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DESIGN AND DEVELOPMENT OF ORAL THIN FILM OF ANTIHISTAMINIC DRUG FEXOFENIDINE

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ABSTRACT

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects. The mucosa is relatively permeable with a rich blood supply. The oral transmucosal drug delivery bypasses first pass effect and avoids pre-systemic elimination in the GI tract. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. A few drugs have been successfully administered via buccal route. The buccal region offers an attractive route of administration for systemic drug delivery. Fexofenadine, H1 antagonist, is a potent antihistamine. Buccal absorption studies of fexofenadine having partition coefficient less than 2 and have lipophilicity in nature, which offers advantages of buccal route over oral route. By observing the above points, it is inferred that fexofenadine has a need to formulate into buccal patches and the drug is suitable for it. Bioadhesive formulations have a wide scope of applications, for both systemic and local effect for management of diseases. Fexofenadine drug will be use for developing a dosage form for a very quick onset of action, which is beneficial in managing severe conditions of allergies, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water. In the present study, Fexofenadine HCl was used as a model drug candidate and nine fast-dissolving films formulations containing different polymer concentrations were prepared. Fast-dissolving films of Fexofenadine HCl were prepared by the solvent casting method on glass molds, using HPMC E15 and Xanthan gum, Sodium starch glycolate as disintegrating agent, glycerin as plasticizer and aspartame as sweetener and distilled water as a solvent. The effect of the nature of polymers was studied by preparing various formulations of oral dispersible films. The various formulations containing a combination of polymers, release was found to be in the following order: OTF7 > OTF8 > OTF9 and formulations OTF7, OTF1, and OTF4

were found to be the best formulations in terms of drug release. The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism.

KEYWORDS: Oral Thin Film, Fexofenidine, Antihistaminic Drug, HPMC E15 and Xanthan gum, Sodium starch glycolate.

INTRODUCTION

Oral thin films have been described as an alternative approach to conventional dosage forms. They are a versatile platform that provides fast, local, or systemic effects. Oral dissolving films or strips can be defined as follows: "These are drug delivery systems that they are quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue". The sublingual mucosa has high membrane permeability due to its thin membrane structure and high vascularization. OTFs drug delivery system works across the buccal or sublingual mucosa has gained great attention in recent years. Mechanical strength, related properties, mucoadhesive properties, and drug release rate can also be adjusted by using combinations of polymers, which are the basic structure of thin films, in different proportions. The pharmaceutical industry is affected by the attractive properties of OTFs, and as a result, they are developing thin-film technologies and are currently patenting these formulations.[1] According to the European Medicines Agency, a thin film that easily dissolves in the oral mucosa is often referred to as an orodispers film. Rapidly dissolving oral films are usually postage stamp-sized OTFs that dissolve/disperse in the oral cavity within 1 min of contact with saliva, resulting in quick absorption and immediate bioavailability of drugs.1,10 These innovative dosage forms are taken orally but do not require water for ingestion and absorption as do conventional drugs. OTFs should not be confused with buccal films that are designed to remain on the cheek mucosa for a long time.[2] Fast-dissolving oral films have many advantages over other solid dosage forms, such as flexibility and increased efficacy of the API. Also, oral films have dissolution and disintegration with very little saliva fluid in less than one minute compared with ODTs.[3]

The oral mucosal epithelium is a 40-50 cell layer called mucus that is made up of carbohydrates and proteins. The mucosal thickness at the mouth base, tongue, and gums ranges from 100 to 200 µm. The lipophilic structure of the cell membranes facilitates the passage of molecules with a high partition coefficient through the cells, while the polar nature of the intercellular space facilitates the penetration of more hydrophilic molecules. The hydrophobic, hydrophilic, or amphiphilic nature of the drug molecule determines its absorption.[4-5] The novel drug delivery system needs to enhance the safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. Thin films have identified as an alternative approach to conventional dosage forms. The thin films are considered to be convenient to swallow, self-administrable, and fast dissolving dosage form, all of which make it as a versatile platform for drug delivery. This delivery system has used for both systemic and local action via several routes such as oral, buccal, sublingual, ocular, and transdermal routes. The new approach is the formulation of mouth dissolving films. A significant drawback of a mouth dissolving films is its weak mechanical strength, which will be addressed. The main objective of the present work is to develop the oral fast dissolving films of Fexofenadine with the purpose of developing a dosage form for a very quick onset of action, which is beneficial in managing severe conditions of allergies, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water.

MATERIAL AND METHODS

Analytical study: The UV spectrophotometric method will used to determine λmax of drug. Calibration curve was prepared with spectrophotometrically based on UV absorption at λmax in PBS pH 6.8 for the quantitative estimation of the drug. Calibration curve was prepared spectrophotometrically based on UV absorption at λmax 224 nm in PBS pH 6.8 for the quantitative estimation of the drug.

Preformulation: The drug powder was determined for specific fundamental physical and chemical properties. This first learning phase is known as preformulation. Before the formulation of drug substances into a dosage form, it should be chemically and physically characterized. The preformulation testing is the first step in the development of dosage forms of a drug substance. These investigations may confirm that there are no significant barriers to dosage form development. Fexofenadine Hydrochloride was obtained as a gift sample from Sanofi pharm. Pvt. Ltd., Ankleshwar India. A various parameters was investigated i.e.

physical appearance (Colour, odour, taste and appearance), melting point, solubility studies, partition co-efficient, FTIR of drug etc.

Formulation of fast dissolving films: In the present study fast dissolving films of Fexofenadine will prepare by solvent casting technique. Flat, square-shaped, aluminum foil coated glass molds a will use for casting the films.

Preparation of casting solutions: Casting solutions was prepared by using selected polymers. The required weighed quantities of polymers HPMC E15 and Xanthan gum (XG) were separately kept for swelling overnight in 5 ml distilled water and dissolved. The drug and aspartame as sweetener were added to the polymeric solution directly as given in **Table 1** along with glycerol as a plasticizer and mixed thoroughly to form a homogenous mixture on magnetic stirrer. Finally polymer solution was added to Xanthan gum solution and volume made up to 10 ml with distilled water. The entrapped air bubbles were removed by applying sonication process.

Preparation of oral thin films: The casting solution (10 ml) was poured into glass molds and dried at 40°C in a vacuum oven for 24 h for solvent evaporation. The films were removed by peeling and cut into a square dimension of 2.0 cm × 2.0 cm (4.0 cm^2). It was dried for 24 hours at room temperature. The thin film was clear and bubble free and removed from the petri dish very carefully, where fast-dissolving films were prepared with different polymers and ratios by maintaining the concentration of the plasticizer and sweetener constant.

Table 1: Formulation casting solution of oral thin films.

F. Code	Otf1	Otf2	Otf3	Otf4	Otf5	Otf6	Otf7	Otf8	Otf9
Fexofenadine hcl (mg)	30	30	30	30	30	30	30	30	30
Hpmc e15 (mg)	50	100	150	-	-	-	25	50	75
Xanthan gum (mg)	-	-	-	50	100	150	25	50	75
Sodium starch glycolate (mg)	10	10	10	10	10	10	10	10	10
Citric acid (mg)	5	5	5	5	5	5	5	5	5
Aspartame (mg)	20	20	20	20	20	20	20	20	20
Glycerol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Distilled water qs (ml)	10	10	10	10	10	10	10	10	10

Evaluation of oral thin films

Weight variation: Mouths dissolving oral films will weigh on digital balance and average weight will determine for each film. It is desirable that films should have nearly constant weight. It is useful to make sure that a film contains the required amount of excipients and drug.

Thickness of films: By using micrometer screw gauge the thickness of the film was measured at 5 totally different places; an average of 3 values was calculated by using screw gauge.

Folding endurance: The folding endurance was expressed as the number of folds (number of times the film is folded at the same place) requires to break the specimen or to develop visible cracks. This also gives an indication of brittleness of the film. A strip of 2.5 cm × 2.5 cm was subject to folding endurance by folding the film at the same place repeatedly several times until a visible crack was observed.

Drug content uniformity: The prepared oral thin films were dissolved in 10ml methanol and 40 ml PBS pH 6.8 mixtures. The mixture was filtered through whatman filter paper. After suitable dilutions, the concentration of the drug was determine by uv method at 224 nm.

Surface pH: The film was placed in a petri dish and moistened with 0.5 ml of distilled water and keep for 30 s. The pH of mixture was noticed by attaching the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min.

Tensile strength: The tensile strength is determined by the apparatus which has two clamps, the upper one is fixed and the lower is movable. The film sample (0.5×3 cm) is clamped between the two clamps. The force at tearing and elongation is determined. The percent elongation (%E) is calculated using the following equation

$$\% E = \{(Ls-Lo) / Lo\} \times 100$$

Where, Lo = Original length

Ls = Length of the film after elongation

The modulus of elasticity of films was calculated from the equation

$$F/A = EM \{(Ls-Lo) / Lo\}$$

Where F = Breaking load (N),

A = Cross- sectional area of the film

EM = Modulus of elasticity

Water vapor transmission rate: The water vapor transmission rate study, vials of equal diameter can be used as transmission cells. Cells are washed thoroughly and dried in an oven. One gm of calcium chloride is taken in the cell and the polymeric films (two cm2 area) are fixed over the brim with the help of an adhesive. The cells are accurately weighed and the initial weight is recorded. Films are then kept in a closed desiccator containing saturated solution of potassium chloride (80-90 % RH). The cells are taken out and weighed after 18, 36, 54 and 72 hours. From increase in weights, the amount of water vapor transmitted and the rate at which water vapor transmitted can be calculated by using the following formula:

Water vapor transmission rate = WL/S

Where, W = Water vapor transmitted in mg

L = Thickness of the film in mm,

S = Exposed surface area in cm2

In vitro disintegration time: In vitro disintegration time is determined visually in a glass dish with 10 ml distilled water with swirling every 10 seconds. The disintegration time is the time when the film starts to break or disintegrate.

In vitro diffusion study: In vitro diffusion study was carried out by using Franz-diffusion cell apparatus with PBS pH 6.8 as a dissolution medium. The temperature was maintained at 37±0.5°C with 50 rotations per minute. 1 ml of aliquots was withdrawn at different time intervals and same amount of fresh dissolution medium was added to maintain sink condition. The aliquots were analyzed for drug content at λ max 224 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported.

RESULT AND DISCUSSION

Identification studies showed that the drug supplied by Pharmaceutical companies matched with the reported official standards. The absorption maximum of FEX in PBS pH 6.8 was found to be 224 nm **(Figure 1)**. λmax found to be very near the λmax reported in reference books. The data of calibration curves were linearly regressed, and the equation of the straight line for the standard curve as well as correlation coefficients was determined. The correlation coefficient for standard curves was found to be very near to one, which indicates an excellent co-linear correlation between concentration 5-50 µg/ml and absorbance **(Figure 2)**. Hence, drugs are following the Beer-Lambert Law in the range of 5-50 µg/ml. The melting point of the drug was found to be similar to the published in reference books. The solubility profile of FEX showed its hydrophobic nature and was insoluble in chloroform and water but freely soluble in methanol. The partition coefficient was found according to their solubility profile

that was indicating the hydrophobic nature of the drug. FEX was studied for compatibility with excipients in different environmental conditions. No drug interaction was observed during the time period of storage, showing their compatibility with all ingredients **(Figure 3 – 4)**. Oral thin films are ideal for many groups of patients including geriatrics, pediatrics, and psychiatrics as well as for those people who have difficulty in swallowing. Many drugs can be formulated in the form of fast dissolving films to provide the advantages of mouth dissolving drug delivery system. In the present study, Fexofenadine HCl was used as a model drug candidate and nine fast-dissolving films formulations containing different polymer concentrations were prepared. Fast-dissolving films of Fexofenadine HCl were prepared by the solvent casting method on glass molds, using HPMC E15 and Xanthan gum, Sodium starch glycolate as disintegrating agent, glycerin as plasticizer and aspartame as sweetener and distilled water as a solvent. The effect of the nature of polymers was studied by preparing various formulations of oral dispersible films. The characterization and evaluation of prepared fast dissolving films were done for various parameters like thickness of the films, drug content uniformity, folding endurance of the films, disintegration time, In-vitro dissolution and stability studies. The Effect of polymer concentration was studied with different formulations (OTF1, OTF2, OTF3, OTF4, OTF5, OTF6, OTF7, OTF8, and OTF9) prepared using HPMC E15, Xanthan gum and a combination of HPMC E15 and Xanthan gum in different concentrations. The weight variations in the films were found to be uniform in all the prepared batches. The film weight was found to be in the range of 35mg to 40mg which ensured uniform distribution of drug in all the formulations (Table 7.1). The thickness of OTF1 to OTF9 was found to be 98-110 µm. From the results obtained for all formulations it can be concluded that the uniformity was achieved during the formulation (Table 7.2). The prepared oral films were studied for folding endurance by number of times, the film could be folded at the same place without breaking gave the value of folding endurance. The mean values of three readings were calculated. The folding endurance value of OTF1 to OTF9 was found to be 48-110. From the results obtained from the above formulations, all formulations showed folding endurance value complies with in the limit 100- 150 except OTF3, OTF5, OTF6 and OTF9 fail to complies with the limit as per previous value (Table 7.3). Percentage of drug content for different formulations was calculated and the results were shown in the Table 6.6. Percentage of drug content of OTF7 was found to be 99.80% and was considered as best formulation compared to the other formulation. The formulations showed percentage drug content 86.12-99.80%. From the results obtained from the above formulations. The pH of surface of oral films was noted after bringing the electrode of the pH meter in contact with

the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken. Surface pH of all films was found to be within the limits 6-7 (Table 7.5). The tensile strength of oral thin films were be in the range of 1.04 – 4.29 (Mpa) and water vapor transmission of oral thin films were be in the range of 8.8 – 29.2. The oral films were evaluated by in vitro disintegration time test for all prepared formulations was carried out using disintegration test apparatus. OTF1-OTF9 showed a disintegration time of 8 to 26 sec. From the results obtained, by increasing the concentration of polymer, disintegration time was increased. The disintegration time of OTF7 was found to be 8 seconds which took less time as compared to all other formulations (OTF1- OTF9). From the results obtained from the above formulations, other than OTF5, OTF6 and OTF9, disintegration time of all films was found to be within the limit as 5-30 seconds as per specification (USP 2007). Based on the disintegration time alone, OTF7 can be lead to develop as fast dissolving film (Table 7.6 and Fig 7.1). The in vitro drug release was observed that in formulations containing a single polymer, the drug release was found to be faster and films formed of HPMC E15 resulted in a fastest release of drug. Further, as the concentration of the polymer increased, the drug release was found to be decreased due to the increase in the time required for wetting and dissolving the drug molecules present in the polymer matrices. The drug release was found to be in the following order: OTF1 > OTF2 > OTF4 > OTF3 > OTF5 > OTF6. For the group of formulations containing a combination of polymers, the drug release was found to be in the following order: OTF7 > OTF8 > OTF9 [Figure 1]. Among the nine formulations (OTF1 to OTF9) prepared, formulations OTF7, OTF1, and OTF4 were found to be the best formulations in terms of drug release (Table 7.13 – 7.22 and Figure 7.5 – 7.8). The results of the release kinetics study showed that all the formulations obeyed first order drug release profile more closely, i.e., the release rate depended upon the initial concentration of drug (Table 7.23 – 7.24). The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism.

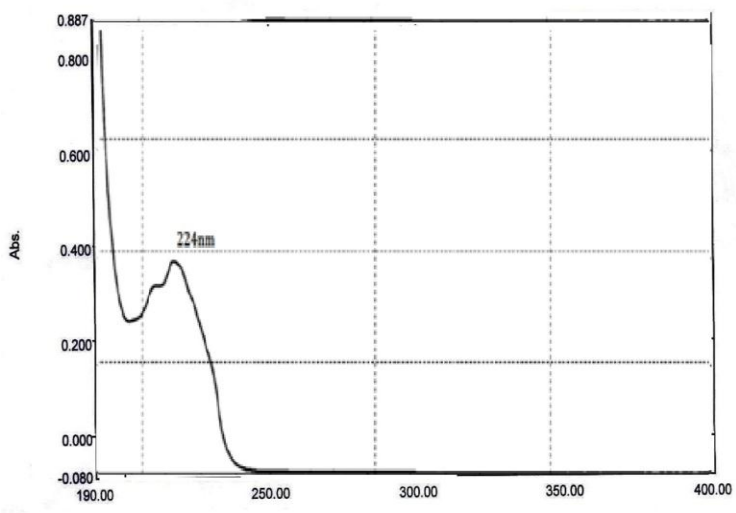

Figure 1: UV-Visible Scan of drug.

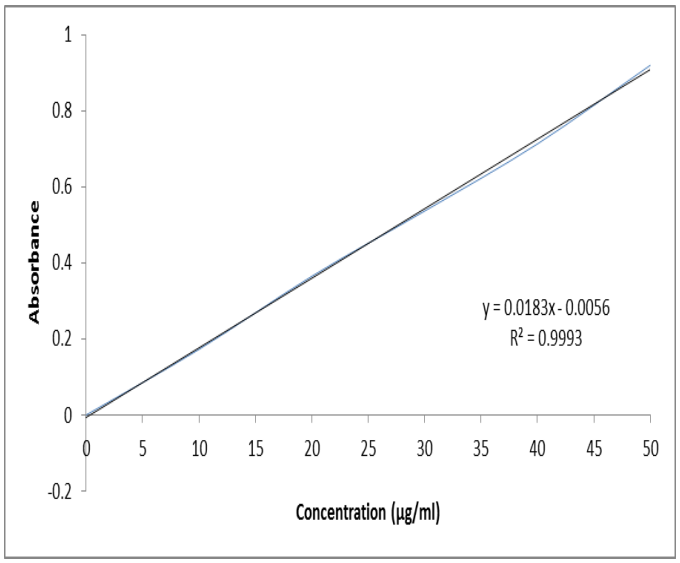

Figure 2: Calibration curve of drug in pH 6.8 phosphate buffer.

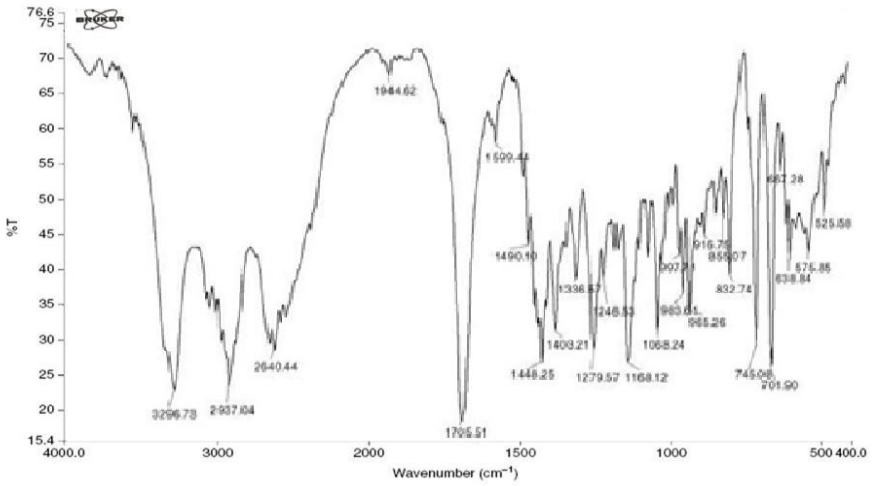

Figure 3: FTIR of drug.

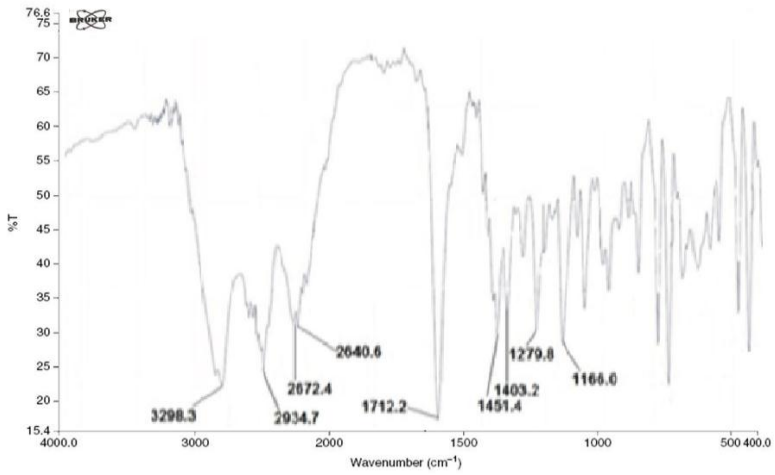

Figure 4: FTIR of Drug and Excipient.

Table 2: Weight variation of oral thin films.

Formulation Code	Weight of film (mg)	Thickness of film (µm)	Folding endurance	Drug content (%)	Surface pH	Tensile strength (Mpa)	Water vapor transmission rate
OTF1	37.24±1.1	98.1±1.1	98	86.11	6.28	1.04	8.8
OTF2	39.22±1.2	100.2±1.2	99	90.41	6.34	1.37	12.1
OTF3	40.8±2.1	102.1±1.6	93	93.12	6.25	1.12	22.2
OTF4	38.25±1.1	101.3±1.4	105	94.17	6.51	3.21	21.8
OTF5	38.90±1.2	105.2±1.2	92	91.17	6.44	1.03	28.4
OTF6	40.01±1.1	109.2±1.3	94	93.21	6.67	1.29	29.2
OTF7	37.16±1.7	99.3±1.2	112	99.19	6.71	4.29	11.2
OTF8	38.13±1.8	106.3±1.1	101	97.22	6.72	3.21	19.3
OTF9	41.15±1.2	110.2±1.1	98	99.51	6.81	4.19	23.1

Table 3: In-vitro drug release study of oral thin films (OTF1 – OTF9).

F. Code	Cumulative percent drug release								
Time (min)	OTF1	OTF2	OTF3	OTF4	OTF5	OTF6	OTF7	OTF8	OTF9
0	0	0	0	0	0	0	0	0	0
2	42± 1.1	36± 0.9	32± 0.8	33± 1.0	31± 1.2	30± 1.2	49± 0.8	41± 1.3	38± 1.2
4	69± 1.7	66± 2.5	62± 1.6	65± 1.3	58± 1.6	55± 2.5	71± 2.5	69± 2.1	67± 2.2
6	81± 1.8	78± 2.9	76± 2.1	77± 1.8	76± 2.2	75± 3.1	88± 3.7	82± 3.1	78± 3.4
8	94± 2.2	91± 3.1	90± 2.8	92± 2.7	89± 2.9	89± 3.4	99± 2.8	98± 3.4	98± 3.7
10	98± 3.4	98± 3.5	97± 3.6	98± 2.6	97± 3.1	96± 2.8	99± 3.1	98± 2.8	98± 3.5
12	99± 3.7	98± 2.6	97± 2.5	98± 3.5	97± 3.2	96± 3.0	99± 3.4	98± 3.2	98± 2.8

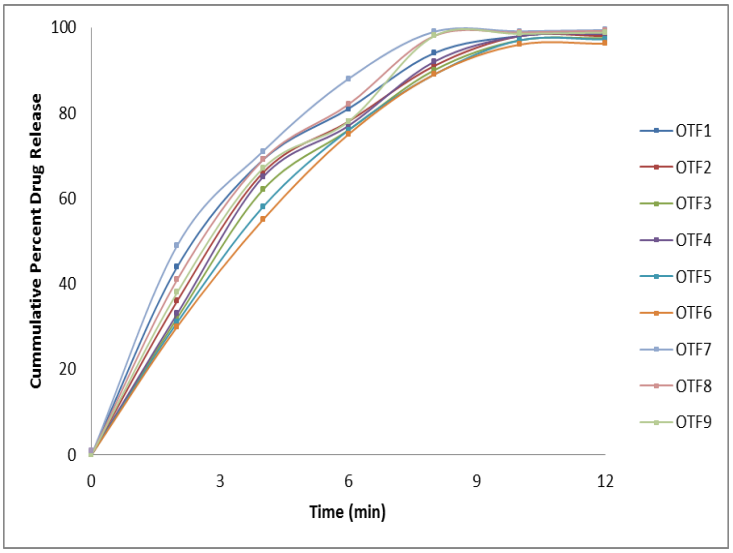

Figure 5: Zero-order plots of oral thin films (OTF1 – OTF9).

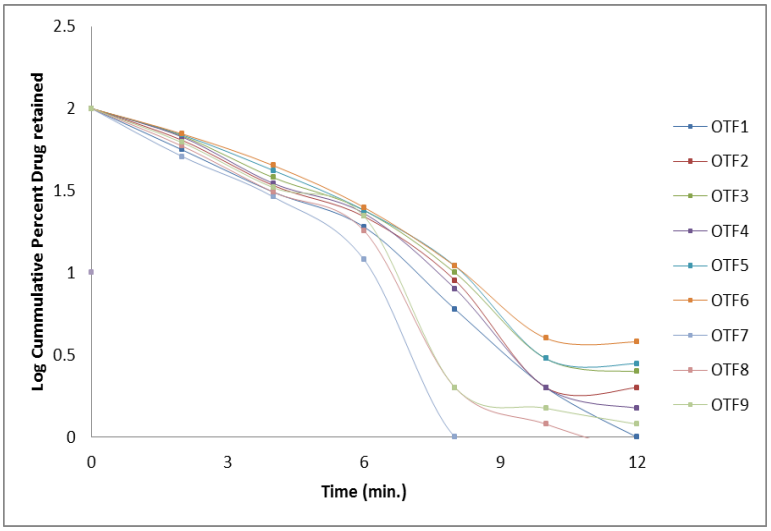

Figure 6: First-order plots of oral thin films (OTF1 – OTF9).

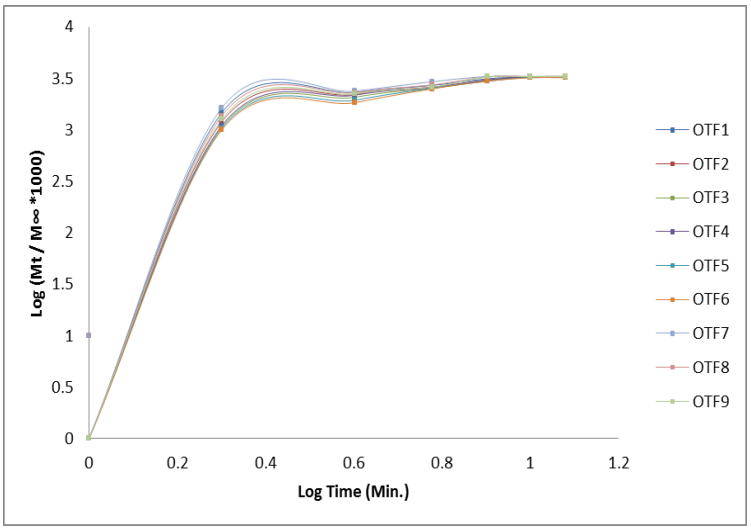

Figure 7: Korsmeyer's-Peppas plot of oral thin films (OTF1 – OTF9).

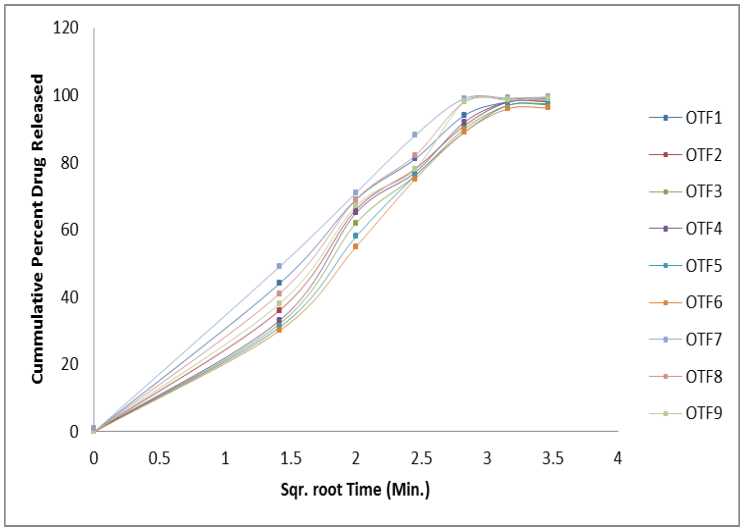

Figure 8: Higuchi kinetic plot of oral thin films (OTF1 – OTF9).

SUMMARY AND CONCLUSION

Oral thin dissolving films or strips is based on as quickly releasing the drug by dissolving or adhering in the mucosa with saliva within a few seconds due to it contains water-soluble polymers when it placed in the mouth cavity or on the tongue. Ideal thin films should possess the desired properties of a drug delivery system, such as a suitable drug loading capacity, rapid dispersion/dissolution, or prolonged application and reasonable formulation stability. Bioadhesive formulations have a wide scope of applications, for both systemic and local effects. The mucosa is relatively permeable with a rich blood supply. Fexofenadine is rapidly absorbed through oral administration and able to increase oral bioavailability by using hydroxyl propyl methyl cellulose, thickening agent as natural polysachride material with using superdisintegrating agents. Fexofenadine drug will be use for developing a dosage form for a very quick onset of action, which is beneficial in managing severe conditions of allergies, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water. In the present study, Fexofenadine HCl was used as a model drug candidate and nine fast-dissolving films formulations containing different polymer concentrations were prepared. The effect of the nature of polymers was studied by preparing various formulations of oral dispersible films. The various formulations containing a combination of polymers, release was found to be in the following order: OTF7 > OTF8 > OTF9 and formulations OTF7, OTF1, and OTF4 were found to be the best formulations in terms of drug release. The slope values of the Korsmeyer-Peppas plot showed that the mechanism was non-fickian or supercase II transport mechanism. Thus the oral thin films of Fexofenadine HCl prepared by the solvent casting

method on glass molds, using HPMC E15 and Xanthan gum, Sodium starch glycolate as disintegrating agent, glycerin as plasticizer and aspartame as sweetener and distilled water as a solvent was valuable dosage form for the future aspects in the field of pharmaceutical sciences.

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