WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 4, 634-649. Research Article ISSN 2277– 7105

DEVELOPMENT AND IN-VITRO EVALUATION OF CHLORHEXIDINE AND FLURBIPROFEN COMPRESSED TABLET LOZENGES

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Article Received on
01 Feb. 2020,

Revised on 21 Feb. 2020,
Accepted on 12 March 2020,

DOI: 10.20959/wjpr20204-10941

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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 Flubiprofen are formulated as lozenges to provide local antiseptic and anti-inflammatory action. The lozenges were prepared using mannitol as base. Hydroxy Propyl Methyl Cellulose K4M and Hydroxy Propyl Methyl Cellulose K15M are used as polymers. Saccharine is used as taste masking agent. These were prepared using wet granulation tablet technology. Some selected formulations were tested for drug excipient interactions subjecting to IR Spectral analysis.

Formulated troches were evaluated for weight variation, crushing strength, friability, thickness, taste, dissolution time, and assay. Crushing strength of optimized troches was found between 8.5-9 kg/cm^2. The Troches can provide an attractive alternative formulation in the alleviation of pain and Inflammation.

KEYWORDS: Hydroxy Propyl Methyl Cellulose K15M are used as polymers.

INTRODUCTION

Lozenges are solid preparations that contain one or more medicaments, usually in a flavoured, 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 soothe irritated tissues of throat. 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 moulding. Moulded 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 anaesthetics for throat pain, aromatics, herbals, zinc salts, decongestants, anti-histamines and cough suppressants and nicotine like substances for smoking cessation etc.

MATERIALS AND METHODS

Chlorhexidine gift sample from Dr.Reddys laboratory, Hyd. Flurbiprofen gift sample from Rawchem, Mannitol from Hi Media Labs, Micro Crystalline Cellulose, Methanol, Propylene Glycol, HPMC K4M, HPMC K15M, HPC, HPMC50CPS, PVP K90 from SD Fine Chemicals.

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 was mixed in equal proportions and subjected to Physical observation and FTIR studies.

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) were 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 (Figures 6 to 12). The spectrum for each sample was recorded over the 450–4000 cm^{-1} spectral region.

FORMULATION

Table 1: Table containing Formulation Codes.

POLYMER USED	CONCENTRATION (%)	Formulation Code
Compressed lozenge (Troch) without polymer	-	DT
HPMC K4M	2	T1
	1.5	T2
	1	T3
	0.5	T4
HPMC K15M	2	S1
	1.5	S2
	1	S3
	0.5	S4
	0.25	S5

Table 2: Composition of Chlorhexidine and Flurbiprofen Troches.

Ingredients (mg)	FORMULATION CODE									
	T1	T2	T3	T4	S1	S2	S3	S4	S5	DT
Chlorhexidine	5	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	8.75
HPMC K4M	25	18.75	12.5	6.25	-	-	-	-	-	-
HPMC K15M	-	-	-	-	25	18.75	12.5	6.25	3.125	-
PEG 6000	50	50	50	50	50	50	50	50	50	50
Mannitol	828.25	804.5	780.75	757	828.25	804.5	780.75	757	760.125	621.25
25# Sugar	150	150	150	150	150	150	150	150	150	150
PVP K90 (7.5%)	qs	qs	qs	Qs	qs	qs	qs	qs	qs	Qs
MCC 101	50	50	50	50	50	50	50	50	50	50
MCC 102	50	50	50	50	50	50	50	50	50	50
saccharin	30	60	90	120	30	60	90	120	120	120
Menthol	5	5	5	5	5	5	5	5	5	5
Aerosil	10	10	10	10	10	10	10	10	10	10
Talc	12	12	12	12	12	12	12	12	12	12
Stearic acid	12	12	12	12	12	12	12	12	12	12
Orange colour	-	-	-	-	_	-	-	_	-	-
Yellow colour	6	6	6	6	6	6	6	6	6	6
Vanilla Flavor	_	-	-	-	_	_	-	_	_	-
Mango flavor	8	8	8	8	8	8	8	8	8	-
Total weight	1250	1250	1250	1250	1250	1250	1250	1250	1250	1250

Preparation of Chlorhexidine and Flurbiprofen Troches

Required amounts of ingredients were weighed and passed through 25- mesh sieve. To the Intra Granular Portion, The blend of Chlorhexidine and Flurbiprofen, MCC 101, polymer, PEG 6000, mannitol, half of the amount of colour and saccharin were mixed for 10min and PVP K-90 was added. The mixture was then granulated and the resulting wet mass passed through 18-mesh Then the granules were dried at 70°C for approximately 15-20min. Then the dried granules were passed through 25-mesh sieve, blended with stearic acid, Aerosil and talc. Flow properties of the dried granules were determined. To the extra Granular portion, the blend of sugar, menthol, MCC 102, flavour and half of the amount of colour and aspartame were mixed for 10min Then it is blended with stearic acid, Aerosil and talc. **(Patel Manisha *et al.*, 2012)**. Now to this extra granular portion, intra granular portion was added and mixed. Then the resulted mixture compressed into tablets having an average weight of 1,250 mg using 16 station rotary tablet compression machine fitted with 16 mm punches.

EVALUATION

The prepared lozenges 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. 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 lozenge in order to break the lozenge. The resistance of the lozenge to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 lozenges 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 of lozenges is calculated and presented with standard deviation. 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 tablets were re-weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage (Table 4) as.

% Friability = $[(W_1 – W_2) / W_1] \times 100$

Where,

W_1 = Initial weight of 20 lozenges

W_2 = Weight of the 20 lozenges 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.

***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.

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, appearance of the lozenges were recorded from them; the results were reported in the table 7, 8.

RESULTS AND DISCUSSIONS

PREFORMULATION STUDIES

Drug-Excipient compatibility studies by physical observation

Chlorhexidine and Flurbiprofen were 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 figure 1. The characteristic peaks of Chlorhexidine are well retained in the spectrum.

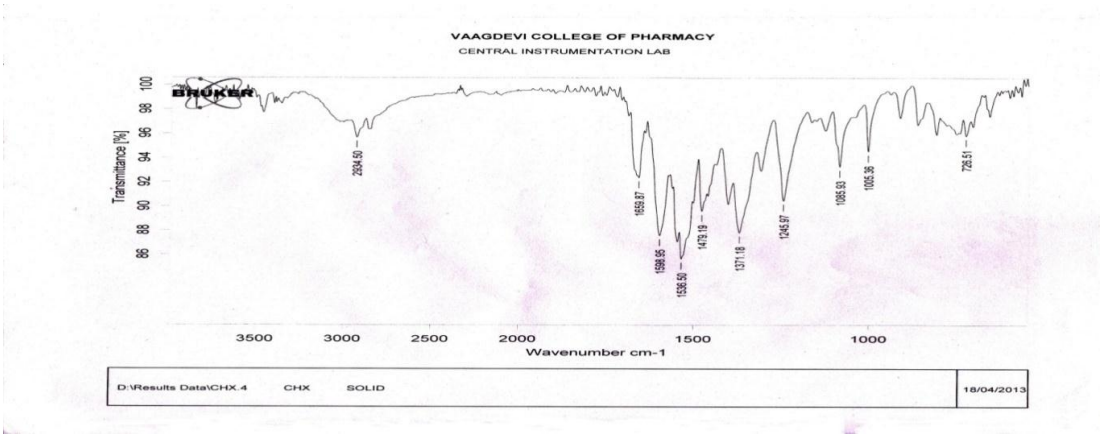

Figure 1: FT-IR spectra of Chlorhexidine pure drug.

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

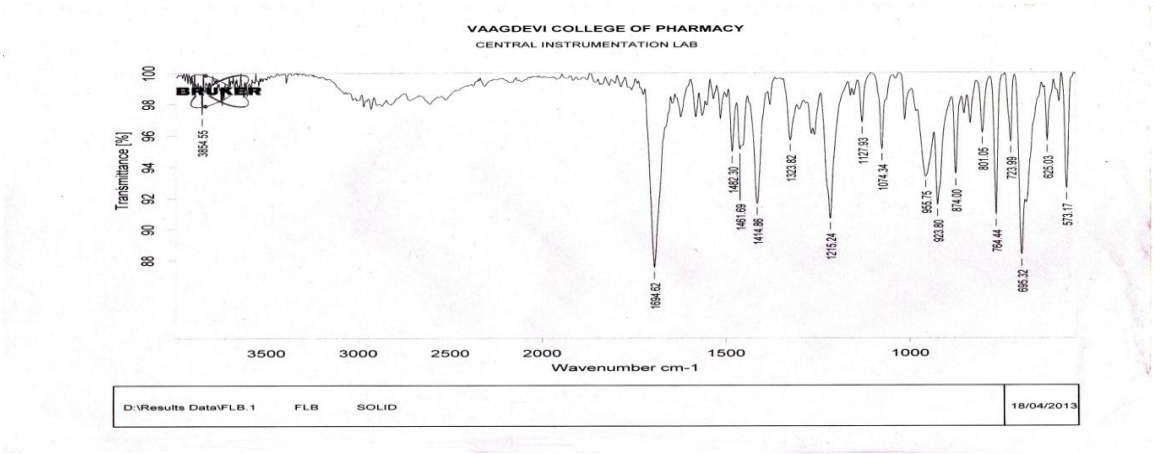

Figure 2: FT-IR spectra of Flurbiprofen pure drug.

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

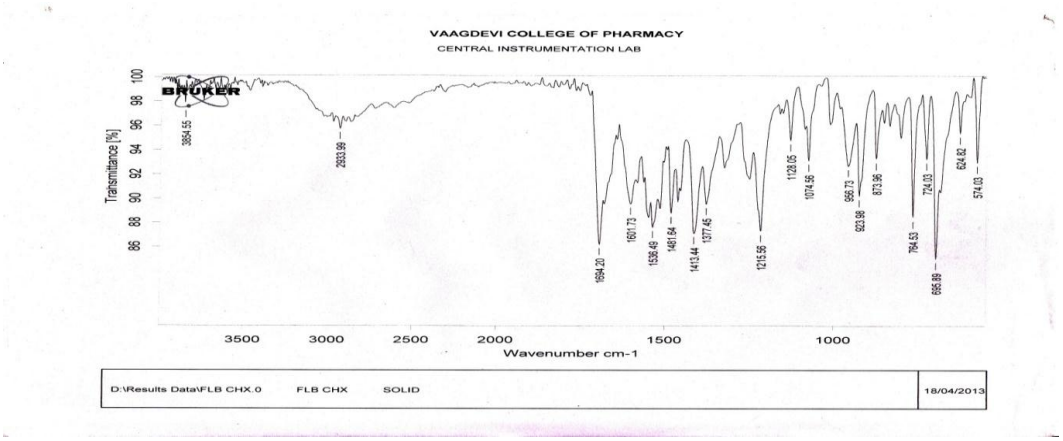

Figure 3: FT-IR spectra of Chlorhexidine and Flurbiprofen pure drugs.

The FT-IR spectra of Chlorhexidine and Flurbiprofen Troches containing HPMC K4M is shown in the figure 4. The characteristic peaks of Chlorhexidine and Flurbiprofen are well retained in the spectrum representing that there is no significant interaction between drugs and excipients.

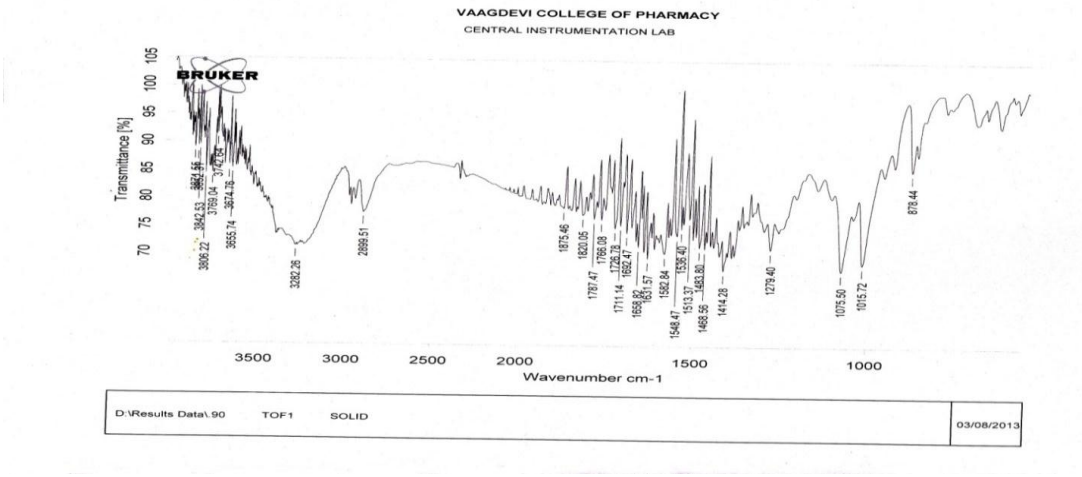

Figure 4: FT-IR spectra of Chlorhexidine and Flurbiprofen Troches containing HPMC K4M.

The FT-IR spectra of Chlorhexidine and Flurbiprofen Troches containing HPMC K15M are shown in the figure 5. The characteristic peaks of Chlorhexidine and Flurbiprofen are well retained in the spectrum representing that there is no significant interaction between drugs and excipients.

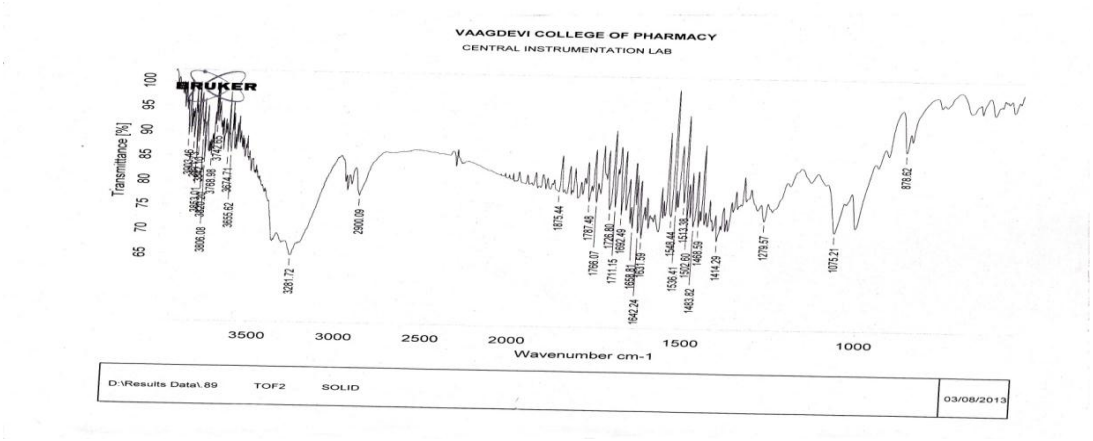

Figure 5: FT-IR spectra of Chlorhexidine and Flurbiprofen Troches containing HPMCK15M.

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 + HPMCK4M	1075.50	3852.31	1279.40	1692.47	2899.51	726.12	1536.40	1536.40
Chlorhexidine+Flurbiprofen + HPMCK15M	1075.21	3853.01	1279.57	1692.49	2900.09	726.32	1536.41	1536.41

From the table 3, 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 (100 µg/ml) were prepared in distilled water. For the selection of analytical wavelength the solutions of Flurbiprofen and Chlorhexidine (10 µg/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.

IN-VITRO EVALUATION OF DEVELOPED CHLORHEXIDINE AND FLURBIPROFEN TROCHES

Evaluation of formulated Troches

All 10 formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopeia limits. The results of the tests were tabulated (Table 4). 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.

Table 4: Physical Parameters of various formulations.

Formulation	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Content uniformity(%)	
					CHX	FLB
T1	1250.65±2.12	4.11±0.03	9.76±0.03	0.12	98.23	98.23
T2	1250.15±4.75	4.12±0.03	9.81±0.03	0.09	99.65	99.65
T3	1250.50±2.52	4.32±0.05	9.80±0.05	0.11	99.12	99.12
T4	1250.50±4.39	4.12±0.04	9.87±0.04	0.08	98.44	98.44
S1	1250.50±4.35	4.32±0.08	9.79±0.08	0.14	99.23	99.23
S2	1250.45±2.12	4.12±0.05	9.85±0.05	0.11	98.63	98.63
S3	1250.33±1.45	4.15±0.06	9.82±0.06	0.10	99.65	99.65
S4	1250.80±1.63	4.12±0.04	9.83±0.04	0.13	98.65	98.65
S5	1250.15±4.75	4.12±0.06	9.79±0.06	0.12	98.45	98.45
DT	1250.31±1.45	2.82±0.06	9.82±0.06	0.10	99.65	99.65

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

The results of the physical tests of the formulations were within the limits and comply with the standards.

In-vitro drug release profile

The percentage drug release profiles from various formulations of Chlorhexidine and Flurbiprofen Troches are represented in figures 6, 7 containing HPMC K4M and figures 8,9 containing HPMC K15M.The percentage drug release profiles from the formulations T1, T2, T3, T4 containing HPMC K4M in 2%,1.5%,1%,0.5% concentrations respectively shown in figures:6,7 respectively. T4 containing HPMC K4M (0.5%) showed 99.2% and 99.6% release of chlorhexidine and Flurbiprofen respectively in 30minutes.

The percentage drug release profiles from the formulations S1,S2,S3,S4,S5 containing HPMC K4M 2%,1.5%,1%,0.5%,0.25% respectively showed in figures: 8, 9 respectively. S5 containing HPMC (0.25%) showed 99.3%and 98.2% drug release in 30minutes.

***In-Vitro* Drug release studies of Chlorhexidine and Flurbiprofen Troches**

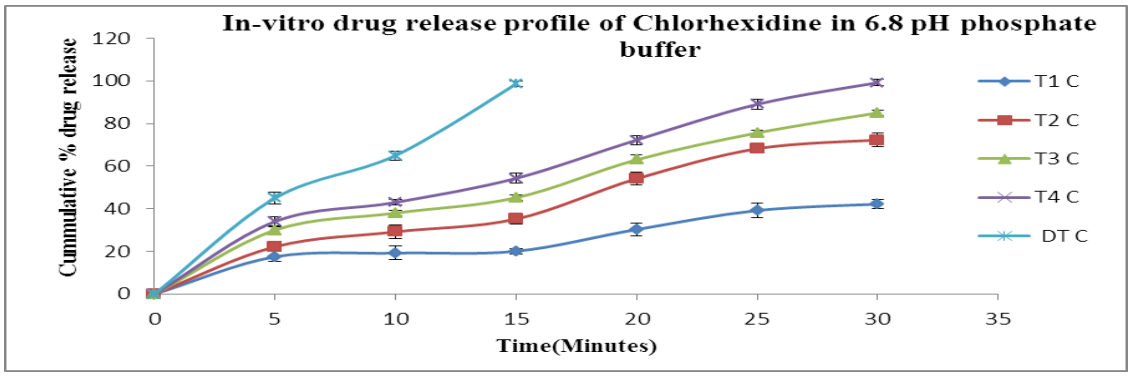

Figure 6: In-vitro drug release profile of Chlorhexidine from Troches containing HPMC K4M.

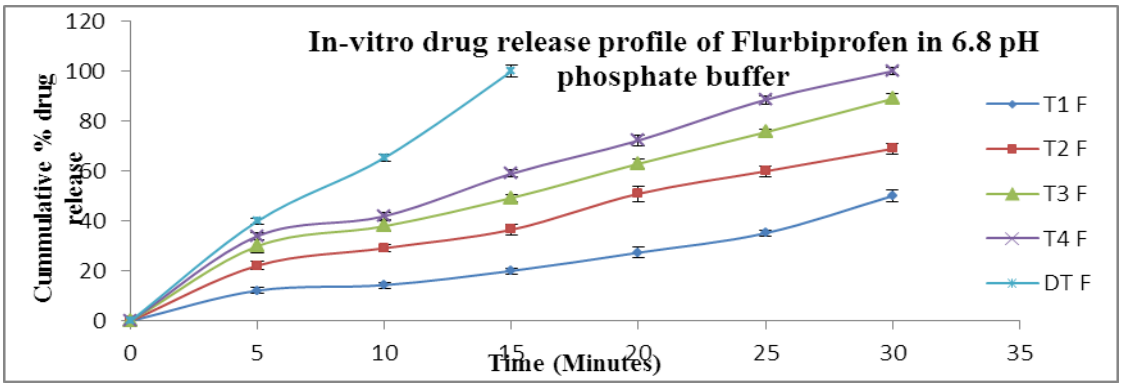

Figure 7: In-vitro drug release profile of Flurbiprofen from Troches containing HPMC K4M.

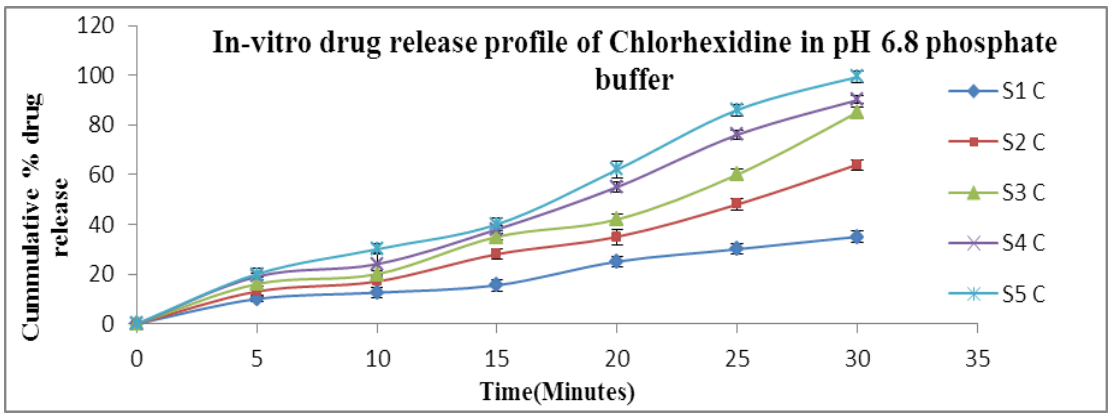

Figure 8: In-vitro drug release profile of Chlorhexidine from Troches containing HPMC K15M.

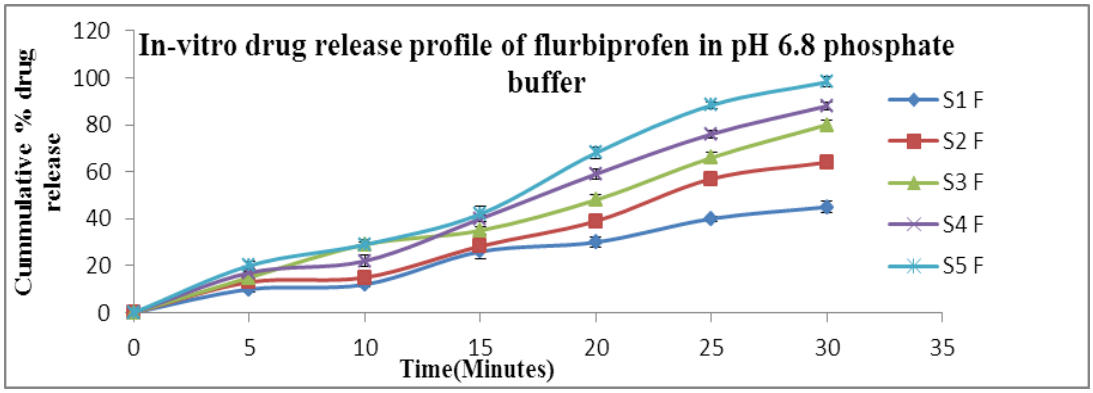

Figure 9: In-vitro drug release profile of Flurbiprofen from Troches containing HPMC K15m.

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, 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**
T4	0.9727	0.7184	0.9702	0.9646
S5	0.9835	0.7023	0.8729	0.9584

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**
T4	0.9732	0.6546	0.9694	0.9641
S5	0.9876	0.7204	0.8832	0.9625

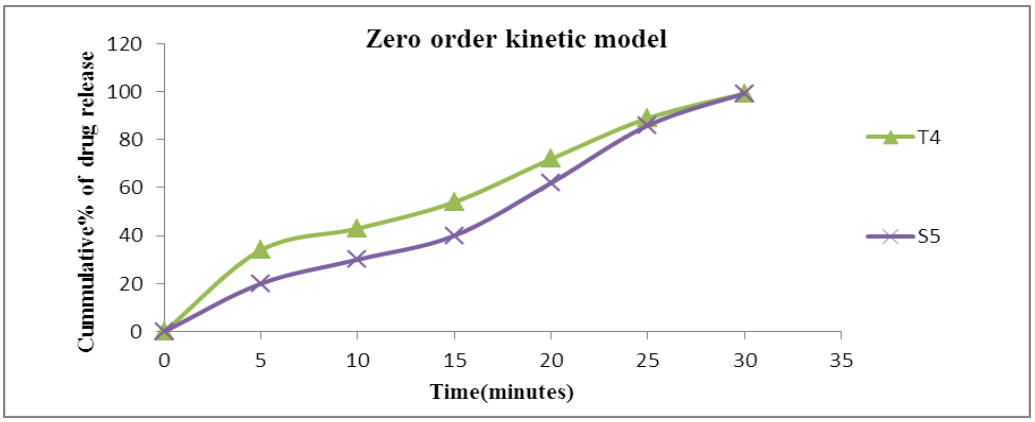

Figure 10: Zero order kinetic model graphs for Chlorhexidine in Formulation T4, & S5.

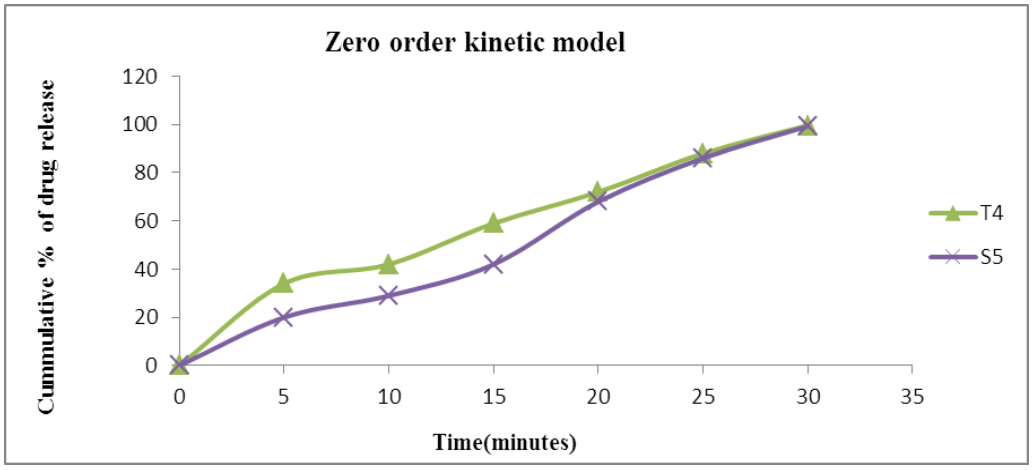

Figure 11: Zero order kinetic model graphs for Flurbiprofen in Formulation T4, & S5.

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.

IN VIVO TASTE EVALUATION CHLORHEXIDINE AND FLURBIPROFEN LOZENGES

Taste evaluation was performed on ten healthy human volunteers by keeping lozenges in mouth for 5 minutes and the results were reported in the table 31. The bitterness of the drug was reduced or even masked by increasing the concentration of sweetner. Troches (compressed lozenges) T4, S4, S5 formulations containing sweetner concentration 120mg were having good taste and odor than other formulation .The results are as follows

Table 7: *In vivo* taste evaluation test for Chlorhexidine and Flurbiprofen lozenges.

Evaluation of taste by human volunteers																
Form--ution Code	Product Elegance					Taste					Mouth feel					
	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	
S1	++	+++	+++	+++	++	+	+	+	+	+	+	+	+	+	+	
S2	++	+++	+++	+++	++	++	++	++	++	++	++	++	++	++	++	
S3	++	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++	
S4	++	+++	+++	+++	++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++	

Table 8: *In vivo* taste evaluation test for Chlorhexidine and Flurbiprofen lozenges.

Evaluation of taste by human volunteers															
Form--ution Code	Product Elegance					Taste					Mouth feel				
	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5	V1	V2	V3	V4	V5
S1	++	+++	+++	+++	++	+	+	+	+	+	+	+	+	+	+
S2	++	+++	+++	+++	++	++	++	++	++	++	++	++	++	++	++
S3	++	+++	+++	+++	++	+++	+++	+++	+++	+++	+++	+++	+++	+++	+++
S4	++	+++	+++	+++	++	++++	++++	++++	++++	++++	++++	++++	++++	++++	++++

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 Compressed Tablet lozenges (Troches) 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. Troches were prepared by wet granulation method. In preparation of the Troches the usage of Microcrystalline cellulose will increase the hardness and drug release of the Troches.

Developed Chlorhexidine and Flurbiprofen Troches were evaluated for various physicochemical evaluation parameters and were found to be within the standard limits. Chlorhexidine and Flurbiprofen Troches with HPMC K4M 0.5% (T4), HPMC K15M (S5) 0.25% were optimized. The optimized formulations showed best release than other formulations. Among the optimized formulations, Troches with HPMC K15M (S5) were showed best drug release within 30minutes. From the mechanisum of drug release kinetics it was found that the optimized formulations fallow zero order kinetics. Based on dissolution studies the Troches showed prolong drug release than Hard candy lozenges.

The bitter taste of Chlorhexidine and Flurbiprofen was masked with artificial sweetener (saccharin) and flavours. From the taste assessment studies it was concluded that the Troches T4,S4,S5 formulations containing vanilla flavor and lemon yellow color and sweetener concentration 120mg were having good taste and odor than other formulations.

Over all it was concluded that the Chlorhexidine and Flurbiprofen Troches 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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