dicyclomine hydrochloride | PEG |
| Metachlopramide hydrochloride | Glycerol |

- **Sweetening agents:**

Sweetening agents should be used for masking the bitter taste of the APIs. Approximately 3 to 6% w/w concentration of sweeteners should be used in the preparation, either alone or in combination. In the formulation, both natural and artificial sweeteners may be used. Natural sweeteners like sorbitol, mannitol, and isomalt and artificial sweeteners include sucrose neotame, alitame, aspartame, cyclamate may ne incorporate in the films. However, artificial sweeteners are mostly preferable, because natural sugars are restricted for diabetic patients as well as in people who are on diet. [13]

- **Saliva stimulating agents:**

Saliva stimulating agents should be used to increase saliva secretion that helps in faster disintegration of the film. Various acids may be used in the preparation of food can be used as saliva stimulant, such as ascorbic acid, citric acid, lactic acid, tartaric acid and malic acid. Among all the examples the most widely saliva stimulating agent used is citric acid. [9]

- **Flavouring agents:**

Flavouring agents are used to impart flavour to any formulation. Flavouring agents should be compatible with drugs as well as with excipients. Flavours can be extracted from different parts of the plants like flowers, leaves, fruits. Flavours used are natural as well as artificial. Examples are peppermint oil, spearmint oil, cinnamon oil, vanillin, chocolate, apple, pineapple, cherry, and raspberry [8]. Flavouring agents used for masking different taste is descried below in table.5.

**Table. 5 Flavouring agents used for masking of different tastes is described as under: [**18]

| Taste | Flavouring agent used |
|---|---|
| Bitter | Mint, anise, walnut, chocolate, wild cherry |
| Salty | Peach, butterscotch, vanilla, apricot, maple, winter green |
| Sweet | Vanilla, fruit, berry |
| Sour | Raspberry, citrus, liquorice root |

- **Surfactants:**

Used as wetting or dispersing or solubilising agent. It is used to dissolve film within seconds and thus immediately release active ingredient. Examples are sodium lauryl sulphate, benzalkonium chloride, tweens, spans, polaxamer 407.Among various examples, mostly Polaxamer 407 is used as wetting, dispersing and solubilising agent [14].Other adjuvant like antioxidants, stabilizers, chelating agent, etc can be used as per need of formulation.

## III. MANUFACTURING METHODS

MDFs can be formulated by different methods:-

- Solvent casting method.
- Semisolid casting method.
- Hot melt extrusion.
- Solid dispersion technique.
- Rolling method.

- **Solvent casting method.**

This method is most commonly used for manufacturing of fast dissolving oral film. In solvent casting method, the water soluble polymers are mixed in water to form homogeneous solution.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 190-210 www.ijprajournal.com ISSN: 2456-4494

Then, the API and remaining excipients are dissolved in smaller amount of other suitable solvent. Both the solutions are combined by stirring and mixing, the air entrapped is removed by sonification. Finally solution is poured in petridish and then dried in the oven. [15]

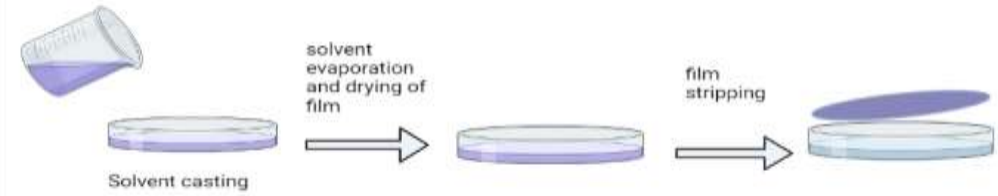



**Fig.2 Solvent casting method.**

Advantages:

- Films have good physical properties as well as flexibility.
- It is low-cost method.
- It does not cause any changes to API when exposed to high temperature.
- Films have better clarity and gloss.
- Films are free from any damage such as die lines.

Disadvantages:

- The polymer should be dissolved in water or volatile solvent.
- Stable solution should be obtained with moderate viscosity.
- The film formed should be homogeneous.[18]

➢ **Semisolid casting method:**

This method is preferred when acid insoluble polymers are used for the preparation of film. Firstly in this method, the solution of water soluble film forming polymer is prepared. The prepared solution is than added to a solution of acid insoluble polymer. Then plasticizer is added in appropriate amount to obtain gel mass. Finally the obtained gel mass is casted in the films or ribbons using heat controlled drums. The ratio of acid insoluble polymer to film forming polymer used should be in 1:4. [16]

➢ **Hot melt extrusion method:**

This method is mostly used for preparation of granules, transdermal drug delivery system, transmucosal drug delivery system and sustained release tablets. This method includes shaping of polymers through heating. In this method, the drug along with other excipients are combined in dry state, without use of any solvent and then subjected to extruder. Then the extruders having heaters that melt the mixture. The molten mass obtained is shaped in to the films. [17]

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

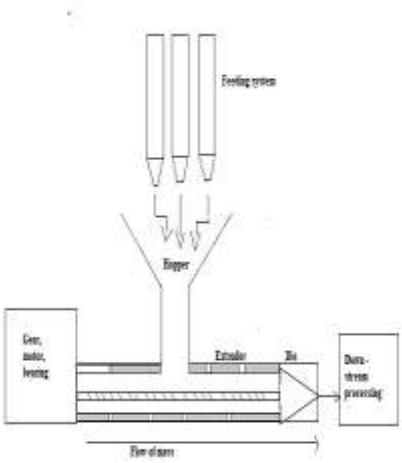


**Fig.3 Hot melt extrusion method**

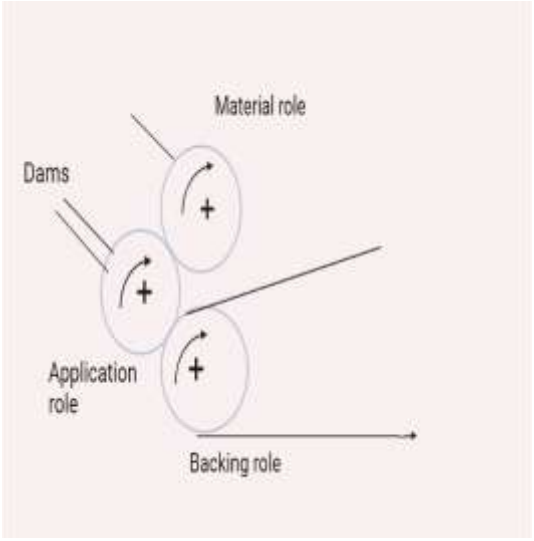



**Fig.4 Preparation of MDFs by Rolling method.**

Advantages:

- Processing steps are less.
- Solvent or water is not used in this method.
- It is more suitable for poorly soluble drugs.
- Energy needed is less than high shear methods.

Disadvantages:

- Thermoliable drugs are not suitable for this method.
- For processing the polymer must have good flow properties.
- It is difficult to maintain dose uniformity.
- Packaging require is expensive.[18]

➢ **Solid dispersion method:**

Solid dispersion method is dispersion of one or more active ingredients in an inert carrier in a solid state in the presence of amorphous hydrophilic polymers. Using suitable liquid solvent, the drug is dissolved. Incorporate solution into the melt of polyethylene glycol, below 70ºC. Atlast the solid dispersions are shaped into the films by means of dies. [1]

➢ **Rolling method:**

In this method, the solvent mainly used are water and mixture of water and alcohol. In small portion of aqueous solvent, the active agent and other ingredients are dissolved by means of high shear processor. Then to prepare homogeneous viscous solution water soluble hydrocolloids is dissolved in water. The solution containing drug is then rolled on a carrier. The films are dried on roller and cutted in desired shape and sizes. [19]

## IV. METHOD OF PREPARATION

**Method of Preparation**

**Solvent Casting Method:**

The solvent casting method was used for the preparation of the film. Take required amount of drug and then dissolve it in Water. Take required amount of film forming polymer and dissolve in water. Mix both the Solution with continuous stirring and then uniformly dispersed to get clear s solution film forming polymer. After that required amount of plasticizer to be added to film forming solution. Other ingredients and excipients were dissolved one by one in previously prepared film forming polymer solution with constant stirring to form clear solution. The prepared solution were kept in undisturbed condition till the entrapped air bubbles are removed. The aqueous solution was casted in a glass petridish having area of 63.58 $cm^2$ and was dried at room temperature. The petridish were put on leveled on surface during drying to avoid variation in the thickness. The film took approximately 24 hours to dry at room temperature. The dried film was carefully removed from the mould and was cut into size required for testing. The films were stored in airtight plastic bags till further use.

## V. EVALUATION PARAMETERS

➢ **Thickness:**

The thickness of film strip is measured by using micrometer screw gauge. The thickness of film must not be more than 5% from 5 different locations. The thickness of film is measured to obtain uniformity of film. This step is important

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

because uniformity in the film thickness is related to the dose accuracy in the film strip. [20, 22]

- **Folding endurance:**

To study the film elasticity, is essential to do folding endurance of film during its handling as well as during its storage. The folding endurance is obtained by cutting a strip of film and continuously folding the film at the same point till it breaks. The number of times, film is folded without breaking considered as folding endurance value.Folding endurance of film is must between 100-150.

- **Swelling study:**

The film swelling studies is determined using simulated saliva solution. One by one every sample of film is weighed and then put it into a stainless steel mesh that is pre-weighed. In a plastic container containing 15 ml of simulated saliva solution, the mesh containing film samples is merged. At each time interval, the increase in weight of film is measured constant weight is obtained. And percentage elongation is calculated by following equation. [20]

The degree of swelling was calculated by below equation:

W=Wt-Wo/Wo

Wt=It is the weight of film at time t.

Wo=It is the weight if film at time zero.

- **Percentage elongation:**

When the stress is applied to the sample of film strip, it stretches that is referred as strain. Increase in concentration of plasticizer causes increase in elongation of strip. Percentage elongation of film is calculated by following equation:

$$\text{Percentage elongation} = \frac{\text{Increase in length of strip}}{\text{Initial strength of strip}} * 10$$

- **Tensile strength:**

The mechanical strength of the film is measured tensile strength measurement. The point at which maximum stress is applied to break a film is termed as tensile strength. Tensile testing machine like Instron and Monsanto tester is use for testing tensile strength of the film. It can be calculated by the load applied divided by cross sectional area of the film as described in the following equation:

Tensile strength= (load at failure/strip thickness*strip width)*100. [17]

- **Surface pH:**

It is important to determine the surface pH of the film to avoid risk of any side effects by placing film in vivo on the surface of 1.5%w/v agar gel than place pH paper on films. The colour change of pH paper is determined and reported. The surface pH value for film must be 7 or near to neutral value.

Another method to measure surface pH of film is by using buffer. Cut a film put it in to petridish than add o.5 ml of buffer solution and measure the surface Ph of film by using Digital pH meter. [1, 21]

- **Assay/drug content and content uniformity:**

For this test standard pharmacopeia is referred, for any particular API, the standard assay method is preferred to determine its content uniformity. Drug content uniformity of the film is measured by UV-Visible spectrophotometer or specify as per pharmacopoeia. In different volumetric flask of 100ml, place films of each formulation and using pH buffer it can be dissolved. The sample of 5ml is withdrawn after 2, 4, 6, 8, 10 and 15 minutes and taken into volumetric flask of 10ml and the volume was made up to the mark. If UV spectroscopy is applied the absorbance is taken, than the value of absorbance is compared against blank in UV spectrophotometer. Using the standard graph, the percentage drug content is determined. [21, 22]

- **Disintegration time:**

For orally disintegrating tablets, the disintegrating time limit is 30 seconds or less that is described in CDER guidance and can be used at development stage or for the quality test as a qualitative guideline. For this study pharmacopeia disintegration test apparatus may be used. Strips have typical disintegration time between 5-30seconds. [23,24]

- **Percentage drug release:**

Ex vivo permeation study was carried out by taking goat oral mucosa using Franz diffusion cell of diameter 2.5 cm.The buccal mucosa than cut and trimmed evenly and then wash it with isotonic solution and immediately keep it between the donor and receptor compartment .Upto 200 ml of buffer is filled in the receptor compartment and temperature maintained at 37±4°C and with contant stirring at 50 rpm was maintained. Than 1 film of 2*2 cm diameter moistened with few drops of buffer solution and placed it in the chamber The donor compartment is filled with 1ml of phosphate buffer. Sample was withdrawn at 2,4, 6, 8, 10 and 15minutes. The amount taken was again filled with fresh buffer solution. The taken sample than diluted and absorbance was taken in UV-visible spectroscopy.

- **Stability study**

Stability study was carried out for 30 days , the optimized formulation was kept at 40±2°C and 75±5% RH. After completion of 30 days, studies

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

were carried out for parameters like physical appearance, folding endurance, disintegration time, drug content and % drug release.

## VI. RESULT AND CONCLUSION

**→Preformulation Study**

**Characterization of Drug**

So, firstly after receiving the drug we have to check out the basic characteristic of API which is described in below table.

**Table 6. Characterization of Drug:**

| **Test** | **Result of Analysis** |
|---|---|
| Description | White crystalline, solid powder |
| Solubility | Soluble in water as well as in methanol |
| Odour | Odourless |
| Melting point | 236°C |

**Interpretation:**

Results are shown in table. API is soluble in water and methanol so solvent casting method can be used for preparation of formulation and the melting point should be in range from 235-238°C described in literature, indicating the purity of drug.

**→UV- visible method for determination of Apixaban**

**Table 7. UV- visible method for identification of Drug:**

| **Conc.** | **Absorbance(λmax)** | | | **Average** | **S.D** |
|---|---|---|---|---|---|
| | **1** | **2** | **3** | | |
| 1 | 0.144 | 0.148 | 0.148 | 0.146667 | 0.002309 |
| 2 | 0.219 | 0.222 | 0.227 | 0.222667 | 0.004041 |
| 3 | 0.336 | 0.345 | 0.355 | 0.345333 | 0.009504 |
| 4 | 0.427 | 0.438 | 0.467 | 0.4444440 | 0.020664 |
| 5 | 0.539 | 0.568 | 0.574 | 0.5603330 | 0.018717 |
| 6 | 0.627 | 0.641 | 0.639 | 0.635667 | 0.007572 |
| 7 | 0.704 | 0.719 | 0.724 | 0.715667 | 0.010408 |
| 8 | 0.838 | 0.840 | 0.840 | 0.839333 | 0.001155 |
| 9 | 0.893 | 0.898 | 0.908 | 0.899667 | 0.007638 |

Calibration curve of Apixaban was prepared using different concentration from 1, 2, 3, 4, 5, 6, 7, 8, 9 µg/ml 6.8 phosphate buffer. Average of 3-determinations

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

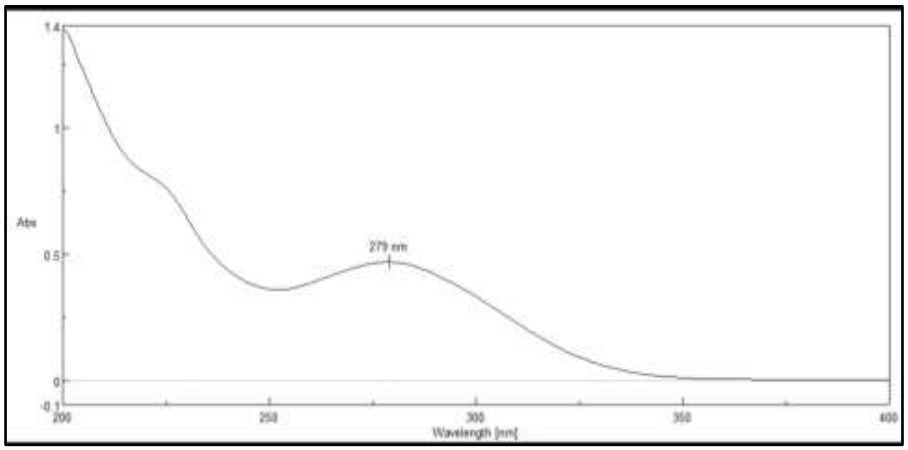



**Fig. 5 Scanning of λmax of API**

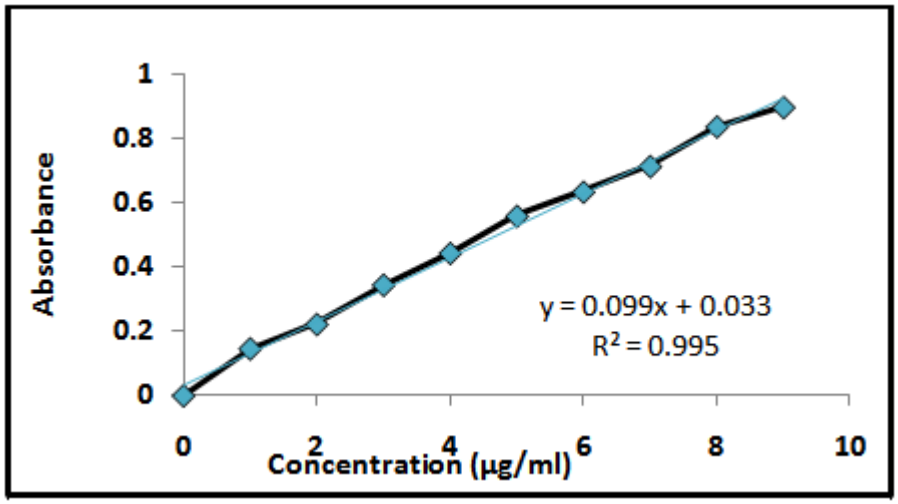



**Fig. 6 Calibration curve of Apixaban**

**→Compatibility study by FTIR**

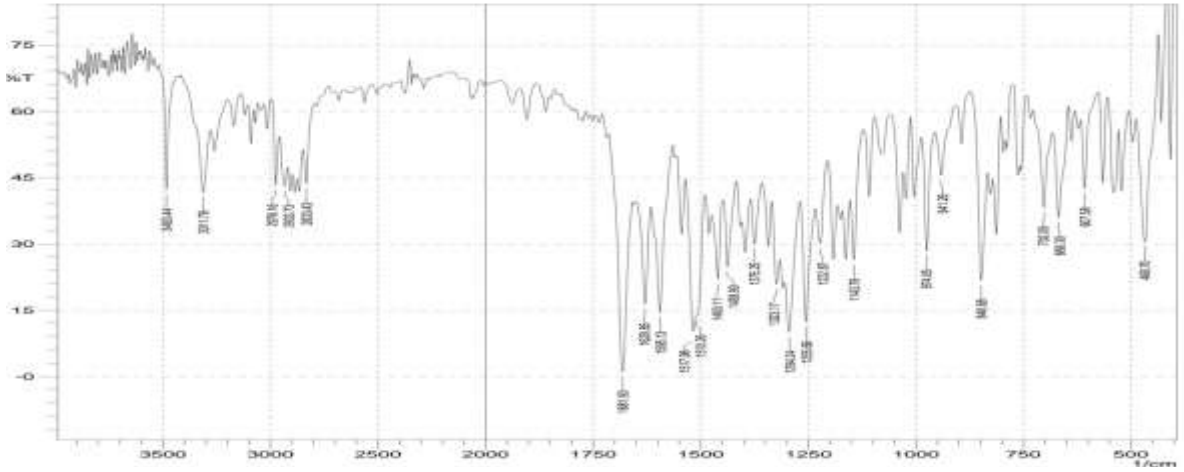



**Fig .7 FTIR spectra of Pure drug**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

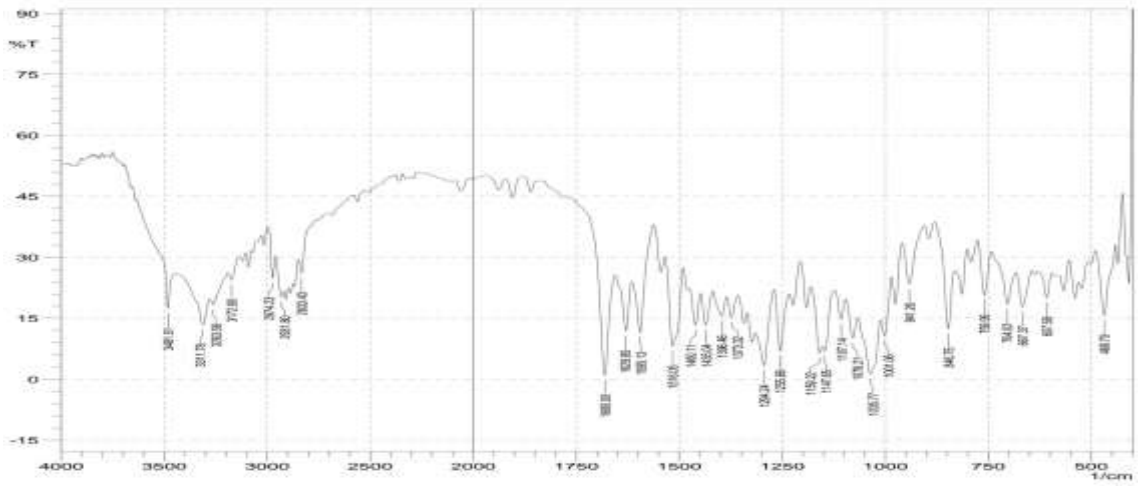



**Fig.8 FTIR spectra of Formulation**

**Table 8. FTIR data of Apixaban and Optimized Formulation:**

| Stretching | Pure drug ($cm^{-1}$) | Formulation($cm^{-1}$) |
|---|---|---|
| N-H | 3311.78 | 3311.78 |
| C-H | 2976.16 | 2974.23 |
| =O-NH | 1510.28 | 1516.05 |
| C=0 (Aromatic stretch) | 1681.93 | 1680.00 |

**Interpretation:**

Characteristic peaks obtained for the pure drug correlated well with the polymer as well as the selected formulation peaks. This indicates that the drug was compatible with the formulation components.

**Trial batches of film**

Initial trials were taken for finalization of polymers.

**Table 9. Composition of Mouth dissolving film:**

| Ingredients (mg) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Apixaban | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| HPMC E3 | 400 | 500 | - | - | - | - |
| HPMC E5 | - | - | 400 | 500 | - | - |
| HPMC E15 | - | - | - | - | 400 | 500 |
| PEG 400(ml) | 0.5 | 1.5 | 0.5 | 1.5 | 0.5 | 1.5 |
| Citric acid | 20 | 20 | 20 | 20 | 20 | 20 |
| Beta cyclodextrin | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

| | | | | | | |
|---|---|---|---|---|---|---|
| Water | q.s | q.s | q.s | q.s | q.s. | q.s. |

The prepared films of trial batches were evaluated for basic evaluation parameters. The results were recorded below in tabulated form.

**Table 10. Evaluation of Trial batches:**

| Formulation Code | Stickiness | Surface appearance | Film clarity | Quality | Folding endurance | Disintegration time (sec) | pH | Weight variation (mg) |
|---|---|---|---|---|---|---|---|---|
| F1 | Non sticky | Non uniform | Clear | Average | 150±20 | 40±11 | 6.8±0.3 | 133±2.7 |
| F2 | Non stocky | Non uniform | Turbid | Average | 200±12 | 38±17 | 7.1±0.2 | 135±4.4 |
| F3 | Non sticky | Uniform | Clear | Good | 204±10 | 33±12 | 7.1±0.1 | 130±2.3 |
| F4 | Non sticky | Uniform | Clear | Good | 248±19 | 35±15 | 7.0±0.2 | 127±3.5 |
| F5 | Non sticky | Non-Uniform | Turbid | Average | 210±15 | 129±17 | 6.92±0.1 | 129±4.1 |
| F6 | Non sticky | Non-Uniform | Turbid | Average | 252±20 | 148±10 | 7.0±0.3 | 139±1.7 |

**Interpretation:**
From the above, F1 and F2 are from HPMC E3, F3 and F4 are from HPMC E5 polymers and F5 and F6 from HPMC E15. HPMC E3 and E15 make average films, while HPMC E5 makes good films.

**Formulation Batches ($3^2$ Factorial Design)**
After Trial batches, HPMC E5 was selected and further by applying $3^2$ factorial designs total 9 formulations were suggested and prepared using solvent casting method.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

**Table 11. $3^2$ Factorial Designs:**

| **Batch NO.** | **X1**<br>**Amount of HPMC E5** | **X2**<br>**Amount of PEG 400** |
|---|---|---|
| A1 | 0 | -1 |
| A2 | 0 | 0 |
| A3 | +1 | -1 |
| A4 | -1 | +1 |
| A5 | 0 | +1 |
| A6 | -1 | -1 |
| A7 | +1 | +1 |
| A8 | +1 | 0 |
| A9 | -1 | 0 |

| **Independent Variables** | **Level** | | |
|---|---|---|---|
| | **Low (-1)** | **Medium (0)** | **High (+1)** |
| HPMC E5 (X1) mg | 400 | 450 | 500 |
| PEG 400 (X2) ml | 0.5 | 1 | 1.5 |
| **Dependent Variables** | | | |
| Response Y1 : Folding endurance | | | |
| Response Y2 : Disintegration time | | | |
| Response Y3 : % Drug release | | | |

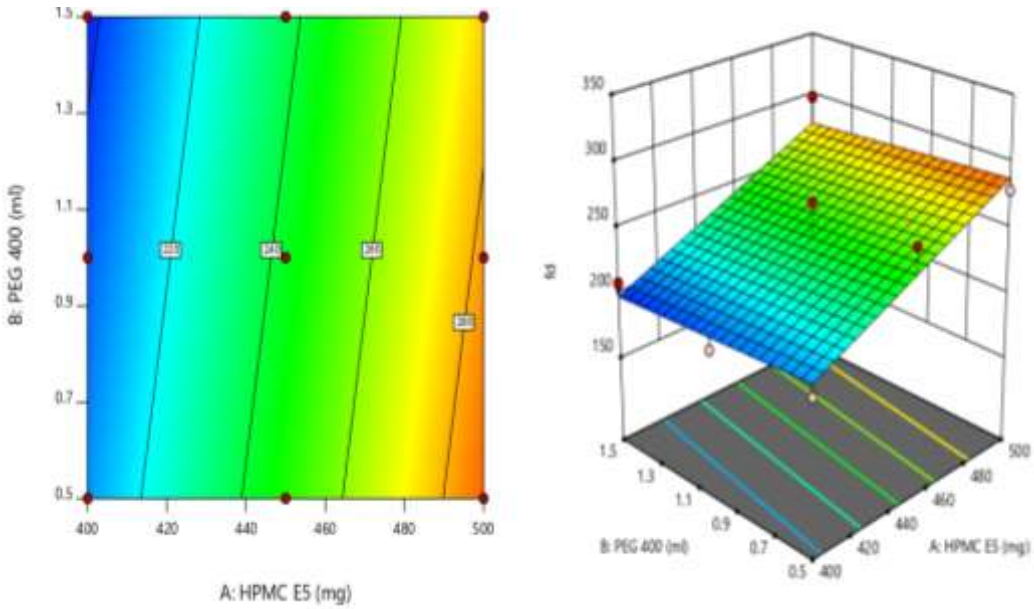
All batches were evaluated for Folding endurance, Disintegration time and % Drug release to find the effect of both X1 and X2 on the film

**Table 12. Factorial Batches of Apixaban Mouth Dissolving Film;**

| **Ingredients(mg)** | **A1** | **A2** | **A3** | **A4** | **A5** | **A6** | **A7** | **A8** | **A9** |
|---|---|---|---|---|---|---|---|---|---|
| Apixaban | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| HPMC E5 | 450 | 450 | 500 | 450 | 400 | 400 | 500 | 500 | 400 |
| PEG 400 (ml) | 0.5 | 1 | 0.5 | 1.5 | 1.5 | 0.5 | 1.5 | 1 | 1 |
| Citric acid | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| Sodium Starch Glyconate | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Beta cyclodextrin | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Water | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s | q.s |

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

➢ **Folding Endurance Contour plot and 3D plot:**




**CONTOUR PLOT** **3D PLOT**

**Fig. 9 3D and Contour plot of folding endurance**

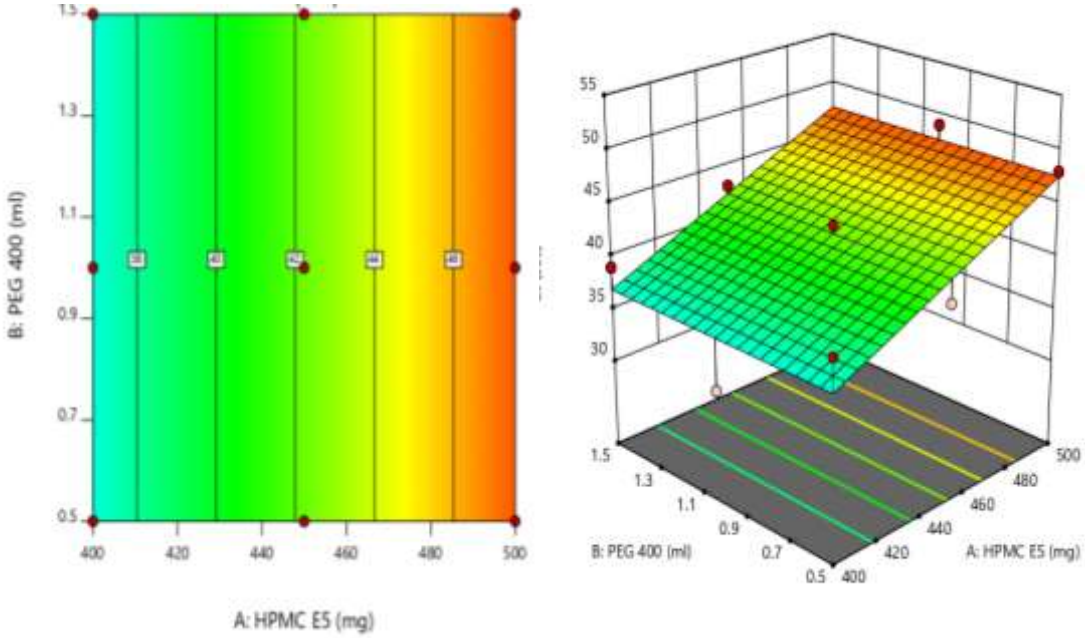
**Table 13. ANOVA for Response 1: Folding endurance**

| Source | Sum of Squares | df | Mean Square | F - value | p- value | |
|---|---|---|---|---|---|---|
| Model | 9486.83 | 2 | 4743.42 | 8.54 | 0.0176 | **significant** |
| A-HPMC E5 | 9282.67 | 1 | 9298.67 | 16.17 | 0.0064 | |
| B- PEG 400 | 204.17 | 1 | 204.17 | 0.3674 | 0.5666 | |
| Residual | 3334.06 | 6 | 555.68 | | | |
| Cor Total | 12820.89 | 8 | | | | |

**For folding endurance, the ANOVA table have significant impact on film.**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

➢ **Disintegration time Contour plot and 3D plot:**




**CONTOUR PLOT** **3D PLOT**

**Fig. 10 3D and Contour plot of Disintegration time**

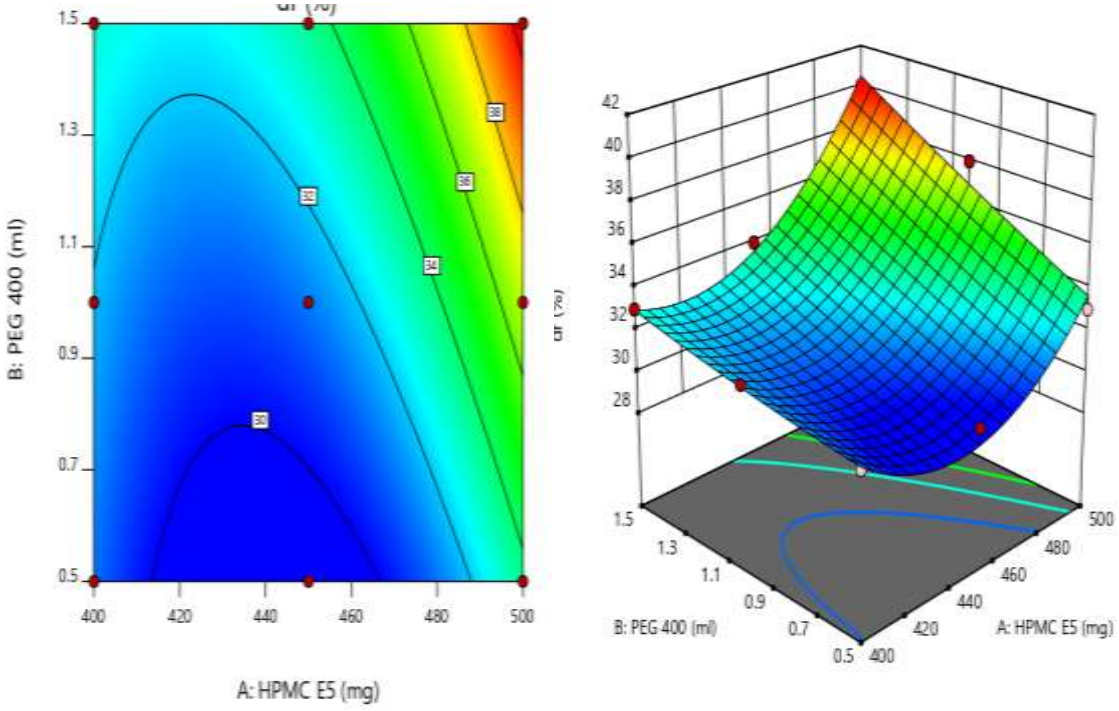
**Table 14. ANOVA for Response 2 : Disintegration time**

| Source | Sum of Squares | df | Mean Square | F - value | p- value | |
|---|---|---|---|---|---|---|
| Model | 170.67 | 2 | 85.33 | 10.47 | 0.0110 | **significant** |
| A-HPMC E5 | 170.67 | 1 | 170.67 | 20.95 | 0.0038 | |
| B- PEG 400 | 0.0000 | 1 | 0.0000 | 0.0000 | 1.0000 | |
| Residual | 48.89 | 6 | 8.15 | | | |
| Cor Total | 219.56 | 8 | | | | |

For Disintegration time ,, the ANOVA table have significant impact on film.

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

➢ **% Drug Release Contour plot and 3D plot:**




**CONTOUR PLOT** **3D PLOT**

**Fig. 11 3D and Contour plot of % Drug release**

**Table 15. ANOVA for Response 3 : %Drug release**

| Source | Sum of Squares | df | Mean Square | F - value | p- value | |
|---|---|---|---|---|---|---|
| Model | 92.03 | 5 | 18.14 | 13.16 | 0.0297 | **significant** |
| A-HPMC E5 | 37.50 | 1 | 37.50 | 26.82 | 0.0140 | |
| B- PEG 400 | 28.17 | 1 | 28.17 | 20.15 | 0.00206 | |
| Residual | 4.19 | 3 | 1.40 | | | |
| Cor Total | 96.22 | 8 | | | | |

For Percentage drug release the ANOVA table have significant impact on film

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

**Table 16. Evaluation of Mouth Dissolving film**

| Formulation | Weight variation(mg) | Swelling index(mg) | Surface Ph | Tensile Strength ($N/mm^2$) |
|---|---|---|---|---|
| A1 | 133±3.5 | 237±1.8 | 6.9±0.2 | 3.33±0.05 |
| A2 | 128±2.5 | 240±1.4 | 7.0±0.1 | 4.52±0.02 |
| A3 | 131±3.4 | 240±2.5 | 6.9±0.3 | 3.60±0.02 |
| A4 | 130±1.2 | 257±3.1 | 6.8±0.3 | 3.42±0.03 |
| A5 | 124±2.9 | 234±2.2 | 6.9±0.2 | 4.16±0.04 |
| A6 | 125±4.1 | 238±1.4 | 6.9±0.3 | 4.62±0.02 |
| A7 | 130±2.2 | 260±1.1 | 6.9±0.2 | 3.47±0.04 |
| A8 | 138±2.5 | 266±1.2 | 7.2±0.1 | 3.78±0.05 |
| A9 | 152±3.4 | 230±2.4 | 7.0±0.4 | 3.49±0.02 |

**Table 17. Evaluation of Mouth dissolving film :**

| Formulation | % Elongation | Thickness(mm) | Folding endurance | Disintegration time(sec) | Drug content (%) |
|---|---|---|---|---|---|
| A1 | 30.12±3.19 | 0.36±0.02 | 208±19 | 39±10 | 98.9+1.2 |
| A2 | 39.44±4.12 | 0.37±0.03 | 270±16 | 40±12 | 99.7+1.0 |
| A3 | 26.66±5.16 | 0.30±0.04 | 298±20 | 46±18 | 97.2+2.2 |
| A4 | 38.54±6.28 | 0.36±0.03 | 194±13 | 32±8 | 85.5+3.1 |
| A5 | 47.11±5.64 | 0.32±0.02 | 279±14 | 48±13 | 98.9+1.3 |
| A6 | 40.22±6.47 | 0.34±0.05 | 261±22 | 49±20 | 98.6+1.1 |

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

| | | | | | |
|---|---|---|---|---|---|
| A7 | 38.66±3.33 | 0.37±0.05 | 269±11 | 40±8 | 88.9+2.1 |
| A8 | 42.18±2.23 | 0.38±0.03 | 207±16 | 43±15 | 99.5+2.2 |
| A9 | 45.19±4.77 | 0.34±0.02 | 200±14 | 40±12 | 99.7+1.8 |

**→Percentage Drug Release:**

**Table 18. % Drug Release :**

| **Formulation** | **Time (min)** | | | | | |
|---|---|---|---|---|---|---|
| | **2** | **4** | **6** | **8** | **10** | **15** |
| A1 | 33.4 | 50.3 | 62.4 | 77.0 | 88.4 | 98.6 |
| A2 | 30.6 | 52.4 | 68.2 | 76.2 | 85 .4 | 99.8 |
| A3 | 31.2 | 45.5 | 53.3 | 67.2 | 78.5 | 85.7 |
| A4 | 32.4 | 45.6 | 58.3 | 79.1 | 89.6 | 99.7 |
| A5 | 48.6 | 52.4 | 60.4 | 73.3 | 84.7 | 96.6 |
| A6 | 49.5 | 55.8 | 61.5 | 73.4 | 84.8 | 97.8 |
| A7 | 40.3 | 42.7 | 57.8 | 68.5 | 79.9 | 83.9 |
| A8 | 43.4 | 48.8 | 56.0 | 70.3 | 77.1 | 82.2 |
| A9 | 40.1 | 53.3 | 64.1 | 75.6 | 83.1 | 94.8 |

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

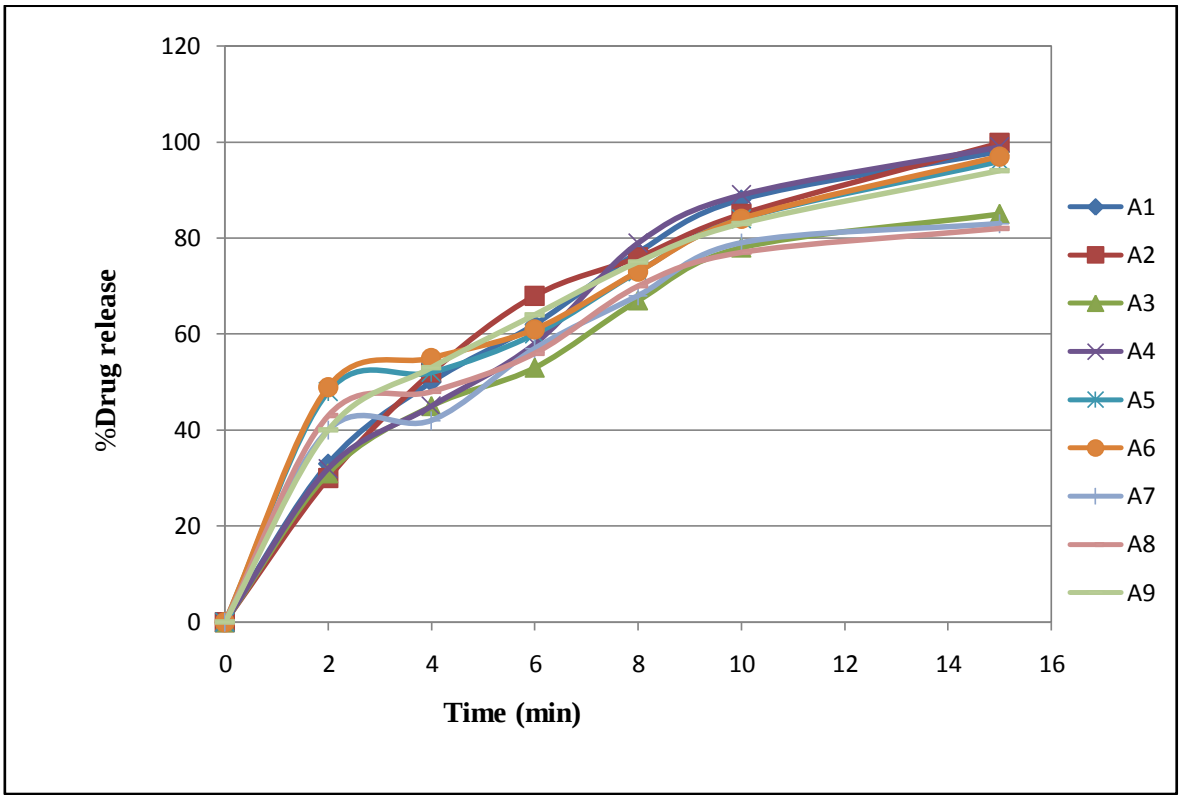



**Fig 12. Drug release study of Factorial batches**

**Interpretation :**

A2 was showing the good dissolution

**→Rate Kinetics Study**

**Table 19. $R^2$ value of Rate kinetics study.**

| FORMULATIONS | ZERO ORDER | FIRST ORDER | HIGUCHI MODEL | KORSMEYER PEPAS |
|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| A1 | 0.9282 | 0.8489 | 0.9952 | 0.9878 |
| A2 | 0.95974 | 0.8895 | 0.9917 | 0.9925 |
| A3 | 0.9408 | 0.8762 | 0.9711 | 0.9836 |
| A4 | 0.9217 | 0.8615 | 0.9638 | 0.9757 |
| A5 | 0.9681 | 0.9503 | 0.9567 | 0.9829 |
| A6 | 0.9786 | 0.9638 | 0.9639 | 0.9357 |
| A7 | 0.8961 | 0.863 | 0.928 | 0.913 |
| A8 | 0.9112 | 0.8876 | 0.9426 | 0.9375 |
| A9 | 0.9475 | 0.8864 | 0.9901 | 0.9986 |

**Kinetic modeling data of Optimized batch A2**

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

**Table 20. Rate kinetics data of Optimized batch A2**

| Kinetic Model | Parameters | Value |
|---|---|---|
| Zero Order | $R^2$ | 0.95974 |
| First Order | $R^2$ | 0.8895 |
| Korsmeyer-Peppas | $R^2$ | 0.9925 |
| Higuchi Model | $R^2$ | 0.9917 |

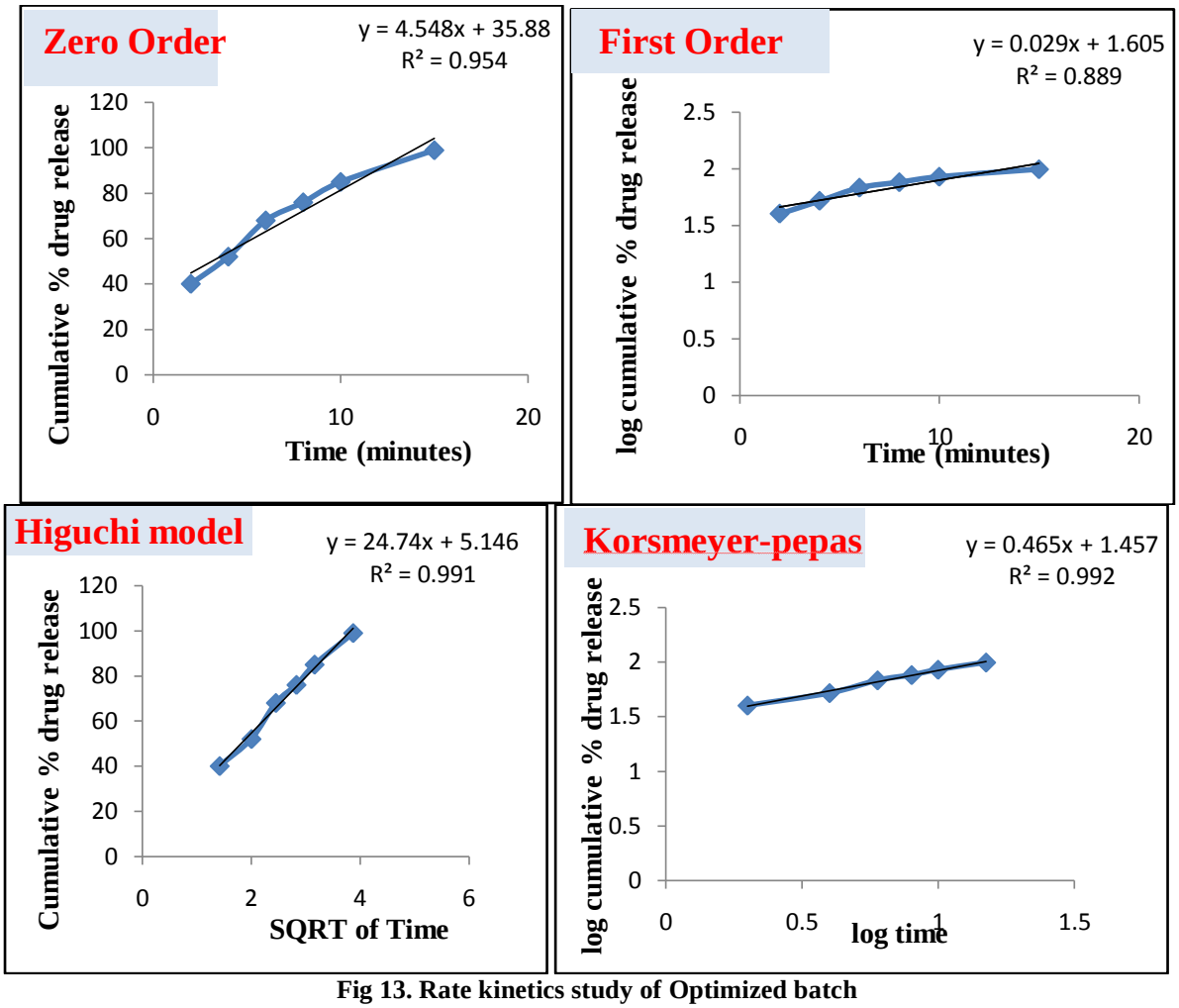



**Fig 13. Rate kinetics study of Optimized batch**

**Interpretation :**

The drug release data of batch A2 is fitted in to different kinetic models. Among all, the best fitted model is Korsmeyer-Peppas model because $R^2$ value of Korsmeyer-Peppas model has 0.9925

International Journal of Pharmaceutical Research and Applications
Volume 7, Issue 3 May-June 2022, pp: 122-126 www.ijprajournal.com ISSN: 2456-4494

➔ **STABILITY STUDY**

**Table : 25 Result of stability study of optimized batch A2**

| Paramters | Initial | After 1 month |
|---|---|---|
| Appearance | Clear and Transparent | Clear and transparent |
| Folding endurance | 270 | 262 |
| Drug content | 99.7 | 99.4 |
| % Drug release | 99.8 | 99.6 |
| Disintegration time (sec) | 40 | 45 |

**INTERPRETATION:**
The A2 batch stability study was found to be satisfactory.

## VII. CONCLUSION:

The aim of the present study was to optimize and characterize mouth dissolving film of Apixaban. Firstly the trial batches of film were prepared using 3 different polymers HPMC E3, HPMC E5 and HPMC E15 and from the result HPMC E5 is selected. Preformulation was performed to investigate the drug-excipient compatibility by doing FTIR of 2 samples that is 1) Pure Drug , 2) Final formulation and the spectra was found to be satisfactory. Further, in UV, the graph obtained was Linear. Then, the formulation was optimized based on $3^2$ factorial design in that, PEG 400 and HPMCE5 was taken as independent variable. Analysis of factorial design done for dependent variables such as Folding endurance, Disintegration time and % Drug release. All the results obtained was found to be satisfactory. Among all, the final formulation A2 was selected based on result obtained by evaluation. Also the F2 formulation shows good Weight variation, Thickness, Surface pH, Tensile strength, % Elongation, Disintegration with in 40 seconds , Drug release is 99.8% in 15 minutes , Drug content is 99.7 and Folding endurance 270.

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International Journal of Pharmaceutical Research and Applications
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