

RESEARCH PAPER

Formulation and Evaluation of soft lozenges of Misopristol for Abortifacient activity in Rat model

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Abstract

Background: Misoprostol is a synthetic prostaglandin E1 analogue commonly used in obstetrics and gynecology. The available dosage forms may present limitations related to administration, patient acceptability, and drug release. Soft lozenges may provide an alternative dosage form by allowing gradual drug release and improving ease of administration. Objective: This study was undertaken to formulate and evaluate misoprostol soft lozenges and to assess their physicochemical properties, in vitro drug release, and short-term stability. Methods: Soft lozenges containing 2 mg of misoprostol were prepared by the melting-moulding method using gelatin, propylene glycol, sucrose, distilled water, and a colouring agent. The formulations were optimized using a factorial design and evaluated for appearance, thickness, weight variation, hardness, friability, drug content, disintegration time, in vitro dissolution, and stability according to standard procedures. Drug release data were analysed using kinetic models. Results: The optimized formulation produced uniform coffee bean-shaped lozenges with a thickness of 0.31 cm, weight of 434 mg, hardness of 15.78 kg/cm², friability of 0.898%, drug content of 82.5%, and a disintegration time of 47 min. The formulation released 91.70% of misoprostol within 50 min, and the release profile was best fitted to the zero order model ($R^2 = 0.9978$). Stability testing carried out for one month under ICH-recommended conditions showed no appreciable changes in the evaluated parameters. Conclusion: The prepared misoprostol soft lozenges showed acceptable pharmaceutical characteristics, sustained drug release, and satisfactory short-term stability. These findings indicate that the developed formulation may be considered a suitable oral dosage form for misoprostol. Further in vivo and clinical studies are required to establish its therapeutic performance.

Keywords: Misoprostol, obstetrics, gynecology, soft lozenges, melting-moulding method, in vitro release study, factorial design.

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1. INTRODUCTION

Abortifacient drugs are available in different dosage forms, including oral tablets, vaginal tablets, buccal tablets, sublingual tablets, and oral solutions. Misoprostol, either alone or in combination with mifepristone, is widely used for medical abortion in early pregnancy. However, the available formulations have certain drawbacks. Oral tablets may undergo first-pass metabolism, which can affect drug availability and may require repeated dosing. Vaginal administration may result in variable absorption due to differences in vaginal conditions and difficulties associated with application. Buccal and sublingual tablets provide faster absorption but may cause an unpleasant taste, oral irritation, increased salivation, and discomfort due to the need to keep the tablet in the mouth until complete dissolution. Conventional tablets may also have limitations related to swallowing difficulty and control over drug release. These challenges indicate the need for alternative dosage forms with improved patient convenience, acceptability, and consistent drug delivery¹.

Lozenges were created in pharmacies during the 20th century and are still produced on a commercial basis. Solid drugs that dissolve in the mouth or throat are called lozenges. They can be used for systemic medication absorption in addition to treating localized oral or pharyngeal irritation or infection. They might contain one or more medications in a base that has been sweetened and flavored. They can disperse medications into the mouth cavity or on the mucosal surface in a number of ways^{2,3}. The patient determines the rate of breakdown and absorption by sucking on the lozenge until it dissolves, even though it takes about 30 minutes. Because of this, the amount of medication administered each time the lozenge is taken may vary significantly⁴. Depending on their type, lozenges are either molded or compressed. Troches are compressed lozenges, whereas molded lozenges are also known as pastilles¹. Lozenges should be smooth, with no sharp edges, and dissolve gradually in the mouth. Lozenges can be flat, circular, octagonal, biconvex, or bacilli, which are short rods or cylinders⁴. While some lozenge formulations are prescribed by doctors, most are available as over-the-counter (OTC) medications that don't need a prescription.

Medicated Soft lozenges:

Because they are simple to make and can be used with a variety of medications, soft lozenges have become increasingly popular. Polyethylene glycols, acacia, or other similar materials are frequently combined to form the bases⁵. Pastilles are a type of soft lozenges that contain a medication in a base of glycerol-gelatin, gelatin, or acacia: sucrose. Soft lozenges have a connection to "confection," a traditional form of medicine that is currently experiencing a resurgence. Soft, saccharinated masses with medicinal ingredients are called confections. Their current use has been significantly enhanced by the use of polymers (polyethylene glycols) as the dosage form matrix⁶. They are easy to use, carry around, taste good, and store easily (at room temperature). Many medications have an unpleasant, bitter taste when taken orally, and this discomfort causes patients to not comply. For medicated soft lozenges, eliminating the bitter taste and increasing bioavailability while simultaneously improving oral feel has been a major concern.

Misoprostol:

A synthetic prostaglandin E1 analogue called misoprostol is sold as an oral medication to prevent and treat gastroduodenal damage brought on by nonsteroidal anti-inflammatory drugs (NSAIDs). Misoprostol, however, is used off-label for a number of purposes in obstetrics and gynecology, such as

medication abortion, medical management of miscarriage, labor induction, cervical ripening prior to surgery, and postpartum hemorrhage treatment. Cervical softening and dilatation, uterine contractions, nausea, vomiting, diarrhea, fever, and chills are among the dose-dependent side effects of misoprostol⁷.

2. MATERIALS AND METHODS

a. Collection of materials

The misoprostol was procured from the SM Pharma Pvt. Ltd. And the remaining chemicals including gelatin, propylene glycol and sucrose were purchased from LOBA CHEMIE Pvt. Ltd. Which are analytical grade.

b. Preparation of soft lozenges

The preparation of misoprostol soft lozenges was based on melting and moulding principle. In a clean and dry beaker gelatin and propylene glycol base was taken, at 45°C base was heated with the help hot plate and magnetic stirrer was stirring. In the heated base sucrose and distilled water was added stirring was continued with 100°C to produce clear solution of sweetener and base. For the addition of Misoprostol the temperature of solution was made to 60°C and stirred to make it homogeneous. Coloring agent added to look bright. The whole solution was gushed into silicon mould and rested it to room temperature to get solidify⁸. Each soft lozenges contains 2mg of Misoprostol as per formula given in table no.01.

Table no.01 Code levels of Design Expert software for Independent variables

Independent variables	Coded levels		
X1 (Gelatin)	-1	0	+1
X2 (Propylene glycol)	-1	0	+1
X3 (Sucrose)	-1	0	+1

Experimental runs by 3³ factorial design in DoE:

Table no.02 DoE Independent variables

Sr.no.	Formulation	X1 Gelatin (gm)	X2 Propylene glycol (ml)	X3 Sucrose (gm)	Misoprostol (mg)	Distilled Water (ml)
1.	F1	3	1	1	20	10
2.	F2	7	1	1	20	10
3.	F3	3	3	1	20	10
4.	F4	7	3	1	20	10
5.	F5	3	1	2	20	10
6.	F6	7	1	2	20	10
7.	F7	3	3	2	20	10
8.	F8	7	3	2	20	10
9.	F9	3	2	1.5	20	10

10.	F10	7	2	1.5	20	10
11.	F11	5	1	1.5	20	10
12.	F12	5	3	1.5	20	10
13.	F13	5	2	1	20	10
14.	F14	5	2	2	20	10
15.	F15	5	2	1.5	20	10
16.	F16	5	2	1.5	20	10
17.	F17	5	2	1.5	20	10

c. Evaluation of soft lozenges

i. Physical appearance

The prepared Misoprostol soft lozenges were physically evaluated with color, shape, etc⁹.

ii. Diameter and thickness

For the lozenges to be uniform in size, diameter and thickness are indispensable was calculated using a Vernier caliper⁹.

iii. Weight variation

To ensure that the weight of lozenges in a batch is consistent, weight variation is used. The USP weight variation test was utilized by weighing 20 medicated soft lozenges from each formulation separately, calculating the average weight, and comparing the individual lozenge weights to the average⁹.

iv. Hardness

The hardness of medicated lozenges establishes how resistant they are to breaking or moving during handling, storage, and transportation before use. The medicated soft lozenges' hardness was examined using Monsanto hardness testers, and the amount of force needed to break them was noted⁹. The hardness was measured in kg/cm².

v. Friability test

The Roche friabilator was used to determine the medicated soft lozenges' friability. After weighing the twenty lozenges from the batch, they were put in a friabilator and rotated for four minutes at 25 rpm. The lozenges were taken out, cleaned of dust, and weighed again after four minutes⁸.

vi. Drug content uniformity

The soft lozenges from the batch were taken and triturated independently. The phosphate buffer of pH 6.4 was added to a beaker containing powder equal to the drug's dosage equal to powder, and the mixture was vigorously shaken for five minutes. Lastly, phosphate buffer pH 6.4 was added to increase the volume up to 100 ml, and Whatman filter paper was used to filter the whole mixture. After the solution was appropriately diluted, the drug content was estimated by spectrophotometrically measuring the absorbance of the filtered solution at 200 nm using a Shimadzu UV visible spectrophotometer 1800 against a blank of phosphate buffer pH 6.4⁸.

vii. Disintegration test

The USP Disintegration apparatus is used to compute the disintegration time of lozenges from the batch. Disintegration time was measured in phosphate buffer with a pH of 6.45 at room temperature (37°C)⁸.

viii. In-vitro release test

The USP II dissolution apparatus (paddle type) was used for this analysis. The vessel was filled with medicated lozenges that contained 2 mg of Misoprostol from the batch. The dissolution study was carried out in 900 ml of phosphate buffer of pH 6.4 at 100 rpm using the USP II paddle method while keeping the temperature at 37±2°C. The absorbance of the solution was measured at 200 nm using the Shimadzu UV visible spectrophotometer. Samples (5 ml) of the solution were taken out every five minutes and substituted right away with an equal volume of fresh Phosphate buffer pH 6.4. The extracted solution was diluted up to 10 ml with Phosphate buffer pH 6.4⁸.

ix. Stability analysis

Drug stability is the ability of a specific formulation in a specific container to stay within its physical, chemical, therapeutic, and toxicological standards. For the stability study parameters like color, shape, thickness, weight variation, drug content, etc. are chose. This study aimed to show how different environmental factors, affect a drug substances or drug product's quality over time. In accordance with the International Council for Harmonization's (ICH) guidelines, medicated soft lozenges of Misoprostol were placed in a container and exposed to 37°C for one months. The physical and chemical characteristics of Misoprostol soft lozenges were assessed¹⁰.

x. Statistical analysis

Design Expert®, version 12.0.3.0 was used to calculate the statistical significance ANOVA with extreme probability level of significance (p<0.05).

3. RESULT

i. Evaluation of formulated soft lozenges

The results of various parameters are enlisted in table no.03.

Table no. 03 Evaluation of different formulations

Parameter	F14	F10	F17
Physical Appearance	Colour: Red Shape: Coffee bean	Colour: Red Shape: Coffee bean	Colour: Red Shape: Coffee bean
Thickness (cm)	0.31	0.29	0.29
Weight Variation (mg)	434	432	430
Hardness (kg/cm ²)	15.78	15.53	15.21
Friability Test (%)	0.898	0.891	0.885
Drug Content (%)	82.5	81.5	81.4
Disintegration time (min)	47	50	51

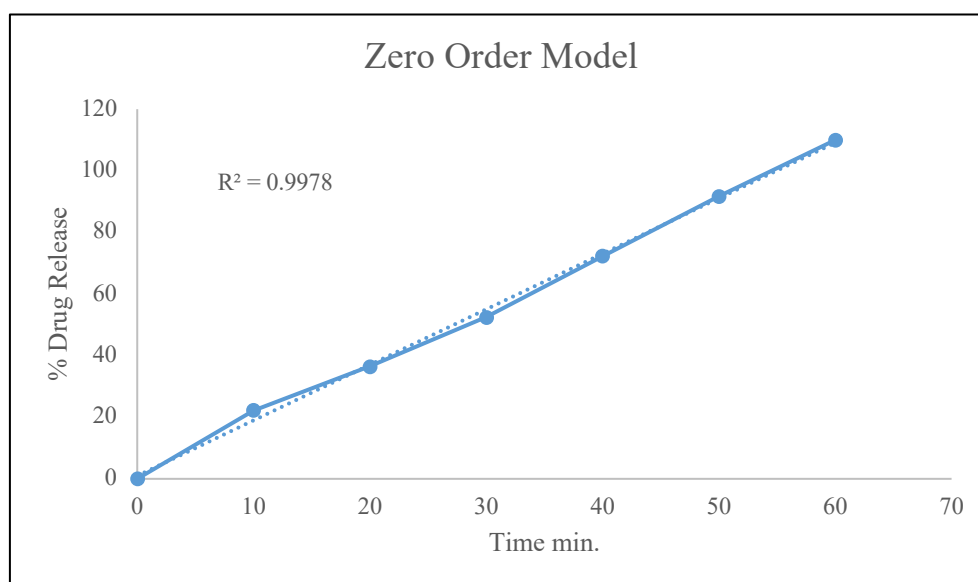
ii. **In- vitro release test**

The in vitro release data are shown below table no.04

Table no.04 In vitro release data of F14th formulation

Time (min)	% Drug release
10	22.25
20	36.49
30	52.47
40	72.34
50	91.70
60	109.98

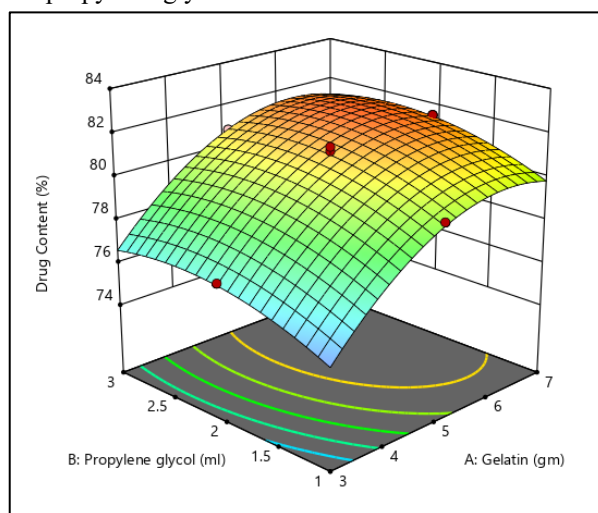
The formulated soft lozenges give 92% of drug release after 50 mins. of dissolution. The release data gives linear graph (Fig. no.000) of percentage drug release against the time in minutes. The plotted graph is of zero order plot with the R^2 of 0.9978.

Fig. no. 01 In vitro dissolution data of Misoprostol soft lozenges (F14)**iii. Statistical Analysis**

The response surface plot obtained using Design-Expert® software shows the combined effect of gelatin (Factor A) and propylene glycol (Factor B) on the drug content (%) of misoprostol soft lozenges. The three-dimensional response surface plot indicate that both variables influenced the drug content. As the gelatin concentration increased from low to intermediate levels, drug content also increased, probably due to better matrix formation and improved entrapment of misoprostol. A similar trend was observed with propylene glycol, where intermediate concentrations improved drug distribution within the formulation. The highest drug content (about 91.70% at 50 min) was obtained with 5 g of gelatin and 2.0 mL of propylene glycol. At

higher concentrations, drug content decreased slightly, which may be related to changes in matrix viscosity affecting drug distribution. The elliptical contour plot indicates an interaction between gelatin and propylene glycol. The predicted values were in close agreement with the experimental results, showing that the Design-Expert® model was suitable for optimization of the formulation.

$$Y1 (\text{Drug Content}) = 7.49051 + 0.310094 * \text{Gelatin} + 0.253326 * \text{Propylene glycol} + 0.273805 * \text{Sucrose} + -0.00416566 * \text{Gelatin} * \text{Propylene glycol} + 0.0114529 * \text{Gelatin} * \text{Sucrose} + -0.0100127 * \text{Propylene glycol} * \text{Sucrose} + -0.0253722 * \text{Gelatin}^2 + -0.0446059 * \text{Propylene glycol}^2 + -0.0689174 * \text{Sucrose}^2$$

**Fig. no.02 3D response surface methodology****iv. Stability study**

The stability study was examined as per ICH guidelines for the soft lozenges after one month and

the data was interpreted in the table no. 000. No any kind of significant change was noticed in the drug content.

Table no.05 Stability data of Misoprostol lozenges (F14) after 35 days

Parameters	Lozenges values
Physical appearance	Colour- Red Shape- Coffee bean
Thickness (cm)	0.28
Weight variation (mg)	429
Friability test (%)	0.894
Drug content (%)	82.5
Disintegration time (min)	49

4. DISCUSSION

The study focused on the formulation and evaluation of misoprostol soft lozenges prepared by the melting–moulding method. The optimized formulation showed acceptable physical characteristics and sustained drug release. Gelatin, propylene glycol, and sucrose produced smooth, coffee bean-shaped lozenges with sufficient mechanical strength for handling. The optimized batch showed a hardness of **15.78 kg/cm²**, friability below **1%**, and uniform weight, indicating good physical quality. The drug content was found to be **82.5%**. Although this confirmed the incorporation of misoprostol into the formulation, the value was lower than the pharmacopeial limit. This may be due to the heat sensitivity of misoprostol, uneven drug distribution, or minor losses during the moulding process. Optimization of processing conditions may improve drug content in future studies. The lozenges disintegrated in **47 minutes**, showing slow erosion of the gelatin matrix. In vitro dissolution studies showed **91.70%** drug release within **50 minutes**, indicating gradual release of the drug from the matrix. Drug-release data fitted the **zero order model ($R^2 = 0.9978$)**, suggesting that release occurred through a combination of diffusion and matrix erosion. The formulation remained stable during one month of storage under recommended conditions. No noticeable changes were observed in appearance, friability, drug content, or disintegration time. These findings indicate that gelatin-based soft lozenges can be developed as a sustained-release oral dosage form for misoprostol. Further work should focus on improving drug content, evaluating long-term stability, and conducting pharmacokinetic, bioavailability, and clinical studies to confirm their therapeutic performance.

5. CONCLUSION

Misoprostol soft lozenges were prepared successfully by the melting–moulding method and showed acceptable physical characteristics, mechanical strength, and short-

term stability. The optimized formulation exhibited uniform appearance, low friability, satisfactory hardness, and a drug release of 91.70% within 50 minutes. The release profile followed the zero order model, indicating controlled drug release from the gelatin-based matrix. No noticeable changes in the evaluated parameters were observed during the one-month stability study. These findings indicate that soft lozenges may serve as a suitable oral dosage form for misoprostol. Further pharmacokinetic, in vivo, and clinical studies are needed to establish their therapeutic performance and clinical applicability.

6. AUTHOR CONTRIBUTION

Bhagyashri Gore- Data curation, original draft writing and editing. Vrunal More- Conceptualization, data validation, reviewing and editing. Prajakta Khule- Data validation, reviewing and editing.

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