**Journal of Innovations in Pharmaceutical and Biological Sciences (JIPBS)**
ISSN: 2349-2759
Available online at www.jipbs.com

Research article

# Formulation and evaluation of metronidazole lozenges for oral thrush

**Siham Abdoun A.*[1], Reem Alenizi[2]**

[1]*Pharmaceutics Department, College of Pharmacy, Qassim University, KSA.*
[2]*Pharm D, College of Pharmacy, Qassim University, KSA.*

**Key words:** Metronidazole, Lozenges, Oral thrush, In-vitro release, Eudragit.

***Corresponding Author: Siham Abdoun A.,** Pharmaceutics Department, College of Pharmacy, Qassim University, KSA.

Vol. 6 (3), 05-10, Jul-Sep, 2019.

**Abstract**

**Background:** Metronidazole is an antimicrobial medication used for the treatment of a variety of parasitic and bacterial infections of the vagina, gynecological area, skin, intra-abdominal cavity, blood, bone, joint, nervous system, and heart. Metronidazole are market as tablet, capsule, cream, lotion, gel, and injection dosage form but still there is a need for new dosage forms which acts effectively and locally. The lozenges dosage forms will increase bioavailability, reducing gastric irritation and increase onset of action. Preparing lozenges dosage forms will provide suitable choice for geriatric and pediatric patients who can't swallow tablets formulation. **Objective:** This study aimed to formulate metronidazole as lozenges to improve delivery of drug to treat oral thrush. **Methods**: Lozenges were formulated using heating and congealing technique. Chocolate, Cherry and Eudragit E100 were used to mask bitter taste of metronidazole. Quality control tests were done to assess the formulated lozenges physically and chemically. **Results:** The quality control results revealed that the formulated lozenges had good quality as the content of metronidazole in lozenges was found 100.25± 0.25, their average weight (4.3g ± 0.19), while the mean thickness and diameter of lozenges were (5.29 mm ± 0.23) and (25.24 mm ± 0.18) respectively. The in-vitro drug release of MTZ-Chocolate and MTZ- Cherry show rapid release (86.92% & 82.5%) respectively in 10minute, while MTZ-Eudrigit show slow release 106.43% in 50 minutes. FTIR Spectral study revealed compatibility of MTZ with eudragit and other excipient. **Conclusion:** The moulded lozenges can provide an attractive alternative formulation of metronidazole medicament for oral thrush.

## Introduction

A dosage form is an integration of Active Pharmaceutical ingredient and excipient to facilitate administration, and delivery of medicine to the patient which variable in their absorption by the human body so different routes of administration are required; hence different dosage forms including many type of liquid, solid, and semisolid dosage forms are recommended [1]. Tablets are widespread use due to the advantages of simplicity, economy of preparation, stability, and convenience in packaging and accuracy of dosage, and ease of administration [2]. The United State Food and Drug Administration (USFDA) defines ''bioavailability' 'as ''rate and extent the active ingredient becomes available at the site of action after absorbed from a drug product'' [3]. The dissolution rate of the drug was a major factor determining the bioavailability of an orally administered drug product [3]. The IV injection is the only route of drug administration that will always result in 100% bioavailability, in which the total administered dose reaching the systemic circulation [4]. After drug is absorbed from stomach or small intestine it will pass through liver before entering systemic circulation, and this will result in large proportion of metabolism [5]. Lozenges are the flavoured medicated buccal tablet prepared to be sucked and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base [6]. Lozenges are used to relieve oropharyngeal symptoms, which are commonly caused by local infections and also for systemic effect provided the drug is well absorbed through the buccal linings or when it is swallowed [6]. It has various shapes, like flat, circular, octagonal, biconvex or cylinders. Depending on the type of lozenges, they may be prepared by moulding or by compression [7]. Lozenges display many advantages over the other dosage form of these are; administer easy to geriatric and paediatric population, has good taste, it prolongs the time of drug in the oral cavity to release a specific effect, prepared easily and no need water intake for administration; however, Lozenges could be accidental swallow by children. Recently single and multiple ingredients lozenges formulated for chronic illness, making patient's friendly use [8]. The mouth is

serving as a site for the absorption of drugs as it lined with a mucous membrane [9]. The main advantages of drugs administration by the buccal route over oral route; the drug is not damaged by acidic media of the stomach, and the achievement of therapeutic serum concentrations of the drug more rapidly [10]. The sublingual route is most favourite route of drug administration because of greater permeability of membranes and rich blood supply leading to more rapid absorption than other route. Metronidazole is an antimicrobial agent, used in medicine for more than 45 years and currently is the drug of choice for all anaerobic infections, it is active against a wide range of Gram-positive and Gram-negative bacteria mainly protozoa and even a few nematode worms. It is the drug of choice at present against trichomonal vaginitis, all forms of amoebiasis caused by *Entamoeba histolytica,* and Vincent's angina - an acute ulcerative condition of the mouth caused by anaerobic bacteria. [11]. Metronidazole appears to be readily absorbed after oral administration; different formulations are available like cream, gel tablets and oral liquid [12]. However, in the present study an attempt was made to develop metronidazole as lozenges to prevent the possible incompliance associated with the drug.

The objective of this study is to prepare metronidazole (MTZ) lozenge using three different types of taste mask agent; Eudragit E100 polymer (EDU), chocolate and cherry and to evaluate the formulated MTZ lozenges using in-vitro release and physicochemical properties of MTZ lozenges.

## Materials and methods

### Chemicals

Metronidazole was obtained as a gift from Ranbaxy Laboratories, Gurgaon, India, sucrose, anhydrous dextrose as additive base, Eudragit E100 was obtained from (El-Gomhouria Co., Cairo, Egypt), chocolate and cherry as taste masking agent and polyethylene glycol (Loba Chemie Pvt. Ltd, Mumbai, India) using as solubilising agent and sodium hydroxide, sodium dihydrogen phosphate from (Loba Chemie Pvt. Ltd, Mumbai, India), all chemicals used is of analytical grade.

### Equipments

UV-Visible Spectrophotometer, Jenway®, UK, Fourier Transform Infra-Red (FTIR), Alpha Bruker, Adam Sensitive balance.

### Method

### Preparation of medicated lozenges

Heating and congealing technique was used for the preparation of lozenges.

### Formula 1 MTZ and EDU

To mask the bitterness of metronidazole (MTZ) different formula were prepared one of which using the polymer Eudragit E100 (EDU). The MTZ and the polymer EDU were weighed in the ratio 1:3 and dissolved in 5ml of ethanol until become solution; the solution was heated in oven at 60°C until the solvent evaporates completely. The dried product was triturated with pestle into a fine powder and passed through sieve size 200 [13].

Syrupy base will be prepared by mixing 30g of sucrose and 8ml of water. A total of 15g Dextrose was dissolved in 4ml of water and was heated in high temperature till dextrose dissolves completely forming clear viscous syrup. Then the dextrose solution was poured into the sugar syrup and heated in high temperature till the colour changes to light yellow. An accurately 1 gram of metronidazole and mixture was weighed and dissolved in 1ml of PEG. The temperature was brought down below 80oC then drug was added. The solution was poured into the mould. The prepared lozenges were stored in room temperature till solidify.

### Formula 2 and 3

0.25 gm of MTZ was triturated separately with **2**ml of chocolate and cherry to mask the bitterness of MTZ, each formula was dissolved in 1 ml polyethylene glycol (PEG) until the particle dissolved and become solution.

The syrup was prepared using same method and the MTZ-Cherry and MTZ- Chocolate formula were added to the syrup and the solutions were poured into the mould and solidified at room temperature.

### Physicochemical analysis study

The prepared tablet lozenges will be subjected to various physico-chemical tests like, diameter, thickness, weight variation, and drug content evaluation [14].

### Diameter and Thickness

Diameter and thickness of the lozenges were measured using vernier callipers. The test was performed for 10 lozenges and standard deviation was calculated

### Weight variations

Ten lozenges were weighed individually on an electronic balance. The average weight was calculated; each lozenge weight was then compared with average weight to assure whether it was within permissible limits or not.

Average weight= weight of 10 lozenges/10

### Drug content

The drug content was tested by powdering the lozenge and dissolving an amount of the powder containing 0.01g of metronidazole in a 100ml volumetric flask using phosphate buffer pH 6.8 the solution was filtered using

whatman filter paper. The filtrate was analysed using spectrophotometer at wavelength 275nm.

### In- vitro drug release

### Preparation of phosphate buffer pH6.8

The buffer was prepared by mixing 175ml of 0.2M sodium hydroxide (NaOH) and 250ml of 0.2M sodium dihydrogen orthophosphate ($NaH_2PO_4$) and the volume was completed to 1000 ml using distilled water [15].

The in-vitro released was done usingphosphate buffer pH 6.8 maintain at 37±0.5°C, as the dissolution media and USP type II -dissolution apparatus; stirred at 100 rpm. 5ml aliquot samples were withdrawn at 5 min. interval and replaced immediately with an equal volume of the buffer the sample was analysed using Jeneway UV-Visible spectrophotometer at 275nm.

### Calibration curve

A stock of 1mg /ml of metronidazole standard solution was prepared using phosphate buffer pH 6.8. Aliquots from stock solution were accurately measured using volumetric pipette and diluted with phosphate buffer to obtain a concentration of 10-80 µg/ ml. This procedure was repeated twice. Each sample was analysed at 275nm using UV-Visible spectrophotometry.

### Drug excipients interaction studies

For studying drug-excipients interaction, prepared lozenges, excipient used and metronidazole were subjected for Fourier Transform Infra-Red (FTIR) studies.

### Statistical analysis

The statistical analyses were performed using SPSS version 2. The average, standard deviation, percentages and t-test were calculated.

## Results

### Organoleptic properties

Visual inspection for the lozenge was done after the solidification. The prepared MTZ - EDU lozenges formula was white in colour while the MTZ- chocolate lozenges were dark brown and MTZ-cherry yellowish as shown in figure 1.

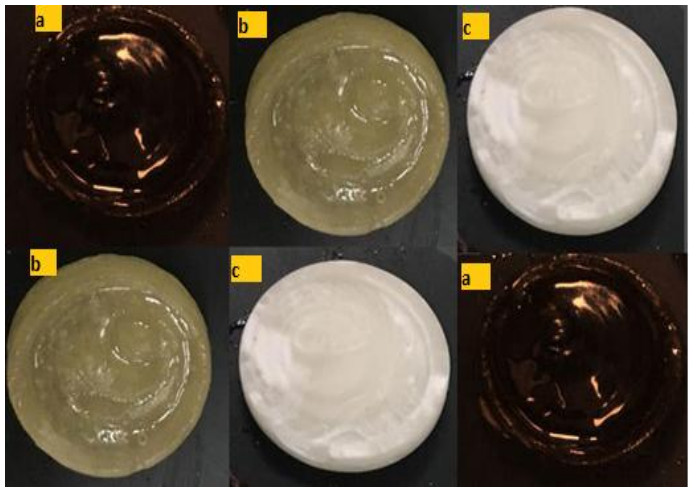


**Figure1. a:MTZ- chocolate, b:MTZ-cherry lozenge's and c:MTZ - EDU lozenges.**

### Physical evaluation of prepared lozenges

The prepared lozenges were subjected to physical evaluation of weight variation, thickness, and diameter. The average weight of lozenges was found (4.3g ± 0.19), while the mean thickness of lozenges was (5.29 mm ± 0.23) and the mean of lozenges diameter were found (25.24 mm ± 0.18) as shown in Table1.

### Drug excipients interaction studies

FT-IR Studies of pure metronidazole drug, eudragit substance and metronidazole lozenge are presented in Figure 2 and 3 respectively. FTIR spectra shows that no interactions between the drug and the excipients being used.

### Calibration curve

A calibration curve was constructed for pure metronidazole standard solution concentration against the corresponding absorbance. It gave linearity in the concentration range (10–80 µg/ml) with a regression of 0.995 as shown in figure 4.

### Drug chemical content

The content was determined using spectrophotometer and the percentage content was calculated, and compared with the USP acceptance criteria [15]. It was found to be in the range from 100.1-100.45% as shown in Table 2.

### In-vitro release test

The percentage release of metronidazole from different type of formulations was presented in figure 5.

**Table1. Physical characteristic of metronidazole lozenges.**

| Type of test / S. No. | Uniformity of weight (g) | Thickness (mm) | Diameter (mm) |
|---|---|---|---|
| **1** | 4.46 | 5.2 | 25.2 |
| **2** | 4.33 | 5.3 | 25.5 |
| **3** | 4.14 | 5.1 | 25.4 |
| **4** | 4.72 | 5.3 | 25 |
| **5** | 4.21 | 5.8 | 25.1 |
| **6** | 4.24 | 5.2 | 25.2 |
| **7** | 4.1 | 5.15 | 25.25 |
| **8** | 4.41 | 5.2 | 25.1 |
| **9** | 4.12 | 5.1 | 25.1 |
| **10** | 4.25 | 5.6 | 25.5 |
| **Average** | **4.30** | **5.29** | **25.24** |
| **SD** | **0.19*** | **0.23*** | **0.18*** |

***USP Acceptance limit: NMT 6.**

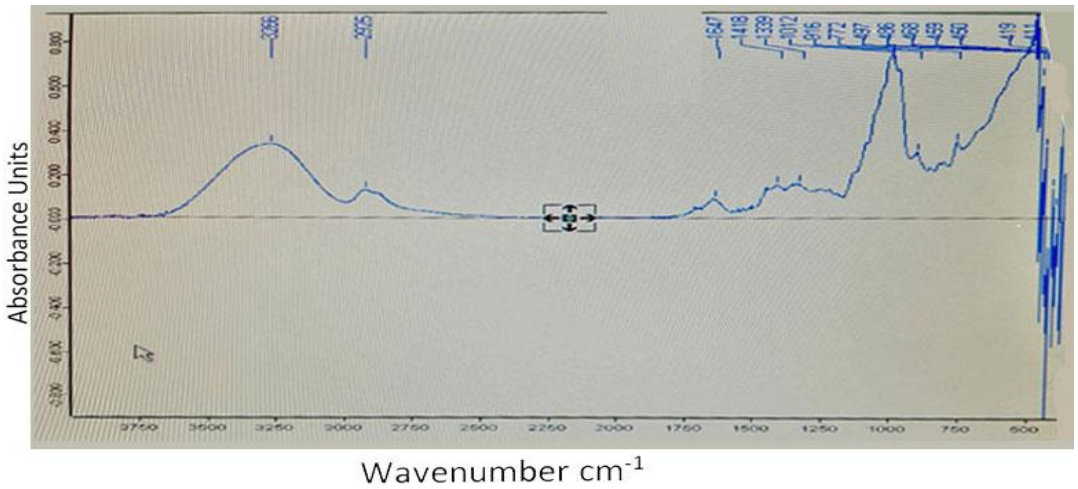


**Figure 2. FTIR spectrum of metronidazole standard substance.**

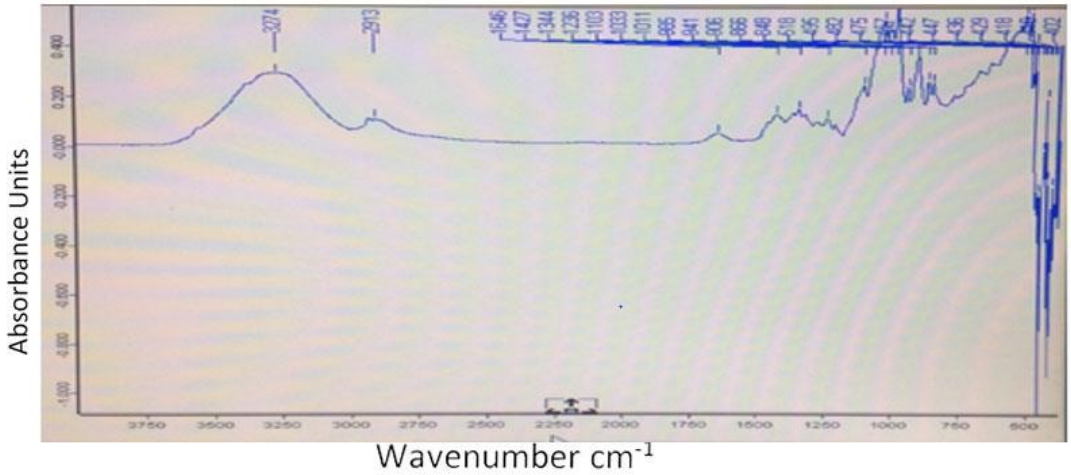


**Figure 3. FTIR spectrum of Metronidazole lozenges with Eudrigit.**

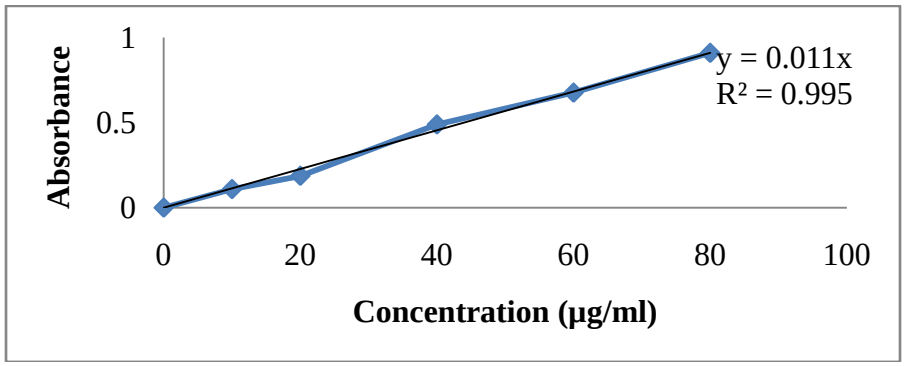


**Figure 4. Calibration curve of metronidazole using UV-Spectrophotometer.**

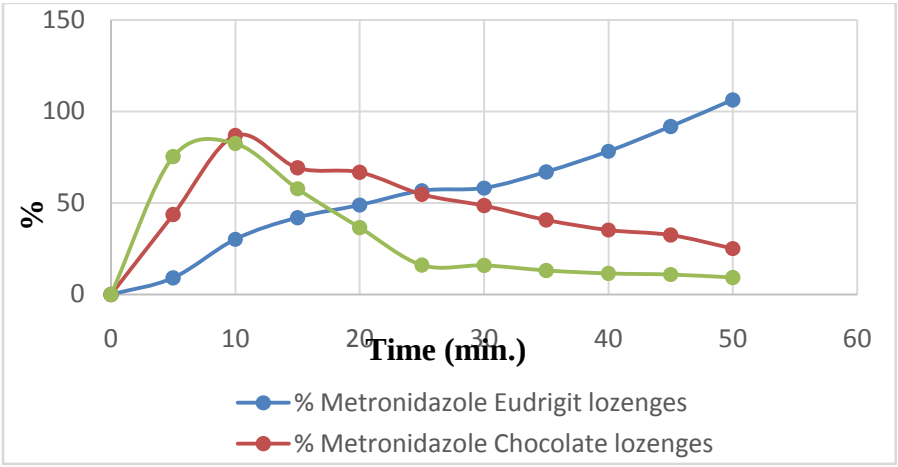


**Figure 5. The release of metronidazole from different type of lozenges.**

**Table 2. Percentage content of the metronidazole in the three formulated lozenges.**

| S. No. | % (w/w) Content MTZ-EDU | % (w/w) Content MTZ-Chocolate | % (w/w) Content MTZ- Cherry |
|---|---|---|---|
| **1** | 100.1 | 99.5 | 98.3 |
| **2** | 100.45 | 98.7 | 97.9 |
| **3** | 100.2 | 100.1 | 99.5 |
| **Average** | 100.25 | 99.43 | 98.57 |
| **SD** | 0.25 | 0.70 | 0.83 |

* USP SD; Acceptance limit NMT 2.

## Discussion

Lozenges display many advantages over the other dosage form of these are; administer easy to geriatric and pediatric population, has good taste, it prolongs the time of drug in the oral cavity to release a specific effect, prepared easily and no need water intake for administration, this study aimed to formulate metronidazole as lozenges to improve delivery to treat oral thrush.

The prepared formulations were subjected to various physical and chemical tests like assay, weight variation and in-vitro release etc. Some selected formulations were tested for drug excipients interactions using FTIR Spectral analysis

Organoleptic properties of MTZ lozenge: All developed lozenge formulae were inspected for their homogeneity, colour, and presence of lumps, no notable change was observed in the sample on visual observation. The prepared MTZ- EDU lozenges were white in colour whereas MTZ –chocolate was dark. Table 1 show the result of weight variation indicting that all prepared MTZ lozenge has an average weight of 4.30g ± 0.19 which is in accordance with requirement of British pharmacopeia [15].

The mean content of lozenge preparation was 100.25% ± 0.25 for MTZ-EDU, and 99.43 ± 0.70 and 98.57 ± 0.83 of the labelled amount for MTZ – Chocolate and MTZ-Cherry respectively, which is in the acceptable range of USP; our results were similar to that of formulated Clotrimazole tablet lozenges prepared by Nagoba Shivappa N. *et al.* [7].

In addition, the physicochemical characteristics revealed that the prepared MTZ lozenges had an average thickness and diameter 5.295mm ± 0.23, 25.235mm ± 0.18 respectively.

FTIR study was performed to investigate if any interaction has been occurred between metronidazole (MTZ) and the excipient in the formulation. The FTIR spectra illustrate compatibility between MTZ, and the formulation excipient as shown in figure 2 and 3 respectively.

The FTIR spectrum of MTZ showed characteristic peak at 3266 $cm^{-1}$ and 2925$cm^{-1}$ while a lozenge of MTZ with EDU polymer showed peak at 3264$cm^{-1}$ and at 2913$cm^{-1}$ which is similar to that of pure drug.

The result of FTIR spectra it revealed that MTZ didn't subjected to interaction by EDU polymer and lozenges base substances which analogous to the study done by Bharkad VB, *et al.,* [13]. As study done for fluconazole lozenges FTIR spectrum which exhibits a characteristic peak at 3071$cm^{-1}$, 3117$cm^{-1}$, 1619$cm^{-1}$, 1506$cm^{-1}$ and 1419$cm^{-1}$ FTIR-spectra of drug and with its formulated excipients, there is no shift of peaks which indicate there were no incompatibility between the drug and additives [16].

The in-vitro drug released was determined using the linearity curve. The results showed that the metronidazole was linear in the concentration range (10-80 µg/ml). The regression coefficient ($R^2$) was found to be 0.995 as shows in figure 4.

MTZ lozenges were prepared using EDU, chocolate and cherry the release of drug from these formulations were done using phosphate buffer pH 6.8 as dissolution media.

Figure 5 illustrate the effect of lozenge bases on the release of MTZ- EDU lozenge bases gave a slower release rate of MTZ than that from chocolate and cherry. In vitro release studies showed 100%, 100% and 80% release of MTZ; after 50min, 10min and 5min from eudragit, chocolate and cherry lozenge bases respectively. We observe the MTZ – EDU lozenges has slower release compare to MTZ -chocolate lozenge so, we chose administer the MTZ- EDU lozenge as we want long acting effect of MTZ medicated, on the other hand administer MTZ -chocolate and MTZ – cherry lozenges have rapid onset and short acting. In study of clotrimazole lozenges formulation in different polymer showed that the drug release in 30 minutes was 97.45% and 91.76% from guar gum methyl cellulose based formulation respectively. However, 97.31% drug release in 7 min. from formulation not containing polymer. Our results revealed that eudragit lozenge bases gave a slower release rate of MTZ than that from chocolate and cherry.

## Conclusion

The present work is focused on the formulation of metronidazole as lozenges, which have various advantages over other dosage form one of which is the increase of bioavailability as it is a major factor responsible for the pharmacological activity of any drug. The three formulation show good quality control test and release of metronidazole, MTZ - EDU show sustain release compared to MTZ-Chocolate and MTZ-Cherry. The lozenges are ease administered to children and elder patient in addition it masks bitterness of most drugs and has prolonged action. Moreover, it is preparation is ease and rapid in addition the less cost and equipment are required for their manufacture in comparing with other solid dosage forms.

## Conflict of interest

The authors confirm that this article content has no conflict of interest.

### References


1. Ritschel WA, Kearns GL. Handbook of Basic Pharmacokinetics: Including clinical applications 6th ed. Washington, DC: American Pharmacists Association, 2004.
2. Linda A. Felton, Oral Solid Dosage Forms. Remington essential of pharmaceutics. Lambeth High Street, London SE1 7JN, UK: Pharmaceutical Press; 2012; 581
3. Chow SC, Liu JP. Design and Analysis of Bioavailability and Bioequivalence Studies. 3. Chapman Hall/CRC Press, Taylor & Francis; New York, New York, USA: 2008.
4. Griffin, J. P. The Textbook of Pharmaceutical Medicine (6th ed.). Jersey: BMJ Books. ISBN 978-1-4051-8035-1, 2009.
5. Susan M Pond, Tozer, Thomas N. "First-Pass Elimination", Clinical Pharmacokinetics. 1984; 9 (1): 1–25.
6. Umashankar M S, Dinesh S R, Rini R, Lakshmi K S, Damodharan N: Chewable Lozenge Formulation- A Review. Int. Res. J. Pharm. 2016; 7 (4): 9-16.
7. Nagoba Shivappa N, Purushotham Rao K, Zakaullah S. Formulation of Clotrimazole as lozenge tablet for improved delivery to oral thrush. Journal of Pharmaceutical and Biomedical Sciences (JPBMS) 2011; 12(12):1-4.
8. Stephen O. Majekodunmi. A review on lozenges. American Journal of Medicine and Medical Sciences 2015; 5(2):99-104.
9. Rakesh H., Mohit T. and Kiran K. A Review on Oral Mucosal Drug Delivery System, The Pharma Innovation 1(1):2012; 15.
10. James C.M. and Carmel M.H. Drug Delivery: Buccal Route, in: Swarbrick J, Boylan JC, editors. Encyclopedia of Pharmaceutical Technology: 3th edition, New York, 2007.
11. Sonja L. Charlotta E. and Carl E. N. Metronidazole is Still the Drug of Choice for Treatment of Anaerobic Infections Metronidazole. Clinical Infectious Diseases 2010; 50:16–23.
12. Committee J. British National Formulary (BNF) 69. London and Chicago: Pharmaceutical Press; 2015.
13. Bhatti A, Singh T. Preparation of tablets rapidly disintegrating in saliva containing bitter taste-masked granules by compression method. Indian Journal of Pharmaceutical Sciences 2007; 69(1):80.
14. Pharmacopoeia US. 30/NF25. US Pharmacopoeial Convention, Rockville, MD 2013 May (Vol. 1691).
15. Pharmacopoeia British. Version 11.0. Appendices: XII A, XII G, XVII G. 2013.
16. Bharkad VB, Kada VS, Shinde SG, Jadhav SB, Zameeruddin M, Shendarkar GR. Formulation and Evaluation of Lozenges Tablet of Fluconazole. American Journal of Pharm Research 2015; 5(01): 32071-32076.