Formulation and In-Vitro Evaluation of Chitosan Based Omeprazole Mucoadhesive Buccal Tablets

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ABSTRACT

The present study is concerned with formulation and evaluation of mucoadhesive buccal tablets containing proton pump inhibitors drug, Omeprazole to circumvent the first pass effect and to improve its bioavailability with reduction in dosing frequency and dose related side effects. The tablets were prepared by direct compression method. Nine formulations were prepared with Chitosan as primary polymer and Carbopol 934, Hydroxy Propyl Methyl Cellulose (HPMC K4M) and Xanthan gum as a secondary polymer. All formulations were evaluated for weight variation, hardness, surface pH, drug Content uniformity, swelling index, and bioadhesive strength and in-vitro drug dissolution study. Physical compatibility studies showed no evidence on interactions between drug, polymers, and excipients. The in vitro release of Omeprazole was performed under sink conditions (Phosphate buffer PH 6.8, 37±0.5ºC, rpm 50) using USP dissolution apparatus type II. The best in-vitro drug release profile was achieved with the formulation F8 which contains the Chitosan combine with Xanthan gum. The surface pH and swelling index of formulation F8 was found to be 6.8, and 60 %, respectively.

Key words: Omeprazole, mucoadhesive buccal tablet, Chitosan, HPMC K4M, Carbopol 934.

1. INTRODUCTION:

Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage form. Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing. Problems such as first pass metabolism and drug degradation in the GIT environment can be circumvented by administering the drug via buccal route. Moreover, the oral cavity is easily accessible for self medication and be promptly terminated in case of toxicity by removing the dosage form from buccal cavity. Mucoadhesive systems remain in close contact with the absorption tissue, the mucous membrane releasing the drug at the action site leading to increase in bioavailability. Successful buccal drug delivery using buccal adhesive system requires at least three of the following (a) a bioadhesive to retain the system in the oral cavity and maximize the intimacy of contact with mucosa (b) a vehicle the release the drug at an appropriate rate under the conditions prevailing in the mouth and (c) strategies for overcoming the low permeability of the oral mucosa. Buccal mucosa makes a more appropriate choice of site if prolonged drug delivery is desired because buccal site is less permeable than the sublingual site. Mucoadhesive polymers have been utilized in many different dosage forms in efforts to achieve systemic delivery of drugs through the different mucosa. These dosage forms include tablets, patches, tapes, films, semisolids. In the case of Omeprazole it is beneficial to overcome the problem of frequent dosing due to its shorter half life (0.5-1 h). Prolonged release of the drug and increased bioavailability leads to the significant reduction in the dose and hence dose related side effects. Hence, in the present work an attempt was made to formulate mucoadhesive buccal tablet for Omeprazole using different mixtures of polymers in order to avoid extensive first pass metabolism, degradation in the stomach and prolonged effect.

2. MATERIALS AND METHODS

2.1 Material

Omeprazole was a gift sample from Micro Lab Pvt. Ltd., Bangalore, Chitosan, HPMC K 4M, Carbopol 934 were gift sample from Glenmark. All other reagents used were of analytical grade.

2.2 Compatibility study:

Compatibility study of drug and excipients were carried out by physical observation (color and odour) by placing the mixture of drug and each excipients separately and physical mixture of all ingredients' at a temperature 45^0C and 75% RH for period of one month.

2.3 Preparation of Omeprazole Mucoadhesive tablet.

Omeprazole Mucoadhesive tablets were prepared using direct compression Method. The drug, polymers and excipients were mixed homogeneously in a glass mortar for 20 min. the powder blend was then screened through sieve no # 80. The mixture was then compressed using an 8 mm, biconcave punch in a single-stroke using 8 station rotary machine.

2.4 Pre compression Evaluation: [3, 5, 6, 7]

2.4.1 Angle of Repose (θ):

It is defined as the maximum angle possible between the surface of a pile of the Powder and horizontal plane. For most pharmaceutical powders, the angle-of repose values range from 25 to 45°, with lower values indicating better flow characteristics. It can be calculated by following formula.

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h/r)$$

Where,

θ = Angle of repose

h = Height of pile

r = Radius of the base of pile

2.4.2 Bulk Density:

Bulk density is defined as the ratio of mass of a powder to the bulk volume. Bulk density of the various ingredients added to the granulation should be maintained as closely as possible, especially when formulating direct-compression products. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another.

$$\textbf{Bulk density} = \frac{\textbf{Weight of the powder (gm)}}{\textbf{Bulk volume (ml)}}$$

2.4.3 Carr's Compressibility Index:

The compressibility index of the granules was determined by Carr's compressibility index (CI). Formula for calculating the CI is given by

$$\textbf{Carr's Index (\%)} = \frac{\textbf{Tapped Density - Bulk Density}}{\textbf{Tapped density}} \textbf{ x 100}$$

2.4.4 Hausners Ratio:

It is determined by comparing tapped density to the bulk density by using following equation

$$\text{Hausners ratio} = \frac{\text{Tapped density}}{\text{Bulk Density}}$$

2.5 Evaluation of Omeprazole Mucoadhesive tablets: [6, 8, 10]

The prepared tablets were evaluated for various parameters as follows.

2.5.1 Weight variation:

Twenty tablets were randomly selected, weighted and average weight was determined. Then individual tablets were weighed and percent deviation from the average weight was calculated.

2.5.2 Thickness:

The thicknesses of prepared tablets were measured by vernier caliper. Tablet thickness should be controlled within a ±2% variation of a standard value. In addition, the average thickness and standard deviation were reported.

2.5.3 Hardness:

It was measured by using a Monsanto hardness tester (in Kg/cm^2). Five tablets from each batch were tested randomly and the average reading noted.

2.5.4 Friability:

Friability of the prepared tablets was determined by using Roche Friabilator. Pre weighed sample of tablets (20 tablets) were placed in the Friabilator and subjected to100 revolutions. That was set at 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches. After that tablets were de dusted using a soft muslin cloth and re weighed. The friability (f) is given by the formula.

$$F\ \% = \left(1 - \frac{W0}{W}\right) \times 100$$

Where,

W0 = Weight of the tablets before the test and

W = Weight of the tablets after test

2.5.5 Content uniformity:

10 tablets were randomly selected, powdered and blend equivalent to 20mg of drug was weighed and dissolved in 100 ml of 6.8 pH phosphate buffer, filtered solution was suitably diluted and drug content analyzed using UV-Visible spectrophotomer at 223nm.

2.5.6 Bioadhesion studies

The mucoadhesive forces of the tablets were determined by means of mucoadhesive measuring device shown in Fig. 1. The sheep buccal mucosa was cut into strips/pieces and washed. At time of testing a section of sheep buccal mucosa (c) was secured keeping the mucosal side out, on the upper glass vial (B) using rubber band and aluminium cap. The diameter of each exposed mucosal membrane was 1 cm. The vial with the sheep buccal mucosa (C) was stored at 37°C for 15 min. Then one vial with section of sheep buccal mucosa (C) and another vial were fixed on height adjustable pan (E). To a lower vial a tablet (D) was placed with the help of bilayered adhesive tape, adhesive side facing downward. The height of the lower vial was adjusted so that a tablet could adhere to the sheep buccal mucosa on the upper vial. A constant force was applied on the upper vial for 2 min, after which it was removed and the upper vial was then connected to the balance. Then the weight on right side pan was slowly added in an increment of 0.5 g, till the two vials just separated from each other. The total weight (g) required to detach two vials was taken as a measure of Mucoadhesive strength. From this Mucoadhesive strength, the force of adhesive was calculated.

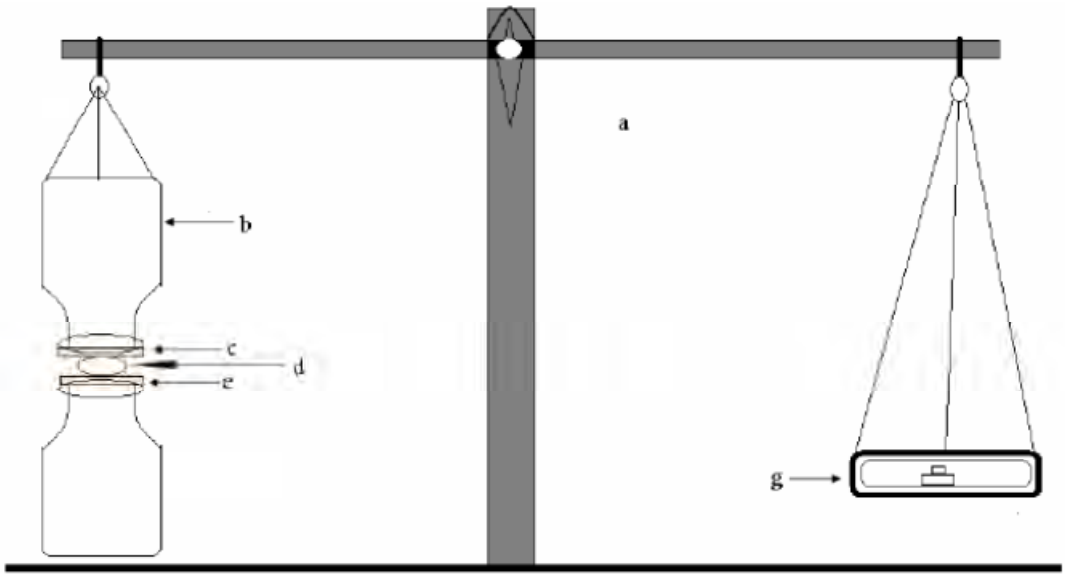

Fig.1. Measurement of bioadhesive strength.
a-scale; b-glass vial; c-sheep buccal mucosa; d-Mucoadhesive tablet; e-adjustable pan; g-weight.

2.5.7 Swelling Studies

For conducting the swelling study, the tablet was weighed (Wo) and placed in a petri dish containing 5 mL of phosphate buffer (pH 6.8) for 8 hours. After that, the tablets were taken out from the petri dish and excess water was removed carefully by using filter paper and weighed again (Wt). The swelling index was calculated using the following formula.

SI = (Wt-Wo) / Wo × 100

Where SI = Swelling index.

Wt = Weight of tablets after time (t)

Wo = Weight of tablet before placing in the Petri dish

2.5.8 Surface pH Study

The tablet is allowed to swell by keeping it in contact with1 mL of phosphate buffer (pH 6.8) for 2 hours at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrating for 1 minute. The experiment was repeated thrice and data.

2.5.9 In-vitro Dissolution studies:

In vitro drug release of Omeprazole mucoadhesive tablets were determined using USP Dissolution Apparatus II (Paddle type) (Electrolab TDT-08L). The dissolution test was performed using 500 ml 6.8 pH phosphate buffer at temperature 37 ± 0.5 ^{0}C. The speed was maintained at 50 rpm. 5 ml of samples were withdrawn at time intervals of 0.5,1, 1.5, 2.5, 3 hrs and same volume was replaced with fresh media. Absorbance of solution was measured at a wavelength of 276 nm and drug release was determined from standard curve.

3. RESULT AND DISCUSSION:

Omeprazole mucoadhesive tablets were prepared and evaluated for the various parameters.

3.1 Compatibility study:

The Compatibility study of drug and excipients were carried out by physical observation (Table 2). There were no any physical change occur between mixture of drug-excipients and physical mixture of all ingredients it shows all the ingredients compatible with drug.

3.2 Evaluation of tablet blends

The physical properties such as bulk density, tapped density, %compressibility index, hausner ratio, angle of repose were determined (table 3) for the all tablet blends.

The angle of repose was found to be varies in between 21.04±0.16 to 31.44±0.05.The F8 shows lowest value i.e. 21.04±0.16 it indicate excellent flow property. Apart from that all formulation was shows the angle of repose in between 25^0 to 30^0 which indicate good flow properties and F5shows angle of repose 31.04±0.16$^{0.}$ It indicates blend had a passable flow.

The value for Carr's index was in between 13.00±0.21 to 22.92±0.21indicating that most batches of powder blends were having good or fair compressibility. Hausner's ratio was found to be within limits (<1.25) except F1, F6 and F9.

3.3 Evaluation of prepared tablets.

In the present work Omeprazole mucoadhesive tablets were prepared by direct compression method using Chitosan as a primary polymer in combination with secondary polymer such as HPMC K4M, Carbopol 934 and Xanthan gum. All the formulations were evaluated for various parameters like hardness, friability, drug content, surface pH, swelling index given in table 4 and in vitro drug release studies given in table 5.

The hardness of the tablets was found to be in between 3.51 ± 0.47 to 4.25 ± 0.42 kg/cm^2 and friability was found to be below 1% indicating good mechanical resistance.

The thickness of the tablets was found to be in between 2.1 ± 0.3 mm to 2.9± 0.4 mm. All the tablets passed weight variation test, as percentage weight variation was within the pharmacopoeial limits i.e. ±1.5%.

The drug content was found to be in between 97.32 ± 0.41 to 101.2 ± 0.34 %, indicating uniform distribution of drug in the tablets.

Surface pH of all the formulations F1 to F9 was found to be 6.4 to 7.2, which is well within the limit of acceptable salivary pH range of 5.69 to 6.8 (Table 4). Hence, it was concluded that all formulations could not produce any local irritation to the mucosal surface.

In vitro drug release of all formulations was above 90% given in Table 5. The formulations F8 were shown 100 % drug release in 3 hrs. All other formulations were shows above 90% drug release.

The swelling studies were conducted for all formulations i.e. F1 to F9 and the results were shown in Table 6. All the formulations were hydrated generally by keeping the tablets in contact with phosphate buffer (pH 8) for 0.5

h to 3 h. The highest hydration (swelling) i.e. 82% was observed with the formulation F3. This may be due to quick hydration of polymers (Carbopol 934 and Chitosan).

4. CONCLUSION:

Omeprazole mucoadhesive tablets were prepared by direct compression method using different hydrophilic polymers such as HPMC K4M, Carbopol and Xanthan gum in different ratios and combinations, to study the effect of these polymers on the physio chemical characters, swelling index and in vitro drug release of Omeprazole from the Omeprazole mucoadhesive tablets. Initially we have prepared all the formulations by altering the polymer quantity randomly (i.e. F1, F2, F3, F4, F5, F6, F7, F8 and F9). Among all the nine formulations, F4 and F8 showed maximum swelling index, bioadhesive strength, and in vitro drug release also. The surface pH indicates that Chitosan alone is not suitable in designing mucoadhesive tablets and a combination of Chitosan with other polymers produces tablets with neutral pH that are safe for mucosal membrane. The swelling behavior of Carbopol is high in all the formulation wherever Xanthan gum is used as more quantity and showed maximum release of Omeprazole from the prepared tablets. The release studies indicated that the prepared Omeprazole mucoadhesive tablets improved the bioavailabity by avoiding the first pass metabolism. The in vitro studies have shown that this is a potential drug delivery system for Omeprazole with a considerably good stability and release profile.

5. ACKNOWLEDGEMENTS:

The authors wish to show their deep gratitude to Micro Lab Pvt. Ltd., Bangalore and Glenmark Pvt. Ltd, Mumbai for providing the gift samples of Omeprazole and polymers, respectively.

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Table no. 1 Composition of Omeprazole mucoadhesive tablets.

Ingredients	Formulation								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Omeprazol	20	20	20	20	20	20	20	20	20
Chitosan	25	30	35	25	30	35	25	30	35
Carbopol 934	20	25	30	-	-	-	-	-	-
HPMC K4M	-	-	-	20	25	30	-	-	-
Xanthan gum	-	-	-	-	-		20	25	30
Microcrystalline cellulose (MCC)	20	20	20	20	20	20	20	20	20
Talc	1	1	1	1	1	1	1	1	1
Aerosil	2	2	2	2	2	2	2	2	2
Lactose	32	22	12	32	22	12	32	22	12
Total weight	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

*All above quantity in mg.

Table no. 2: Compatibility study of drug and excipients by physical observation

Days	Drug+ Chitosan	Drug + Carbopol 934	Drug + HPMC K4M	Drug + Xanthan gum	Drug + MCC	Drug + Aerosil	Drug + Talc	Physical mixture
1	N	N	N	N	N	N	N	N
2	N	N	N	N	N	N	N	N
3	N	N	N	N	N	N	N	N
4	N	N	N	N	N	N	N	N
5	N	N	N	N	N	N	N	N
6	N	N	N	N	N	N	N	N
8	N	N	N	N	N	N	N	N
10	N	N	N	N	N	N	N	N
12	N	N	N	N	N	N	N	N
14	N	N	N	N	N	N	N	N
16	N	N	N	N	N	N	N	N
18	N	N	N	N	N	N	N	N
20	N	N	N	N	N	N	N	N
22	N	N	N	N	N	N	N	N
24	N	N	N	N	N	N	N	N
26	N	N	N	N	N	N	N	N
28	N	N	N	N	N	N	N	N
30	N	N	N	N	N	N	N	N

N – No physical change (colour, Odour)

Table No. 3: Evaluation of Pre compression Parameters

Formulation code	Angle of Repose(^{0}) (n=3)	Bulk Density (n=3)	Tapped Density (n=3)	% compressibility Index (n=3)	Hausner Ratio (n=3)
F1	28.02±0.15	0.35±0.02	0.45±0.05	22.92±0.21	1.30±0.04
F2	27.25±0.08	0.39±0.03	0.48±0.03	19.64±0.17	1.24±0.07
F3	22.05±0.10	0.40±0.07	0.45±0.01	15.33±0.06	1.15±0.02
F4	29.01±1.10	0.42±0.02	0.50±0.06	13.00±0.21	1.19±0.03
F5	31.44±0.05	0.33±0.04	0.41±0.05	14.63±0.23	1.17±0.01
F6	29.87±0.85	0.44±0.01	0.56±0.02	21.43±0.21	1.27±0.04
F7	25.35±0.20	0.40±0.03	0.47±0.07	14.89±0.10	1.18±0.03
F8	21.04±0.16	0.36±0.02	0.43±0.03	16.28±0.27	1.19±0.07
F9	29.02±0.15	0.37±0.08	0.46±0.02	21.92±0.11	1.30±0.05

Mean ± SD (n)

Table No. 4: Evaluation of prepared Omeprazole mucoadhesive tablets.

Formulation Code	Weight Uniformity (mg) (n=20)	Thickness (mm) (n=10)	Hardness (Kg/cm^2) (n=3)	% Friability (n=3)	Surface pH	% Drug Content (n=3)
F1	120 ± 0.5	2.7 ± 0.4	3.51 ± 0.47	0.36 ± 0.01	6.8	98.24 ± 0.20
F2	118 ± 1.4	2.4 ± 0.2	3.25 ± 0.25	0.42 ± 0.04	7.1	97.32 ± 0.41
F3	122 ± 1.3	2.1 ± 0.3	4.12 ± 0.38	0.35 ± 0.02	6.5	99.41 ± 0.34
F4	121 ± 1.2	2.9 ± 0.4	3.54 ± 0.25	0.39 ± 0.01	6.9	100.3 ± 0.37
F5	119 ± 1.5	2.6 ± 0.5	3.51 ± 0.14	0.41 ± 0.02	7.2	101.1 ± 0.33
F6	120 ± 1.8	2.2 ± 0.6	4.25 ± 0.42	0.47 ± 0.06	6.4	97.56 ± 0.47
F7	118 ± 1.5	2.2 ± 0.4	3.72 ± 0.25	0.34 ± 0.07	6.6	99.42 ± 0.52
F8	120 ±1.2	2.1 ± 0.8	3.05 ± 0.36	0.32 ± 0.04	6.8	101.2 ± 0.24
F9	121 ±1.3	2.5 ± 0.4	3.45 ± 0.26	0.48 ± 0.02	6.5	101.2 ± 0.34

Mean ± SD (n)

Table No. 5: In vitro drug release study of prepared Omeprazole mucoadhesive tablets**.**

Time (hrs)	% Drug release(n=3) F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	36± 0.35	31± 0.10	38± 0.28	42± 1.47	41± 0.12	43± 0.27	45± 0.30	43± 0.21	42± 0.21
1.0	58± 1.15	59± 1.15	57± 0.13	58± 1.06	57± 0.23	59± 0.35	59± 1.35	60± 0.30	59± 0.30
1.5	69± 0.05	71± 0.25	74± 1.05	73± 0.61	72± 0.44	73± 1.07	74± 0.98	76± 1.28	74± 1.28
2.0	78± 0.02	83± 1.63	82± 0.41	85± 0.22	86± 1.30	81± 0.33	86± 0.11	88± 0.92	87± 0.92
2.5	85± 0.87	91± 0.52	92± 0.87	93± 0.90	91± 0.21	89± 0.74	91± 0.42	94± 1.02	92± 1.02
3.0	96± 0.47	97± 0.88	97± 0.28	98± 0.62	98± 0.61	96± 1.20	99± 1.08	100± 0.27	99± 0.27

Mean ± SD (n)

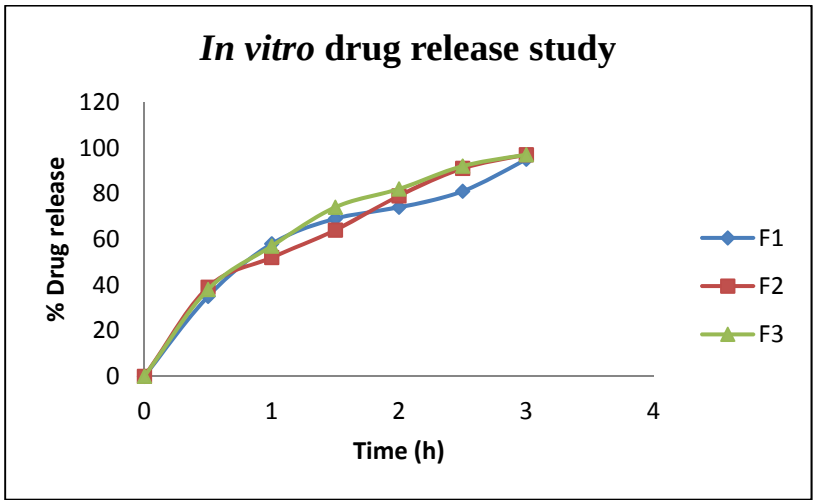

Fig. 2: In vitro drug release study of Omeprazole mucoadhesive tablets (F1-F4).

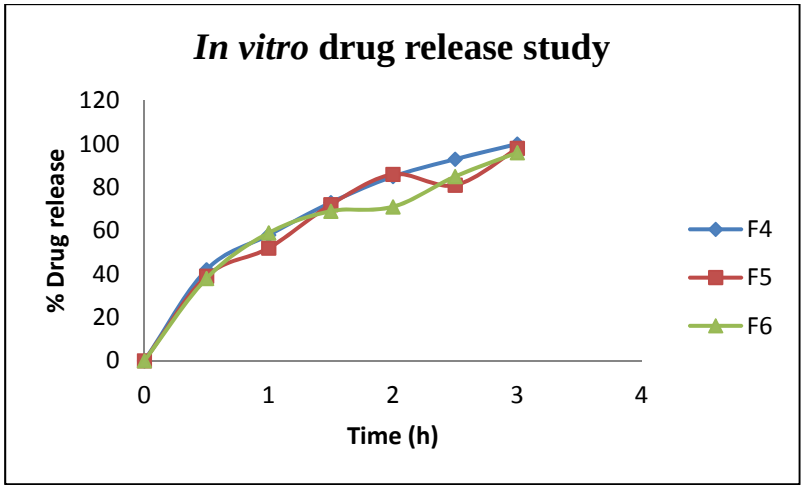

Fig. 3: In vitro drug release study of Omeprazole mucoadhesive tablets (F4-F6).

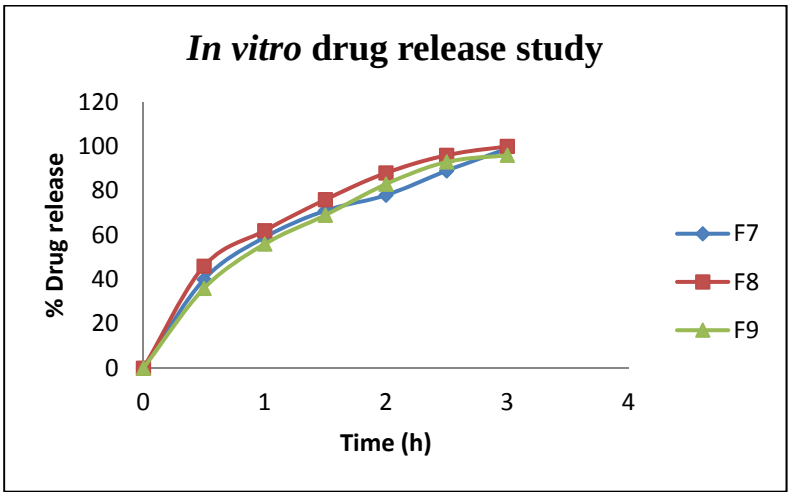

Fig. 4: In vitro drug release study of Omeprazole mucoadhesive tablets (F7-F8).

Table No. 6: Swelling data of Omeprazole mucoadhesive tablets.

Time (h)	Percentage weight change (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
0	0	0	0	0	0	0	0	0	0
0.5	35	30	32	33	29	31	32	30	28
1.0	45	41	47	49	36	39	42	36	31
1.5	50	52	54	54	42	48	53	42	46
2.0	57	60	62	61	51	56	63	48	50
2.5	62	69	70	66	59	63	71	53	56
3.0	68	79	82	74	68	71	76	60	65

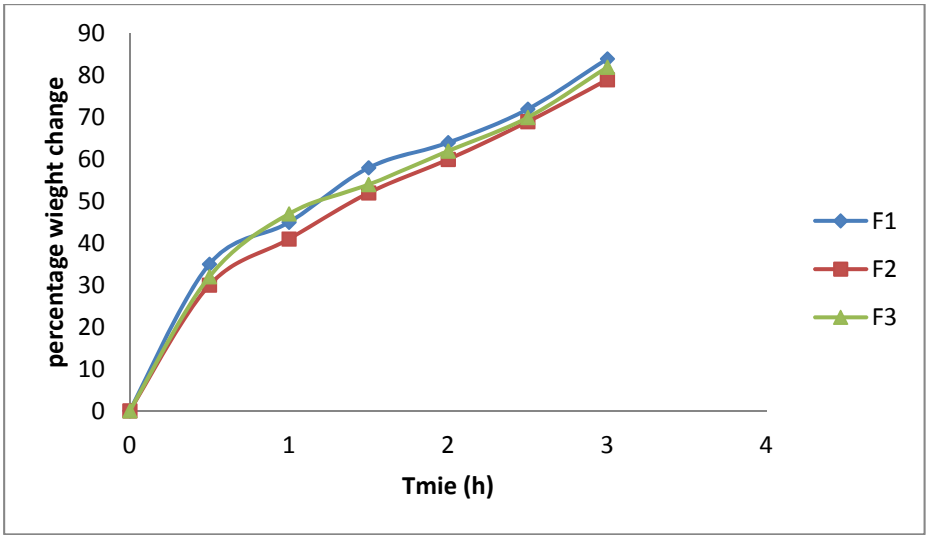

Fig. 5: Swelling data of Omeprazole mucoadhesive tablets containing Chitosan and Carbopol 934.

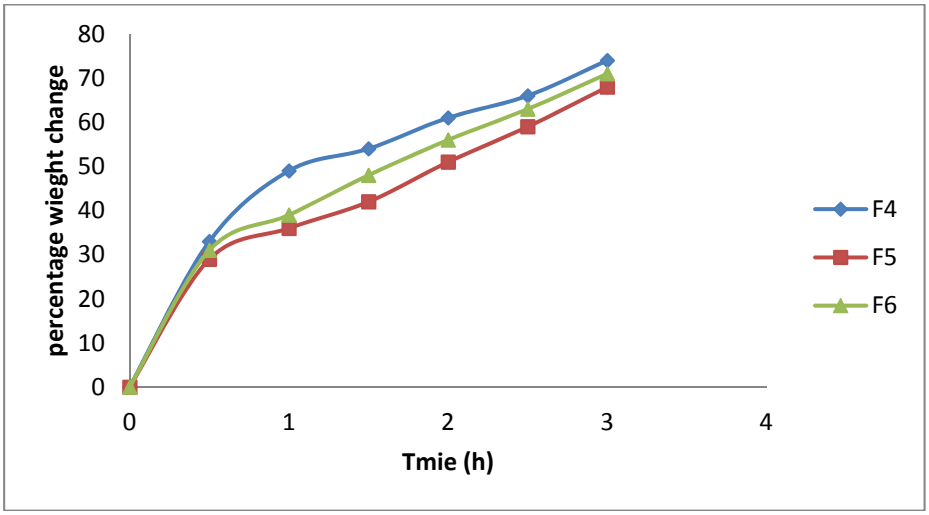

Fig. 6: Swelling data of Omeprazole mucoadhesive tablets containing Chitosan and.HPMC K4M.

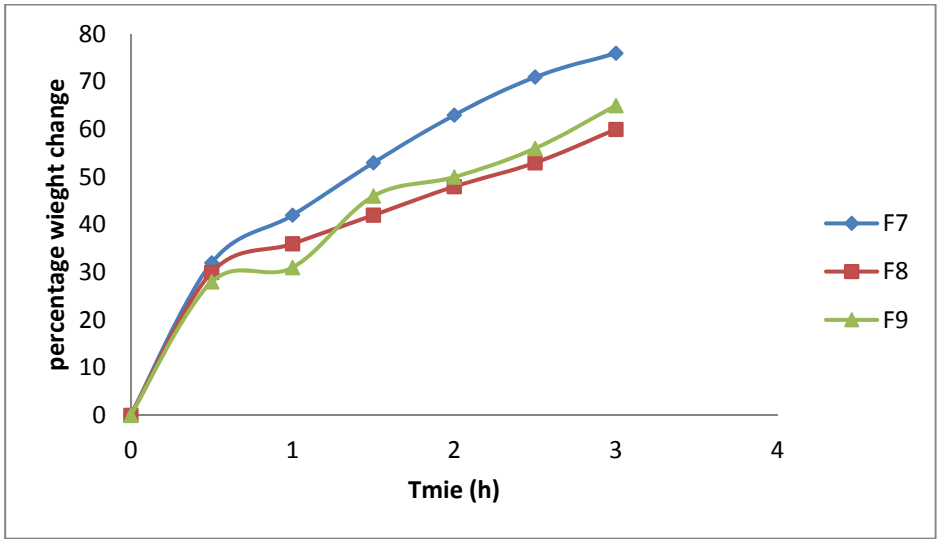

Fig. 7: Swelling data of Omeprazole mucoadhesive tablets containing Chitosan and Xanthan gum