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PREPARATION AND IN VITRO EVALUATION OF FAMOTIDINE MUCOADHESIVE MICROSPHERES USING DIFFERENT MUCOADHESIVE AGENTS

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ABSTRACT

The present study involves preparation and characterization of mucoadhesive microspheres with famotidine as model drug for prolongation of gastric residence time. Mucoadhesive formulation has been accepted as a process to achieve controlled release and drug targeting. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive microspheres exhibited a prolonged residence time at the site of application or absorption and facilitate an intimate contact with the underlying absorption surface and thus contribute to improved and/or better therapeutic performance of drugs. In recent years such mucoadhesive microspheres have been developed for oral, buccal, nasal, ocular, rectal and vaginal routes for either systemic or local effects. The microspheres were prepared by Orifice Ionic-Gelation method using mucoadhesive polymers like HPMC (hydroxy propyl methyl cellulose), CMC (carboxy methyl cellulose) MC (methyl cellulose) and a release controlling polymer Sodium alginate. *In Vitro* drug release studies were performed and drug released evaluated. The effect of polymer concentration on size of microspheres and drug release were observed. The prepared microspheres exhibited prolonged drug release the mean particle size increased as the concentration of sodium alginate increased, as the sodium CMC polymer concentration increases the mucoadhesion increased and the drug release rate decreased at higher concentration of Sodium alginate.

KEYWORDS: Microspheres, famotidine**,** hydroxy propyl methyl cellulose, carboxy methyl cellulose.

INTRODUCTION

Famotidine is a histamine H2 receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, zollinger-elison syndrome in the management of benign gastric and duodenal ulceration the dose is 40 mg daily by mouth at bed time, for 4-8 weeks. The low bioavailability (40-45%) and short biological half life (2.5-4 hr) of famotidine for the oral administration it favors the development of sustained release formulation. It has been reported that oral treatment of gastric disorders with H2 receptor antagonists like famotidine or ranitidine used in combination with antacids promotes local deliver of these drugs to parietal cell wall. Local delivery also increases the stomach wall receptor site bioavailability and increases the efficacy of the drugs to reduce acid secretion. Hence this principle may be applied for improving systemic as well as local delivery of famotidine, which would efficiently reduced gastric acid secretion. Therefore it is expected that if local delivery of antimicrobial agents from gastric lumen into the mucous layer can be achieved, H.pylori eradication rate will be increased. Mucoadhesive microspheres have the ability to adhere to the stomach wall and there by remain in the GIT for an extended period. Famotidine is very soluble in water, so complete releasing of drug is not possible by preparing simple microspheres, because these microspheres escapes from the stomach part before complete release of drug, complete release of drug can be enhanced by increasing the gastric residence time by addition of mucoadhesive agent. The purpose of this study is to prepare famotidine mucoadhesive microspheres using different mucoadhesive agents like HPMC, CMC, MC and to determine mucoadhesive property, drug release profile, particle size etc., and to select the appropriate ratio of polymer to copolymer which shows the better properties

PREPARATION OF MICROSPHERES[1]

Solvent evaporation method

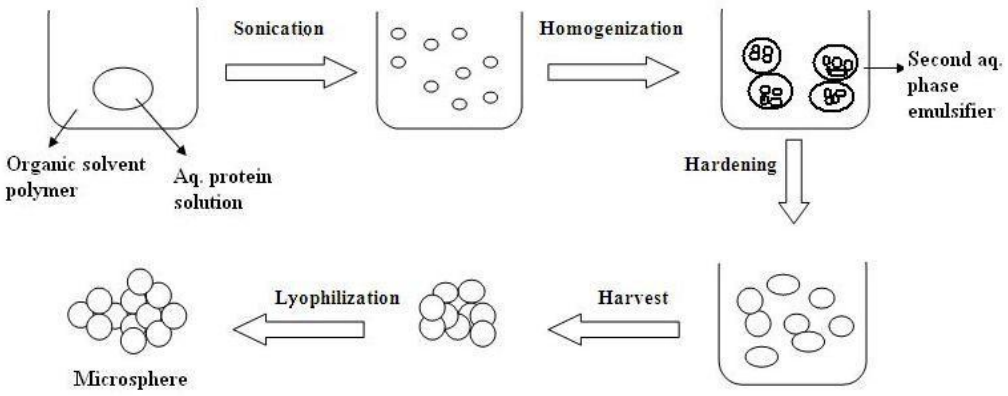


Fig 1.1: Solvent evaporation method.

It is the most extensively used method of microencapsulation. In this method a buffer or plain aqueous solution of the drug (may contain a viscosity building or stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents like dichloromethane (or ethyl acetate or chloroform) with vigorous stirring to form the primary water in oil emulsion. This emulsion is then added to a large volume of water containing an emulsifier like PVA or PVP to form the multiple emulsions (w/o/w). The double emulsion, so formed, is then subjected to stirring until most of the organic solvent evaporates, leaving solid microspheres. The microspheres can then be washed, centrifuged and lyophilize to obtain the free flowing and dried microspheres.

METHODOLOGY

Preparation of Famotidine Microspheres[17]

- Accurately weighed measured quantity of sodium alginate and kept aside. Then it was dispersed in 100 mL of distilled water by using magnetic stirrer at 40^0C.
- Then after complete dispersion, add accurately required quantity of famotidine. Then the stirring was continued until complete and uniform dispersion was obtained.
- The resulting bubble free dispersion was added manually drop wise with a 5 mL syringe (18 guaze needle) into 100 mL of (20 % w/v) calcium chloride solution ($CaCl_2$) stirred in a 250 mL beaker.
- The gelatin time of 15 min was allowed to complete the curing reaction and produce spherical and rigid micro beads. The beads so prepared were collected by decantation, washed with water and dried in hot air oven at 60^0c for 2 hrs.

Table No. 4.1: Formulations with different formulation variables.

Formulation	AH1	AH2	AH3	AC4	AC5	AC6	AM7	AM8	AM9
Ratios	3:1	1:1	1:3	3:1	1:1	1:3	3:1	1:1	1:3
Conc. of polymeric solution (%)	2	2	2	2	2	2	2	2	2
Wt.taken (in g) SA:HPMC	1.5:0.5	1.0:1.0	0.5:1.5	---	---	---	---	---	---
SA:CMC	---	---	---	1.5:0.5	1.0:1.0	0.5:1.5	---	---	---
SA:MC	---	---	---	---	---	---	1.5:0.5	1.0:1.0	0.5:1.5
$CaCl_2$(%w/v)	20 %	20 %	20 %	20 %	20 %	20 %	20 %	20 %	20 %
Curing time(in min)	15	15	15	15	15	15	15	15	15

EVALUATION TESTS

Particle size measurement

The prepared micro beads were mounted in light liquid paraffin, and the diameters of 100 particles were measured by means of an optical microscope fitted with a stage and an ocular micrometer. The mean diameter was calculated by measuring the number of division of ocular micrometer covering the micro beads. The stage micrometer was previously used to standardize the ocular micrometer.

$$\text{Mean particle size} = \Sigma n.d / \Sigma n$$

Drug entrapment Efficiency

The drug entrapment efficiency of beads was estimated by crushing the dried beads and extracting the drug in phosphate buffer (pH 6.8) by vigorous shaking on mechanical shaker for 24 hrs and analyzed the drug content. The entrapment efficiency of micro beads was calculated as follows:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Estimated percentage drug loading}}{\text{Theoretical drug content}} \times 100$$

Mucoadhesion study

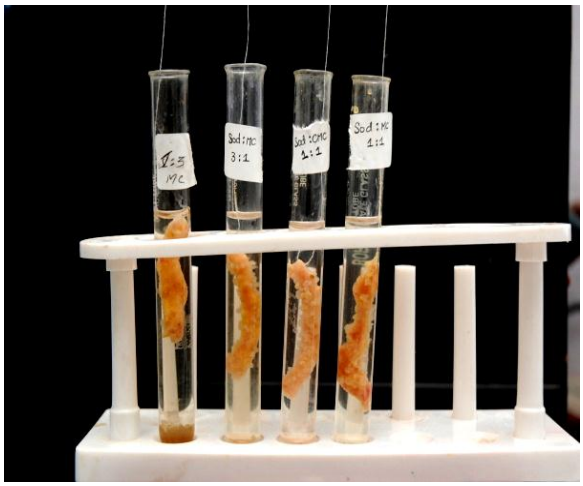


Fig 4.1 Chicken intestine suspended In 8 mL of saline.

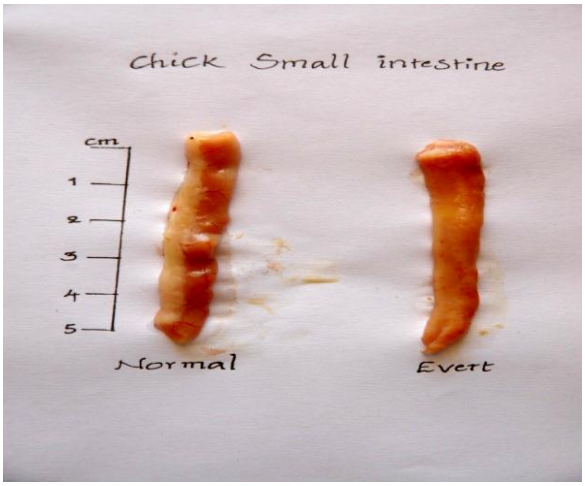


Fig 4.2 Normal and everted positions of chicken intestine.

Apparatus used

Chicken intestine, glass rod, test tubes, measuring cylinder, thread.

Method

The *in vitro* mucoadhesive test was carried out using small intestine from chicken. The small intestine tissue was excised and flushed with saline. 5 cm segment of jejunum were everted using a glass rod. Ligature was placed at both ends of segment. 100 microspheres were scattered uniformly on an everted sac from the position of 2cm above. Then the sac was suspended in 10 mL tube containing 8mL of saline by the wire, to immerse in the saline completely. The sac was incubated at 37^{o}c and agitated horizontally. The sac was taken out of medium after immersion for 0.5, 1, 1.5, 2 and 2.5 hrs, immediately repositioned as before in the similar tube containing 8 mL of fresh saline and unbound microspheres were counted. The adhering percent was presented by the following equation:

Mucoadhesion= (no. of microspheres adhered/no. of microspheres applied) x100

***In vitro* drug release of core microspheres[18]**

The prepared formulation was evaluated for *in vitro* release by USP dissolution apparatus 1 at 50 rpm and at 37^{o}c in order to determine 100 % release. To evaluate microspheres containing Famotidine were exposed to 900 mL of Hcl (pH 1.2). The samples were collected in predetermined time intervals from 0 to 480 min (8 hrs). Famotidine concentrations were determined by UV at 265 nm.

RESULTS AND DISCUSSION

Determination of Particle Size

Table No. 4.2 Comparison of particle sizes of mucoadhesive microspheres prepared using HPMC as copolymer.

Particle size(µm)	No. of particles			Mean particle size(µm)			Average particle size(µm)		
800-900	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
	12	06	--	833.4	846.8	866.0	1056.44	1276.4	1432.33
900-1000	09	10	07	912.3	954.2	932.2			
1000-1100	27	11	14	1034.22	1054.9	1066.4			
1100-1200	13	19	18	1156.4	1173.2	1187.2			
1200-1300	18	26	31	1222.1	1243.9	1284.0			
1300-1400	21	28	30	1312.4	1334.6	1393.9			

OBSERVATION

- The particle sizes of different microspheres prepared using different combinations of Sodium alginate and HPMC (hydroxy propyl methyl cellulose).

- From the above results we have known that as the concentration of the co-polymer increase the particle size increases. This is due to the increase in viscosity, which in turn increase the droplet size during addition of the polymer solution to the cross-linking solution. Particle size also increases by increasing the drug load.

Table No. 4.3: Comparison of particle sizes of mucoadhesive microspheres prepared using CMC as copolymer.

Particlesize(µm)	No. of particles			Mean particle size(µm)			Average particle size (µm)		
1500-1600	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
	09	09	02	1533.4	1566.7	1518.0	1623.54	1863.4	2010.02
1600-1700	27	12	04	1612.3	1645.2	1623.2			
1700-1800	12	14	12	1734.22	1784.9	1726.4			
1800-1900	21	23	14	1856.4	1873.2	1818.2			
1900-2000	18	29	25	1912.1	1943.9	1984.0			
2000-2100	--	13	43	2037.4	2056.6	2086.9			

OBSERVATION

- The particle sizes of different microspheres prepared using different combinations of Sodium alginate and CMC (carboxy methyl cellulose).
- From the above results we have known that as the concentration of the co-polymer increase the particle size increases. This is due to the increase in viscosity, which in turn increase the droplet size during addition of the polymer solution to the cross-linking solution. Particle size also increases by increasing the drug load.

Table No. 4.4 Comparison of particle sizes of mucoadhesive microspheres prepared using MC as copolymer.

Particlesize(µm)	No. of particles			Mean particle size(µm)			Average particle size(µm)		
4700-4800	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**	**F1**	**F2**	**F3**
	17	06	--	4763.4	4736.7	4782.0	4843.7	4967.4	5116.8
4800-4900	20	12	--	4810.9	4863.2	4891.2			
4900-5000	27	13	12	4973.28	4924.8	4962.2			
5000-5100	36	22	14	5016.4	5055.2	5078.2			
5100-5200	--	21	25	5134.9	5182.0	5192.8			
5200-5300	--	29	43	5264.9	5248.9	5278.4			

OBSERVATION

- The particle sizes of different microspheres prepared using different combinations of Sodium alginate and MC (methyl cellulose).

- From the above results we have known that as the concentration of the co-polymer increase the particle size increases. This is due to the increase in viscosity, which in turn increase the droplet size during addition of the polymer solution to the cross-linking solution. Particle size also increases by increasing the drug load.

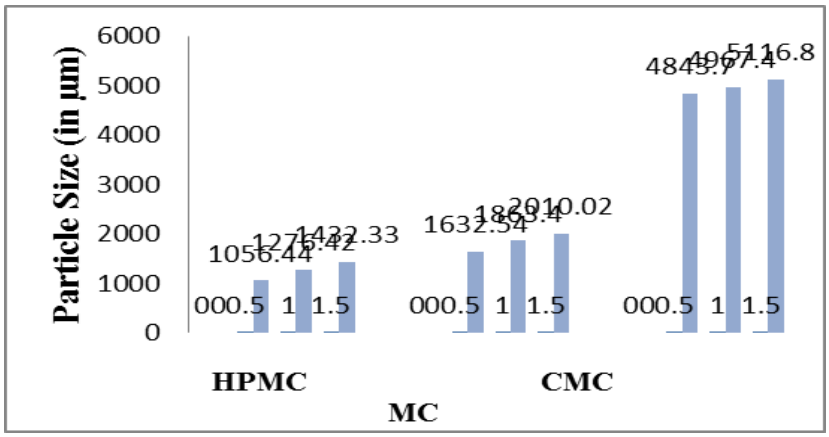


Fig 4.5 Comparison of particle sizes of mucoadhesive microspheres Prepared using different co-polymers.

- Out of all the different mucoadhesive microspheres prepared using different combinations of mucoadhesive agents, the microsphere prepared using sodium alginate and Methyl Cellulose are larger in size when compared to all other different microspheres and microspheres prepared using Sodium alginate and HPMC (hydroxy propyl methyl cellulose) are smaller in size among all formulations.

Entrapment efficiency

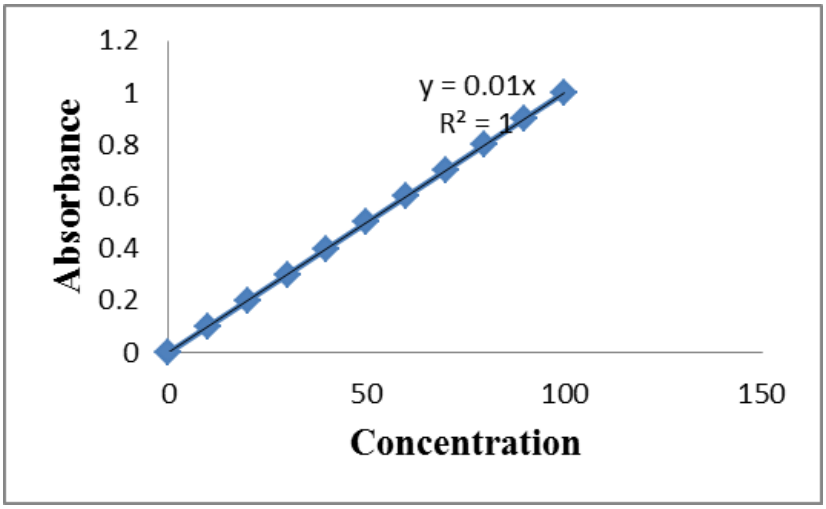


Fig 5.2 Standard plot for entrapment efficiency of Famotidine.

Table No. 4.6 Entrapment efficiency of mucoadhesive microspheres.

Composition	Weight(in g)	Media(inmL)	Absorbance	Entrapment efficiency (%)
(SA:HPMC)3:1	0.1	100	0.313	31.37 %
1:1	-do-	-do-	0.492	49.26 %
1:3	-do-	-do-	0.580	58.07 %
(SA:CMC) 3:1	-do-	-do-	0.368	36.88 %
1:1	-do-	-do-	0.456	45.68 %
1:3	-do-	-do-	0.495	49.50 %
(SA:MC) 3:1	-do-	-do-	0.283	28.34 %
1:1	-do-	-do-	0.401	40.18 %
1:3	-do-	-do-	0.355	35.50 %

Observation

- The drug entrapment efficiency of different formulations has been summarized.
- The Famotidine being highly soluble in water, is having tendency to diffuse out to the aqueous medium even though the sufficiently higher drug entrapment to the gel beads prepared with the combination of polymer and copolymer could be achieved that might be resulted due to hindered diffusion of the medicament through the gel barrier formed by the copolymer. It was observed that, as the concentration of copolymer increases, viscosity of resulting gel increases and thereby increases in entrapment efficiency.
- An increase in drug load was also observed by increasing the concentration of drug. The decrease in entrapment efficiency in case of coated beads may be due to leakage of drug into coating solution during coating.

***IN VITRO* DRUG RELEASE STUDIES**

Standard graph

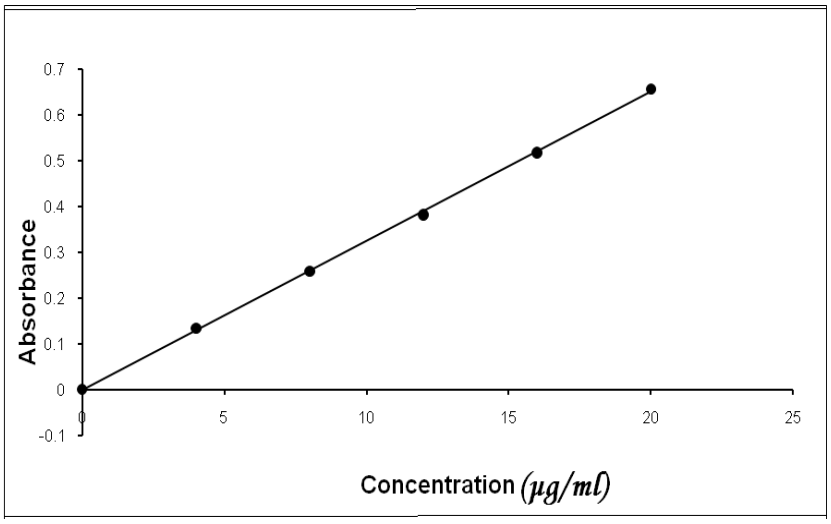


Fig. 5.3: Standard Plot for *In vitro* Drug release of Famotidine.

Table No. 4.7 *In vitro* drug release study of mucoadhesive microspheres prepared. Using SA: HPMC in 3:1 concentration.

S.NO	Time (hrs)	Dissolution medium p^H	Absorbance	Concentration(µg/mL)	Amount of drug released	%of Drug release
1.	00:30	1.2	0.802	24.464	22017.6	22.01
2.	01:00	-do-	0.896	27.217	24490.8	24.49
3.	01:30	-do-	0.967	29.357	26421.3	26.42
4.	02:00	-do-	0.992	30.275	27247.5	27.24
5.	02:30	-do-	1.071	32.721	29448.9	29.44
6.	03:00	-do-	1.113	33.944	30549.6	30.54
7.	03:30	-do-	1.146	34.862	31375.8	31.37
8.	04:00	-do	1.214	37.003	33302.7	33.30

Table No. 4.8 *In vitro* drug release study of mucoadhesive microspheres prepared. Using SA: HPMC in 1:1 concentration

S.NO	Time (in hrs)	Dissolution Media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900mL of D.M	% of drug released
1.	00:30	1.2	1.663	50.764	45687.6	45.68
2.	01:00	-do-	1.746	53.211	47889.9	47.88
3.	01:30	-do-	1.794	54.740	49266.2	49.26
4.	02:00	-do-	1.822	55.657	50091.3	50.09
5.	02:30	-do-	1.871	57.186	51467.4	51.46
6.	03:00	-do-	1.964	59.938	53944.2	53.94
7.	03:30	-do-	2.013	61.467	55320.3	55.32
8.	04:00	-do-	2.066	62.996	56696.4	56.69

Table No. 4.9 *In vitro* drug release study of mucoadhesive microspheres. Prepared using SA: HPMC in 1:3concentration

S.NO	Time (in hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released	%of drug release
1.	00:30	1.2	1.814	55.351	49815.9	49.81
2.	01:00	-do-	1.846	56.269	50642.1	50.64
3.	01:30	-do-	1.918	58.409	52568.1	52.56
4.	02:00	-do-	1.935	59.021	53118.9	53.11
5.	02:30	-do-	1.994	60.856	54770.4	54.77
6.	03:00	-do-	2.016	61.467	55230.3	55.23
7.	03:30	-do-	2.112	64.525	58072.5	58.07
8.	04:00	-do-	2.144	65.443	58898.7	58.89

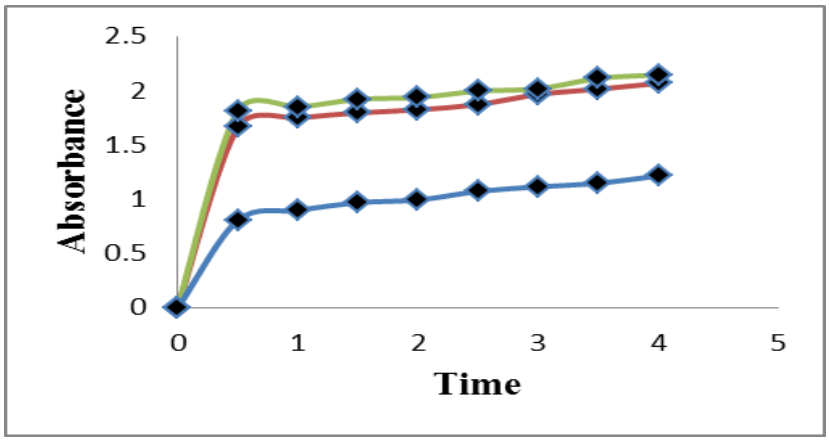


Fig 5.4 Comparison of *In vitro* drug release of mucoadhesive microspheres. Prepared using different concentrations of HPMC

Table No. 5.0 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:CMC in 3:1 concentration.

S.NO	Time (in hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900 mL of D.M	% of drug release
1.	00:30	1.2	1.061	32.415	29173.5	29.17
2.	01:00	-do-	1.155	35.168	31651.2	31.65
3.	01:30	-do-	1.047	31.804	28623.6	28.62
4.	02:00	-do-	1.203	36.697	33027.3	33.02
5.	02:30	-do-	1.286	39.143	35228.7	35.22
6.	03:00	-do-	1.348	40.978	36880.2	36.88
7.	03:30	-do-	1.414	43.119	38807.1	38.80
8.	04:00	-do-	1.532	46.788	42109.2	42.10

Table No. 5.1 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:CMC in 1:1 concentration.

S.NO	Time (in hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900 mL of D.M	% of drug release
1.	00:30	1.2	1.564	47.706	42935.4	42.93
2.	01:00	-do-	1.433	43.730	39357.2	39.35
3.	01:30	-do	1.592	48.623	43760.7	43.76
4.	02:00	-do-	1.611	49.235	44311.5	44.31
5.	02:30	-do-	1.664	50.764	45687.6	45.68
6.	03:00	-do-	1.756	53.516	41164.4	41.16
7.	03:30	-do-	1.833	55.963	50366.7	50.36
8.	04:00	-do-	1.881	57.492	51742.8	51.74

Table No. 5.2 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:CMC in 1:3 concentration

S.NO	Time (in hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900 mL of D.M	% of drug release
1.	00:30	1.2	1.324	40.366	36329.4	36.32
2.	01:00	-do-	1.361	41.590	37431.2	37.43
3.	01:30	-do-	1.481	45.259	40733.1	40.73
4.	02:00	-do-	1.532	46.788	42109.2	42.10
5.	02:30	-do-	1.602	48.926	44033.4	44.03
6.	03:00	-do-	1.646	50.152	45136.8	45.13
7.	03:30	-do-	1.691	51.681	46512.9	46.51
8.	04:00	-do-	1.802	55.045	49504.5	49.50

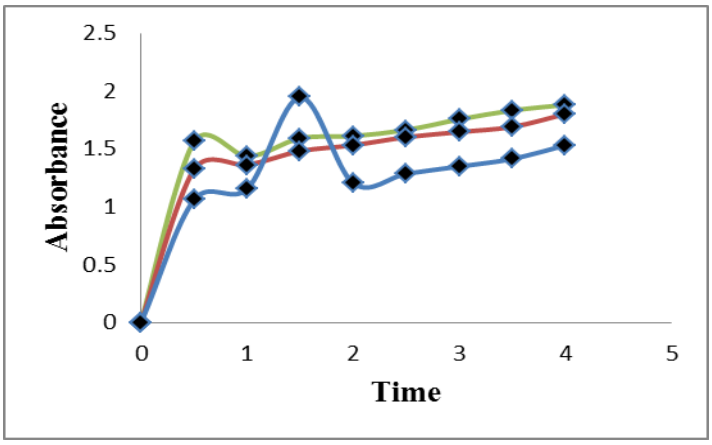


Fig 5.3 Comparison of *In vitro* drug release of mucoadhesive microspheres Prepared using different concentrations of CMC

Table No. 5.4 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:MC in 3:1 concentration

S.NO	Time (hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900 mL of D.M	% of drug release
1.	00:30	1.2	0.735	22.324	20091.6	20.09
2.	01:00	-do-	0.752	22.935	20641.5	20.64
3.	01:30	-do-	0.747	22.629	20366.1	20.36
4.	02:00	-do-	0.776	23.547	21192.3	21.19
5.	02:30	-do-	0.862	26.299	23669.1	23.66
6.	03:00	-do-	0.918	27.828	25645.2	25.64
7.	03:30	-do-	0.994	30.275	27247.5	27.24
8.	04:00	-do-	1.036	31.498	28348.2	28.34

Table No. 5.5 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:MC in 1:1 concentration

S.NO	Time (hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released in 900 mL of D.M	% of drug release
1.	00:30	1.2	1.435	43.730	39357.2	39.35
2.	01:00	-do-	1.524	46.483	41834.7	41.83
3.	01:30	-do-	1.463	44.648	40183.2	40.18
4.	02:00	-do-	1.542	47.094	42384.6	42.38
5.	02:30	-do-	1.591	48.623	43760.7	43.76
6.	03:00	-do-	1.634	49.847	44862.3	44.86
7.	03:30	-do-	1.688	51.376	46238.4	46.23
8.	04:00	-do-	1.776	54.128	48715.2	48.71

Table No. 5.6 *In vitro* drug release study of mucoadhesive microspheres prepared using SA:MC in 1:3 concentration

S.NO	Time (in hrs)	Dissolution media p^H	Absorbance	Concentration (µg/mL)	Amount of drug released	% of drug release
1.	00:30	1.2	1.012	30.886	27797.4	27.79
2.	01:00	-do-	0.973	29.663	26693.7	26.69
3.	01:30	-do-	1.084	33.027	29724.3	29.72
4.	02:00	-do-	1.132	34.556	31100.4	31.10
5.	02:30	-do-	1.183	36.085	32476.5	32.47
6.	03:00	-do-	1.204	36.697	33027.3	33.02
7.	03:30	-do-	1.296	39.449	35504.1	35.50
8.	04:00	-do-	1.324	40.366	36329.4	36.32

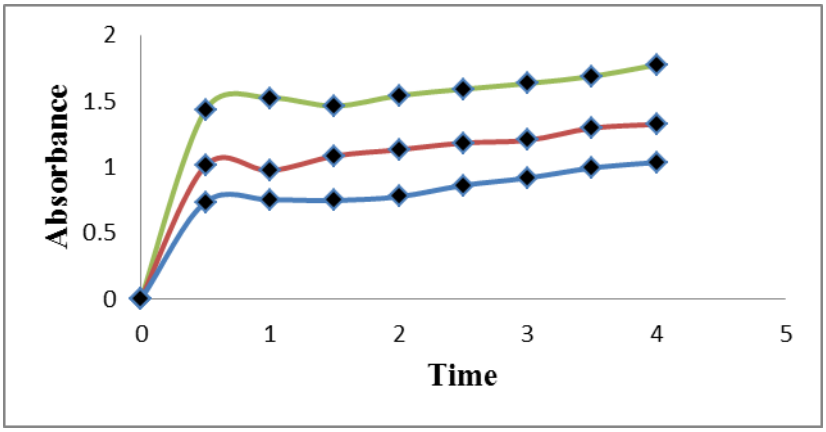
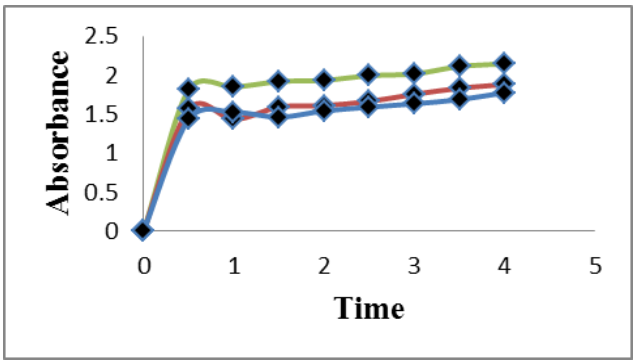


Fig 5.6 Comparison of *In vitro* Drug release of mucoadhesive microspheres Prepared using different concentrations of MC

OBSERVATION

- The prolongation of the release rate and increase in drug release occurs by increasing the concentration of copolymer (HPMC, CMC, MC). This is due to increase in gel strength which is determining in this case, since the release of drugs in polymer matrices are mainly through the diffusion of the drug through the pores of the polymer network which can be significantly reduced in size by increasing the polymer concentration.
- At higher drug-polymer ratio the drug release from the mucoadhesive microspheres was faster as compared to lower drug/polymer ratio.



HPMC

CMC

MC

Fig 5.7Comparison of *in vitro* drug release of best combination among threeDifferent Co-polymers

Observation

- The results showed that out of all nine formulations, the mucoadhesive microspheres prepared with HPMC (hydroxy propyl methyl cellulose) as co-polymer has good drug release profile when compared to other formulations and the mucoadhesive microspheres prepared with MC (methyl cellulose) as Co-polymer has poor drug release profile when compared to other formulations.
- Other factors like p^H of the dissolution medium, rotating speed of the stirrer also influence up to a certain extent.

MUCOADHESION STUDIES

Table No. 5.7 Mucoadhesion study of mucoadhesive microspheres.

Formulation	No. of Microspheres		Percentage of adhesion %
	Initial	Final	
SA:HPMC 3:1	100	60	60
1:1	100	52	52
1:3	100	81	81
SA:CMC 3:1	100	46	46
1:1	100	42	42
1:3	100	59	59
SA:MC 3:1	100	36	36
1:1	100	41	41
1:3	100	47	47

CONCLUSION

Famotidine release from these mucoadhesive microspheres prepared using different mucoadhesive agents was slow and extended over longer period of time and dependent over ratio of polymers.

Mucoadhesive property was increased due to the usage of these copolymers (HPMC, CMC, MC) when compared to older conventional polymers.

Out of all Co-polymers used in the preparation of mucoadhesive microspheres HPMC has been showing better properties in term of Mucoadhesion, Drug release, Drug entrapment.

REFERENCES

1. Sanju Dhawan, Anil Kumar Singla, and Vivek Ranjan Sinha, "Evaluation of Mucoadhesive Properties of Chitosan Microspheres Prepared by Different Methods", *AAPS Pharm SciTech*, 2004; 5(4): 123-8.
2. Patil Ganesh B, Belgamwar veena S, Surana Sanjay J, Bioadhesive based drug delivery system, *Int J Pharma Excip*, 2007; 3(5): 76-80.
3. Kora Pattabhi Rama Chowdary and Yarraguntla Srinivas Rao, "Mucoadhesive microspheres for Controlled drug delivery", *Biol. Pharm. Bull*, 2004; 27(11): 1717-24.
4. G. Rajput, F Majmudar, J Patel, R Thakor, NB Rajgor, Stomach specific mucoadhesive microsphere as a controlled drug delivery system, 2010; 1(1): 70-78.
5. A.C Guyton, "Pathophysiology of Ulcer", Textbook of medicinal physiology, 456-64.
6. K D Tripathi, "Drugs used in treatment of Gastrointestinal disorders", Essentials of Medical Pharmacology, 6th Edition, 233-7.

7. P K Choudhury and Mousumi Kar, "Preparation of Alginate Gel Beads Containing Metformin Hydrochloride Using Emulsion- Gelation Method", *Tropical Journal of Pharmaceutical Research,* Dec. 2005; 4(2): 489-93.
8. M L Soni, M Kumar and K P Namdeo, "Sodium alginate microspheres for extending drug release: formulation and in vitro evaluation", *International Journal of Drug Delivery,* 2010; 2(14): 64-8.
9. K. P. R. Chowdary and Y. Srinivasa Rao, "Design and In Vitro and In Vivo Evaluation of Mucoadhesive Microcapsules of Glipizide for Oral Controlled Release: A Technical Note", *AAPS PharmSciTech,* 2003; 4(3): 356-67.
10. Pradnya Patil, N G Raghavendra Rao, Doddayya Hiremath, "Preparation and characterization of mucoadhesive microcapsules of salbutamol sulphate", *Asian Journal of Pharmaceutics,* June 2010; 5(21): 141-8.
11. Singla, Gupta K.C, "Preparation of Microspheres by Emulsification and Ionotropic Gelation by Sodium hydroxide", *International Journal of Biological Macromolecules,* 2006; 14(38): 272-83.
12. Hemanta Kumar Sharma, Siba Prasad Pradhan, Babita Sarangi,"Preparation and In Vitro Evaluation of enteric controlled release Pantoprazole loaded Microbeads using Natural Mucoadhesive Substances", *Int. J. Pharm. Tech. Res,* 2010; 2(1): 542-51.
13. Davis, S. S. Illum L, "Chitosan Microspheres prepared by Spray-drying", *International Journal of Pharmaceutics,* 1999; 187(1): 53-65.
14. Ram S. Gaud, Saloni Kakkar., "Controlled release Formulations of Lansoprazole Coating of microspheres", *J.Control Release,* Nov. 2009; 4(2): 345-9.
15. Renata P. Raffin., Denise Jomada., Sandra Hass, Adriana R. Pohlmann, "Pantoprazole Sodium loaded controlled release Microparticles prepared by Spray-drying", *15th International Journal of Pharmaceutics,* 2005; 9(11): 59-68.
16. Uchida Takahiro, Yasuda Noriko, Matsuyama Kenji, "In Vitro Studies of Enteric coated Diclofenac sodium-carboxymethylcellulose Microspheres", *Journal of Microencapsulation,* 1996; 13(6): 689-99.
17. Rajeshwar Kamal Kant Arya, Ripudam Singh, Vijay Juyal, "Mucoadhesive microspheres of Famotidine: Preparation characterization and in vitro evaluation", *International Journal of Engineering Science and Technology,* 2010; 2(6): 1575-80.
18. Lachman LA, Liberman HA, Kanig JL. The theory and practice of pharmacy. Mumbai, India: *BI publication,* 2006; 21st(1): 924.

19. Ajay Semalty, "*Mucoadhesive Polymers- A Review*", 2006; 4(5).
20. P. Venkatesan, R. Manavalan and K. Valliappan, Microencapsulation: A Vital Technique in Novel Drug Delivery system, *J. Pharm. Sci. & Res*., 2009; 1(4): 26-35.