Preparation and Evaluation of Novel Candy Lozenges Containing Fluoxetine Hydrochloride

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***Abstract*: The present work is focused on development of candy lozenges which serves the purpose of increasing the bioavailability. To check if there are any interactions between the drugs and various components of formulation, FT-IR was performed and there were no interactions seen. The lozenges of Fluoxetine Hydrochloride were prepared by using different polymers like HPMC K4M and sodium alginate with different ratios. The average weight of the prepared lozenges was found to be in the range of 2.16±0.006 to 3.08±0.004 gram, the percent friability was found to be in the range of 1.86±0.008 to 2.14±0.003, the hardness was found to be in the range of 10.15±0.004 to 12.27±0.003 kg/cm^2, the disintegration time was found to be in the range of 23.35±0.007 to 24.25±0.0012 minutes, the percent drug content was found to be 96.5±0.006 to 99.4±0.005, and the percent moisture content was found to be in the range of 0.5±0.015 to 0.8±0.026. From all the evaluation parameters FL2 was considered as the optimized formulation. The in-vitro drug release was carried out in phosphate buffer of pH 6.8 and was found that the drug release depends on the concentration of the polymer. The drug release kinetics of optimized formulation FL2 fitted best to the zero order kinetics with the mechanism of Korsmeyer-peppas drug release. The stability study of the optimized formulation shows no significant changes in the product. In the view of above findings, effect of polymers like, HPMC K4M shows better result in heat congealing technique for preparation of lozenges.**

***Keywords*: Lozenges, Fluoxetine Hydrochloride, HPMC E15, HPMC E5, Heat Congealing Technique, Candy.**

Introduction[1-4]:

Lozenges are the flavored medicated dosage forms intended to be administered and held in the mouth or pharynx containing one or more medicaments usually in the sweetened base. Lozenges are used for pediatric and geriatric 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.

Lozenges are one of the very popular and novel drug delivery system as well as a better innovative dosage form and oral confectionary products. It is a probably helpful for means that of administration of medication either regionally or consistently through the mouth. The reasons for this preference because of the easy to administered for the geriatric and pediatric patient and wide spread acceptance by patients. The development of new drug delivery systems for existing drug with an improved efficacy, avoid first pass hepatic metabolism, no need of water intake and increase bioavailability together with reduced dosing frequency.

Fluoxetine belongs to the category of selective 5-hydroxytryptamine uptake matter (SSRI). It blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on 5HT1A auto receptors, which leads to an increase in 5-hydroxytryptamine levels and enhances the mood of the patients. Fluoxetine is used to treat depression, major depressive disorder, bulimia nervosa (a binge eating disorder) obsessive-compulsive disorder (OCD), panic disorder, and pre-menstrual dysphoric disorder (PMDD). The bioavailability of selective-serotonin reuptake inhibitor complex is concerning 60-80% and having 94-95% of protein binding with a biological half-life of 1-3 days and it's a BCS category I drug

Advantages of Lozenges

1) Ease of administration to pediatricand geriatric patients
2) Local and systemic effect through oralcavity
3) Increased contact time of thedrug
4) Prolonged drugaction
5) Avoid hepaticmetabolism ofdrugs
6) Do not require water forintake
7) Suitable for patients having difficulty swallowing (Dysphagia)
8) Drug therapy can be withdrawn if dose is notneeded
9) Modification of formula as per the patient'srequirement
10) Less productiontime
11) Cost of production islow
12) Provides flavorand pleasant taste to themouth
13) Better patientcompliance

Disadvantages of Lozenges

1) Non-omnipresent distribution of drug in the saliva for localtherapy
2) Possible clearing out of drug into thestomach
3) Accidental swallowing of entire dosageform

Materials and Methods:
Fluoxetine Hydrochloride was procured from Yarrow Chem, Mumbai, HPMC E15, HPMC E5was obtained as a gift sample from Colorcon Ltd. Goa, Citric Acid, Mannitol, Sucralose, Menthol, Dextrose,was procured from Loba Chem Pvt.Ltd, Mumbai.

Drug-Excipient Interaction Study by FT-IR[5-6]:
The FT-IR spectroscopy approach was used for the detection of any possible chemical and physicalinteraction between the drug and the excipients. A mixture of drug and polymer was prepared in the ratio of 1:1 and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a pellet using a hydraulic press. It was scanned from 4000 to 150 cm-1 in FT-IR spectrophotometer. The IR spectrum of the physical mixture was compared with the standard value of pure drug and excipients and it was matched for any disappearance of any peak to detect any of interaction between the drug and excipient.

Standard Calibration Curve of Fluoxetine Hydrochloride:
A UV absorption maximum was determined by scanning 10µg/ml solution of Fluoxetine Hydrochloride in phosphate buffer of pH 6.8, at 226 nm by using UV-visible spectrophotometer. Further a representative spectrum was drawn of Fluoxetine Hydrochloride in phosphate buffer of pH 6.8.

Preparation of Lozenges[5-7]:
The lozenges were prepared by the heating and congealing technique.Required quantity of sucralose syrup was prepared mixing sucralose and water. Dextrose was dissolved in little quantity of water and heated it to 110ºC till it dissolves completely forming as clear viscous solution.Then the prepared dextrose solution was poured into the sucralose syrup and heated to 160ºC till the colour changes to golden yellow. The temperature was brought down to 90ºC. Fluoxetine Hydrochloride was dissolved in the small quantity of water and then polymer was dissolved in the drug solution with other ingredients. The drug solution was mixed with the sucralose and dextrose solution mixed well and the solution was poured into the mould. The prepared tablets were wrapped in aluminum foil and stored in desiccators for the better storage conditions for the evaluation study and also to prevent the moisture uptake

Table No.1 Formulation Chart of Fluoxetine Hydrochloride Lozenges.

Ingredients	FL1	FL2	FL3	FL4	FL5	FL6
Drug	5mg	5mg	5mg	5mg	5mg	5mg
HPMC E15	20mg	40mg	60mg	-	-	-
HPMC E5	-	-	-	20mg	40mg	60mg
Aspartame	2025mg	2000mg	1075mg	2025mg	2000mg	1075mg
Dextrose	1000mg	1000mg	1000mg	1000mg	1000mg	1000mg
Citric Acid	10mg	10mg	10mg	10mg	10mg	10mg
Orange Flavor	1ml	1ml	1ml	1ml	1ml	1ml

Evaluation[8-12]:
Organoleptic Characteristics:
- **Color:** Yellowish Orange
- **Texture:** Smooth and no grittiness
- **Shape:** Spherical

The characteristics like shape, texture, color were analyzed by visual inspection of each formulation.
Average weight: 5 Lozenges of each batches were selected and weighed on an electronic balance. From the collective weight, average weight was calculated with ±SD.

$$\text{Average Weight} = \frac{\text{Total weight of Lozenges}}{5}$$

Friability test: The friability of the 5Lozenges from each batch was tested by a fribilator (Total 30 Lozenges were used). At a speed of 25 rpm for 4 min. The lozenges were then dedusted, reweighed and percentage weight loss was calculated by the equation,

$$\% \text{ Friability} = \frac{(\text{Initial Wt.} - \text{Wt. after friability}) \times 100}{\text{Initial Weight}}$$

Hardness test:
To evaluate the diametrical crushing strength, 3 tablets from each formulation were tested using a Pfizer hardness tester. The mean±SD values were calculated.

***In-vitro* Disintegration Study:**

Disintegration study was determined by each batch formulation using USP disintegration apparatus, where lozenges were placed in each tube of the apparatus previously filled with artificial salivary fluid at 37^0C and time taken for the prepared lozenges to dissolve fully was noted. This test was performed in triplicate. The average dissolving time for lozenges was calculated and presented with ±SD.

Preparation of Artificial Salivary Fluid[13-14]:

In a beaker of 1000ml take the appropriate quantity of Sodium chloride (0.844gm), Potassium Chloride (1.2gm), Calcium Chloride (0.193gm), Magnesium Chloride (0.111gm), and Potassium Phosphate dibasic (0.342gm) and were added one by one to the beaker filled with 500ml of distilled water and mixed well. After mixing all of the ingredients the volume was made up with 1000ml of distilled water and the pH was adjusted up to 5.7 with adding few drops of 0.1N Hydrochloric Acid.

Drug Content Uniformity:

The drug content uniformity was tested by powdering one lozenge in a mortar pestle and dissolving the powder content in 60ml of methanol in a 200ml volumetric flask and shaken until completely dissolved and then make up the volume by using phosphate buffer of pH 6.8. From this 10ml was taken in another volumetric flask diluted with phosphate buffer of pH 6.8 up to 100mland sonicated for 30 min and then the solution was filtered and the absorbance was recorded at 226nm.

Percent Moisture Content:

The prepared lozenges were crushed in a mortar (3 lozenges of each batch) and weighed. From each crush lozenge 1 gm of sample was weighed and placed on a butter paper and then placed in the desiccator for 24 hours. After that the sample were removed and weighed again. The weight reduced was then calculated for the % moisture content by the following formula:

$$\% \text{ Moisture Content} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

***In-vitro* Dissolution Study:**

In vitro dissolution was carried out in USP XXIV dissolution test apparatus. 900ml Phosphate buffer of pH 6.8 solution was used as dissolution medium. The stirrer was adjusted to rotate at 100 rpm. The temperature of dissolution medium was maintained at 37± 0.5°C throughout the experiment. One lozenge was used in each test. 5ml of samples from the dissolution medium were withdrawn by means of syringe.The volume withdrawn at each timeinterval was replaced with fresh quantity of dissolution mediumto maintain the sink condition. Solution was filtered with whatman filter paper. Samples were withdrawn after 5, 10, 15, 20, 25, 30, 35, 45 minute intervals of time and analyzed for drug release by measuring the absorbance at 226 nm [15]. The volume withdrawn at each time interval was replaced with fresh quantity of dissolution medium to maintain the sink condition.

Stability Study[16-20]:

In the present study, stability studies were carried out at Room Temperature and Accelerated testing: 40°C ± 2°C / 75 % RH ± 5% RH for 3 months for the optimized formulation. The optimized formulation was analyzed for the Physical appearance, Drug content, Disintegration Time, average weight, percent friability, moisture content.

The optimized formulation was wrapped in aluminum foil for the studies and then kept in the testing chamber for 90days and the testing was carried out in every 15 days for up to 3 months.

Results and Discussions:

The lozenges of Fluoxetine Hydrochloride were prepared with the hot congealing method by using the various polymers like HPMC E15 and HPMC E5 and Dextrose and sucrose as the sweetening agent. The prepared lozenges were then evaluated for the various parameters of which the results were noted down.

Drug-Excipients Interaction Study by FT-IR Study:

From the figures obtained of the FT-IR spectrum it was seen that there was no disappearance of any peak which concludes that there was no physical and chemical interaction between the drug and excipients.

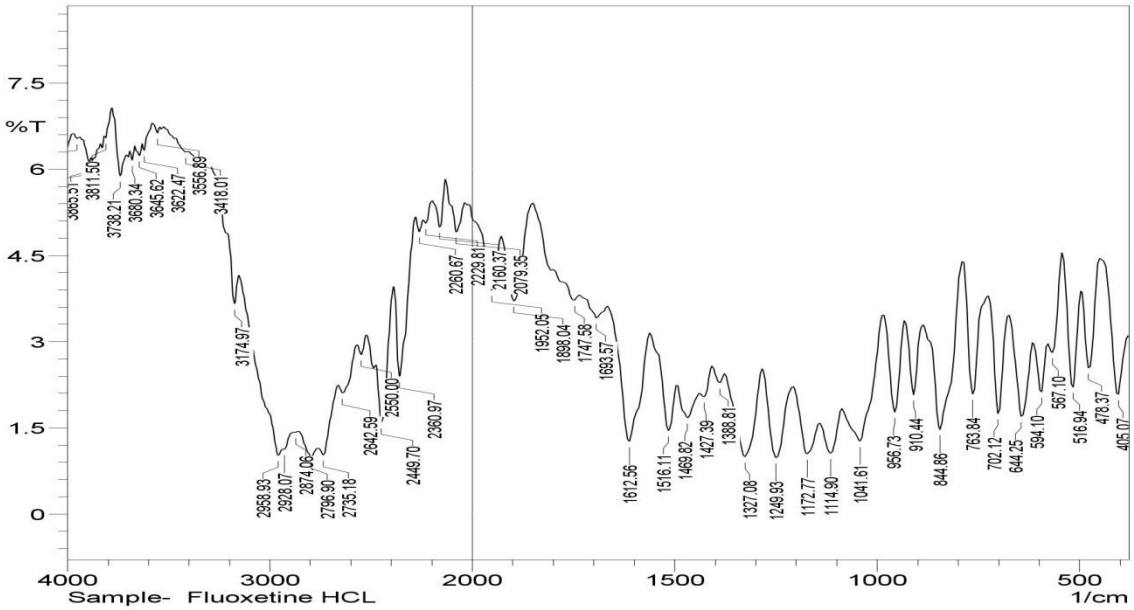

Figure No.1: FT-IR Spectrum of pure drug Fluoxetine Hydrochloride

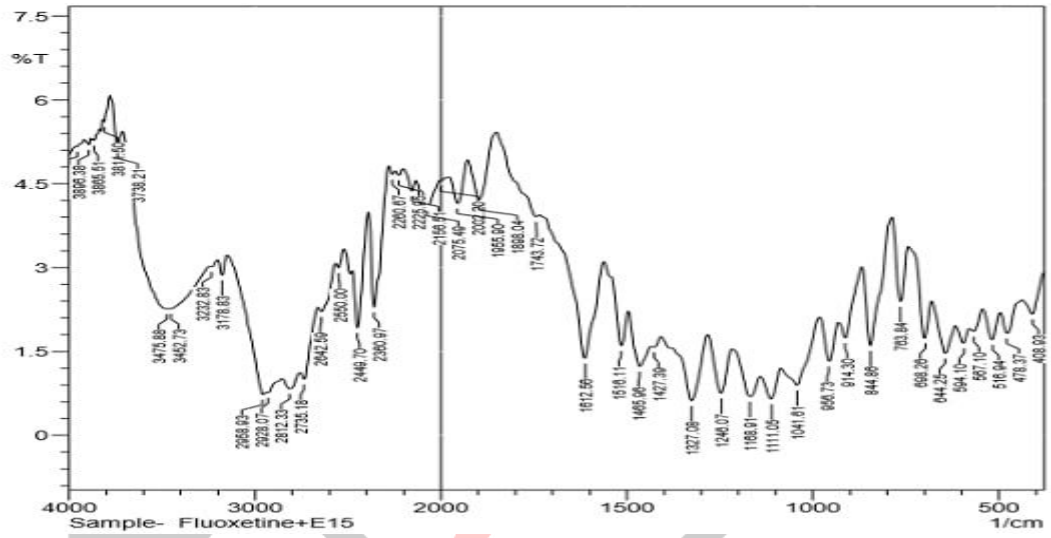

Figure No.2: FT-IR Spectrum of Optimized Formulation

Standard Calibration Curve: The standard calibration curve was plotted concentration Vs absorbance according to the absorbance reading and the obtained equation was found to be y = 0.0827x + 0.0665 and the r^2 value was found to be 0.9767.

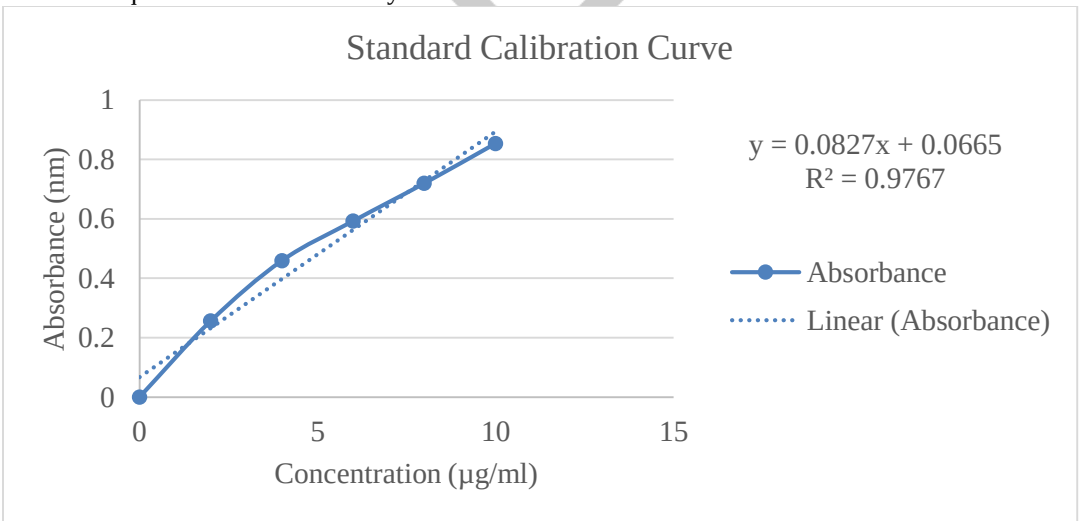

Figure No.4: Standard Calibration Curve of Fluoxetine Hydrochloride

Evaluation Parameters:

Table No.2: Evaluation Study of the Prepared Lozenges

Batch	Average Weight (gm)	% Friability	Hardness (Kg/cm^2)	Disintegration Time (min)	% Drug Content	% Moisture Content
FL1	3.06±0.002	2.14±0.003	10.15±0.006	23.50±0.005	98.2±0.002	0.5±0.020
FL2	3.05±0.004	1.86±0.008	12.27±0.003	23.35±0.007	99.4±0.005	0.5±0.015
FL3	2.16±0.006	1.79±0.015	11.14±0.004	24.25±0.012	97.3±0.004	0.7±0.024
FL4	3.08±0.004	2.06±0.007	10.15±0.004	24.10±0.003	96.5±0.006	0.6±0.018
FL5	3.03±0.007	1.96±0.006	10.27±0.012	23.40±0.018	99.1±0.003	0.7±0.019
FL6	2.20±0.005	1.87±0.011	12.24±0.019	23.50±0.005	98.4±0.004	0.8±0.026

The average weight of the prepared lozenges was found to be in the range of 2.20±0.005-3.08±0.004 gm. The percent friability of the lozenges was found to be between 1.79±0.015- 2.14± 0.003%. The hardness of the lozenges was found to be in the range of 10.15±0.004- 12.27±0.003 kg/cm^2. Disintegration time of the prepared lozenges was found to be in the range of 23.35±0.007-24.10±0.003 minutes. Percentage drug content was found to be in the range of 98.2±0.002- 99.4±0.005%. The moisture content in the lozenges was found to be in the range of 0.5±0.015- 0.8±0.026 %.

***In-vitro* dissolution test:** The dissolution test of the lozenges revealed that the prepared lozenges shows that about 50% of the drug is released within 15 minutes and the maximum amount of drug release is released is of 98.91% in 45 minutes of the FL2 formulation which was considered as optimum formulation.

Table No.3: % Cumulative Drug Release of the Prepared Lozenges.

Time (min)	Batches					
	FL1	FL2	FL3	FL4	FL5	FL6
0	0	0	0	0	0	0
5	38.71	27.79	28.21	40.51	40.48	35.82
10	54.53	40.12	36.66	55.15	53.51	50.46
15	62.38	49.71	48.03	69.09	63.98	61.72
20	78.95	59.89	53.97	82.91	81.19	70.03
25	89.59	71.84	69.18	92.42	86.76	75.83
30	92.11	85.05	79.35	93.06	89.24	85.29
35	95.45	90.25	88.42	95.58	90.41	90.41
40	96.87	95.67	92.35	96.80	95.68	94.38
45	97.90	98.91	98.41	97.25	97.82	96.79

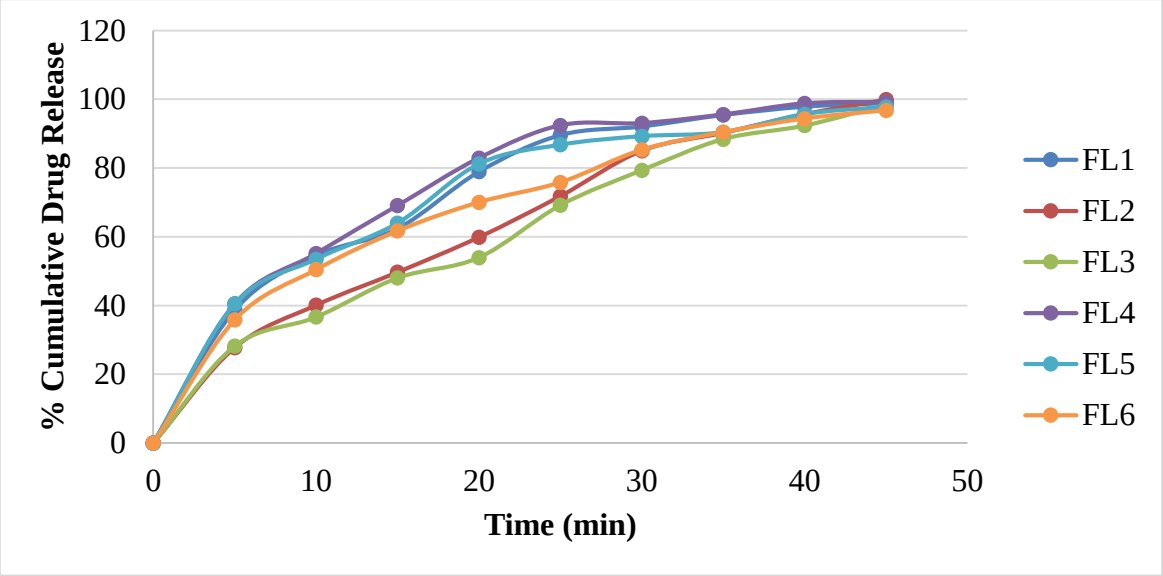

Figure No.5: % Cumulative Drug Release

Kinetics: The kinetics study of the optimized formulation shows the value of 0.896 for first order kinetics, 0.9546 for zero order kinetics**,** 0.9877 for higuchi diffusion and 0.9915 for korsmeyer-peppas model of diffusion. From which it was concluded that the optimized formulation shows zero order kinetics with release mechanism of korsmeyer-peppas.

Table No.4: Kinetics Study Data

Sr. No.	First Order	Zero Order	Higuchi Diffusion	Korsmeyer - Peppas
FL2	0.896	0.9546	0.9877	0.9915

Stability Studies: The formulated lozenges were studied for the parameters such as average weight, percent friability, hardness, disintegration time, percent drug content, and percent moisture content. The stability of the prepared lozenges was carried out accordingly as per the guidelines of International Council for Harmonization (ICH). The stability study was carried out as accelerated study at 40°C ± 2°C / 75 % RH ± 5% RH for 90 days.The study revealed that there were no significant changes in the product quality.

Table No.5: Evaluation Parameters on Stability Study of Optimized Batch.

Days (40°C ± 2°C / 75 % RH ± 5% RH)	Average Weight (gm)	% Friability	Hardness (kg/cm^2)	Disintegration Time (min)	% Drug Content	% Moisture Content
0	3.05±0.004	1.86±0.008	12.27±0.003	23.35±0.007	99.4±0.005	0.5±0.015
15	3.03±0.002	1.86±0.007	12.27±0.002	23.35±0.003	99.4±0.002	0.5±0.011
30	3.03±0.005	1.85±0.008	12.26±0.003	23.30±0.006	99.3±0.002	0.4±0.017
45	3.02±0.003	1.85±0.006	12.26±0.002	23.28±0.001	99.1±0.006	0.4±0.020
60	3.02±0.006	1.83±0.005	12.25±0.006	23.21±0.007	98.9±0.003	0.3±0.018
75	3.02±0.004	1.84±0.007	12.26±0.006	23.23±0.004	98.8±0.009	0.4±0.012
90	3.01±0.001	1.84±0.006	12.26±0.004	23.23±0.008	98.9±0.005	0.3±0.016

Conclusion:

As bioavailability is a major factor responsible for the pharmacological activity of any drug, the present work is focused on the formulation of the active pharmaceutical ingredient (APIs) as lozenges due to their various advantages. Lozenges increase bioavailability by increasing the solubility. First of all, FT-IR studies were performed and from the FT-IR spectra it was evident that there were no physical and chemical interactions between the drug and the excipients being used. The lozenges of Fluoxetine Hydrochloride were prepared by using different polymers of different concentrations by heat congealing technique (FL1-FL6), among the six formulations FL2 (HPMC E15) showed the highest percentage of drug release, drug content, less disintegration time. Hence, it was considered as the optimized formulation among the six formulations The optimized formulation shows the average weight of 3.05±0.004 gram, the percent friability was found to be 1.86±0.008, the hardness of the lozenges was found to be 12.27±0.003 kg/cm^2, the disintegration time was found to be 23.35±0.007 minutes, the percentage drug content of the formulation was found to be maximum of 99.4±0.005 and the percentage moisture content in the lozenges was found to be 0.5±0.015. The drug release kinetics of optimized formulation FL2 fitted best to the zero order kinetics with the mechanism of Korsmeyer-peppas drug release. The stability studies were performed as per the guidelines of the International Council for Harmonisation (ICH) of accelerated stability studies of 90 days at 40°C ± 2°C / 75 % RH ± 5% RH and it was noted that there was no significant change in drug content, disintegration time, hardness, friability, weight variation, moisture content.

Enhancement of bioavailability is the current interest of research. Drug administration by lozenges helps to bypass the hepatic metabolism therefore, avoiding the hepatic metabolism metabolism helps in bioavailability enhancement. Thus by this work, we could conclude that candy lozenges can be used as efficient means of formulation to enhance bioavailability of the drug as carried through oral cavity.

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