FORMULATION AND EVALUATION OF ANTIFUNGAL LOZENGES FOR ORAL CANDIDIASIS

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Abstract

Oral candidiasis is the most common oral fungal infection in man and caused by different species of Candida, usually Candida albicans. Many dosage forms like tablets, capsules, creams and gel are available in the market for the treatment of oral candidiasis, but still there is need of novel dosage forms which is acts locally and effectively. The Candy based lozenges of antifungal agent prepared using hydrophilic natural polymers (gelatin, acacia and tragacanth) by heating and congealing method in order to enhance bioavailability, reduce gastric irritation, by-pass first metabolism and increase onset of action. These lozenges were evaluated for various parameters like hardness, friability, thickness, drug content, mouth dissolving time, moisture content and in vitro dissolution etc. The optimized formulation was having good transparency and pourability with mouth dissolving time, in vitro drug release 98.23% and follows first order release kinetics and the mechanism of drug release was found to be Non-fickian. The DSC and FTIR studies indicated that there was no drug-excipients interaction. Accelerated stability study conducted as per ICH guidelines at 45°C and 75% relative humidity over a period of one month found that there wasn’t any substantial interaction between the drugs, flavor and colour and the prepared formulation were stable. The antifungal studies showed that they retained similar antifungal activity of pure drug. It was concluded that development of Ketoconazole loaded gelatin lozenges tablets were successfully formulated cost effectively and has high efficiency in treatment of oral candidiasis.

Keywords: Ketoconazole, Lozenge, Oral Candidiasis.

Introduction

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. Lozenges are most often used for localized
effects in the mouth. They can also be used for systemic effects if the drug is well absorbed through the buccal lining or is swallowed.²

Oral candidiasis is a disorder caused by infection of the mouth due to yeast like fungus called *Candida albicans*³. Oral candidiasis appears the adherent white, curd like plaque present anywhere in the oral cavity. There are many dosages forms are available in the market for the treatment of oral candidiasis⁴. Lozenges are the one of the dosage form.

The present work is designed the Ketoconazole loaded lozenges. The Advantages of Ketoconazole lozenges as increase bioavailability, reduction in dose size, gastric irritation, bypass first pass metabolism and improve the patient compliance⁵.

When it is not effectively treated, oral candidiasis often leads to hospitalization, limitation on physical activity, insomnia nights and in some cases death. The present investigation is aimed at developing a Ketoconazole lozenge which provides prolonged retention time up to 30 min in oral cavity for relief of oral candidiasis⁶.

**Materials and Methods**

**Materials**

Ketoconazole was received a gift sample from Aarti Drug Limited, Mumbai, acacia, gelatin, tragacanth gum was obtained from Spectrum chemicals, Cochin. Sucrose and dextrose was obtained from Nice pharmaceuticals, Kottayam, Kerala. All other chemicals and solvents were of analytical reagents grade and distilled water was used throughout the study.

**Methods**

**Drug- Excipients Compatibility Studies**⁷

During the studies, possible interaction of drug with various ingredients proposed for use in final dosage form was checked.

The drug-excipients compatibility study was carried out by using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared (FTIR) spectroscopy. DSC study of pure drug and optimized batch was performed using DSC instrument (DSC-60, Shimadzu).

The samples were prepared by mixing the drug and the excipients in 1:1 ratio. Accurately weighed samples were sealed in aluminum pans, and analyzed in an inert atmosphere of nitrogen at flow rate of 25 ml/min. A temperature range of 0°C to 300°C was used.
FTIR study was conducted using KBr mixing method on FTIR spectrophotometer (FTIR-8400, Shimadzu) and the spectrums were recorded in the wavelength region of 2000 - 400 cm\(^{-1}\).

**Analytical methods**

10 mg of Ketoconazole was accurately weighed and was transferred to 100 ml volumetric flask. Small quantity of methanol was added to dissolve drug. The volume was made up to 100 ml using phosphate buffer 6.8 to prepare stock solution of 100µg/ml.

From the stock solution 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8 and 2.0 ml of solution was pipette into 10 ml volumetric flasks and volume was made up to 10 ml to form concentrations of 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20µg/ml with phosphate buffer 6.8. The absorbance was measured with the help of UV Spectrophotometer at 222nm by taking a phosphate buffer 6.8 as reference solution. All study done in triplicate (n=3) with the same instrument.

The absorbance values were plotted against concentration to obtain the standard graph.

**Preparation of Lozenges**

Candy based Lozenges are prepared by heating and congealing technique. Various steps are involved in the preparation of lozenges. Syrup base was prepared by dissolving required amounts of sugar in water while heating it and stirring continuously for 30 minutes at the temperature of 80ºC.

Dextrose was added to the syrupy base to prevent crystallization of sugar, and the syrupy base was heated and stirred continuously till the plastic mass was obtained. The drug is dispersed in the methanolic solution, binders, color and flavor were added and the materials were stirred for few minutes. The mixture was poured into desired shape lozenges mould and air for 1 hour. Then the prepared lozenges were wrapped in aluminum foil.

**EVALUATION OF LOZENGES**

**Organoleptic Evaluation**

The formulated lozenges were evaluated for organoleptic characteristics like color, odor and shape. All the lozenges were inspected for color and shape.

**Weight Variation**

According to weight variation test, 20 Lozenges were selected randomly and each one weighed individually and collectively on a digital weighing balance. Average weight per Lozenges was calculated from the collective weight. Then the weights of the individual Lozenge were compared with the average weight to determine the weight variation.
Hardness test / crushing strength

The Monsanto hardness tester was used which consists of a barrel containing a compressible spring held between two plungers. The lower plunger is placed in contact with the lozenges, and zero reading is taken. The upper plunger is then forced against a spring by turning threaded bolt until the lozenges breaks. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of break is recorded and zero force reading is deducted from it.

Friability

Friability of lozenges was determined using Roche Friabilator. 20 lozenges were taken in a friabilator and were operated for 100 revolutions in 25 rpm. The resulting lozenges were re-weighed and % loss was calculated. Lozenges should not more than 1% of their weight. Friability can be calculated using the formula,

\[
\text{Friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100
\]

Thickness

The thickness of the Lozenges was measured using calibrated Vernier caliper. The Lozenges was inserted between the jaws after making sure that the pointer was set to zero. The reading from the main scale and Vernier scale were measured. The mean thickness was calculated.

Moisture Content Analysis

Moisture content in the prepared lozenges was determined by weighed the lozenges and crushed in a mortar. From this, 1 gm of the sample was weighed and placed in desiccators for 24 hr. After 24 hr the sample is weighed. The moisture content is determined by the subtracting the final weight from initial weight of lozenges.

\[
\% \text{ Moisture content} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100
\]

Drug Content

10 Lozenges were randomly selected and crushed in a motor. 100mg lozenges was accurately weighed and dissolved in the methanol and made up 50 ml with methanol. The solution was then filtered and absorbance was measured by UV spectrophotometer at 222 nm against methanol as the blank.
Mouth Dissolving Time

The mouth dissolving time was determined using USP disintegration device which consist of 6 glass tubes of 3 inches length, open at the top and 10 mesh screen at the bottom end of the basket rack assembly. To test mouth dissolving time, one lozenge was placed in each tube and the basket rack is positioned in a 1 L beaker containing phosphate buffer pH 6.8 at 37 ± 2°C.

Moved the basket rack assembly up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per min. The time taken for the complete dissolving of the lozenges was noted.

In vitro Dissolution Studies

The rate of dissolution is related to the efficacy of the Lozenge. In vitro drug dissolution studies were carried out using Electro Lab dissolution tester USP type II paddle method.

Method

Dissolution medium : Simulated salivary pH 6.8 solution
Dissolution volume  : 900 ml
rpm                : 100 rpm
Temperature       : 37°C ± 0.5°C
Samples withdrawn : 5 ml

At appropriate time intervals, 5 ml of samples were withdrawn and filtered through filter paper, the initial volume of dissolution medium was maintained by adding 5ml of fresh dissolution medium. Then determine the absorbance of Ketoconazole at λ max of 222nm by UV-Visible spectrophotometer.

Release Kinetics

Kinetic study was carried out by fitting the in vitro drug release data into Zero order, First order, Higuchi model, Hixson-Crowell Cube Root Law model and Korsmeyer- Peppas models. The best fit model was confirmed by the value of R² which is near to 1.

In vitro Antimicrobial Studies

The Antifungal activity was determined by agar diffusion technique using Candida albicans [ATCC NO 10231] as microorganism. Candida albicans (0.1 ml of 10⁶ CFU/ml) were inoculated into 20 ml of Sabouraud Dextrose Agar medium; the contents were swirled gently to produce uniform mixture. The agar plates were allowed to cool and solidify. Sterile cork borer were used to form equidistant wells in the agar plate. 1 ml of prepared lozenge solution
was introduced into the respective wells using sterile micropipette. Pure drug solution was used as standard. The plates were incubated at 37°C for 24 hr. The clear zone was measured.

**Stability Studies**

The stability studies were carried out as per ICH guidelines. The optimized formulation (F3) was packed in amber colored screw capped bottles. It was subjected to accelerated stability study for a period of 6 months using stability chamber at a temperature of 40 ± 2°C and RH 75 ± 5 %. The physical stability of the lozenges was inspected at initial, third and sixth month by checking physical appearances, hardness, friability, mouth dissolving time, % drug content and in vitro drug release profile.

**Results and Discussions**

1. **Drug- Excipients compatibility studies**

1.1 FTIR.

The FTIR spectrum of Ketoconazole exhibits a characteristics peak of C=O starching vibration of carbonyl group, C-O stretching of aliphatic ether group and C-O stretching of cyclic ether at 1647 cm⁻¹, 1031 cm⁻¹, 1244 cm⁻¹ respectively.

FTIR spectra of drug and its physical mixture with excipients are nearly same, and there is no shift of principle peaks or disappearance of principle peaks or modification of the principle peaks indicating that there is no interaction between the drug and excipients.

1.2 DSC

When drug was studied in combination with Excipients no change in melting point of drug was observed, no additional peaks were observed indicating compatibility of drug and excipient.

2. **Analytical methods**

The drug was analyzed using UV visible spectrophotometer. The drug exhibited λmax at 222 nm. The calibration curve was generated using different concentration (2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 µg/ml) of drug solution in the Beer-Lambert law. The data for calibration curve are shown in table and calibration curve is shown in figure no. 12.

3. **Evaluation of Lozenges**

The prepared formulations were evaluated for weight uniformity, hardness, friability, thickness, moisture content, mouth dissolving time, drug content for all batches. The hardness of the candy based lozenges ranges from 12.2-12.6 kg/cm². The friability was found to be designed formulation within the ranges of 0.11-0.43%. The mean
thickness of the prepared lozenges was found to be ranges from 4.96-5.27mm. The % of moisture content of all the formulation found to be below 1%.

This is due to fewer amounts of water soluble polymers and less water uptake. The mouth dissolving time of prepared lozenges is within the range of 30 minutes. Drug content was found to be in the range of 90.55-98.94%. So values of all the evaluation parameters are within the pharmacopoeial limits. Hence all the prepared lozenges have good physical appearance.

3.1 In vitro dissolution study

The rate at which lozenges dissolves is important because it is directly related to the rate at which the active drug is to the body. If the lozenges dissolve too fast, some of the drug may be lost as it is swallowed. Drug formulations to be dissolves at the designed rate. If the dissolution is too fast, the formulation is adjusted to dissolve more slowly.

In vitro drug release of lozenges tablets using standard USP dissolution apparatus, percentage of drug dissolution in buffer pH 6.8 for a period of 60 minutes at temperature 37°C are analyzed by using UV-spectrophotometer at 222.4 nm wavelength. The formulation batches F1,F2,F3,F4,F5,F6,F7,F8,F9,F10,F11,F12 shows percentage drug release of 94.44,93.55,98.23,97.14,90.38,89.01,96.77,95.13,93.54,91.45,93.83,95.21% respectively.

Weight 9.99gm, thickness is 5.14 mm, hardness 12.6 kg/cm², friability .11% and uniformity of drug content is 98.94%.

F3 batches shows better drug release compared with other batches. So we selected F3 is the optimized batch from all other formulations. Gelatin has a better drug release than other 2 hydrophilic polymers.

3.2 Release Kinetic Profile of Different Formulation

To determine the release mechanism that gives the best description to the pattern of drug release, the in vitro release data were fitted to zero order, first order, Hixson Crowell equation and Higuchi matrix model. The release data were also kinetically analyzed using the Korsmeyer- Peppas model. The accuracy and prediction ability of the models were compared by calculation of R² values as summarized in Table No. 31. The model giving R² close to unity was taken as the best fit model.

The value of ‘n’ indicates the drug release mechanism. The ‘n’ value is used to characterize different release mechanism concluding that value n=0.5 indicates Fickian diffusion and values of n between 0.5 and 1.0 or n=1.0 indicate non- Fickian mechanism.
The release kinetics data indicates that the release of drug from Lozenges best fits to first order release kinetics. \( R^2 \) values of first order kinetic equations were found to be close to unity indicating that the release from Lozenges was dependent on the concentration of drug present in the formulation. The data was fitted with Higuchi equation which gave almost a linear plot with highest \( R^2 \) indicating the mechanism of drug release was diffusion. The dissolution data was also plotted in accordance with Hixson-Crowell cube root law. To determine whether fickian or non-fickian diffusion existed, data was analyzed using the Korsmeyer-Peppas equation. The \( n \) value determined lies between 0.5 and 1.0 indicates it follows non-Fickian diffusion.

These observations showed that mechanism of drug release for all the formulation was Non-fickian diffusion following first order kinetics and Higuchi model of drug release.

From each plot the formulation F3 showed better results when compared to other formulations.

On the basis of percent drug content, *in vitro* drug release profile, and release kinetics the Lozenges formulation (F3) of 150 mg Gelatin was selected as the best formulation. The optimized formulations were evaluated for Antimicrobial and stability studies.

### 3.3 Antimicrobial studies

The prepared Lozenges formulations showed antifungal activity when tested microbiologically by the agar diffusion technique using drug solution as standard. The result obtained as shown in fig. no 25. The study indicates that the formulated Lozenges film F3 containing Ketoconazole retained their antifungal activity and also it shows the similar effect as the standard Ketoconazole drug.

### 3.4 Stability Studies.

Stability studies were conducted in the optimized Lozenges formulation. The stability data are illustrated in the table no.4, 5. As observed from the data shown, the formulation showed that there was no significant change in the physical appearance, drug content (no loss of drug more than 5%), hardness, friability, mouth dissolving time and *in vitro* drug release profile. Hence, it is confirmed that the formulation were stable at elevated temperatures.

**Table no 1: Formulae for the Development of Ketoconazole Lozenges**

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<th>F6</th>
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Table no. 2: Calibration Curve Data of Ketoconazole
Table no 3: Evaluation Parameters of Lozenges.

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<th>Batch Code</th>
<th>Evaluation Parameters (mean ± S.D)*</th>
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Table no 4: % Cumulative drug release of formulations.

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Table no 5: R² values for Drug Release Kinetics

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<td>0.949</td>
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<tr>
<td>F6</td>
<td>0.705</td>
<td>0.918</td>
<td>0.962</td>
<td>0.868</td>
<td>0.744</td>
<td>0.935</td>
</tr>
<tr>
<td>Evaluations</td>
<td>Initial</td>
<td>After 3 month</td>
<td>After 6 month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>---------</td>
<td>---------------</td>
<td>---------------</td>
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<td></td>
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<tr>
<td>Hardness (Kg/cm²)</td>
<td>12.6</td>
<td>12.0</td>
<td>11.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Friability (%)</td>
<td>0.11</td>
<td>0.18</td>
<td>56.20</td>
<td></td>
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<tr>
<td>Mouth dissolving time (min)</td>
<td>30</td>
<td>26</td>
<td>22</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Drug content (%)</td>
<td>98.94</td>
<td>96.91</td>
<td>95.72</td>
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</table>

Table no. 6: stability studies data of optimized formulation.

<table>
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<tr>
<th>Time (min)</th>
<th>Initial % Drug Release</th>
<th>% Drug Release After 3 Month</th>
<th>% Drug Release After 6 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>58.03</td>
<td>53.47</td>
<td>51.36</td>
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<td>10</td>
<td>63.83</td>
<td>58.82</td>
<td>56.20</td>
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<td>20</td>
<td>76.68</td>
<td>72.15</td>
<td>69.87</td>
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<tr>
<td>30</td>
<td>82.07</td>
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<td>40</td>
<td>87.46</td>
<td>82.61</td>
<td>80.45</td>
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<tr>
<td>50</td>
<td>93.26</td>
<td>89.17</td>
<td>86.53</td>
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<td>60</td>
<td>98.23</td>
<td>95.11</td>
<td>93.87</td>
</tr>
</tbody>
</table>

Table no. 7: stability data of % drug release
Fig 1: FTIR of Ketoconazole

Fig 2: FTIR of Ketoconazole + Gelatin

Fig 3: FTIR of Ketoconazole + Acacia

Fig 4: FTIR of Ketoconazole + Tragacanth

Fig 5: DSC of Ketoconazole

Fig 6: DSC of Ketoconazole + Gelatin

Fig 7: DSC of Ketoconazole + Acacia

Fig 8: DSC of Ketoconazole + Tragacanth

Fig 9: Calibration Curve of Ketoconazole

(A) Drug Release of Lozenges Containing Gelatin

(B) Drug Release of Lozenges Containing Acacia
Fig 10: Comparison of *in vitro* drug release profile of Lozenges containing (A) Gelatin, (B) Acacia, (C) Tragacanth.

Fig 12: Zone of inhibition of optimized formula.

Fig 13: Lozenges of F1-F4 (Gelatin).

Fig 14: Lozenges of F5-F8 (Acacia).
Conclusion

The present study was focused on the formulation and evaluation of Ketoconazole Lozenges which dissolve slowly in the mouth which prevail over the problem of oral candidiasis which is commonly associated with pediatric, geriatric patients having a problem in swallowing tablets. Lozenge is a better delivery system as the effective concentration of drug can be maintained in oral cavity for a more prolonged period of time. Different types of Ketoconazole lozenges were formulated using addition of hydrophilic gum like Gelatin, Acacia, Tragacanth and the formulations were evaluated for various physicochemical parameters. In vitro drug release studies were carried out using USP dissolution apparatus type II. F3 were optimized based on in vitro drug release studies. F3 yield good result to sustain the drug release in salivary pH conditions for a period of 30 minutes. The stability studies proved that the prepared lozenges tablets were found to be stable when stored at 40ºC. The formulation F3 retained sufficient antifungal activity. These finding could be of potential use in designing such formulations for patients.

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Reference


