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# Formulation Characterization and Evaluation of Bioadhesive Orodispersible Film of Enalapril Maleate For Soft Palate Drug Delivery

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## ABSTRACT

The present experimental study involves the preparation and characterization of Orodispersible film of enalapril maleate. In this method HPMCK100 and propylene glycol are used to formulate orodispersible film and two disintegrating agent was used by using solvent casting method. Enalapril maleate is a antihypertensive drug which class of ACE inhibitor (Angiotensin converting enzyme). It is used in the treatment of hypertension congestive heart failure. It show low bioavailability due to high hepatic first pass metabolism so the soft palate drug delivery provide an excellent route to deliver the drug into systemic circulation and the present experimental work to formulate bioadhesive orodispersible of enalapril maleate to improve the therapeutic efficacy, patient compliance and its bioavailability by avoiding the first pass metabolism. After proper preformulation studies various orodispersible film which were prepared subjected for several evaluation study like thickness, weight uniformity, surface pH, drug uniformity, folding endurance, In vitro disintegration time the drug is rapidly disintegrate within seconds. It means it show that best for the those patient who have difficult to swallowing the drug and .*Invitro* dissolution study of prepared orodispersible film was carried out in phosphate buffer 7.4 as a medium and it was clearly observed that the F6 formulation a best formulation because it rapidly drug release. All the formulation provide a well controlled drug release at a sustainable rate. From the experimental result it was clearly concluded that orodispersible film of enalapril maleate may use as an effective drug delivery with an enhance bioavailability.

**Keywords:** Orodispersible film, Hydroxypropylmethylcellulose(HPMCK100), Crosspovidone, Solvent casting , Emalapril maleate

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## INTRODUCTION

The Orodispersible is an advance drug delivery system it consist of thin film when placed on the patient tongue mucosal tissue film get wet by a saliva dissolve within few seconds releasing the drug for oral absorption. Oral route is a simplest route when compared other routes of delivery of drugs. The main advantage of this film there is no needed of water or chewing the film. Oral route is a perfect route because they easily administered specially those patient who have pain to swallow the drug and low cost therapy. Oral dispersible dosages are useful in paediatric and geriatric patients who have difficult to swallowing conventional tablet. Orodispersible film mainly formulated those drugs having a low bioavailability because during the formulation the film improve the bioavailability and therapeutic efficacy due to extensive first pass metabolism and faster the onset of action as compared to capsules and tablets.[1]There is no definition of oral film but in practical purpose it define as A thin film, flexible, non friable polymeric film having dispersed pharmaceutical and after swallowing for delivery into the GIT. The oral mucosa can be categorized into sublingual, gingivae, buccal, hard and soft palate mucosa comparison the route. The buccal and sublingual dosage form short acting because the limited contact between the dosage form and oral mucosa. In these routes generally considered unsuitable for prolonged administration whereas the soft palate drug delivery at steady state infusion of drug over an extended period of time due to the soft palate to cover a epiglottis while swallowing, it is more fitted for sustain and control drug delivery system[2]

Preparing the Orodispersible film the Enalapril maleate was chosen because it is a antihypertensive drug which class of ACE inhibitor (Angiotensin converting enzyme).It is a pharmaceutical drug used for the treatment of hypertension and congestive heart failure. It is low bioavailability but after preparing the orodispersible film it increase the bioavailability, it increase its solubility and rapid onset of action for hypertensive patients. A orodispersible film is prepared by using HPMCK100 as a polymer and propylene glycol used as a plasticizer, and various ingredients used in the combination cross povidone, citric acid and sodium starch glycolate used as a superdisintegranting agent. Orodispersible film was evaluated various parameters like weight uniformity, average thickness, folding endurance, surface pH, disintegration time, drug content uniformity and *invitro* diffusion study[4].

## MATERIALS AND METHOD

**Material used:**

Enalapril Maleate was obtained from Sun pharma pharmaceutical pvt ltd,HPMCK100 was

received from Central drug house ltd Delhi and all other ingredients was obtained from Central drug house ltd Delhi. All other instruments used were of analytical grade.

**Preformulation Study**

Preformulation study is the first step in the rationale development of dosage form to a drug. It can be defined as the investigation of physical and chemical properties if drug substance alone or in combination with excipients . The overall objectives of preformulation studies is to generate information useful to formulator in developing stable and bioavailable dosage form which can be mass produced.

**Identification of drug:**

**Physical appearance of drug:**

**Physical appearance and surface texture of films**

The physical appearance was checked with visual inspection by touch or mouth feel.

**Determination of pH**

1gm of ENL was dissolved in 100ml of water and pH of the solution was found to be 3.2, this value is same as given in literature between 2-5

**Determination of Melting point:**

The sample was loaded in to sealed capillary (melting point capillary) which was then placed in melting point apparatus. The sample was then heated and as the temperature increase the sample was observed to detect the phase change from solid to liquid phase. The temperature which the phase changes occur gives the melting point.

**Solubility:**

The solubility of drug may be expressed in number of ways. The US Pharmacopoeia and national formularies list the solubility of the drugs as the number of mill liters of solvent in which 1 gram of solute will dissolve. 1 gm of Enalapril Maleate was dispersed in the solvent and based on the following table number solubility was determined. Solubility of Enalapril Maleate was determined in water,ethanol,methanol,water and dimethylformamide.

**Drug Excipient compatibility study by FTIR**

**Fourier transform infrared (F.T.I.R)**

Infrared spectrum of enalapril maleate was determined by using Fourier Transform.Infrared Spectrophotometer using KBr disks method. The sample (0.5 to 1.0 mg) is finely. grounded d intimately mixed with approximately 100 mg of dry potassium bromidepowder. Grinding and mixing can be done with mortar and pestle. The mixture is the pressed intotransparent disk in an evaluable die at sufficiently high pressure. SuitableKBr disks or pellets can often be made using a

simpler device such as a hydraulic press.The base line correction was done using dried potassium bromide. Then, the spectrum of dried mixture of drug and potassium bromide was scanned from 2000 cm -1 to 400 cm -1

**Preparation of Calibration Curve**

**Instrument:**UV spectrophotometer

Accurately weight 100mg of pure enalapril maleate was dissolved in few ml of methanol and volume was made upto 100ml with methanol to get conc. of about 1000 µg mL-1 from the above stock solution.Working standards were prepared by taking 10ml of the solution in 100ml volume flask and made upto the mark with methanol to get concentration of about 100 µg ml.

From the stock solution the 1ml pipette out and transferred into the 10ml volumetric flask and diluted in phosphate buffer 7.4separately to get final concentration range 5-30µg/ml.The solution were scan in UV spectrophotometer. The wavelength was found to be 232nm.The calibration curve plot against the absorbance *vs* concentration.

**In phosphate buffer pH 7.4:**

Dissolving 6.8gn of potassium dihydrogen phosphate buffer and 1.56g of sodium hydroxide in 1000ml in distilled water. The pH was adjusted to 7.4

**Preparation of Orodispersible film:**

Formulation of Orodispersible film containing Enalapril Maleate can be prepared by solvent casting method. Firstly in solution 1 the HPMCK100 is added into the ethanol and placed in magnetic stirrer. After a few minutes the propylene glycol is added in sample 1.Similarly the solution 2 were prepared in this solution the drug and other excipient added in ethanol. The calculate amount of polymer and PG were dispersed in three-fourth amount in solvent(ethanol) with continuous stirring using the magnetic starrier and final volume(10ml) adjusted by the solvent. Then the solution was poured into the petri dish and dry at 24 hrs at room temperature. After drying these film were removed from petridish and cut into definite shape and are packed.

**Table: 1 Formulation chart of ENL Maleate Film**

| Formulation Code | Drug (mg) | HPMCK100 (mg) | Propylene glycol(ml) | Citric acid(mg) | Cross povidone(%) | SSG(%) | Ethanol (ml) |
|---|---|---|---|---|---|---|---|
| F1 | 10 | 100 | 0.2 | 20 | 2 | 1 | 10 |
| F2 | 10 | 100 | 0.2 | 20 | 4 | 2 | 10 |
| F3 | 10 | 200 | 0.3 | 20 | 6 | 3 | 10 |
| F4 | 10 | 200 | 0.3 | 20 | 8 | 4 | 10 |
| F5 | 10 | 200 | 0.4 | 20 | 10 | 5 | 10 |
| F6 | 10 | 200 | 0.4 | 20 | 12 | 6 | 10 |

**Evaluation parameters of Orodispersible films:**

**Physical appearance:**

The physical appearance was with visual inspection by mouth. The observation suggest that the film having smooth surface and they enough to see.

**Weight uniformity:**

Weight uniformity can be determine to weight of each film of every formulation was taken and average weight of film can be determine by using analytical balance[5].

**Thickness:**

Film was measured at five different places by screw gauge vernier caliper and to determine the average film thickness was calculated. It show the accuracy of dose in Orodispersible film formulation.

**Surface pH:**

The surface pH was determine by dissolving the film in 10ml water and to placed in pH meter and it show the uniformity pH value of surface.

**Folding endurance:**

Folding endurance to study the elasticity of film. It was to determine by more time folded film at same place till it break and it computed as a folding endurance value[6].

**Drug content uniformity:**

The film was cut and placed into the beaker the beaker was containing 100ml of phosphate buffer pH 7.4 solution. The solution was stirred in magnetic stirrer to dissolve the film in solution. The solution was transferred into the 100ml volumetric flask. The absorbance of the solution was measured at 232nm.

**In vitro disintegration time:**

The disintegration time was determine by using disintegration test apparatus. In this method the film was placed into the basket the time was noted when the film dissolved into the basket and check no traces required in the basket.

**In vitro diffusion study:**

In vitro diffusion study of prepared Orodispersible film was conducted by using diffusion cell drug loaded dispersible film subjected for diffusion study using dialysis membrane.After preparing the solution check the absorbance at 232 nm in UV spectrophotometer.

## RESULTS AND DISCUSSION

**Preformulation studies**

**Identification of drug**

The various parameters were performed for Enalapril Maleate. The result shown in tables 3.1.

**Organoleptic Properties of Enalapril Maleate**

Organoleptic property of Enalapril Maleate determine by physical and visual inspection

**Table: 2 Organoleptic Property Data**

| S,No | Properties | Result |
|---|---|---|
| 1. | Description | Solid |
| 2. | Color | White or off white powder |
| 3. | Odor | Odourless |
| 4. | Taste | Characteristics |

The observed organoleptic property of obtained sample is similar with given standard value so it can be used as preliminary device for identification of drug.

**Solubility of Enalapril Maleate:**

**Table: 3 Solubility of Enalapril maleate**

| Solvent | Concentration µg/ml | Solubility |
|---|---|---|
| Water | 0.986 | Sparingly soluble |
| Ethanol | 4.58 | Soluble |
| Methanol | 6.32 | Freely soluble |

The quantity based on solubility suggested that drug was freely soluble in methanol, sparingly soluble in water and soluble in ethanol.

**Melting point determination was done by capillary method.**

The sample was loaded in to sealed capillary (melting point capillary) which was then placed in the melting point apparatus. The sample was then heated and as the temperature increase the sample was observed to detect the phase change from solid to liquid phase. The temperature which the phase changes occur gives the melting point.

**Table:4 Melting Point Data**

| S.no | Standard range of melting point | Experimental value of melting point Mean±SD(n=3) |
|---|---|---|
| 1. | 144°C | 145.6±0.667°C |

Melting point of Enalapril Maleate was found to be 145±0.66°C by the capillary method. So it may used as an identification of drug.

**Identification of drug by UV**

**Figure1: Enalapril maleate pure drug identification.**

UV spectrum of Enalapril Maleate in phosphate buffer pH 7.4 was observed value of absorbance obtained 232 nm which is similar to that of standard given value.

**Analytical Method:**

**UV spectroscopy:**

Standard curve of Enalapril maleate inmethanol. The standard curve of enalapril maleate was drawn absorbance vs concentration. The result shown in table 4

**Standard curve of Enalapril maleate in methanol**

**Table: 5 Calibration data of Enalapril Maleate in methanol**

| S.No | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 5 | 0.135 |
| 2 | 10 | 0.245 |
| 3 | 15 | 0.463 |
| 4 | 20 | 0.598 |
| 5 | 25 | 0.743 |
| 6 | 30 | 0.987 |

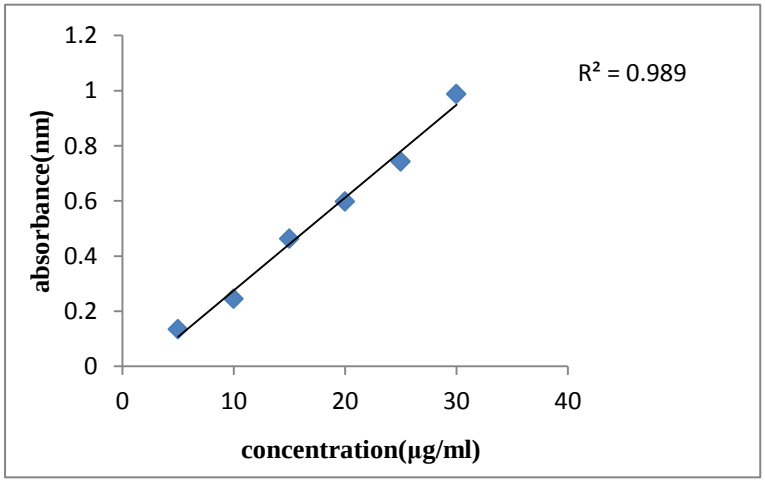


**Figure:2 Calibration curve of Enalapril Maleate in Methanol**

**Observed λ max of drug** - 232nm

**Observed Beer's range of drug** 5-30ug/ml

**Line of equation and r2 value** = (y = 0.033x + 0.060)

**R² value** = 0.989

**Standard curve of Enalapril Maleate in phosphate buffer pH( 7.4)**

The standard curve was drawn absorbance vs concentration.The result shown in table no 3.5

**Table: 6 Calibration date of Enalapril maleate in phosphate buffer ph (7.4)**

| S.No | Concentration(µg/ml) | Absorbance(nm) |
|---|---|---|
| 1 | 5 | 0.295 |
| 2 | 10 | 0.342 |
| 3 | 15 | 0.495 |
| 4 | 20 | 0.578 |
| 5 | 25 | 0.789 |
| 6 | 30 | 0.934 |

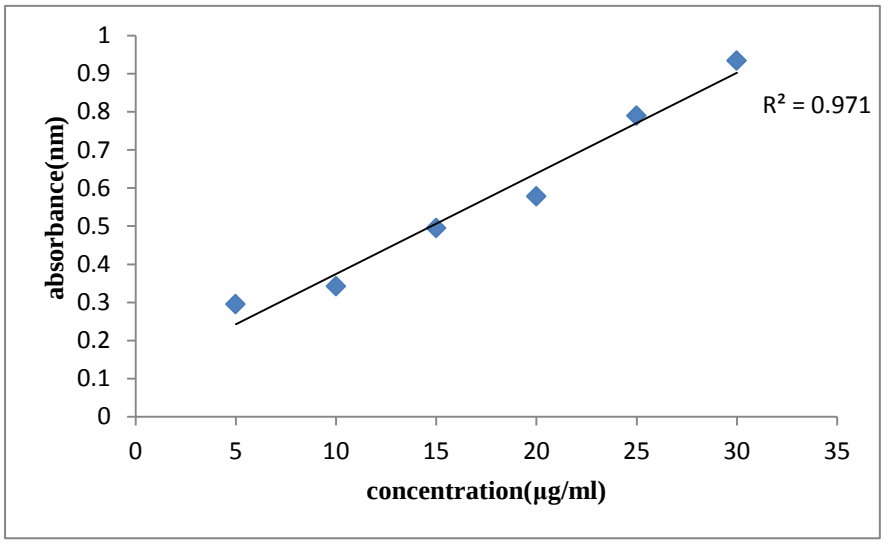


**Figure:3 Calibration curve of Enalapril Maleate in phosphate buffer(7.4)**

**Observed λ max of drug:** 232nm

**Observed Beer's range of drug:** 5-30ug/ml

**Line of equation and r² value** = (y = 0.026x + 0.110)

**R² value** = 0.971

Standard curve of Enalapril Maleate was prepared in methanol as well as phosphate buffer pH(7.4).Higher regression value conform the linearity of equation.

**Infrared spectroscopy:**

The FITR of drug Enalapril Maleate were obtained using FTIR spectrophotometer in the frequency range 4000cm-¹ to 400 cm-¹

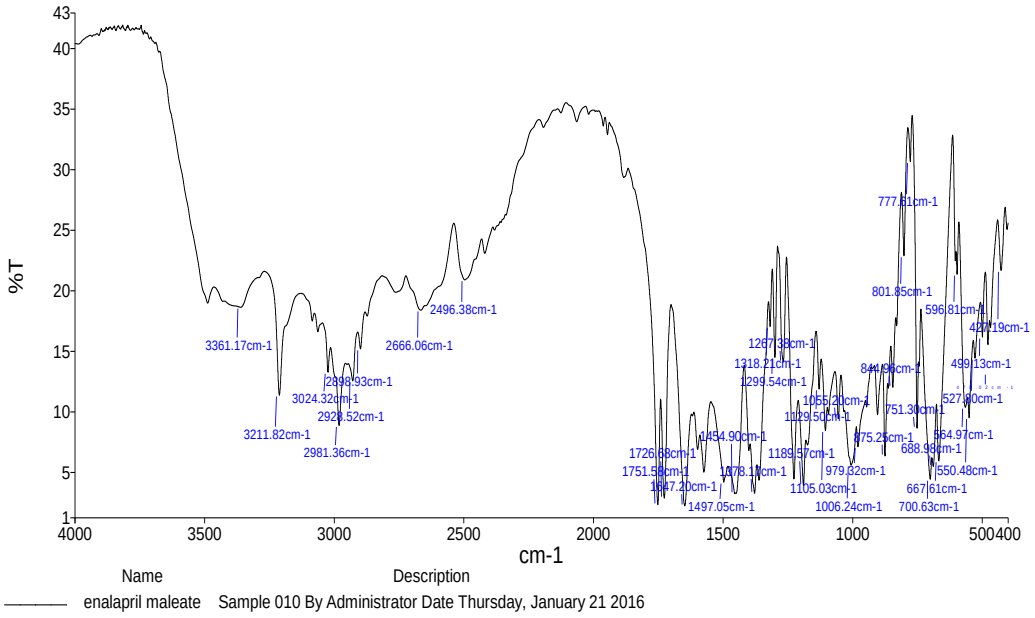


**Figure: 4 FTIR spectra of pure Drug Enalapril Maleate**

**Compatibility Studies:**

Compatibility studies of the pure drug of Enalapril maleate with the different polymers and disintegrate agent and it show in figure: 5

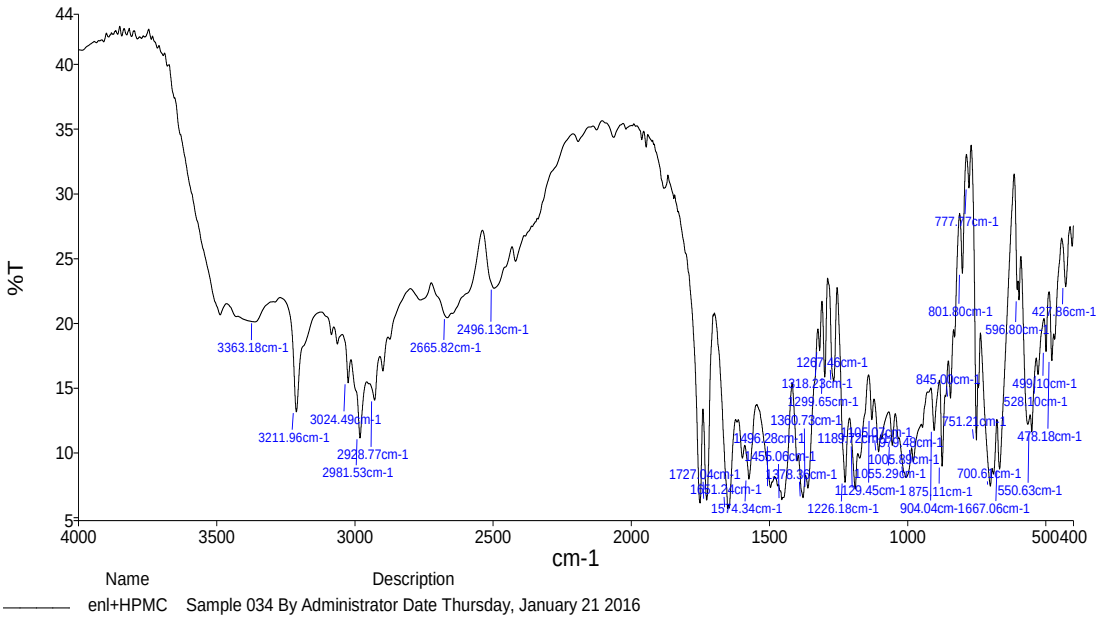


**Figure: 5 FTIR spectra of Drug + HPMCK100**

Compatibility study between drug and excipient was conducted by means of FTIR. The evaluation based on matching the pure drug with drug and excipient that revealed there is no significantly change finger print region which conform there is no incompatibility between the drug and excipients.

**Evaluation of Orodispersible film of Enalapril Maleate:**

**Physical appearance:**

The physical appearance was with visual inspection by mouth. The observation suggest that the film having smooth surface and they enough to see.

**Weight uniformity of films:**

**Table: 7 Weight uniformity different variation form of Orodispersible film**

| Formulation code | Average weight (mg) |
|---|---|
| F1 | 92.70±0.25 |
| F2 | 72.82±0.68 |
| F3 | 80.02±0.29 |
| F4 | 83.25±1.20 |
| F5 | 85.53±0.31 |
| F6 | 76.13±0.32 |

The range of weight uniformity of Orodispersible film lies between the range 92.70±0.25.

**Thickness of films:**

**Table: 8 Average thickness different variation form of Orodispersible film**

| Formulation code | Average thickness (mm) SD |
|---|---|
| F1 | 0.145±0.07 |
| F2 | 0.149±0.05 |
| F3 | 0.153±0.08 |
| F4 | 0.168±0.04 |
| F5 | 0.183±0.09 |
| F6 | 0.186±0.09 |

The range of thickness of Orodispersible film lies between the range 0.145±0.05 to 0.186±0.09.It was observed that as the polymeric is increased that thickness of film increased significantly.

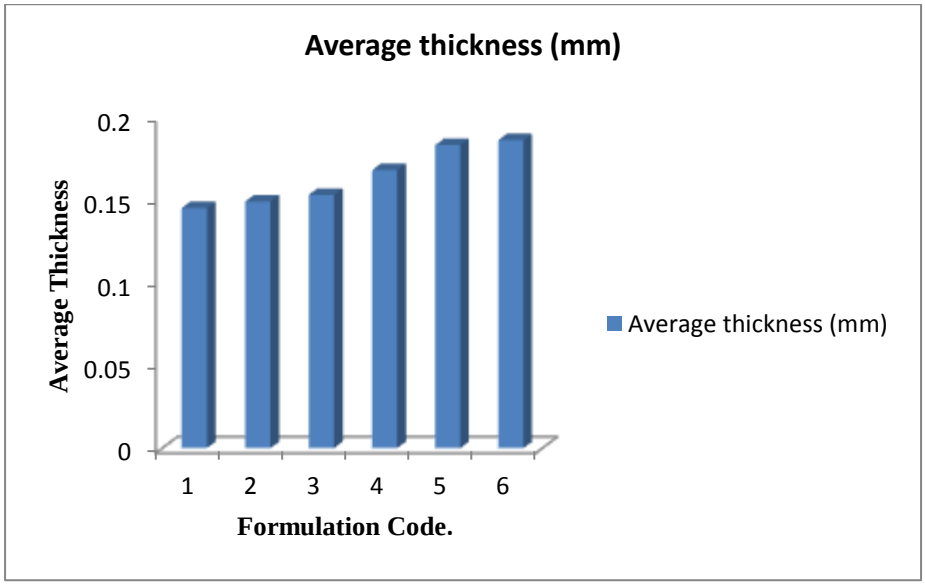


**Figure: 6 average thickness different variation of Orodispersible film**

**Table: 9 folding endurance variation different form of Orodispersible form**

| Formulation code | Folding Endurance (±SD) |
|---|---|
| F1 | 185±4.98 |
| F2 | 186±8.12 |
| F3 | 198±1.76 |
| F4 | 190±9.87 |
| F5 | 191±5.34 |
| F6 | 171±2.12 |

The folding endurance of Orodispersible film lie between the range185±4 to 171±2.It suggest that prepared film having a enough tensile strength which required with stand the pressure.

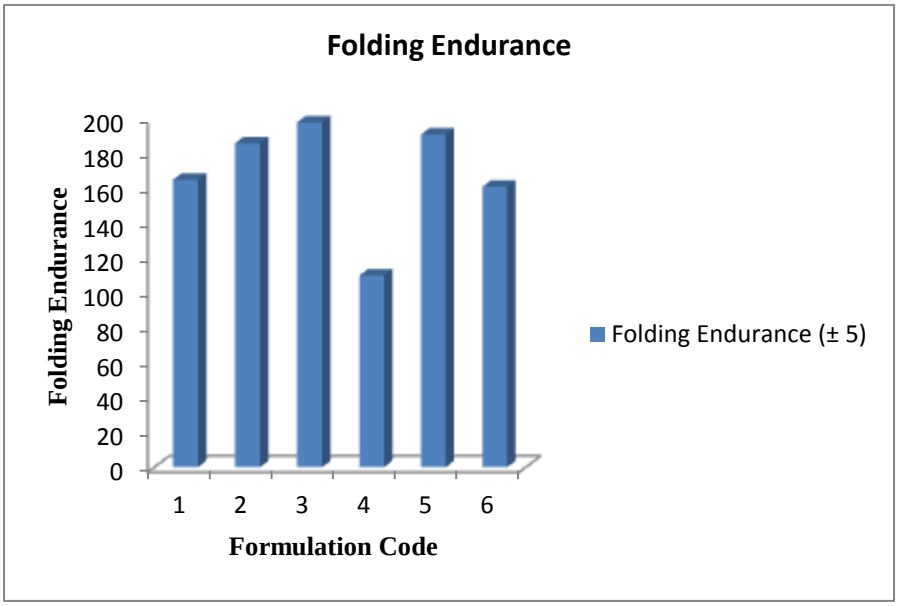


**Figure: 7 Folding endurance different variation form of Orodispersible film**

**In vitro disintegration time of films:**

**Table: 10 Average disintegration time variation form of Orodispersible film**

| Formulation code | Average disintegrating time (sec) ± SD, n=3 |
|---|---|
| F1 | 13±0.342 |
| F2 | 12±0.129 |
| F3 | 11±0.179 |
| F4 | 10±0.157 |
| F5 | 09±0.116 |
| F6 | 07±0.076 |

Prepared film disintegrate rapidly in salivary pH and release the drug at a faster rate. which helps in rapid absorption of drug in systemic circulation. It overcome the problem of conventional

dosage form i.e first pass metabolism effect bypassing it hence improve the bioavailability as well as patient compliance.

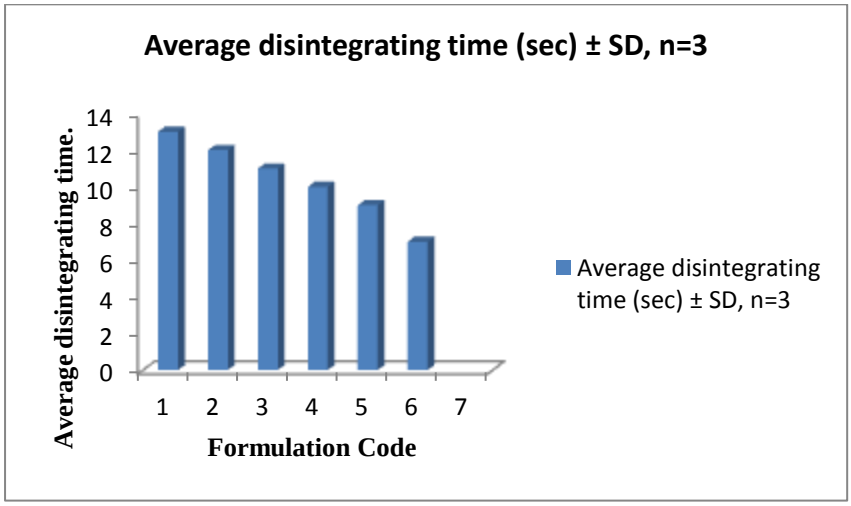


**Figure: 8 Average disintegration variation different form of Orodispersible film**

**Surface pH of films:**

**Table 11 Evaluation of Orodisperible film**

| Formulation code | Drug content mean SD | Average surface pH Mean SD |
|---|---|---|
| F1 | 86.21±0.56 | 6.17±0.1 |
| F2 | 83.76±0.32 | 6.29±0.1 |
| F3 | 81.65±.93 | 6.57±0.1 |
| F4 | 85.23±0.75 | 6.35±0.1 |
| F5 | 88.43±0.45 | 6.68±0.1 |
| F6 | 83.02±0.21 | 6.36±0.1 |

The surface pH of orodispersible films lies within the range6.17±0.to 6.36±0.This neutral pH range matched with salivary pH which is desirable for orodispersible films.

**Drug content uniformity:**

The drug content uniformity of orodispersible film lies within the range86.21±0.56 to83.02±0.21.Higher the value of drug content signified proper drug loading is prepared orodispersible film.

**In vitro diffusion study of films:**

**Table: 12 Percentage cumulative drug release**

| Time (mins) | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| 2 | 48.91 | 50.09 | 54.09 | 52.23 | 44.12 | 59.34 |
| 4 | 64.24 | 57.13 | 63.19 | 62.24 | 56.14 | 76.34 |
| 6 | 72.14 | 64.20 | 72.78 | 76.34 | 64.91 | 88.43 |
| 8 | 80.87 | 80.57 | 80.91 | 81.09 | 75.07 | 92.78 |
| 10 | 88.91 | 86.54 | 92.10 | 88.04 | 86.02 | 98.45 |
| 12 | 92.82 | 94.09 | 95.16 | 98.10 | 96.45 | - |

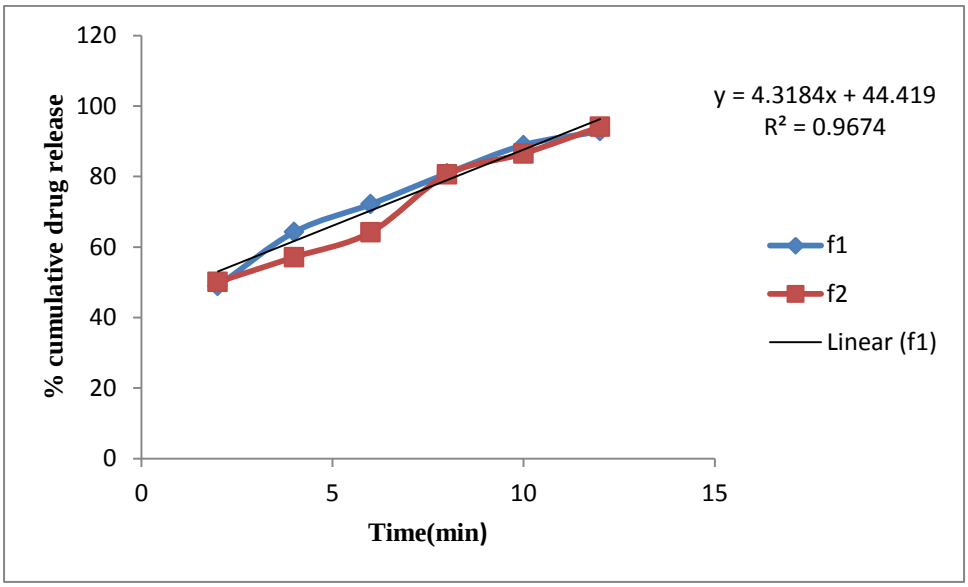


**Figure: 9 percentage cumulative drug release of F1-F2**

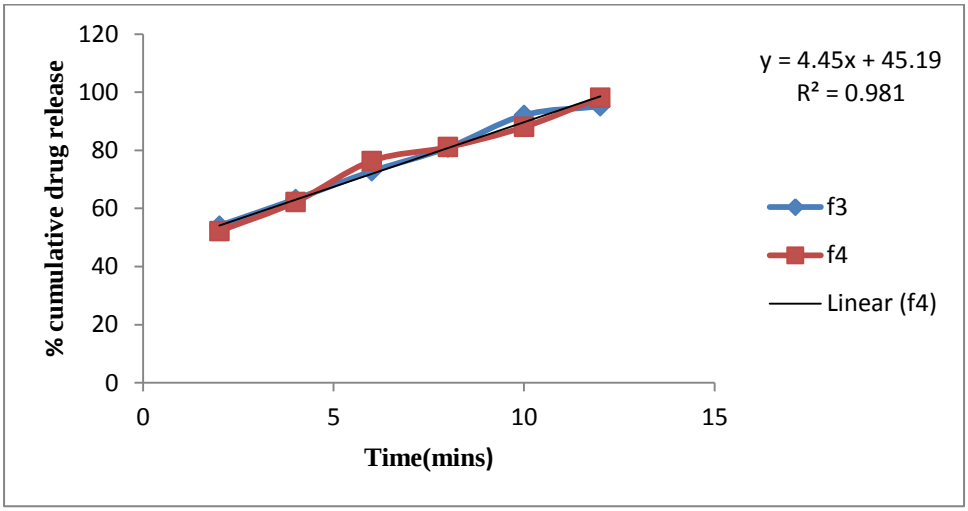


**Figure: 10 percentage cumulative drug release of F3-F4**

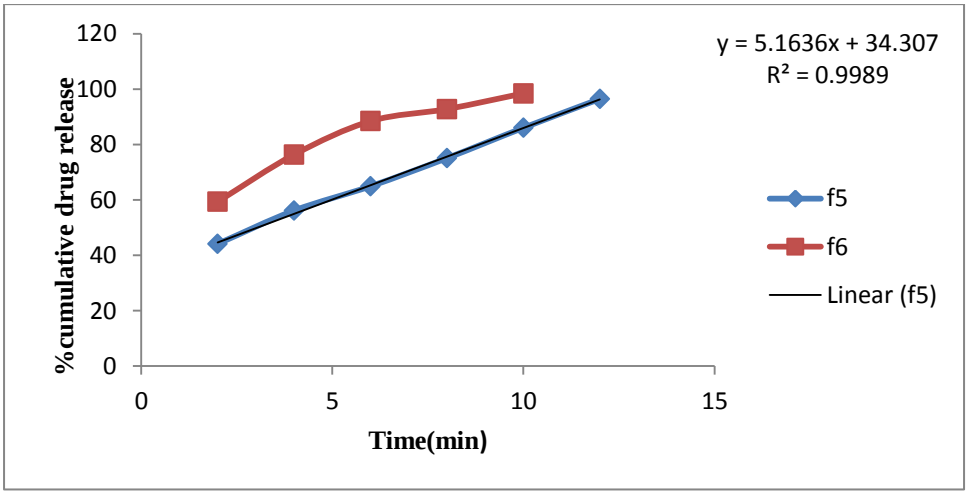


**Figure: 11 percentage cumulative drug release of F5-F6**

In vitro diffusion study of prepared Orodispersible film was conducted by using diffusion. All drugs loaded orodispersible film subjected for diffusion study using dialysis membrane molecular weight 70.All the film prepared release the drug with a predetermine rate result showed table Most of the formulation release more than 90% drug within 12 minutes of study period.

On the basis of all evaluation parameters formulation F6 selected as optimized formulation physical appearance, surface pH , thickness, folding endurance, weight uniformity, *In vitro* disintegration time and *Invitro* diffusion study.

## CONCLUSION

Orodispersible film are used those patient who have difficulty to swallow the conventional tablet paediatric and geriatric patient. In the present study Enalapril maleate was selected for the preparation of Orodispersible film to improve its bioavailability as well as therapeutic efficacy. Prepared film disintegrate rapidly in salivary pH and release the drug at a faster rate which helps in rapid absorption of drug in systemic circulation. It overcome the problem conventional dosage form i.e first pass metabolism effect by passing it hence improve the bioavailability as well as patient compliance.

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