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Formulation and Evaluation Famotidine Fast Dissolving Buccal Films

Ch. Saibabu, Kothapalli Kalyani*, and Karavadi Thejomoorthy

Department of Pharmaceutics, Malineni Lakshmaiah College of Pharmacy, Kanumalla, Singarayakonda-523101

ABSTRACT

The present research work was to formulate and evaluate famotidine fast dissolving buccal filmSFormulations F12, F13, F14 and F15 has shown release 94.4% , 96.2% ,98.2% and 97% respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 1.310326, 0.907833, 0.871323, 1.087838 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F14 and Super case II transport type in of case of formulations F12, F13 and F15. At pH 6.8, carbopol is present in ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of PVP decreases the Famotidine release may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, there by controlling the drug release approximately 12 h.

Key words: Famotidine,HPMC,PVP and Carbapol.

Introduction

Famotidine is a histamine H_2-receptor antagonist that inhibits stomach production, and it is commonly used in the treatment of peptic ulcer disease (PUD) and gastro esophageal reflux disease (GERD/GORD)[1-4]. It is commonly marketed by Johnson/Merck under the trade names Pepcidine and Pepcid and by Astellasunder the trade name Gaster. Unlikecimetidine, the first H_2 antagonist, famotidine has no effect on the cytochrome P450 enzyme system, and does not appear to interact with other drugs.Certain preparations of famotidine are available over the counter (OTC) in various countries. In the United States, preparations of 10- and 20-milligram tablets, sometimes in combination with a more traditional antacid, are available OTC. Larger doses still require a prescription.Famotidine is given to surgery patients before operations to prevent postoperative nausea and to reduce the risk of aspiration pneumonitis. Famotidine is also given to some patients taking NSAIDs, to prevent peptic ulcers. It serves as an alternative to proton-pump inhibitors[5-9]. It is also given to dogs with acid reflux. Famotidine has also been used in combination with an H1 antagonist to treat and preventurticaria caused by an acute allergic reaction.Side effects are associated with famotidine use. In clinical trials, the most common adverse effects were headache, dizziness, and constipation or diarrhea.[6] Antacid preparations such as famotidine, by suppressing acid-mediated breakdown of proteins, lead to an elevated risk of developing food or drug allergies. This happens due to undigested proteins then passing into the gastrointestinal tract where sensitization occurs. It is unclear whether this risk occurs with only long-term use or with short-term use as well[10-14].

MATERIALS AND METHODS

Famotidinewere obtained from Torrent Pharmaceuticals Ltd.,Gujrat India. HPMC,PVP AND Carbapol were obtained from Loba chemie Pvt. Ltd., Mumbai.

Table No: 1

THE COMPOSITION OF BUCCAL FILMS PREPARED USING FAMOTIDINE

Formulation code	Polymers in mg			Solvents in ml	
	HPMC	CP	PVP	Ethanol (70 % v/v)	PG
F1	200	0	-	9.5	0.5
F2	190	10	-	9.5	0.5
F3	180	20	-	9.5	0.5
F4	170	30	-	9.5	0.5
F5	160	40	-	9.5	0.5
F6	150	50	-	9.5	0.5

F7	190	-	10	9.5	0.5
F8	180	-	20	9.5	0.5
F9	170	-	30	9.5	0.5
F10	160	-	40	9.5	0.5
F11	150	-	50	9.5	0.5
F12	150	40	10	9.5	0.5
F13	150	30	20	9.5	0.5
F14	150	20	30	9.5	0.5
F15	150	10	40	9.5	0.5

Famotidine: 20 mg

PHYSICOCHEMICAL EVALUATION OF BUCCAL FILMS OF FAMOTIDINE

Formulation Code	Surface pH ± SD	PMA ± SD	PML± SD	Swelling Index ± SD	WTR ± SD	Thickness (mm) ± SD
F1	6.73±0.005	5.21±0.07	5.97±0.12	69.4±1.04	10.58±0.35	0.24±0.01
F2	6.79±0.005	7.32±0.04	5.14±0.72	99.67±0.69	7.67±0.34	0.62±0.01
F3	6.71±0.015	9.24±0.09	4.74±0.1	118.4±0.72	7.17±0.34	0.47±0.01
F4	6.64±0.050	10.32±0.11	4.14±0.2	124.15±0.99	6.4±0.35	0.59±0.01
F5	6.6±0.015	12.13±0.09	4.08±0.03	132.36±0.61	5.98±0.08	0.85±0.02
F6	6.52±0.03	14.21±0.06	3.88±0.02	138±0.85	5.39±0.32	0.31±0.01
F7	6.7±0.03	7.86±0.27	6.44±0.1	67.53±0.65	10.87±0.35	0.22±0.02
F8	6.8±0.015	6.18±0.13	7.13±0.08	69.7±0.72	11.48±0.52	0.2±0.01
F9	6.77±0.005	5.34±0.12	9.12±0.07	71.6±0.62	11.58±0.43	0.23±0.01
F10	6.8±0.001	4.12±0.13	10.06±0.06	78.6±1.07	12.3±0.59	0.25±0.01
F11	6.81±0.001	3.56±0.25	11.21±0.06	82.6±1.1	12.44±0.48	0.31±0.01
F12	6.71±0.001	13.02±0.23	4.84±0.08	86.9±0.9	5.69±0.2	0.48±0.02
F13	6.67±0.005	11.26±0.24	5.72±0.01	77.4±0.7	5.91±0.38	0.43±0.01
F14	6.63±0.005	9.89±0.22	6.13±0.02	72.53±0.6	6.32±0.2	0.36±0.01
F15	6.61±0.017	7.02±0.06	7.45±0.52	69.56±0.65	6.94±0.31	0.32±0.01

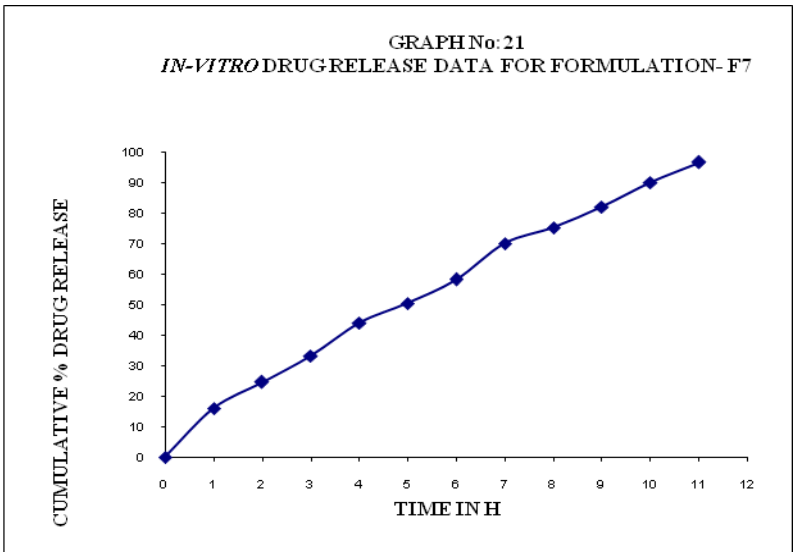
MEASUREMENT OF BUCCOADHESIVE STRENGTH OF BUCCAL FILMS OF FAMOTIDINE

Formulation code	Buccoadhesive strength in g
F1	15.4
F2	15.5
F3	16.6
F4	20.5
F5	27.8
F6	32.5
F7	15.3
F8	17.4
F9	19.8
F10	24.8
F11	26.7
F12	34.2
F13	34.8
F14	35.6
F15	33.4

IN-VITRO DRUG RELEASE STUDIES

The *in-vitro* release studies were performed in phosphate buffer solution (pH 6.8, 100 ml) at 37 ºC using a modified dissolution apparatus. The modified dissolution apparatus consisted of a 250 ml beaker as a receptor compartment and an open end tube as a donor tube. The magnetic stirrer assembly with an attached hot plate was adopted for the study. The dissolution medium consisted of 100 ml of phosphate buffer (pH 7.5) maintained at 37 ± 1°C by means of a thermo-regulated hot plate. Film was placed into the donor chamber of the assembly separated from the medium by a semi-permeable

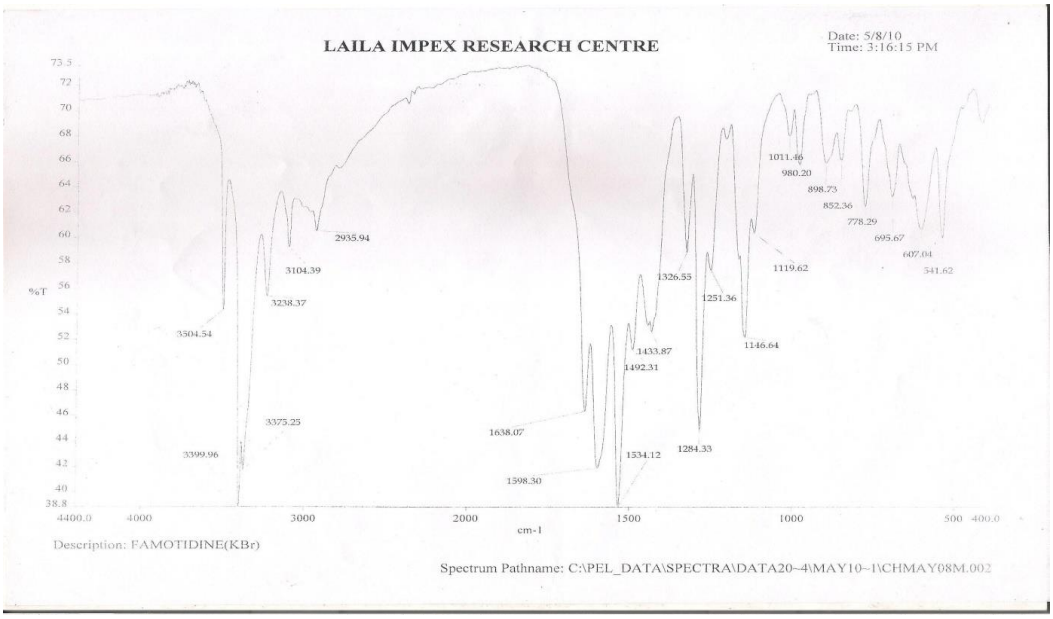
membrane. The donor tube was then dipped into the receptor compartment containing dissolution medium, which was maintained at 37 ± 1°C and stirred at a constant speed of 100 rpm using a magnetic bead. One milliliter samples were withdrawn at predetermined time intervals for all the batches. For each sample withdrawn, an equivalent volume of phosphate buffer was replaced to the dissolution medium to maintain constant volume and sink condition. A ten-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 272 nm.

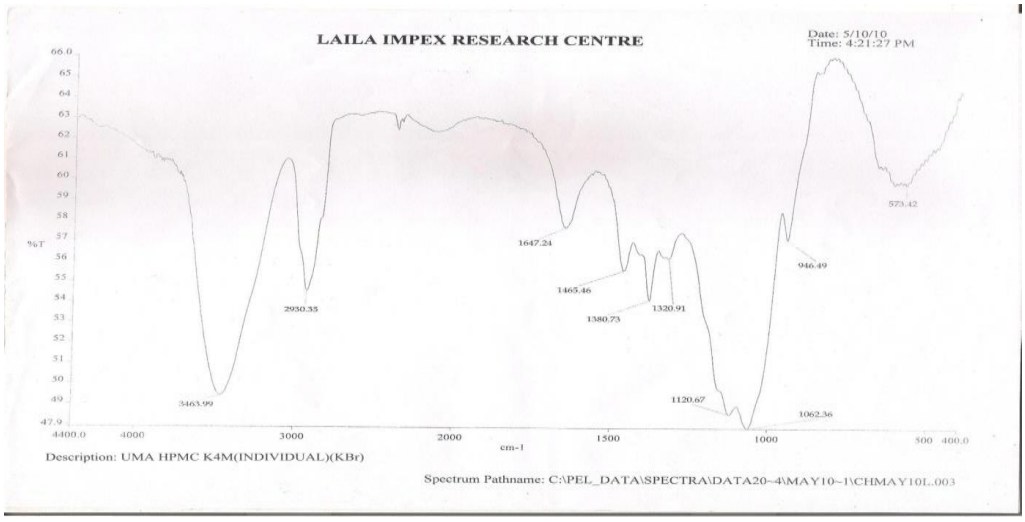


DRUG –POLYMER COMPATIBILITY STUDIES BY FTIR

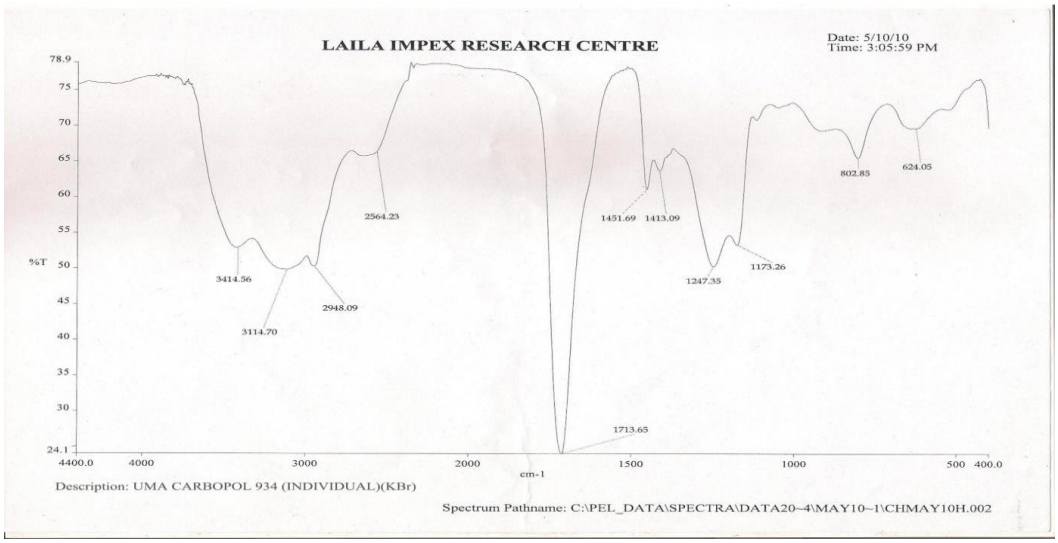
Drug polymer compatibility studies were performed by FTIR[57] (Fourier transform infrared spectroscopy). In order to confirm that the entrapment of drug within the polymeric systems involve only the physical process and no interaction between drug and polymer. FTIR absorption spectra ofpure drugand all the polymers used like HPMC, CP, PVP and the combination of drug and polymers were shows no significant interaction between drug and polymers. The graphs obtained were shown in the figure 2-6.

FTIR SPECTRA OF FAMOTIDINE





FTIR SPECTRA OF CARBOPOL



FTIR SPECTRA OF PVP

RESULTS AND DISCUSSION

The Famotidine buccal mucoadhesive films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Poly vinyl pyrrolidone (PVP). Ethanol (70 % v/v) is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. Triethanolamine was used to neutralize the carbopol polymeric solution.

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy).

The prepared Famotidine buccal films were characterized based upon their physico chemical characteristics like surface pH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content. (Table No.3)

The stability studies performed would be more accurate to mimic the stability of drug and buccal film in the oral cavity *in-vivo*. The stability study of the optimized patch (F 14) was done in natural human saliva. The patches were evaluated by their appearance characteristics, such as color and shape, and their drug content in natural human saliva.

Ex-vivo buccoadhesive strength has determined by using a modified balance method using Fresh sheep buccal mucosa. The strength of bond formed between the buccoadhesive Famotidine formulation and the mucosal membrane sheep buccal mucosa was determined. The weights required to detach the patch from the buccal mucosa was noted as buccoadhesive strength.

The *in- vitro* drug release studies were performed as the release of the drug from the dosage form plays an important role in buccal drug delivery and in**Drug –polymer compatibility studies by FTIR**

The FTIR spectra of Famotidine, HPMC, CP, PVP and the combination of drug and polymers were shows no significant interaction between drug and polymer. The FTIR spectra's of Famotidine, HPMC, Carbopol, PVP, and mixture of drug along with polymers are shown in figure 2 to 6.

The physicochemical compatibility of the drug and the polymer was established through FTIR studies. IR spectral analysis of Famotidine showed the peaks at wave numbers of 3504, 3399, 3375 (N-H Asymmetric stretching), 3238, 3104 (Associated N-H stretching), 2938 (CH_2 Asymmetric stretching), 1638 (C=C Stretching), 1433 (CH_2 Bending), 1326, 1284(C=S Stretching), 1251 (C-NStretching), 1146, 1119 (SO_2 Asymmetric stretching), 980 (Ring Stretching), 778, 698, 607 (C-S Stretching) confirming the purity of drug with standard respectively.

In the physical mixture of Famotidine with Hydroxy propyl methyl cellulose, Carbopol and Poly vinyl pyrrolidone the major peaks of Famotidine 3504.04, 3399.89, 3375.11 (N-H Asymmetric stretching), 3237.51, 3104.97 (Associated N-H stretching), 2937.22 (CH_2 Asymmetric stretching), 1638.48 (C=C Stretching), 1449.09 (CH_2 Bending), 1325.39, 1283.56 (C=S Stretching), 1251.23 (C-N Stretching), 983.62 (Ring Stretching), 778.79, 691.14, 609.23 (C-S Stretching) wave numbers. However, additional peaks were absorbed in physical mixtures which could be due to presence of polymers and indicated that there was no chemical interaction between Famotidine and other excipients.

Surface pH

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films was determined. The observed surface pH of the formulations was found to be in the range of 6.52±0.03 to 6.81±0.01. The results are found that there is no significant difference of surface pH in all the formulations and the pH range lies with in the range of salivary pH i.e. 6.5 to 6.8, hence do not cause irritation and achieve patient compliance. Surface pH values of all the formulations are represented in table no: 3.

Percentage Moisture Absorption and Percentage Moisture Loss

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML. The observed results of PMA and PML were shown in the tabular column. (Table No. 3). The percentage Moisture uptake in the formulation F6 (150 mg, HPMC, 50 mgCP) has shown the highest value of moisture absorption 14.21±0.06. This may be due to the presence of higher concentrations of CP along with HPMC.

The formulation F11 (150 mg, HPMC, 50 mg PVP) shows higher value of Moisture loss 11.21±0.06which is due to presence of higher concentration of PVP and formulation F6 (150 mg, HPMC, 50 mg CP) shows low value of 3.88±0.02. The Results were tabulated in table no.3

Swelling percentage

Table 3 shows the swelling percentage of the formulated buccal films. The swelling behaviour of the polymer was reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to over hydration.

The formulation F6 (150 mg, HPMC, 50 mg CP) shows higher value of Swelling percentage 138±0.85 which is due to presence of higher concentration of carbopol. The Results were tabulated in table no.3

Water Vapour Transmission

Water vapor transmission rate through various films was given in table 3. Water vapor transmission studies indicated that all the films were permeable to water vapour. The formulation F11 (150 mg, HPMC, 50 mg PVP) has shown maximum water vapor transmission of 12.44±0.48 among all the films. This may be due to the presence of high amount of PVP.

The formulation F6 (150 mg, HPMC, 50 mg CP) has shown lower water vapor transmission of 5.39±0.32among all the films. This may be due to the presence of high amount of carbopol. The Results were tabulated in table no.3

Thickness and Weight of films

The film thicknesses were observed by using digital vernier caliper and found to be in the range of 0.20±0.01 mm to 0.62±0.01 mm. The weight of the films was found to be in the range of 210.12±1.06 mg to 163.18±0.9 mg. The Results were tabulated in table no.3

Folding endurance

The folding endurance was found to be greater than 300 times in case of all the formulations. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. Folding endurance test results indicated that the films would maintain the integrity with buccal mucosa when applied.

Drug content estimation

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability. Recovery was possible to the tune of 18.1 to 19.9. The Results were tabulated in table no.3

Stability in human saliva

The stability study of the optimized patches (F 14) was done in natural human saliva. The films did not exhibit any significant changes in their color, shape and satisfactory physical stability.

Measurement of Buccoadhesive Strength

The buccoadhesive properties of the fabricated films were shown in table 4. Carbopol being an anionic polymer gives the highest bioadhesive force. The bioadhesive strength exhibited by Famotidine buccal films was satisfactory for maintaining them in oral cavity. The combination of HPMC and Carbopol shows good adhesion. Upon addition of PVP the bioadhesive strength increases which maybe due to hydrogen bond formation and vanderwaals forces. The highest Buccoadhesive strength was found to be in formulation F 14. Ref, Graph No.2.

***In-vitro* drugrelease studies**

Distinguishable difference was observed in the release of Famotidine in all formulations. The results and data of *in vitro* studies are shown in the Table No: 6 to 20, and the individual graphs were shown in 3-47, The comparative *in-vitro* drug release, Higuchi's and peppa's models was shown in the Graph No: 49- 57.

Formulations F1, F2, F3 containing HPMC alone and Combination of carbopol and HPMC gave a reasonable Famotidine release up to 10 h.

Formulations F4, F5 and F6 containing Combination of carbopol and HPMC gave a reasonable Famotidine release up to 11 h.

The formulations F1, F2, F3, F4, F5 and F6 has shown release 95.2%, 96%, 95.6 %, 98.1 %, 96.2 % and 94.4 % respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). The diffusion exponent (n) obtained by peppas plot showing 0.713705, 0.880056, 1.092273, 1.157541,1.13872, 1.118578 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F1 and F2 and Super case II transport type in of case of formulations F3, F4, F5 and F6.

Formulations F7, F8, F9, F10 and F11 containing Combination of HPMC and PVP gave a reasonable Famotidine release up to 11 h.

The formulations F7, F8, F9, F10, F11 and F12 has shown release 96.6 % , 95.2 % ,94 %, 93.2 %, and 91 % respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shownslope value of 0.712362, 1.062854, 1.098589, 1.073329, 1.1027 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F7 and Super case II transport type in of case of formulations F8, F9, F10 and F11.

Formulations F12, F13, F14 and F15 containing Combination of HPMC, CP and PVP gave a reasonable Famotidine release up to 12 h.

Formulations F12, F13, F14 and F15 has shown release 94.4% , 96.2% ,98.2% and 97% respectively The *in-vitro* drug release and higuchi's plot has shown that the drug release followed by zero order kinetics, which was envinced from the regression value (R). Peppa's plot was drawn which has shown slope value of 1.310326, 0.907833, 0.871323, 1.087838 respectively, which confirms that the diffusion mechanism involved in the drug release was Non fickian release in case of formulations F14 and Super case II transport type in of case of formulations F12, F13 and F15.

At pH 6.8, carbopol is present in ionized state and as a result the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of PVP decreases the Famotidine release may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, there by controlling the drug release approximately 12 h.

The incorporation of carbopol and PVP into HPMC films, the drug release was found to maximum at the end of 12^{th} h.

CONCLUSION

The project work was certified as "formulation and characterization of oral muco adhesive buccal films of famotidine"The Famotidine buccal films were prepared by solvent casting technique using ethanol(70%v/v) as a solvent, employing o shape ring placed on a glass surface as substrate and by using different polymers like Hydroxy Propyl Methyl Cellulose-15cps (HPMC), Carbopol (CP)and Poly Vinyl Pyrrolidine (PVP).The polymeric solutions are levigated with 30%w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. Drug polymer interaction studies by FTIR shows there is no significant interaction between drug and polymers. The prepared famotidine buccal films were characterized based upon their physico-chemical characteristics like surface PH, PMA, PML, swelling percentage, WVT, thickness, weight, folding endurance and drug content. the ex-vivo bucco adhesive strength, Ex-vivo permeation studies, in-vitro release studies and in-vivo release studies in rabbits were performed.

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