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Influence of guar gum, tragacanth and HPMC E-5 on fluconazole release from lozenzes

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ABSTRACT

Topical application of drug prevents several drug interactions and lozenge is a better delivery system as the effective concentration of drug can be maintained in the oral cavity for a more prolonged period of time. The aim of study was to develop and evaluate fluconazole lozenges for topical therapy of oropharyngeal candidiasis. The current investigation was designed to improve patient compliance and its efficacy by delivering anti-fungal drug in the form of lozenges. Fluconazole is having poor flowing property it was decided to go for wet granulation in order to increase its ability to flow. For the formulation of compressed tablets lozenges guar gum, tragacanth and HPMC E-5 was used as drug release polymer. Other excipients used were gelatin 6% solution (as binder), sucrose (taste masking agent), methyl paraben (as preservative) and Magnesium stearate (lubricating agent). Among all the formulations F8 showed 98.33 % drug release at 35 min, thickness 4.0±0.1mm, hardness 3.3±0.3 kg/cm3, Friability 0.72±0.26%. F8 batch showed better drug release than other batches, hence F8 was the optimized batch from all formulations.

Keywords: Fluconazole lozenges, Guar gum, Tragacanth, HPMC E 5.

INRODUCTION

Oral drug delivery is the most preferred and simplest means as the oral route provides a maximum active surface area of all drug delivery system for administration of various drugs. The oral route of drug administration has been widely used for both conventional as well as novel drug delivery. The lozenges are solid medicated, flavored and sweetened base dosage forms intended to be sucked and hold in the mouth or pharynx to treat local irritation, mouth or pharynx infection. [1]

Lozenges should dissolve slowly in mouth and possess some degree of smoothness, with their shape being without corners. Lozenges may be formulated with various shapes, like flat, circular, octagonal, biconvex or bacilli, meaning short rods or cylinders. Lozenges are placed in oral cavity. Since the sublingual lozenges may be impractical due to their size, buccal lozenges are formulated and have been

extensively used and are intended to be placed between the cheek and the gums. Depending on the type of lozenge, they may be prepared by molding or by compression. Molded lozenges are called pastilles while compressed lozenges are called troches [2].

Fungal infections are very common among individuals in daily clinical practice. Topical treatments for fungal infections are considered preferable to systemic treatment in various individuals [3].

Candidiasis, especially that caused by *Candida albicans*, is extremely common; however, it is not clear why these usually harmless commensal organisms become pathogenic. Candidias can occur in most parts of the body. Infection is particularly common in young children and elderly people following antibiotic treatment. People with diabetes and suppressed immune systems are also vulnerable to candidiasis. Most infections are local, but for immune-suppressed patients they can become systemic and life-threatening, especially if they are infected with a drug-resistant strain [4].

The choice of antifungal agent used in the treatment of candidiasis is dependent upon the severity and nature of the infection [5]. In case of local infections, only topical therapy is preferred and in case of systemic infections, a combination of topical and systemic therapies is used as treatment regimen [6].

Fluconazole is a first-generation triazole antifungal medication. It differs from earlier azole antifungal (such as ketoconazole) in that its structure contains a triazole ring instead of an imidazole ring. While the imidazole antifungals are mainly used topically, fluconazole and certain other triazole antifungals are preferred when systemic treatment is required because of their improved safety and predictable absorption when administered orally. Fluconazole's spectrum of activity includes most *Candida* species (but not *Candida krusei* or *Candida glabrata*), *Cryptococcus neoformans*, some dimorphic fungi, and dermatophytes, among others [7].

Lozenges can be made by molding or by compression at high pressures, often following wet granulation, resulting in a mechanically strong tablet that can dissolve in the mouth. Compressed lozenges (or troches) differ from conventional tablets in that they are nonporous and do not contain disintegrate. As the formulation is designed to release drug slowly in the mouth, it must have a pleasant taste, smoothness, and mouth feel. The choice of binder, filler, colour, and flavour is most important [8].

The present investigation designed to improve patient compliance by formulating, fluconazole lozenges for topical therapy of oropharyngeal candidiasis. Lozenges are the flavored medicated dosage forms intended to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. Advantages of the fluconazole tablet lozenges as dosage forms include increase in bioavailability, reduction in dose size and gastric irritation, by first pass metabolism [9].

Lozenges are intended to relieve oropharyngeal symptoms, which are commonly caused by local infections. Topical application of drug prevents several drug interactions. [10] Lozenges are considered to be better delivery system as the effective concentrations of the drug can be maintained in the oral cavity for a prolonged period as the lozenge is sucked slowly in the mouth. We have reported the formulation and evaluation of fluconazole lozenges containing maize starch, acacia, HPMC E-15 as binders along with gelatin. [11, 12]

The present work was aimed formulation of fluconazole tablet lozenges and the influence of guar gum, tragacanth and HPMC E-5 as rate controlling polymers on fluconazole release from lozenzes, which provide prolonged action in oral cavity for relief of oral thrush.

MATERIAL AND METHODS

MATERIALS

Fluconazole was a gift sample from Aurobindo Pharma, Hyderabad. Pvt. Ltd. Guar gum was obtained from Molychem Chemical Corporation, Mumbai. Tragacanth was obtained from Molychem, Mumbai. HPMC E5 was obtained from Micro Lab, Bangalore. Sucrose and Gelatine were obtained from, Molychem Chemicals Pvt. Ltd., Mumbai. All other chemicals and solvents were of analytical reagent grade and distilled water was used throughout the study.

METHODOLOGY

Melting point

The melting point of the drug was determined using capillary method. The drug was filled in small

quantity into one side sealed capillary tube which was tied to thermometer at its mercury bulb. The thermometer was inserted into Thieles tube containing liquid paraffin in such a way that the upper open end of capillary tube remains above the oil layer. The side arm of Thieles tube was then heated with burner till solid drug melts, and the melting temperature was noted.

Solubility [13]

The solubility of the drug was carried out in buffer pH 6.8 as well as in methanol. The excess amount of drug was dissolved in 5 ml of solvent. The solution was then subjected to ultrasonication for 30 min. It was then allowed to stand for 24 h at RT (room temperature) in tightly closed vials to attain saturation equilibrium. After 24 h the solution was filtered through Whatman filter paper no. 41. It was then diluted appropriately with the solvent and its absorption was observed through UV spectrophotometer at 200-400 nm in buffer pH 6.8.

Standardization of fluconazole by UV-spectrophotometer [14]

Standard stock solution of fluconazole

Accurately weighed 10mg of Fluconazole was transferred into a 100ml volumetric flask and dissolved in 30ml of methanol. It was then sonicated for 10 min and made up to the mark with methanol to give a stock solution having 100 µg/ml concentration.

Form this standard stock solution, a series of dilution (10, 20, 30, 40, 50 µg/ml) were prepared using Phosphate buffer pH 6.8. The absorbance of these solutions was measured spectrophotometrically against blank of methanol at 260 nm for fluconazole.

Drug-excipient compatibility study [15]

The interaction was studied for prediction of stability and compatibility between drug and polymer which was analyzed using IR spectroscopy.

FTIR can be used to investigate and predict any physiochemical interaction between different excipients. IR spectra matching approach was used for detection of any possible chemical interaction between the drug and polymer. A physical mixture of drug, polymer and other excipients were prepared and mixed with suitable quantity of potassium bromide. It was scanned from 4000 to 400 cm^{-1} in a FTIR spectrophotometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymer and peak matching was done to detect any appearance or disappearance of peaks.

Pre-compression characteristics [16]

Bulk density is defined as the mass of a power divided by the bulk volume. Procedure:-A sample of powder of fluconazole (5 gm) was introduced into 25 ml graduated cylinder. The volume of material was noted on graduated cylinder. The bulk density was calculated by the formula,

$$\text{Bulk density } (\rho) = \frac{\text{Mass of powder (gm)}}{\text{Bulk Volume (ml)}}$$

Fluconazole powder was filled in graduated cylinder and then tapping was done 100 times initially and the tapped volume (Va) was measured to nearest graduated unit. The tapped density was calculated by the formula,

$$\text{Tapped density} = \frac{\text{Mass of powder (gm)}}{\text{Tapped Volume (ml)}}$$

The compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed. Compressibility index of fluconazole was calculated by the formula,

$$\text{Compressibility} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped Density}} \times 100$$

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}} \times 100$$

The flow characteristics are measured by angle of repose. Improper flow of powder is due to fractional forces between the particles. These fractional forces are quantified by angle of repose.

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. Angle of repose, $\tan \theta = h/r$ or $\theta = \tan^{-1}(h/r)$, where, h is height of pile, r is radius of the base of the pile and θ is angle of repose.

Formulation of lozenges tablet of fluconazole [17]

Formulations of compresed tablet lozenges of fluconazole are given in Table 1. Lozenges Tablet of fluconazole the formulation was prepared by Wet granulation process using different grades of polymer with varying concentration. Using gelatine solution as binder and passed through #8 sieve and the granules obtained were dried at 25±1°C for 40 min. Dried granules were to then passed through sieve #16 and collected on sieve #44, 10% fines were added, which passed through a sieve #44 remaining magnesium stearate, was then added to dried granules and subjected to blending process and compressed using 13 mm punch on a double stroke punching machine.

Table 1: Formulation of compresed tablet lozenges of fluconazole

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fluconazole	50	50	50	50	50	50	50	50	50
Guar gum	30	60	90	-	-	-	-	-	-
Tragacanth	-	-	-	30	60	90	-	-	-
HPMC E-5	-	-	-	-	-		20	40	60
Gelatin (6%)	60	60	60	60	60	60	60	60	60
Sucrose	854.5	824.5	794.5	854.5	824.5	794.5	864.5	844.5	824.5
Methyl Paraben	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Stearate	5	5	5	5	5	5	5	5	5

Total Tablet wt.-1000 mg

Post compression parameters [18]

All the prepared Lozenges tablets were evaluated for following official parameters. The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of the lozenges was determined using Monsanto hardness tester, where the force required to break the lozenges was noted.

The thickness and diameter of lozenges were determined using vernier callipers. Three lozenges from each batch were used and average values were calculated.

Friability is the measure of tablet strength. The friability of the lozenges was determined using Roche Friabilator. Weighed lozenges were placed in the friabilator and operated for 4 min at 25 rpm. The tablets were then made free from dust and reweighed. The percentage friability was calculated.

The percentage friability was measured using the formula, $\% F = \{W1-W2/W1\} \times 100$; where % F is friability in percentage, W1 is initial weight of tablet before test, and W2 is weight of tablets after test.

The weight variation was conducted by weighing 20 tablet lozenges individually and calculating the average weight and comparing the individual lozenges weight to the average value. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviates from the average weight by more than the percentage

In-vitro drug dissolution studies

The release of fluconazole for different formulations of compressed lozenges tablets was determined using USP dissolution test apparatus (type II). The dissolution medium was 900 ml in buffer pH 6.8 at 37±0.2 °C with a stirring speed of 50 rpm. Aliquots of 5 ml were withdrawn at predetermined intervals of 5 min, filtered and replaced by equivalent volume of fresh dissolution media. The test sample was filtered through membrane filter, (0.45 µm) and the concentration of drug release was determined using UV-visible spectrophotometer at λ_{max} 260.00 nm.

Mechanisms of drug release kinetics

To analyse the mechanism for the drug release and drug release rate kinetics of the dosage form, the data obtained was fitted into zero order and first order. By comparing the R^2-values obtained from the above equations, the best-fit model was selected.

RESULTS AND DISSCUSSION

The standard calibration curve of fluconazole in pH 6.8 phosphate buffer showed a good linear relation with R^2 value of 0.998 following Beer's limit from 0-50 µg (Figure 1).

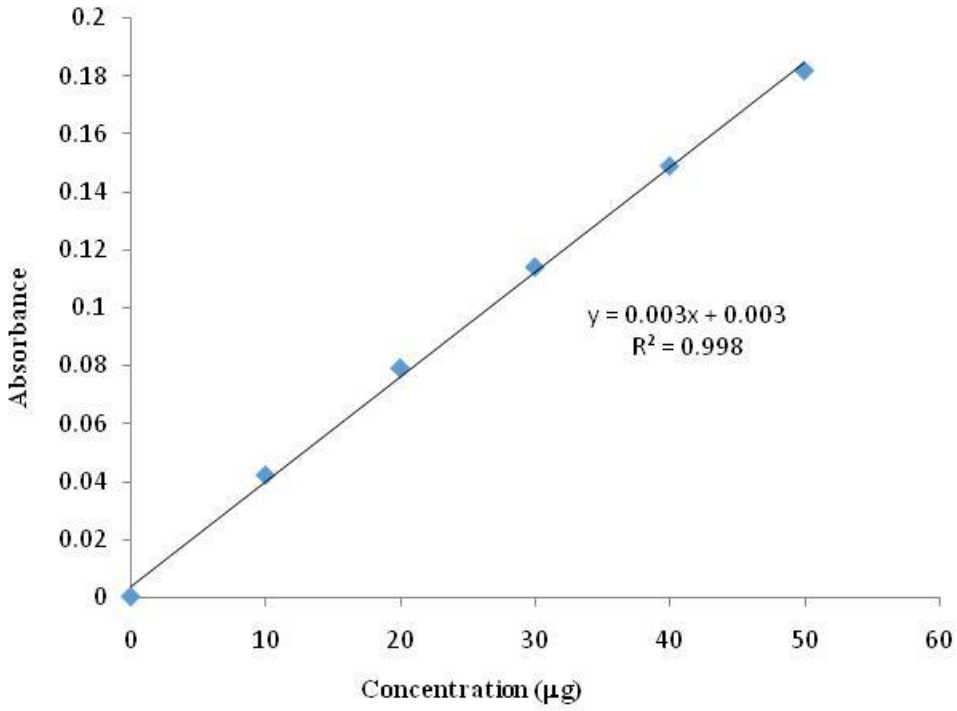

Figure 1: Standard calibration curve of fluconazole in 6.8 pH buffer

Drug-excipient compatibility studies using FTIR

The results of FTIR studies are shown in Figure 2. The FTIR spectrum of fluconazole exhibits a characteristic peaks at 3071cm^{-1}, 3117cm^{-1}, 619cm^{-1}, 1506cm^{-1} and 1419cm^{-1} FTIR-spectra of drug and its physical mixture with excipients are nearly same, and there was no shift of peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.

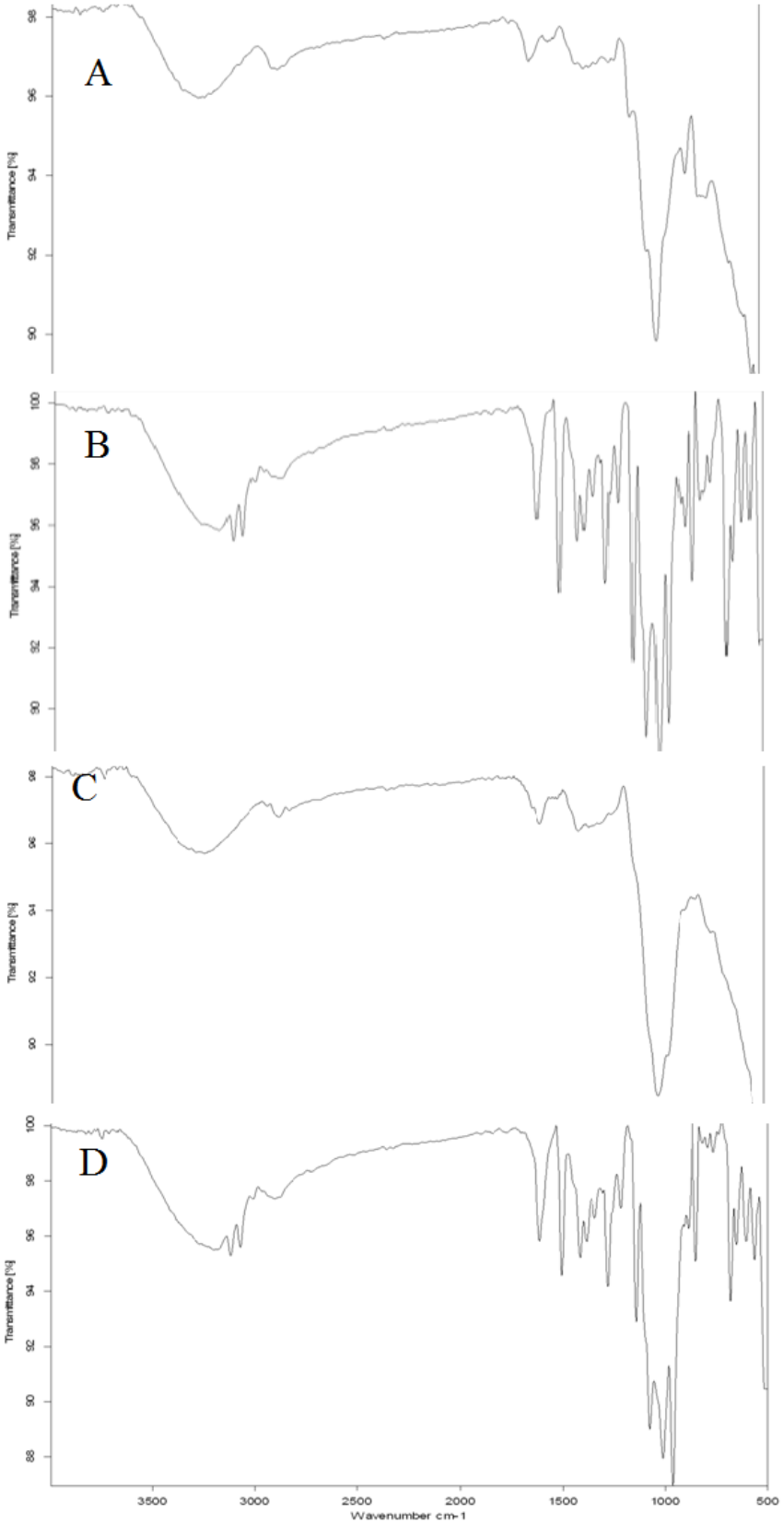

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Figure 2: FTIR Spectra of (A) fluconazole, (B) fluconazole + guar gum, (C) fluconazole + tragacanth and (D) fluconazole + HPMC E-5

The evaluation of fluconazole lozenges was performed and the results are summarized in Table 2. All the formulations of lozenges fulfilled the official requirements of uniformity of dosage units, *in-vitro* dissolution. It was observed that drug fluconazole was compatible with all excipients so it was decided to use appropriate polymer which would increase its solubility, buccal residence time and gave acceptable mouth feel of the lozenges in the oral cavity. The thickness of all the developed batches ranged from 4.0 – 4.1 mm. The hardness and percentage friability of all batches ranged from 3 – 4 kg/cm^2 and less than 1 % respectively.

Table 2: Evaluation parameters of Lozenges Tablet

Batch Code	Evaluation Parameters				
	Thickness (mm) N=3	Diameter (mm)N=3	Hardness (Kg/cm^2) N=3	Friability%	Weight variation N=20
F1	4.0±0.1	13±0.1	3.4±0.40	0.86±0.38	990.5±9.5
F2	4.0±0.1	13±0.1	3.5±0.45	0.78±0.56	999.0±0.1
F3	4.0±0.1	13±0.1	3.2±0.22	0.81±0.23	990.5±9.5
F4	4.1±0.1	13±0.2	3.7±0.70	0.67±0.72	995.0±4.5
F5	4.0±0.2	13±0.1	3.8±0.17	0.74±0.12	980.5±19.5
F6	4.0±0.1	13±0.1	4.0±0.24	0.87±0.66	986.5±14.5
F7	4.1±0.3	13±0.1	3.0±0.16	0.89±0.32	990.5±9.5
F8	4.2±0.4	13±0.2	3.3±0.32	0.72±0.26	987.5±12.5
F9	4.0±0.2	13±0.1	3.1±0.12	0.66±0.36	995.5±4.5

In-Vitro drug release studies

The percentage release of drug in buffer pH 6.8 at temperature 37^{o}C is analyzed using UV-Spectrophotometer at 260.60 nm wavelength.

Effect of guar gum concentration on drug release

The dissolution was carried out with combination of fluconazole and Guar gum in different concentration. The results are shown in Figue 3. The F3 formulation showed drug released which is 94.33 % up to 40 min. The formulation of F2 batch showed drug released i.e. 96 % up to 40 min and the formulation F1 batch which showed drug released i.e. 91.66 % up to 40 min.

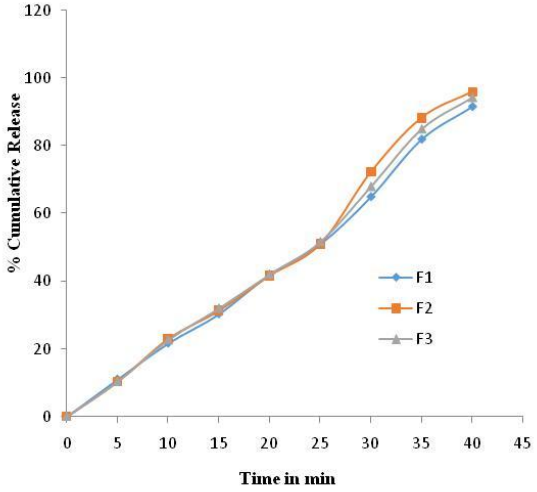

Figure 3: *In-vitro* release profile of F1, F2 and F3 batch

Effect of tragacanth concentration on drug release

The dissolution was carried out with combination of fluconazole and Trgacanth in different concentration and the results are summarized in Figure 4. The formulation of F6 batch showed the percent drug released up to 94.66% to 40 min. The formulation of F5 batch showed the percent released 95% up to 40 min. The formulation F4 showed the percent released 93% up to 40 min.

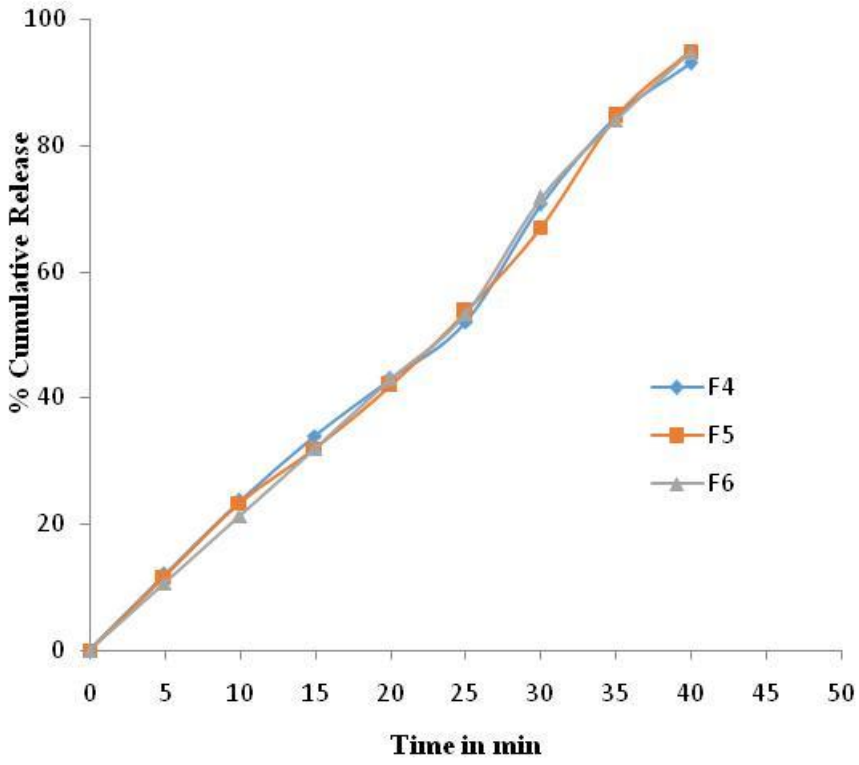

Figure 4: *In-Vitro* release profile of F4, F5 and F6 batch

Effect of HPMC E-5 concentration on drug release

The dissolution was carried out with combination of fluconazole and HPMC E-5 in different concentration. The results are summarized in Figure 5. The formulation of F9 batch showed the percent drug released up to 91 % to 40 min. The formulation of F8 batch showed the percent released 98.33% up to 40 min. The formulation F4 showed the percent released 96% up to 40 min.

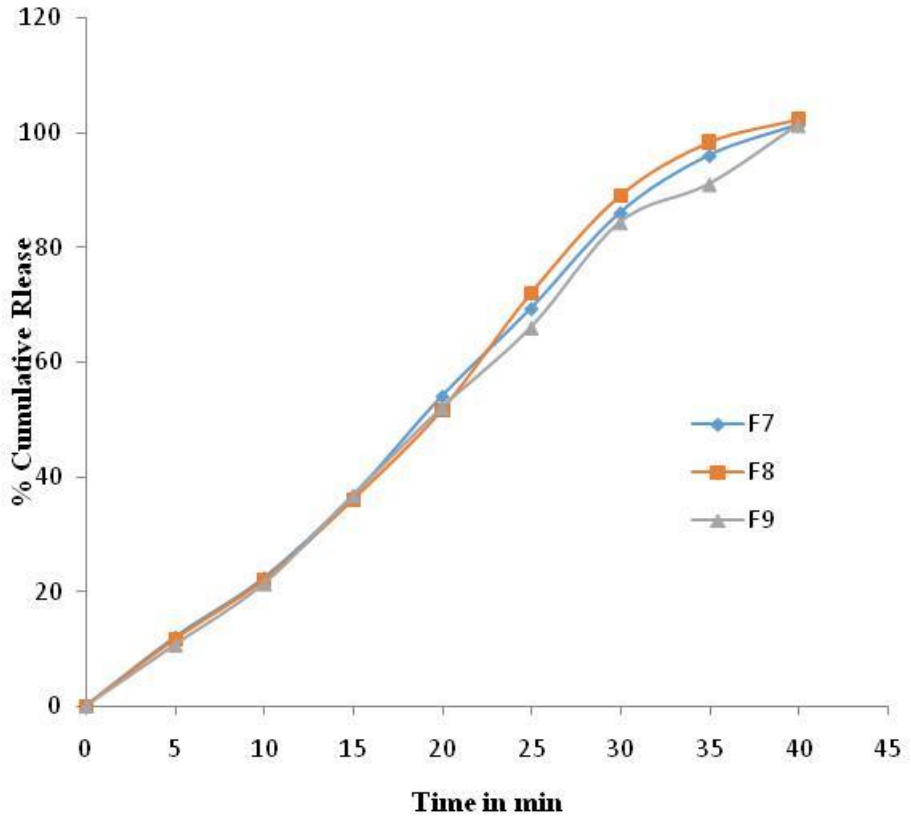

Figure 5: *In-vitro* release profile of F7, F8 and F9 batch

Among all the formulations F8 shows 98.33 % best drug release at 35 min, thickness 4.0±0.1mm, hardness 3.3±0.3 kg/cm3, Friability 0.72±0.26%. F8 batch showed better drug release than other batches. Hence, F8 was the optimized batch from having polymer HPMC E-5 which was release in 35 min.

Kinetic analysis of F8 batch

The results of *in-vitro* release profile obtained for the optimized batch F8 formulation were plotted in kinetic release as follows. The results of dissolution kinetics are plotted in Figures 5 and 6. Formulation F8 was subjected for zero order and first order equations and the regression co-efficient was found to be 0.990 and 0.784 respectively. F8 batch formulation best fit in zero order model by giving the values 0.990 that indicated the formulation had constant slow release of the drug over period of 30 min.

Topical treatment for oropharyngeal candidiasis was considered preferable to systemic treatment in various individuals. However, there are some limitations for traditional topical therapies including short contact time with the oral mucosa and multiple dosing each day. The current investigation was designed to improve patient compliance and its efficacy by delivering anti-fungal drug in the form of lozenges.

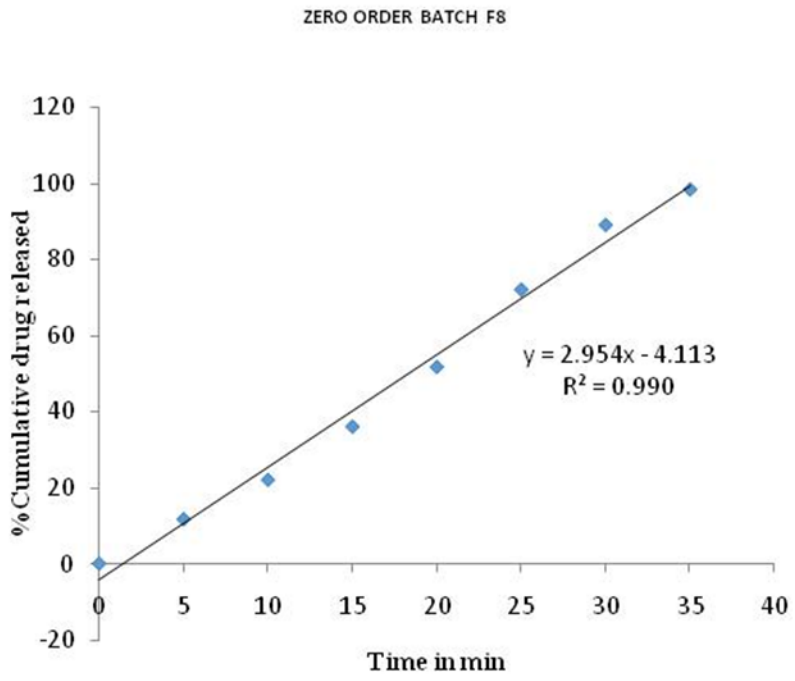

Figure 6: Zero order release of batch F8, Cumulative % drug released versus T

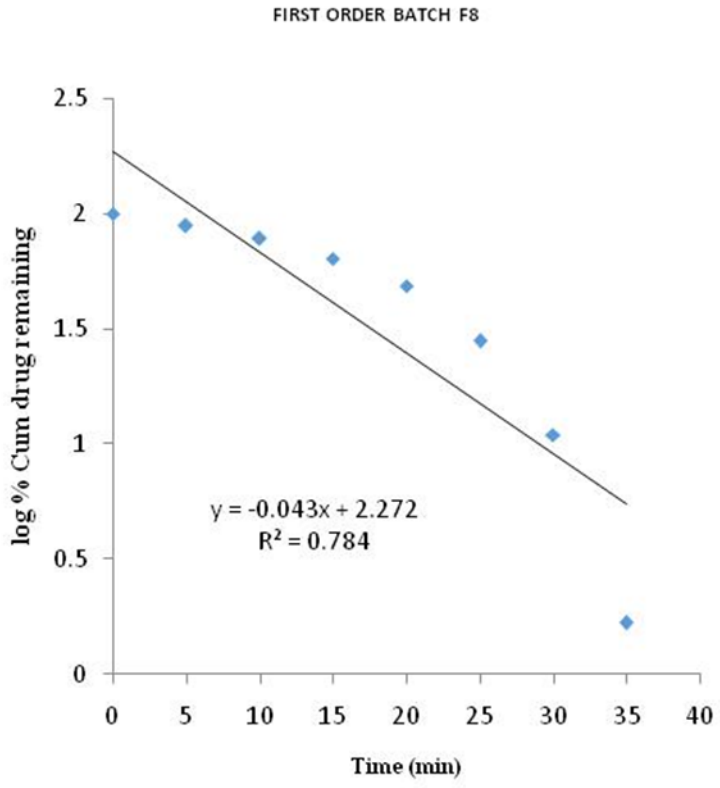

Figure 7: First order kinetic model F8, Log cumulative % drug remains Versus T

CONCLUSION

The physico-chemical characterization revealed that all the formulations were found to show acceptable thickness, weight and hardness. Suitable analytical method based on UV-Visible spectrophotometer was validated for Fluconazole in pH 6.8 buffer at λ max 260.60 nm. No drug-excipient interactions were seen. Wet granulation technique was established for preparation of granules for the Lozenges tablet of Fluconazole. *In-vitro* release rate studied showed that the maximum drug release was observed in batch F8 formulations up to 98.33% using polymer HPMC E-5. The addition of natural hydrophilic gums like, guar gum and tragacanth, yielded good results to sustain the drug release in salivary pH conditions for a period of 40 min. From the study it was concluded that a promising compressed tablets lozenges of fluconazole prepared. It can be stated that the objective of the study was met. Fluconazole lozenges were successful in delivering the drug for topical application orophangyl candidiasis.

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