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Original Article

Formulation and Evaluation of Mouth Dissolving Films Containing Tizanidine Hydrochloride

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ABSTRACT

The formulation of a mouth dissolving film for Tizanidine, a muscle relaxant, BCS Class II drug has been an interesting topic of research compared to other oral dosage forms. Oral film of this drug is very essential to overcome the lack of compliance and also to protect the drug degradation from hepatic metabolism which can result in undesired pharmacological action. In the present study oral film was prepared and evaluated for all the physical parameters and *in vitro* drug dissolution studies. Tizanidine is a short-acting muscle relaxant used to treat spasticity and acts by temporarily relaxing muscle tone. It was prepared by using single Buffer System, thus avoiding the patent issues. Formulations were prepared by using different polymers like Hydroxy Propyl Methyl Cellulose and Polyvinyl alcohol. Propylene glycol is used as plasticizer and Citric acid is used as a saliva stimulating agent. Drug-excipients compatibility studies were conducted by FT-IR studies. *In vitro* dissolution was carried out by using USP Apparatus Type-II at 50 rpm, using 6.8 pH phosphate buffers as dissolution medium recommended by office of generic drugs (OGD). The effect of polymers on the disintegration time and dissolution was clearly studied in the present research work. Based on disintegration time and drug release, formulation F1 has less disintegration time compared to formulation F2 and formulation F2 has still less disintegration time than formulation F6, which having HPMC E5 at 30% w/v . Formulation containing 500 mg of HPMC E15 film exhibited required tensile strength, folding endurance and percentage elongation. HPMC E15 at 10% w/v concentration level showed highest release of more than 99% of the drug in 3min. So ODF formulated with HPMC E15 at 10 % w/v is best formulation among all formulation batches.

Keywords: Tizanidine, mouth dissolving fiolm, BCS Class II, muscle relaxant, FT-IR

1. INTRODUCTION

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The oral route of drug administration is the most important method of administration for systemic effect; despite of tremendous advancement in drug delivery system due to its ease of administration, pain avoidance and various advantages over other routes is the reason that the oral route achieved such popularity. But the most evident drawback of oral dosage forms like tablets and capsules is difficulty in swallowing which leads to patient's incompliance particularly in case of pediatric and geriatric, bedridden, nauseous patients. A renewed interest has been addressed to oral solid dosage forms designed for prompt availability of therapeutic dose i.e. Mouth dissolve products (tablets and films) which shows greater patient acceptability and convenience. Fast-dissolving oral delivery systems are solid dosage forms, which disintegrate or dissolve within minutes when placed in the mouth without drinking of water or chewing. After disintegrating in mouth it will enhance the clinical effect of drug through pre-gastric absorption from mouth pharynx and esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form. More recently, it is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements [1]. FDFs are also applicable when local action in the mouth is desirable such as local anesthetic for toothaches, oral ulcers, cold sores or teething. Fast dissolving films are prepared using hydrophilic polymers that rapidly dissolve/disintegrate in the mouth within few seconds without water and eliminate the fear of chocking as an alternative to fast dissolving tablets. Basically the fast dissolving film can be considered as an ultra thin strip of postage stamp size with an active pharmaceutical ingredient and other excipients. Most fast dissolving films are having taste masked active ingredients. These masked active ingredients are swallowed by the saliva of patients along with the soluble and insoluble excipients. These films are to be placed on the tongue and produce immediate systemic effect by enabling the drug absorbed directly through mucosal lining of the mouth beneath the tongue or inside buccal cavity. The drug absorbed from stomach goes to mesenteric circulation which connects to stomach via portal vein Thus, absorption through oral cavity avoids first-pass metabolism [2]. The film must dissolve quickly allowing the API to be absorbed quickly. It's designed to dissolve in small quantity of saliva; the drug can enter the blood stream enterically, buccally or sublingually. One or a combination of the processes can be used to manufacture the Mouth dissolving films such as solvent casting, Hot-melt extrusion, Semisolid casting, Solid dispersion extrusion and rolling method. Tizanidine is a centrally acting α2-agonist that exerts its antispastic effect by causing presynaptic inhibition of motor neuron hyperactivity. Tizanidine is a potent, central-acting myotonolytic agent that principally affects spinal polysynaptic reflexes. This action arises from agonistic activity of the compound at noradrenergic alpha 2 receptors, resulting in both direct impairment of excitatory amino acid release from spinal interneurons. Similar alpha 2-receptor-mediated inhibition of interneuronal activity appears to underlie the additional antinociceptive and anticonvulsant activity of tizanidine reported in several species and test paradigms. Despite its structural and biochemical similarity to Clonidine, the cardiovascular properties of tizanidine are mild and transitory in relation to its activity as a muscle relaxant. The effects of tizanidine are greatest on polysynaptic pathways. The overall effect of these actions is thought to reduce facilitation of spinal motor neurons [3, 4, 5 & 6]. Tizanidine hydrochloride is a short acting drug for the management of increased muscle tone with spasticity.

The oral bioavailability of tizanidine is about 21% mainly due to extensive first-pass metabolism and its mean elimination half-life is approximately 3h.[7]

2. MATERIALS AND METHODS

Tizanidine Hydrochloride was obtained as gift sample from SYMED Lab Ltd., Hyderabad. HPMC and Polyvinyl alcohol were gift sample from Drugs India, Hyderabad. Propylene glycol was obtained as gift sample from Karnataka fine chem. Industries, Bangalore. Citric acid was obtained from Universal laboratories Pvt. Ltd., Mumbai. All other reagents and chemicals used were of analytical reagent grade.

2.1 Pre Formulation Studies[9]

Solubility

The solubility of a drug may be expressed in number of ways. The U.S. pharmacopoeia and national formularies list the solubility of the drugs as the number of ml of solvent in which 1 gm of solute will dissolve. One gm of Tizanidine was dispersed in different solvent and solubility was determined. The solubility of the drug was determined in water, ethanol, methanol, chloroform and acetone.

Determination of pH

pH of the drug solution was tested by using previously calibrated pH meter. 4 % w/v solution of Tizanidine was prepared using methanol as a solvent and sonicated for 30 minutes. The glass electrode of the pH meter was immersed in the prepared solution and the pH of the solution was recorded.

Moisture content

The moisture content was determined using sartorious moisture determining apparatus. 5gm of the Tizanidine was transferred to an aluminum plate and the moisture content was determined at 105^0C

Melting point

Melting point of the drug was determined by using Scientek digital melting point apparatus.

Drug –Polymer compatibility studies by FT-IR

Drug polymer compatibility studies were performed by FT-IR (Fourier transform infrared spectroscopy). In order to confirm that the entrapment of drug within the polymeric systems involve only the physical process and no interaction between drug and polymer. FTIR absorption spectra of pure drug and the combination of drug and polymers were shows no significant interaction between drug and polymers.

Preparation of Calibration Curve

A standard graph of pure drug in suitable medium was prepared by plotting the concentration on X-axis and absorbance on Y-axis. An accurately weighed 100 mg of Tizanidine was dissolved in pH 6.8 phosphate buffer as per I.P and make up the volume up to 100 ml in a volumetric flask, (Stock Solution: I, This stock solution concentration is 1mg/ml or 1000 µg/ml). From this stock solution 5 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 50µg/ml). Then the aliquots were prepared, whose concentration ranging from 0 to 60 µg/ml and the absorbance were measured at 228nm by using UV Spectrophotometer Labomed, (Model No: 2602) against the reagent blank.

2.2 Formulation of Oral Dissolving Films of Tizanidine Hydrochloride [8]

Tizanidine Hydrochloride Oral dissolving films were prepared using different water soluble polymers like HPMC E-series (E5, E15) and polyvinyl alcohol by solvent casting method. Different formulations of Tizanidine Hydrochloride ODFs were prepared using the polymers in different concentrations keeping all other ingredients constants. The calculated quantities of polymers were dispersed in water and form aqueous solution. Allow it for swelling for 12 hrs. An accurately weighed amount of TZH was incorporated in polymeric solutions after levigation with propylene glycol which served the purpose of plasticizer as well as penetration enhancer. Sweeteners, flavors and other

ingredients were also added. The solution was mixed occasionally to get semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles. Then this were casted on surface having a 8×24cm a glass plate covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were carefully separated from the glass plate, checked for imperfection and cut to the required size to deliver the equivalent dose ($2\times2cm^2$) per strip. Film samples with air bubbles, cuts, or imperfection were excluded from the study. Then the formulations were stored in desiccators until further use. They are assigned with formulation codes shown in Table 1.

2.3 Evaluation of Tizanidine Hydrochloride ODFs [9, 10]

Thickness

This is essential to ascertain uniformity in the thickness of the film as this is directly related to the accuracy of dose in the strip. The thickness of each film was measured by using a digital Vernier caliper at six different positions of the film and the average thickness in mm was calculated.

Dryness/Tack test

About eight stages of film drying process have been identified and they are set-to-touch, dust-free, tack-free (surface dry), dry-to-touch, dry-hard, dry through (dry-to-handle), dry-to-recoat and dry print-free. Although these tests are primarily used for paint films, most of the studies can be adapted intricately to evaluate pharmaceutical orally fast dissolving film. Tack is the tenacity with which the strip adheres to an accessory (a piece of paper) that has been pressed into contact with the strip.

Tensile strength [11]

Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. It is calculated by the applied load at rupture divided by the cross-sectional area of the strip. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation. The rate of change of stress was kept constant with the increment of 0.5g per 2minutes. The tensile strength was calculated by using following formula.

Tensile strength = Load at breakage/ Strip thickness × Strip Width

Percent elongation

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

The percent elongation at break was measured by formula given below.

% Elongation = Increase in length ×100 / Original length

Tear resistance

Tear resistance of film or sheet is a complex function of its ultimate resistance to rupture. Basically very low rate of loading 51mm (2 in)/min is employed and measure the force (that is generally found near the onset of tearing) required to tear the specimen which is recorded as the tear resistance value in Newton's (or pounds-force).

Folding endurance [12]

The folding endurance is expressed as the number of folds (number of times of film is folded at the same

plain) required for breaking the specimen or developing visible cracks. This gives an indication of brittleness of the film. A small strip of 4 square cm was subjected to this test by folding the film at the same plane repeatedly several times until a visible crack was observed.

Assay/ Content uniformity [13]

Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85–115%. The films were tested for content uniformity. Films of size two square inches was cut, placed in 100 ml volumetric flask and dissolved in methanol, volume was made upto 100 ml with methanol. Solution was suitably diluted. The absorbance of the solution was measured at 228nm.

Disintegration time

The disintegration time limit is 30 sec or less for orally disintegrating tablets described in CDER guidance which can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films strips, this may be used as a qualitative guideline for quality control test or at development stage. Pharmacopoeial disintegrating test apparatus may be used for this study. Typical disintegration time for strips is 5–30secs. A size of two square inch film was subjected for this study.

***In vitro* Dissolution test [14]**

ODFs of desired formulation were taken and placed in the vessels of dissolution apparatus. Samples were collected from the vessels at different time intervals, refill with the same volume of the blank solution and analyzed using UV-Visible spectrophotometer. Drug concentration was calculated from the standard graph and expressed as % of drug dissolved or released. The release studies were performed in 6 replicates and mean values were taken. Dissolution was taken according to lotter et.al using type-II apparatus of USP (DBK instruments, Mumbai) in 6.8 pH phosphate buffer (900ml) medium, at 50 rpm, and at 37±0.5ºc. All formulation equivalents to 160 mg of Tizanidine HCl was placed in dissolution media and 5ml of sample was withdrawn at time (min) 1, 3, 5, 10, 15, 20 and 30 respectively and diluted up to 50ml and then analyzed with double beam spectro photometer.

3. RESULTS AND DISCUSSION

3.1 Pre Formulation Studies

Solubility

Tizanidine Hydrochloride is slightly soluble in water, soluble in methanol. Solubility in water decreases as the pH increased. It is freely soluble in 0.1 N hydrochloric acid solution and combination of dichloromethelene and methanol.

Determination of pH

Tizanidine Hydrochloride 4% W/V solution in methanol showed pH of 4.68.

Moisture content

Moisture content of Tizanidine Hydrochloride was found to be 0 .39 %

Melting point

Melting point of the Tizanidine Hydrochloride was found to be 280^0 C -290^0 C

Calibration Curve

The prepared aliquots, whose concentration ranging from 0 to 60 µg/ml absorbance was measured at 228nm by using UV Spectrophotometer against the reagent blank. A standard graph of pure drug in suitable medium was prepared by plotting the concentration (µg/ml) on X-axis and absorbance (nm) on Y-axis (Figure 1). An excellent correlation co-efficient (r^2=0.999) was observed.

Drug Polymer Compatibility Studies by FTIR

Tizanidine Hydrochloride with polymers showed no significant variation in height, intensity and position of peaks, suggest that drug and excipients were compatible and there is no interaction present between drug and polymer. (Figure 2) Hence, it can be

concluded that the drug is in Free State and can release easily from the formulation.

3.2 Evaluation of Tizanidine Hydrochloride ODFs

HPMC E15 formulation F3 has high viscosity due to this it was unable to casted and also dispersion of polymer in distilled water was difficult. Formulation F4, F5 (HPMC E5) and formulation F7 (PVA) resulted in high brittle films compared with the formulation F6 (HPMC E5) and formulation F8 (PVA), formulation F9 (PVA) which separated easily. The reason for the brittle film formation was insufficient concentration of polymer for the formation, which were difficult to remove from the mould. Thus HPMC & PVA films which are transparent, thin, without any imperfections were used for further study.

Thickness

The thickness of the drug loaded films were measured with the help of screw gauge by combining of five films of film F1, F2, F6, F8 & F9 formulations, as it was difficult to measure the thickness of the single film, thickness varies from 0.10 to 0.16 mm. the results were reported in Table 2.

Table 1: Composition of Tizanidine Hydrochloride ODFs

Ingredients/ Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
TZH (mg)	160	160	160	160	160	160	160	160	160
HPMC E15 (mg)	500	1000	1500						
HPMC E5 (mg)				500	1000	1500			
PVA (mg)							500	1000	1500
Propylene glycol (mg)	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Citric acid (ml)	60	60	60	60	60	60	60	60	60
Mannitol(mg)	80	80	80	80	80	80	80	80	80
Menthol (ml)	2	2	2	2	2	2	2	2	2

Table 2: Thickness of the films

Formulation code	Average thickness in mm			Mean thickness ±S.D
	Trial-1	*Trail-2*	*Trial-3*	
F1	0.10	0.11	0.10	0.10±0.04mm
F2	0.14	0.16	0.12	0.14±0.05mm
F6	0.14	0.12	0.13	0.13±0.02mm
F8	0.16	0.12	0.14	0.14±0.2mm
F9	0.17	0.15	0.16	0.16±0.2mm

Weight variation

Mouth dissolving films were prepared by solvent casting method. Five Films each of one square inch were cut at five different places from casted films and weight variation was measured. Weight variation varies from 23 to 49mg. The results of weight variations are shown in Table 3.

Table 3: Weight variation of the ODF films

Formulation code	Average weight of the 2cm square film in mg			Mean weight ±S.D
	Trial-1	*Trail-2*	*Trial-3*	
F1	23.40	24.10	22.26	23.25±2.43
F2	34.11	36.09	35.06	35.08±3.12
F6	47.13	49.42	47.20	49.25±2.51
F8	35.58	36.00	36.87	36.15±2.51
F9	47.13	49.42	46.20	49.25±2.51

Tensile Strength

The film of 3 inch×10mm was taken for the studies. From the results it is clear that when the concentration of the polymer increases, the tensile strength of the film also increases. The formulation F8, F9 shows the maximum tensile strength. Presence of polyethylene glycol as a plasticizer imparts the flexibility to the film. Tensile strength measures the ability of the film to withstand rupture. The formulation F9 shows the maximum value of tensile strength 1.573 ± 0.05 was as shown in Table 4 .This might be due to the formation of strong hydrogen bonds between polymer and plasticizer there by imparting flexibility to withstand rupture.

Folding endurance

The folding endurance was measured manually. A strip of film 2×2squre cm was cut and subjected for the folding endurance studies until it broke at the same place. Folding endurance increases with increase in polymer concentration. The no of times the film fold until it broke was reported. This data revealed that the patches had good mechanical strength along with flexibility. (Figure 3)

Table 4: Tensile Strength of the ODF

Formulation code	Tensile Strength in Kg			Mean ±S.D
	Trial-1	*Trail-2*	*Trial-3*	
F1	1.159	1.205	1.105	1.156 ±0.05
F2	1.396	1.374	1.290	1.356±0.05
F6	1.436	1.447	1.395	1.426±0.05
F8	1.466	1.497	1.595	1.519±0.05
F9	1.595	1.547	1.578	1.573±0.05

Table 5: %Assay of the ODF

Formulation code	%Assay
F1	99.4
F2	104
F6	100.5
F8	105
F9	103

Percentage elongation

The film of 3 inch X 10 mm was taken for the studies. Percentage elongation was found to increase in increase concentration of polymer in the film. The % elongation was found to be in the range of 20.73 to 37.1%. The formulation F1 showed minimum % elongation among all the other patches .The result obtained for all the formulations is shown on figure 4.

Disintegration time

Time of the disintegration was done by using tablet disintegration test apparatus. A size of two square inch film was subjected for this study. Mouth dissolving time and disintegration time of the films were found to be increased with increase in the concentration of the polymer. The formulation F1 shows 16 Sec (disintegration time). Disintegration time of the films was reported in figure 5.

Drug content uniformity/Assay

The prepared film formulations were analyzed for drug content and it was observed that all the formulation found to contain almost uniform quantity of drug as per content uniformity studies indicating reproducible technique. The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. The Results were shown in Table 5.

Dissolution time

No significant differences were observed from *in vitro* dissolution studies for the film F1, F2, F6, F8 and F9 due to film instantly get wet by dissolution medium and disintegrate. Percentages of drug release at different time intervals were shown in Figure 6. In F1 formulations 100% drug released within 3 mins but in F2 100% drug is released within 5mins.Because of high viscosity and concentration of polymer, so it took time to dissolve the polymers.

4. DISCUSSION

The prepared Tizanidine Hydrochloride oral films were characterized based upon their physiochemical characteristics like tensile strength, percentage elongation, Disintegration time, mouth dissolving time, thickness, weight, folding endurance and drug content. The *in vitro* release studies in 6.8 Phosphate buffer were performed. The films were evaluated for weight variation and thickness which shows satisfactory results in all prepared formulation. Tensile strength, percentage elongation and folding endurance of the films were increased with increase in the concentration of polymer due to increase in the elasticity nature of the polymer. Mouth dissolving time and disintegration time of the films were increased with increase in the concentration of the polymer, as more fluid is required to wet the film in the mouth. Content uniformity study showed that the drug is uniformly distributed in the film. Based on the results formulation F1 [HPMC E15,

10% w/v] was the best one when compared to other. Based on disintegration time and drug release, formulation F1 has less disintegration time compared to formulation F2 and formulation F2 has still less disintegration time than formulation F6, which having HPMC E5 at 30% w/v . Formulation containing 500 mg of HPMC E15 film exhibited required tensile strength, folding endurance and percentage elongation. HPMC E15 at 10% w/v concentration level showed highest release of more than 99% of the drug in 3min. So ODF formulated with HPMC E15 at 10 % w/v is best formulation among all formulation batches.

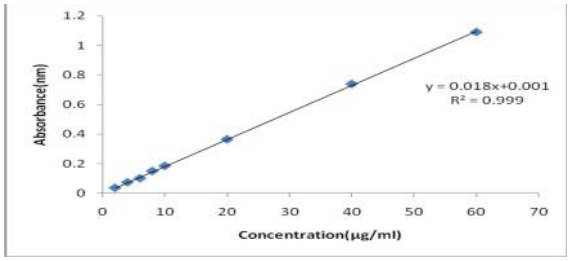

Fig 1: Standard graph of Tizanidine hydrochloride

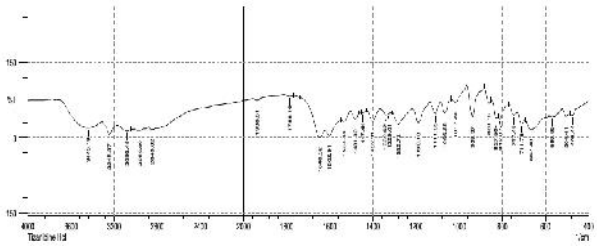

Fig 2.1: FTIR spectra of Tizanidine Hydrochloride .

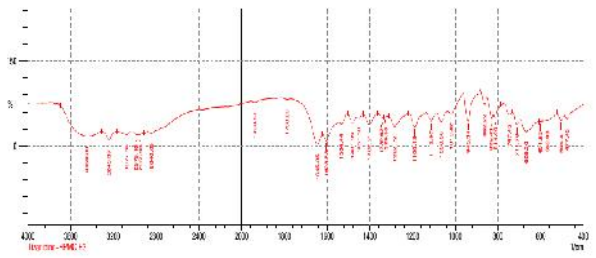

Fig 2.2: FTIR spectra of Tizanidine HCl + Hydroxy Propyl methyl cellulose

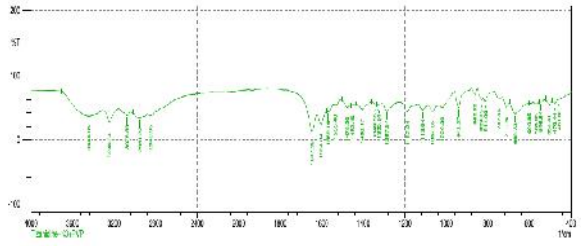

Fig 2.3: FTIR spectra of Tizanidine HCl+ PVA

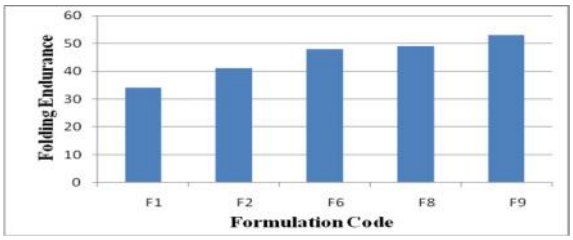

Fig 3: Graphical representation of folding endurance of the films

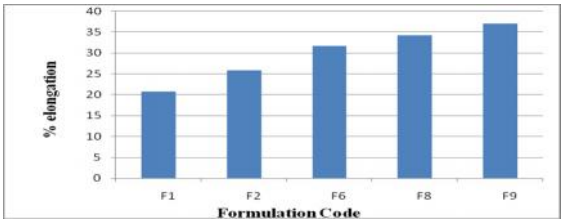

Fig 4: Graphical representation of percentage elongation of the films

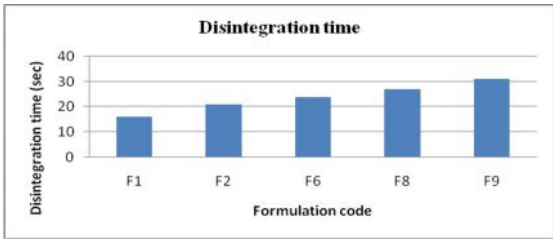

Fig 5: Graphical representation of Disintegration time of the films

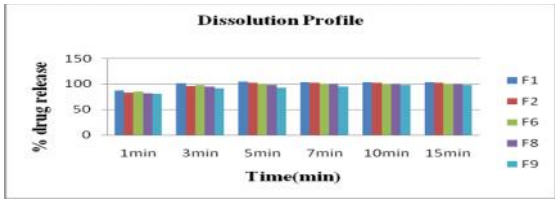

Fig 6: Graphical representation of dissolution profile of the films

5. CONCLUSION

Hence TZH oral films could be promising one as they, increase bioavailability, minimize the dose, reduces the

side effects and improve patient compliance and also TZH might be a right and suitable candidate for oral delivery. Low dose of drug can be suitable for oral films with low density of polymers. ODF are the thin film with more surface area they get wet quickly and disintegrate then dissolve faster than other formulations. From the present investigation it can be concluded that mouth dissolving film formulation can be a potential novel drug dosage form for pediatric, geriatric and also for general population

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