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FORMULATION DEVELOPMENT AND EVALUATION OF ANTIEMETIC LOZENGES OF ONDANSETRON HYDROCHLORIDE

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Abstract: The present investigation aims to design, prepare and evaluate the medicated lozenges of Ondansetron hydrochloride for the treatment of chemotherapy induced nausea and vomiting. Ondansetron hydrochloride is a selective serotonin receptor (5-HT₃) antagonist. Taste masking was done by complexing Ondansetron HCl with Eudragit E100 in ratio 1:1. The benefits of these prepared lozenges showed increase in bioavailability, reduction in gastric irritation by passing of first pass metabolism and increase in onset of action. The lozenges were prepared by heating and congealing method using sucrose as base; sodium carboxy methyl cellulose (NaCMC), hydroxy propyl methyl cellulose (HPMC K₄M) and methyl cellulose (MC) are used as polymers and comparing with lozenges of without hydrocolloids. It was found that the formulation without hydrocolloids (F₀) was more stable compare to other formulations. All the prepared formulations were characterized for drug content uniformity, hardness, thickness, diameter, weight variation, moisture content, *in-vitro* dissolution by pharmaceutical standard methods. Accelerated stability study conducted as per ICH guidelines (zone IV) at 45°C and 75% relative humidity over a period of seven weeks found that there wasn't any substantial interaction between the drugs, flavor and color and the prepared formulations were stable.

Keywords: Medicated Lozenge, Mold, Ondansetron hydrochloride, Chemotherapy induced nausea and vomiting (CINV).

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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^(1,2). Lozenges are used for patients who cannot swallow solid oral dosage forms as well as for medications designed to be released slowly to yield a constant level of drug in the oral cavity or to bathe the throat tissues in a solution of the drug³.

Chemotherapy-induced nausea and vomiting (CINV) is one of the most feared and severe side effects of cancer treatment⁴. CINV may jeopardize the nutritional status of patients; thereby it may reduce the performance status and ability to tolerate further cycles of chemotherapy⁵.

Ondansetron hydrochloride is a competitive serotonin receptor (5-HT₃) antagonist. It is effective in treatment of nausea and vomiting caused by cytotoxic chemotherapeutic drugs, including cisplatin and has reported anxiolytic and neuroleptic properties⁶. The present investigation is design to improve patient compliance. Lozenges are commonly used for the purpose of local and systemic effect through the buccal mucosa. The present work is aimed at to antiemetic lozenges meant for systemic effects.

MATERIALS AND METHODS

Materials

Ondansetron HCl was obtained as a gift sample from Sozin Flora Pharma, Kalaamb, (H.P.). HPMC K₄M, Eudragit E100 and citric acid (Yarrow Chem products, Mumbai), Sucrose (Merck specialties private limited, Mumbai), MC and NaCMC (Sd-fine chem. Limited, Mumbai). All chemicals were of analytical reagent grade and distilled water was used throughout the study.

Methods

Taste masking of drug by forming drug polymer complex

Complex of Ondansetron HCl and Eudragit E-100 was done by pressurized homogenization method. Saturated solutions of both drug and polymer (1:1 w/w) were prepared in isopropyl alcohol and injected with the help of needle into 20 ml of distilled water with constant stirring at 500 rpm for about 45 mins with the help of IKA homogenizer. Volatile solvent was evaporated by solvent evaporation method and mixture was dried at 65° C in hot air oven for 24 hours under vacuum. The dried mixture used for further studies⁷.

Method of preparation of medicated lozenges^{8,9}

The methodology include-Heating and congealing method.

Procedure: Heating and congealing technique

1. Syrupy base to be prepared by dissolving the required amount of sugar by heating at 110°C for about 90 mins.
2. Cooling to obtain the plastic mass.
3. Addition of drug, polymer, colour, flavour with mixing.
4. Pour the mixture into mold of desired shape and allow cooling it at room temperature.
5. Wrapping the lozenges with polyethylene wraps.

FORMULATION TABLE

Table-1:- Working formula for lozenges

BATCH	WITHOUT HYDROCOLLOIDS (F ₀)	METHYL CELLULOSE (F ₁)	SODIUM CMC (F ₂)	HPMC K ₄ M (F ₃)
DRUG- ONDANSETRON HYDROCHLORIDE	8 mg	8 mg	8 mg	8 mg
EUDRAGIT E100	8 mg	8 mg	8 mg	8 mg
SUCROSE	q.s	q.s	q.s	q.s
METHYL CELLULOSE	-	50 mg	-	-
Na-CMC	-	-	50 mg	-
HPMCK4M	-	-	-	50 mg
CITRIC ACID	30 mg	30 mg	30 mg	30 mg
FLAVOURING AGENT	5 mg	5 mg	5 mg	5 mg
Total Weight	3gm	3gm	3gm	3gm

- Each lozenge contains 8 mg of Drug.
- Each lozenges weight 3gm only

EVALUATION¹⁰

All the formulations prepared were subjected to different evaluation parameter as subjected below:

a) Weight Variation

The weight of the lozenges being made was routinely determined to ensure that a lozenge contains the proper amount of drug. The USP weight variation test is done by weighing 20 lozenges individually, calculating the average weight and comparing the individual weights to the average. The lozenges met the USP specification that not more than 2 lozenges are outside the percentage limits and no lozenges differs by more than 2 times the percentage limit.

b) Hardness

The hardness of each batch of lozenges was checked by using Monsanto hardness tester. The hardness was measured in terms of kg/cm². 3 lozenges were chosen randomly and tested for hardness.

c) Thickness and Diameter

Thickness and diameter was measured using Vernier Calipers. It was determined by checking the thickness and diameter of ten lozenges of each formulation. The extent to which the thickness of the each lozenge deviated from $\pm 5\%$ of the standard value was determined.

d) Content Uniformity

The drug content was calculated for all the four formulations of Medicated lozenges. Three replication of each test were analysed for mean and standard deviation. All the formulations were found to be within the standard limits, which states that the drug content should be in the range of 95%- 105% for Ondansetron hydrochloride.

$$\text{Drug content} = \frac{\text{Conc.}^n \times \text{vol.} \times \text{DF}}{1000}$$

e) Moisture content analysis

The sample was weighed and crushed in a mortar. From this, one gram of the sample was weighed and placed in a desiccator for 24 hours. After 24 hours the sample is weighed. The moisture content is determined by the abstracting the final weight from initial weight of lozenges.

$$\% \text{ Moisture content} = \frac{\text{initial weight} - \text{final weight} \times 100}{\text{initial weight}}$$

f) *In-Vitro* Release Studies:

All the four formulation prepared were subjected to *in-vitro* release study. The *in-vitro* method for studying the release rate should be so that it must simulate the mouth condition. In the present work *in-vitro* release study was carried out using dissolution apparatus. For different time interval, sample was withdrawn and cumulative drug release was calculated. The dissolution apparatus USP paddle type Π was used. The temperature was maintained at $37 \pm 0.5^\circ\text{C}$ and stirred at 100 rpm. The dissolution medium being phosphate buffer of pH 6.8 and phosphate buffer of pH 1.2. The samples were withdrawn at predetermined time intervals with the same volume of fresh medium being added after each withdrawal. The sample was suitably diluted and absorbance was measured at 246 nm for phosphate buffer of pH 6.8 and at 310 nm for phosphate buffer of pH 1.2.

g) Stability Studies: Stability studies for the lozenges were carried out at 40°C at 75%RH for a period of 90 days. For every 15 days the parameters like, drug content, weight variation, colour, hardness and moisture content were determined.

RESULTS

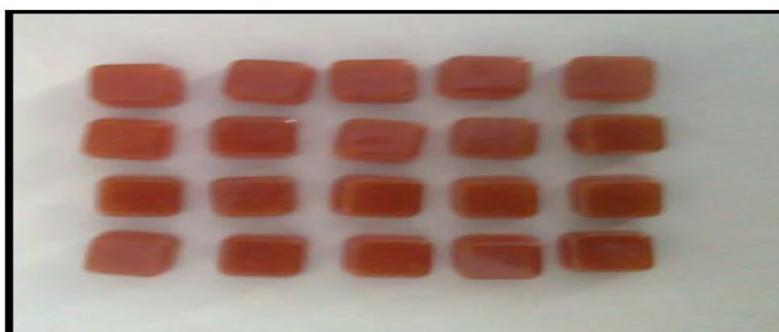


Figure.1: Physical Appearance of prepared Medicated lozenges

A. Physicochemical parameters of prepared lozenges

Table-2:- Physicochemical parameters of prepared lozenges

Batch no	Weight Variation (gm)	Hardness (kg/cm ²)	Thickness (mm)	Diameter (mm)	Drug content (%)
F ₀	2.925±0.051	10.16±0.288	9.14±0.015	15.65±0.015	100.38±3.052
F ₁	2.982±0.063	11.16±0.288	9.15±0.030	15.66±0.015	96.67±0.889
F ₂	3.031±0.111	11.83±0.288	9.14±0.015	15.66±0.020	98.30±2.284
F ₃	2.923±0.062	13.16±0.288	9.14±0.020	15.65±0.020	97.81±1.556

n=3 (Mean± S.D.)

B. Moisture content of prepared lozenges

Table-3:-Moisture content of lozenges

S.No.	Formulation	Moisture content (%)
1.	F ₀	1.4
2.	F ₁	0.8
3.	F ₂	1
4.	F ₃	1.6

C. *In-vitro* release profile of medicated lozenges

a) Dissolution study of medicated lozenges Formulation in phosphate buffer pH-6.8

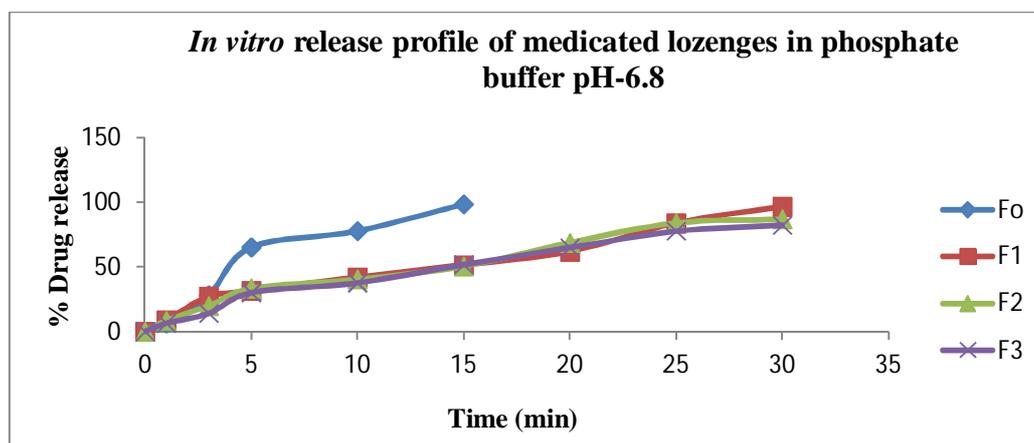


Figure-2:- In-vitro dissolution study in pH-6.8

b) Dissolution study of medicated lozenges Formulation in phosphate buffer pH-1.2

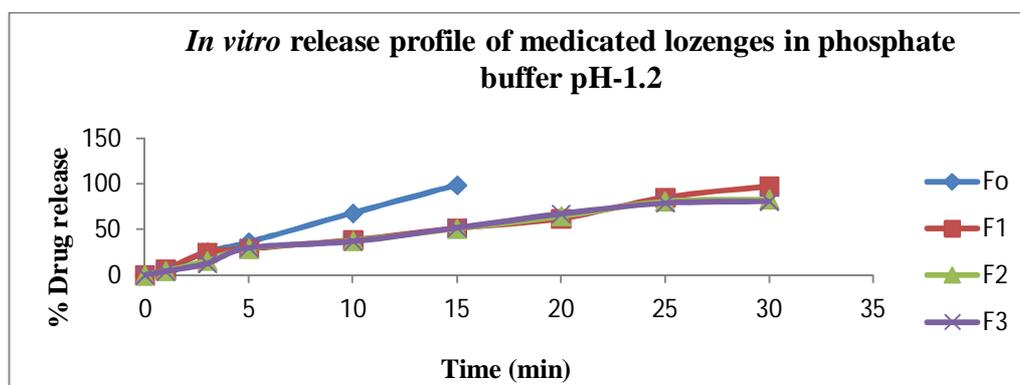


Figure-3:- In-vitro dissolution study in pH-1.2

D. Drug content after stability study

Table-4:- Drug content after stability study

S.No.	Days	Drug content (%)			
		F ₀	F ₁	F ₂	F ₃
1.	15	99.37	96.14	97.30	96.14
2.	30	98.85	95.88	96.92	95.56
3.	49	98.59	95.48	96.56	95.19

DISCUSSION

All the formulations showed good physical appearance. The diameter of all the formulation was found to be 15.65 ± 0.015 - 15.66 ± 0.020 mm. The thickness was in range of 9.14 ± 0.015 - 9.15 ± 0.030 mm. All the formulations had good hardness and passed drug content uniformity. Thus, it can be concluded that all the formulations passed physicochemical evaluation. The details of physicochemical properties are given in **Table-2**. The moisture content of all the formulation found to be below 2%. This is due to fewer amounts of water soluble polymer and less water uptake; details of moisture content are given in **Table-3**. The *in-vitro* dissolution studies for the formulations were in range of 82.25-98.38% for phosphate buffer pH-6.8 and 80.88-98.50% for phosphate buffer pH-1.2. The details of the drug release is shown in **figure-2** and **figure-3**. **Table-4** shows that there is no change in drug content after performing stability studies.

CONCLUSION

Following conclusions can be drawn from the results obtained in the present investigation:

It is found that sucrose based medicated lozenges will be an alternative dosage forms. These will have additional advantages of patient compliance, convenience and comfortness for efficient treatment including low dose, immediate onset of action, reduced dosage regimen and economy.

- The physico-chemical characterization revealed that all the formulations were found to show acceptable thickness, weight and hardness.
- The drug content estimation showed uniform drug content in all the formulations.
- The moisture content test reveals that the prepared formulations were within the limits.

- Addition of hydrophilic mucoadhesive polymer HPMC yields good result to prolong dissolution time and the drug release in salivary pH conditions for a period of 30 minutes. Increasing the concentration of polymers will lead to formulation of extended release formulation.
- The stability studies proved that the prepared lozenges were found to be stable when stored at air tight containers at 40 ± 2 °C & 75% RH.

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