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DEVELOPMENT AND *IN-VITRO* EVALUATION OF CHLORHEXIDINE AND FLURBIPROFEN HARD CANDY LOZENGES

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ABSTRACT: The mouth of human body provides non-shedding surfaces (teeth) for natural microbial colonization. This can result in the accumulation of large masses of bacteria and their products at stagnant sites. Dental plaque, Periodontitis and gingivitis are some of this type of conditions, which can develop due to microbial accumulation on teeth and Infections of throat leading to tonsillitis, pharyngitis, laryngitis, sour throat etc. Chlorhexidine is widely used antimicrobial drug in the treatment of dental plaque and gingivitis and Flurbiprofen is used as anti-inflammatory drug to reduce pain and inflammation. Lozenges are designed to deliver medications directly to the mucus membranes of the mouth and oropharengial cavity by dissolving slowly when placed between the tongue and gums. Lozenges provide maximum amount of local action thus Chlorhexidine and Flurbiprofen are formulated as lozenges to provide local antiseptic and anti-inflammatory action. The candy based lozenges were prepared by heat and congealing method by sugar as lozenge base, HPC, HPMC as polymers, citric acid artificial flavours and colours and other essential excipients. Some selected formulations were tested for drug excipient interactions subjecting to IR Spectral analysis. Formulated lozenges were evaluated for weight variation, crushing strength, friability, thickness, taste, dissolution time, and %assay. Crushing strength of optimized troches was found between 8-9.50 kg/cm^2. The candies can provide an attractive alternative formulation in the alleviation of pain and Inflammation.

INTRODUCTION: Lozenges are solid preparations that contain one or more medicaments, usually in a flavored, sweetened base, and are intended to dissolve or disintegrate slowly in the mouth or these are medicated candy intended to be dissolved slowly in the mouth to lubricate and sooth the irritated tissues of throat.

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Two types of lozenges are used widely because of their ready adaption to modern high speed methods, they are hard candy lozenges and compressed tablet lozenges. Hard candy lozenges are prepared by molding. Molded lozenges are sometimes referred to as pastilles, whereas compressed lozenges may be referred to as Troches.

They are intended to be dissolved on the back surface of the tongue to provide drug delivery locally to the mouth, tongue, throat, etc., to minimize systemic and maximize local drug activity. These contain a variety of active ingredients including antimicrobials and local

anesthetics for throat pain, aromatics, herbals, zinc salts, decongestants, anti-histamines and cough suppressants and nicotine like substances for smoking cessation etc [1, 2].

MATERIALS & METHODS:

Chlorhexidine was obtained as a gift sample from Dr. Reddys Laboratory, Hyd, Flurbiprofen was obtained as a gift sample from Dr. Reddys Laboratory, Hyd , liquid glucose from Deccan bottle traders, Hyd, HPC, HPMC 50 cps from Hi Media Labs.

Preformulation Studies:

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

Drug- Drug Compatibility study:

Chlorhexidine and Flurbiprofen were mixed in equal proportions and subjected to Physical observation and FTIR studies[3].

Drug-Drug Compatibility study by physical observation:

Chlorhexidine and Flurbiprofen was mixed in equal proportions and kept at 40°C/75%RH conditions for two months. The physical properties (Color change) were monitored regularly. The change in color of mixture was considered as incompatibility and the blend was discarded from study.

Drug-Excipient Compatibility study by physical observation:

Chlorhexidine and Flurbiprofen mixture was mixed in equal proportions with all excipients which were used in the formulation, in different ratios and kept at 40°C/75%RH conditions for two months. The physical properties (Color change) monitored regularly. The change in color of any mixture was considered as incompatibility and the excipient blend was discarded from study.

Drug-Excipient Compatibility study by FT-IR:

A Fourier Transform-Infra Red spectrophotometer (Spectrum BX series, 51658, Perkin Elmer BX, UK) equipped with spectrum v2.19 software was used to study the non-thermal analysis of drug-drug and drug-excipient (binary mixture of drug: excipient 1:1 ratio) compatibility (**Fig.6 to 12**). The spectrum for each sample was recorded over the 450–4000 cm^{-1} spectral region

TABLE 1: LIST OF FORMULATION CODES

Polymer Used	Concentration (%)	Formulation Code
HPC	1	C1
	2	C2
	3	C3
	4	C4
HPMC 50CPS	1	M1
	2	M2
	3	M3
	4	M4
Hard candy lozenges without polymer	-	DC

TABLE 2: FORMULATION OF CHLORHEXIDINE AND FLURBIPROFEN HARD CANDY LOZENGES

Ingredients (mg)	FORMULATION CODE								
	C1	C2	C3	C4	M1	M2	M3	M4	DC
Chlorhexidine	5	5	5	5	5	5	5	5	5
Flurbiprofen	8.75	8.75	8.75	8.75	8.75	8.75	8.75	8.75	8.75
Sucrose	2038.25	1998.25	1958.25	1918.25	2038.25	1998.25	1958.25	1918.25	2038.25
Liquid Glucose	900	900	900	900	900	900	900	900	900
Saccharin	-	10	20	30	-	10	20	30	30
HPC	30	60	90	120	-	-	-	-	-
HPMC 50CPS	-	-	-	-	30	60	90	120	-
Citric acid	10	10	10	10	10	10	10	10	10

Menthol	2	2	2	2	2	2	2	2	2
Methyl paraben	2	2	2	2	2	2	2	2	2
Orange colour	2	2	2	2	-	-	-	-	-
Yellow colour	-	-	-	-	2	2	2	2	2
Orange Flavour	2	2	2	2	-	-	-	-	-
Mango flavor	-	-	-	-	2	2	2	2	2
Total weight	3000	3000	3000	3000	3000	3000	3000	3000	3000

Preparation of Chlorhexidine and Flurbiprofen Hard Candy Lozenges:

Hard candy Lozenges were made just like hard candies. The hard candy lozenges were prepared as per the formulae shown in **Table 2**. All the ingredients like sucrose, liquid glucose, color, and polymer except flavors were mixed together along with the medicament and added to molten mass of sugar. Now the mass is mixed thoroughly to get a uniform distribution of medicament. Flavors were added when the temperature was brought to 40-45 °C. Now this semisolid mass was poured into pre-lubricated moulds and subjected to cooling. Then the hard candy lozenges were taken out from the moulds and packed in aluminum foil pouches**.** The above drugs give bitter taste so in order to mask the bitter taste of drugs we included saccharin (artificial sweetener), Menthol (cooling agent) in the above formulations[4].

Evaluation:

The prepared lozenges were smooth, round and good in appearance. They are shown in **Fig**. They were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

Twenty lozenges were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one lozenge was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula [5, 6]. The results are presented in **Table 4**.

% Deviation =

(Individual weight – Average weight / Average weight) × 100

Lozenge hardness:

Hardness of lozenge is defined as the force applied across the diameter of the tablet in order to break the lozenge. The resistance of the lozenge to chipping, abrasion or breakage under condition of storage transport and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using Pfizer hardness tester and the average was calculated and presented with standard deviation. The results are presented in **Table 4**.

Lozenge thickness:

Lozenges thickness is an important characteristic in reproducing appearance. Twenty Lozenges were taken and their thickness was recorded using Digital Micrometer (Digital Caliper, Aerospace, India). The average thickness for Lozenges is calculated and presented with standard deviation[5, 6]. The results are presented in **Table 4**.

Friability:

It is a measure of mechanical strength of tablets. Roche friabilator (Electro lab, Mumbai, India) was used to determine the friability by following procedure. Pre-weighed lozenges (20 tablets) were placed in the friabilator. The lozenges were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the lozenges were re-weighed, loss in the weight of lozenges is the measure of friability and is expressed in percentage [5, 6] (**Table 4**) as:

$$\% \text{ Friability} = [(W_1 - W_2) / W_1] \times 100$$

Where,

W_1 = Initial weight of 20 tablets

W_2 = Weight of the 20 tablets after testing

Determination of drug content: 20 lozenges were randomly selected, weighed and finely powdered

and quantity of powder equivalent to one lozenge was added to 100 ml solvent of pH 6.8 phosphate buffer in a conical flask. Conical flasks were placed on a rotary shaker overnight. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 255nm and 247nm against pH 6.8 phosphate buffer as blank. Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated[7, 8, 9].

***In vitro* drug release studies:**

Dissolution conditions:

- Apparatus **:** USP Type 2 apparatus
- Dissolution medium**:** 250ml of pH 6.8 Phosphate buffer
- Temperature **:** 37 ± 0.5^0 C
- Rotating speed of the paddle **:** 50 rpm
- Sample time intervals **:** 5, 10, 15, 20, 25, 30 minutes
- Detection**:** UV-VIS spectrophotometer at λ_{max} 255 nm and 247nm for Chlorhexidine and Flurbiprofen respectively.
- The samples were withdrawn at predetermined time points, diluted appropriately and were analyzed spectrophotometrically at λ_{max} 255 nm and 247nm for Chlorhexidine and Flurbiprofen respectively [6, 7, 9].

***In Vivo* Taste Evaluation of Chlorhexidine and Flurbiprofen Lozenges:**

Taste evaluation was performed on ten healthy human volunteers by asking them to taste the lozenges for 5 minutes. After 5 minutes they are supplied with water to rinse the oral cavity. Data of the taste, mouth feel, and appearance of the lozenges were recorded from them[10, 11, 12]. The results were reported in the **Table 10.**

RESULTS AND DISCUSSION:

Preformulation Studies:

Drug-Excipient compatibility studies by physical observation:

Chlorhexidine and Flurbiprofen When mixed with various proportions of excipients showed no color change at the end of two months, hence proving no drug-excipient interactions.

Drug-Excipient compatibility studies by FT-IR:

The FT-IR spectra of pure drug chlorhexidine is shown in the **Fig. 1**. The characteristic peaks of Chlorhexidine are well retained in the spectrum.

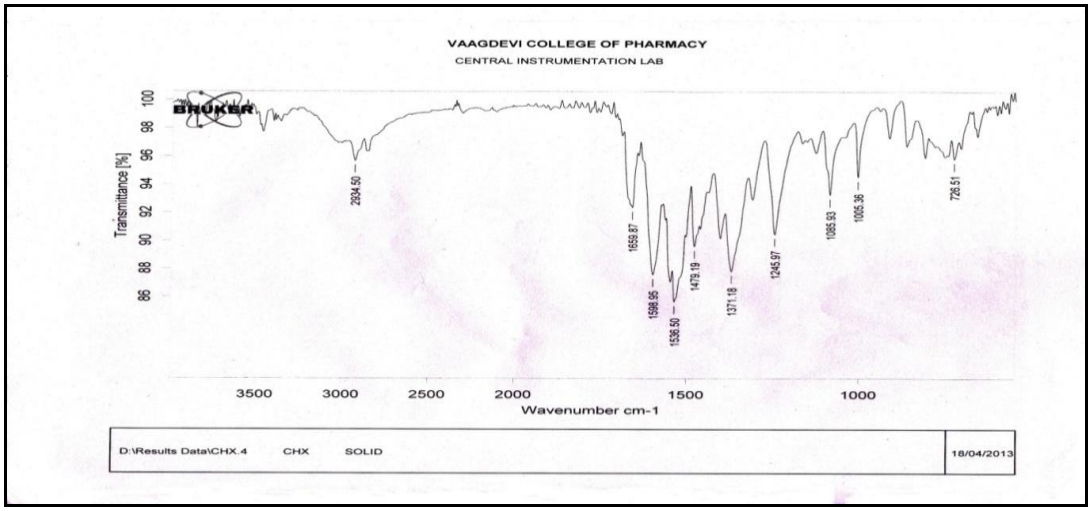

FIG.1 : FT-IR SPECTRA OF CHLORHEXIDINE PURE DRUG

The FT-IR spectra of pure drug Flurbiprofen is shown in the **Fig. 2**. The characteristic peaks of Flurbiprofen are well retained in the spectrum.

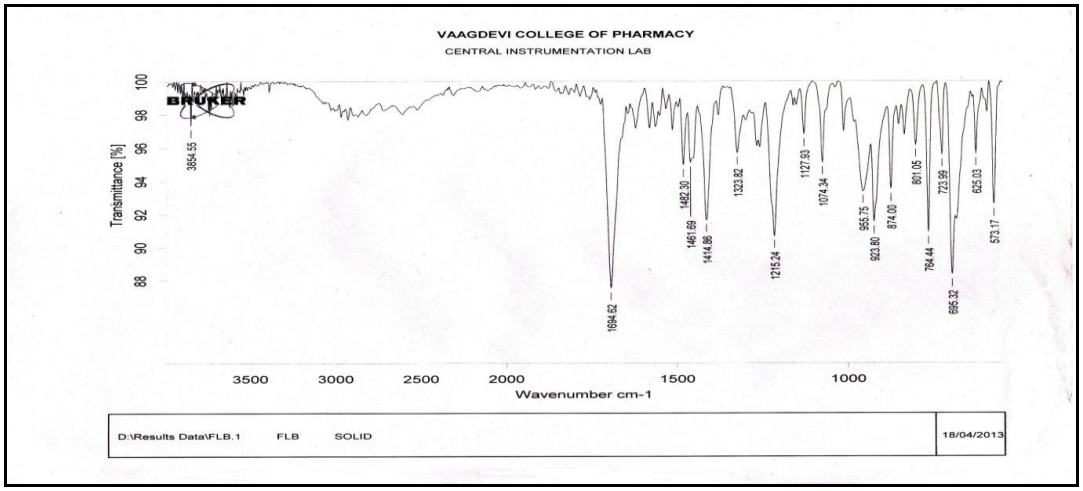

FIG.2 : FT-IR SPECTRA OF FLURBIPROFEN PURE DRUG .

The FT-IR spectra of pure drugs Chlorhexidine and Flurbiprofen is shown in the **Fig. 3**. The characteristic peaks of both drugs are well retained in the spectrum.

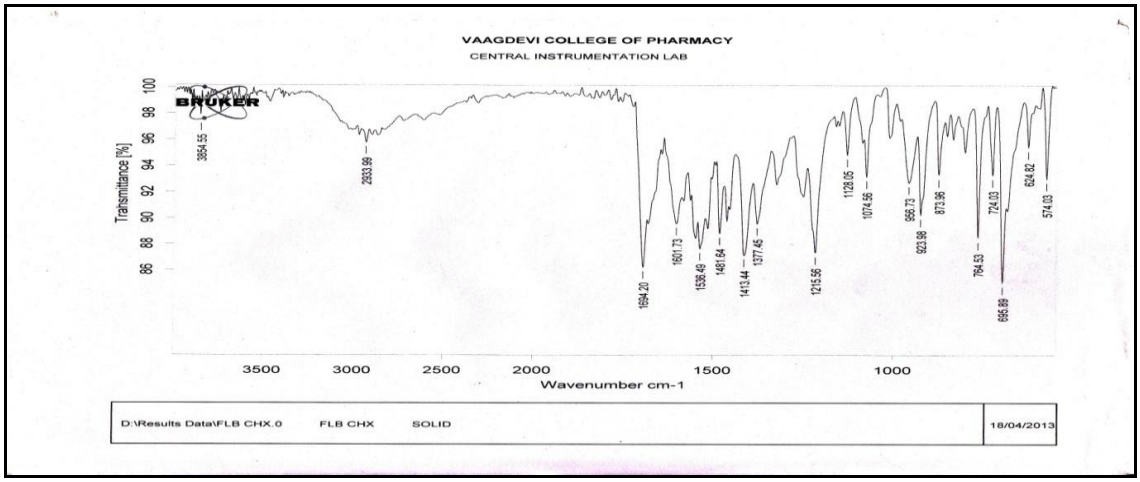

FIG. 3 : FT-IR SPECTRA OF CHLORHEXIDINE AND FLURBIPROFEN PURE DRUGS.

The FT-IR spectra of Chlorhexidine and Flurbiprofen hard candy lozenges containing HPC, HPMC 50 Cps are shown in the **Fig. 4, 5** respectively. The characteristic peaks of Chlorhexidine and Flurbiprofen are well retained in the spectrum representing that there is no significant interaction between drugs and excipients.

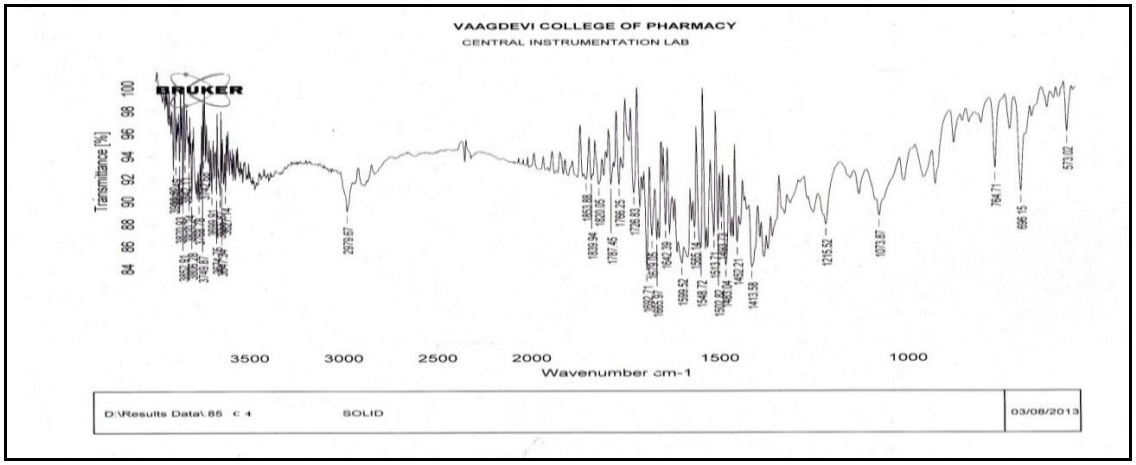

FIG.4: THE FT-IR SPECTRA OF CHLORHEXIDINE AND FLURBIPROFEN HARD CANDY LOZENGES CONTAINING HPC

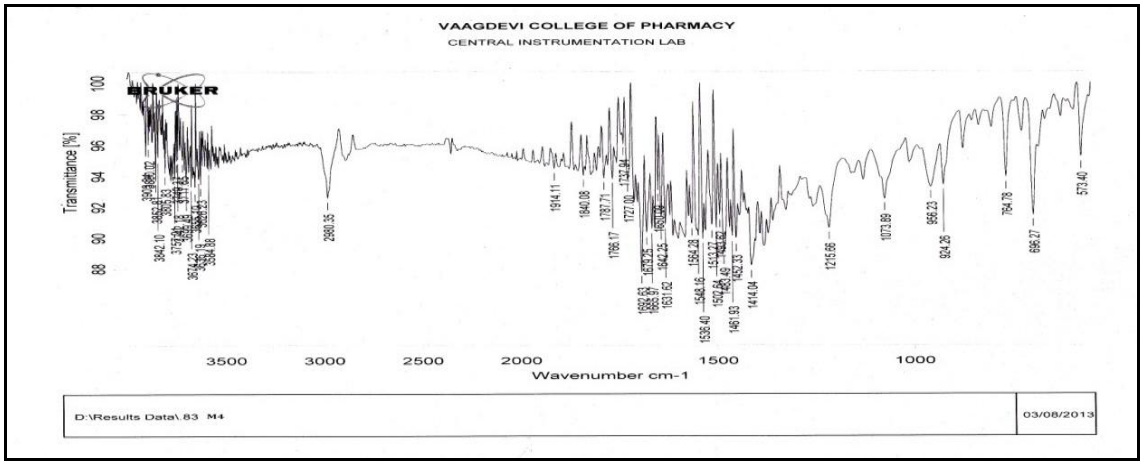

FIG.5: FT-IR SPECTRA OF CHLORHEXIDINE AND FLURBIPROFEN HARD CANDY LOZENGES CONTAINING HPMC 50 CPS

TABLE 3: DATA FOR FTIR SPECTRA OF CHLORHEXIDINE AND FLURBIPROFEN

FT IR spectra of Drurs and formulations with different polymers	Peak of Functional groups [Wave length (cm-1)]							
	C–F Stretch	O–H stretch	C– O Stretch	C=O Stretch	C–H Stretch	C-Cl strech	Aromatic C–C stretch (in–ring)	N-H Bend
Chlorhexidine					2934.50	726.51	1536.50	1598.95
Flurbiprofen	1074.34	3854.55	1215.24	1694.62				
Chlorhexidine+Flurbiprofen	1074.56	3852.55	1215.56	1694.20	2933.99	724.03	1536.49	1536.49
Chlorhexidine+Flurbiprofen +HPC	1073.84	3852.91	1215.52	1692.71	2979.67	764.71	1548.72	1548.72
Chlorhexidine+Flurbiprofen + HPMC 50 CPS	1073.89	3852.81	1215.66	1692.63	2980.35	764.78	1536.40	1536.40

From the table it was observed that the characteristic peaks of Chlorhexidine and Flurbiprofen are well retained in the spectrum representing that there is no significant interaction between drugs and excipients.

Determination of Absorptivity Values:

Standard stock solutions of Flurbiprofen, Chlorhexidine (100µg/ml) were prepared in distilled water. For the selection of analytical wavelength the solutions of Flurbiprofen and Chlorhexidine (10µg/ml) was prepared separately by appropriate dilution of standard stock solution with distilled water and scanned in the spectrum mode from 200 to 300 nm separately. From the overlay spectra of the drugs, wavelengths 247nm (λmax of flurbiprofen), 255(λ max of Chlorhexidine) was selected for analysis [1, 4].

Evaluation of Developed Chlorhexidine and Flurbiprofen Hard Candy Lozenges:

All 9 formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopeial limits. The results of the tests were tabulated (**Table 5**). The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were acceptable. The results of the physical tests of the formulations were within the limits and comply with the standards.

TABLE 4: PROCESS PARAMETERS OF VARIOUS FORMULATIONS:

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity	
					CHX	FLB
C1	3000±2.21	7.23±0.03	8.20±0.5	0.12	98.23	99.64
C2	3002±3.45	7.20±0.03	8.30±0.5	0.09.	99.65	98.12
C3	3000±2.63	7.30±0.05	7.50±0.5	0.11	99.12	99.72
C4	3001±2.43	7.23±0.04	8.30±0.5	0.08	98.44	97.13

M1	3005±4.23	7.23±0.08	8.40±0.5	0.14	99.23	99.12
M2	3003±3.45	7.21±0.05	9.50 ±0.5	0.11	98.63	98.12
M3	3002±4.63	7.20±0.06	8.50±0.5	0.10	99.65	99.72
M4	3004±2.12	7.22±0.04	8.80±0.5	0.13	98.65	97.13
DC	2505±4.75	7.32±0.06	7.50±0.5	0.12	98.45	99.72

(Values are expressed as mean percentage release ± SD with n=3)

***In-vitro* drug release profile:**

The percentage drug release profiles from various formulations of Chlorhexidine and Flurbiprofen hard candy lozenges containing HPC hard candy lozenges with a dose of Chlorhexidine 5mg, and Flurbiprofen 8.75mg containing HPC are represented in **Fig. 6.** The percentage drug release profiles from the formulations C1, C2, C3, C4 containing HPC in 1%, 2%, 3%, 4% concentrations respectively are shown in **Fig.7**. C4, (optimized formulation) containing 4 % HPC showed 98.7% and 99.7% release of Chlorhexidine and Flurbiprofen respectively in 30min. Formulations DC (Hard candy lozenges without polymer) showed 100% drug release within 10 minutes .The percentage drug release profiles from the formulations M1, M2, M3, M4 containing HPMC 50 CPS 1%, 2%, 3%, 4% concentrations respectively are shown in **Fig. 8** and **9**. M4, (optimized formulation) containing 4% HPMC 50 CPS showed 99.9% and 99.8% release of Chlorhexidine and Flurbiprofen respectively in 30minute.

***In-Vitro* Drug Release Studies of Chlorhexidine and Flurbiprofen** Hard **Candy Lozenges:**

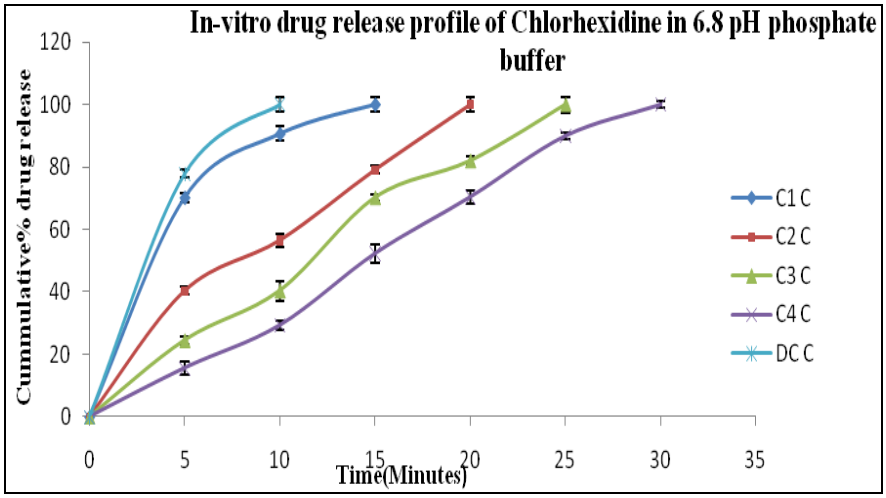

FIG.6: *IN-VITRO* DRUG RELEASE PROFILE OF CHLORHEXIDINE FROM HARD CANDY LOZENGES CONTAINING HPC.

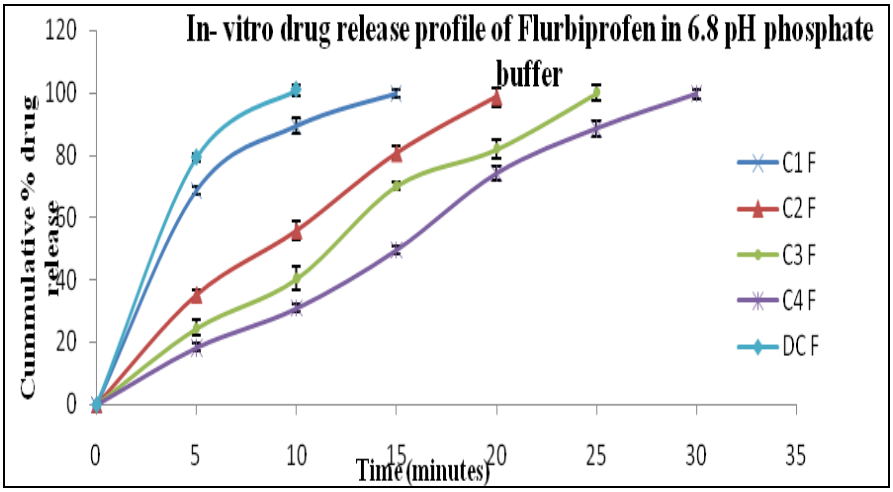

FIG. 7: *IN-VITRO* DRUG RELEASE PROFILE OF FLURBIPROFEN FROM HARD CANDY LOZENGES CONTAINING HPC

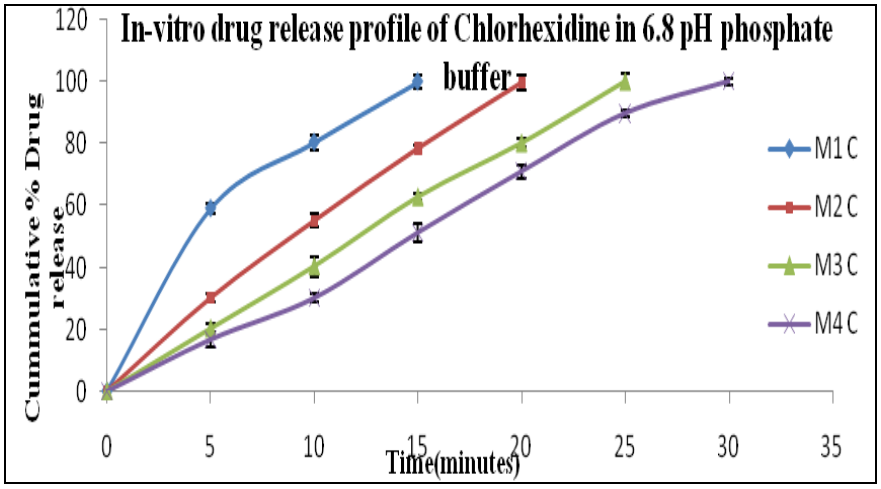

FIG. 8: *IN-VITRO* DRUG RELEASE PROFILE OF CHLORHEXIDINE FROM HARD CANDY LOZENGES CONTAINING HPMC 50 CPS.

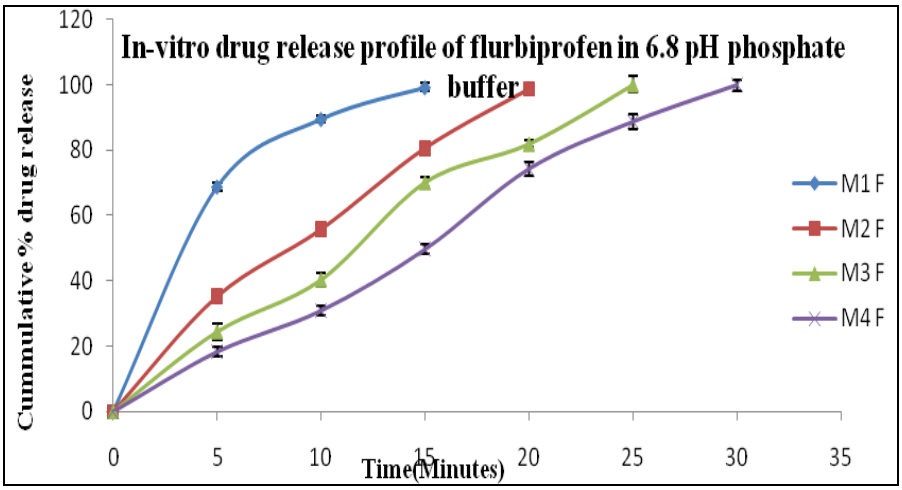

FIG. 9: *IN-VITRO* DRUG RELEASE PROFILE OF FLURBIPROFEN FROM HARD CANDY LOZENGES CONTAINING HPMC 50 CPS.

Drug Release Kinetics: The mechanism of drug release from lozenges was determined by fitting the *in vitro* release profiles of optimized batches with zero order, first order, Higuichi and Korsmeyer-Peppas models. The obtained correlation coefficient values are given in the **Table 5** and **6**.

TABLE 5: CORRELATION COEFFICIENT (R^2) VALUES FOR CHLORHEXIDINE

Correlation coefficient (R^2) values of different drug release kinetic models				
Formulation code	**Zero order**	**First Order**	**Higuichi**	**Peppas**
C1	0.9933	0.8048	0.9012	0.9930
M4	0.9947	0.6117	0.9021	0.9935

TABLE 6: CORRELATION COEFFICIENT (R^2) VALUES FOR FLURBIPROFEN

Correlation coefficient (R^2) values of different drug release kinetic models				
Formulation code	**Zero order**	**First Order**	**Higuichi**	**Peppas**
C4	0.9922	0.7161	0.9058	0.9887
M4	0.9938	0.6824	0.9074	0.9833

From the dissolution profile modeling of the final formulations the R^2 value of zero order kinetic models is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows zero order kinetics.

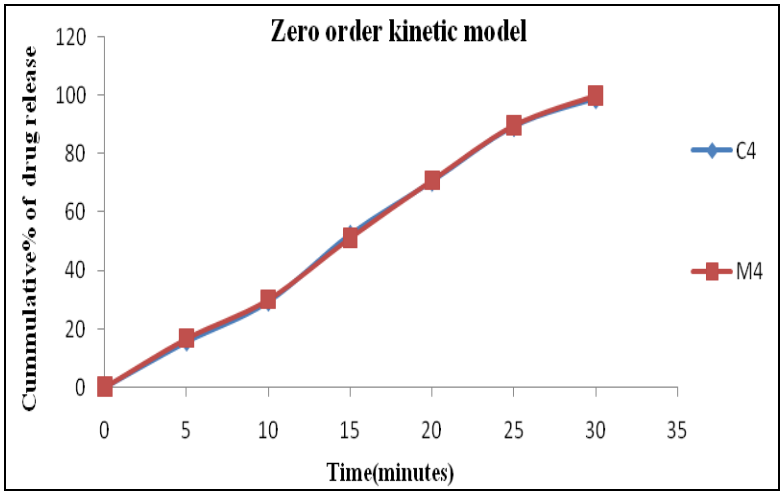

FIG.10: ZERO ORDER KINETIC MODEL GRAPHS FOR CHLORHEXIDINE IN FORMULATION C4&M4

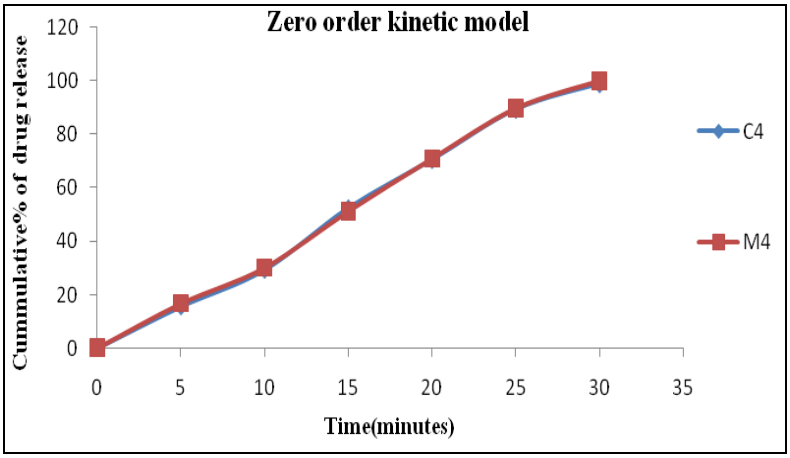

FIG.11: ZERO ORDER KINETIC MODEL GRAPHS FOR FLURBIPROFEN IN FORMULATION C4&M4

***In Vivo* Taste Evaluation Chlorhexidine and Flurbiprofen Lozenges:**

Taste evaluation was performed on five healthy human volunteers by keeping lozenges in mouth for 5 minutes and the results were reported in the **Table 7, 8**. The bitterness of the drug was reduced or even masked by increasing the concentration of sweetener. The hard candy lozenges C4, M4, DC formulations containing sweetener concentration 30 mg and Troches (compressed lozenges) T4, S4, S5 formulations containing sweetener concentration 120mg were having good taste and odor than other formulation. The results are as follows.

TABLE 7: EVALUATION OF TASTE BY HUMAN VOLUNTEERS

Formation Code	Product Elegance					Taste					Mouth feel				
	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5
C1	+++	++++	++++	++++	+++	+	+	+	+	+	+	+	+	+	+
C2	+++	++++	++++	++++	+++	++	++	++	++	++	++	++	++	++	++
C3	+++	++++	++++	++++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
C4	++	++++	++++	++++	++	++++	++++	++++	++++	++++	++++	++++++++++++++++			

TABLE: 8 EVALUATION OF TASTE BY HUMAN VOLUNTEERS

Formation Code	Product Elegance					Taste					Mouth feel				
	V6	V7	V8	V9	V10	V6	V7	V8	V9	V10	V6	V7	V8	V9	V10
C1	+++	++++	++++	++++	+++	+	+	+	+	+	+	+	+	+	+
C2	+++	++++	++++	++++	+++	++	++	++	++	++	++	++	++	++	++
C3	+++	++++	++++	++++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
C4	++	++++	++++	++++	++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

TABLE 9: GUIDE FOR *IN VIVO* TASTE EVALUATION OF LOZENGES

Product Elegance	Taste	Mouth feel	Result
Bad	Slightly bitter	Bad	+
Unplesant	Tolerable	Acceptable	++
Good	Acceptable	Very good	+++
Plesant	Good	Excellent	++++

SUMMARY AND CONCLUSION:

Chlorhexidine and Flurbiprofen Hard candy lozenges with a dose of 5mg of Chlorhexidine and 8.75mg of Flurbiprofen was developed and evaluated because Chlorhexidine was widely used as antimicrobial drug in treatment of dental plaque, periodontitis and gingivitis and Flurbiprofen as anti inflammatory agent. Combination of Chlorhexidine and Flurbiprofen has antimicrobial and anti inflammatory effect on periodontitis, dental plaque and oral inflammatory conditions.

Drug excipient compatibility studies by FTIR showed that there was no incompatibility between drugs and excipients. The hard candy lozenges of Chlorhexidine and Flurbiprofen were prepared by heat and congealing method. In the preparation of Hard candy lozenges the proper ratio of sugar and Liquid glucose (7:3) only give lozenges of good hardness and other physical properties.

Developed Chlorhexidine and Flurbiprofen Hard candy lozenges were evaluated for various physicochemical evaluation parameters and were found to be within the standard limits. Chlorhexidine and Flurbiprofen Hard candy lozenges with HPC 4% (C4), HPMC 50cps (M4) were optimized. The optimized formulations showed best release than other formulations. Among the optimized formulations hard candy lozenges with HPC 4% (C4) showed best drug release within 30minutes. From the mechanisum of drug release kinetics it was found that the optimized formulations follow zero order kinetics.

The bitter taste of Chlorhexidine and Flurbiprofen was masked with artificial sweetener (saccharin) and flavors. From the taste assessment studies it was concluded that the hard candy lozenges C4, M4, DC formulations containing yellow color and mango flavor containing sweetener concentration 30 mg were having good taste and odor than other formulations and it also concluded that hard candy lozenge have better mouth feel and taste.

Over all it was concluded that the Chlorhexidine and Flurbiprofen Hard Candy lozenges were found to improve the versatility, convenience, economic and patient compliance leading to an enhanced approach for the administration of drugs to treat local oral microbial and inflammatory conditions effectively.

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