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A Research Article on Formulation And Evaluation of Enteric Coated Tablet Loaded With Rabeprazole for Mucoadhesive Drug Delivery

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Rabeprazole is a substituted Benzimidazole is a proton pump inhibitor. PPIs block gastric acid secretion from the gastric parietal cells. The subsequent rise in gastric pH relieves symptoms and aids healing in GORD and peptic ulcer disease**.** Rabeprazole sodium is acid labile and formulated as an enteric coated tablet. Absorption occurs rapidly after the tablet leaves the stomach.In this present study an attempt was made to formulate and evaluate Rabeprazole as enteric coated mucoadhesive tablet. Delayed release tablets of Rabeprazole were prepared by wet granulation method using HPMC, HPMC-P, Xanthan gum and Carbapol as polymer, Avicel PH 102 (MCC) as filler and starch as binder. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards.The prepared tablets were coated using enteric coating polymer such as Hydroxypropyal methyl cellulose-Phthalate by spray dried method. The in vitro release was studied using pH 1.2 acidic buffer and pH 7.2 phosphate buffer. The in vitro release study revealed that the prepared tablets were able to sustain release drug in to the intestine.The Rabeprazole sodium enteric coated formulations F9 at a dose of 10 mg/kg body weight showed a protection index of 100%.

Keyword: Rabeprazole, Delayed release, HPMC, Carbapol, Xanthan gum.

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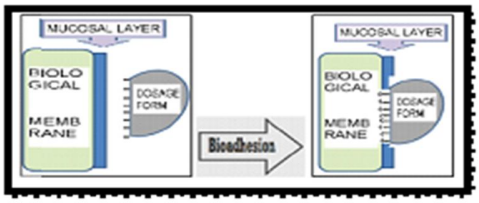
INTRODUCTION: Bioadhesion is an interfacial phenomenon in which two materials at least one of which is of biological nature are held together with the other (bioadhesive material) by means of interfacial forces for extended period of time.

When the biological substrate is mucosal coat of surface tissues then the phenomenon is called Mucoadhesion[1-4].

Figure.1. Mucoadhesive systems[5, 6]



Bio/mucoadhesive systems are those which bind to the gastric epithelial cell surface or mucin and serve as a potential means of extending the Gastro retention of drug delivery system (DDS) in the stomach or in the intestine by increasing the intimacy and duration of contact of drug with the biological membrane[7].

Enteric coating is meant to protect the drug from the gastric acidic environment, to prevent or reduce the side effect of the drug by protecting the gastric mucosa from some drugs, to deliver some drugs intended for local action in the intestine, to provide a delayed-release component for repeat-action tablets and to deliver drugs, which are primarily absorbed in intestine. The enteric coating of the tablets utilizes the pH differences of gastric pH 1-3 and intestinal pH 6-8[8].

An enteric coating is a barrier applied to oral medication that controls the location in the digestive system where it is absorbed. Enteric refers to the small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine.

2. MATERIALS AND METHODS

2.1 MATERIALS:-

- ✓ The drug Rabeprazole was obtained as a gift sample from Reagent pharmaceutical, Selaqui, Dehradun.
- ✓ The polymers HPMC, HPMC-P, Xanthun gum, Carbapol are obtained as a gift sample from Reagent pharmaceutical, Selaqui, Dehradun.
- ✓ Carbapol was purchased from C.D.R.I, Lucknow

2.2 METHODS:-

2.2.1 Identification of pure drug

Identification of Rabeprazole was examined by FT-IR and compared with the reference spectrum of drug.

2.2.2 Method used to estimate Rabeprazole sodium

The drug Rabeprazole Sodium was dissolved in phosphate buffer 7.2 to get 10 µg/ml solutions. Further diluted with the same and scanned for maximum absorbance (λmax) in a double beam UV-VIS Spectrophotometer, between a U.V ranges from 200 to 400 nm against phosphate buffer pH 7.2 as blank and λ max is found to be 287 nm.

2.2.3 Preparation of Rabeprazole sodium tablet

Rabeprazole sodium granules for tabletting were prepared by wet granulation method. Specified quantity of Rabeprazole, Polymer (Hydroxypropyl methylcellulose (HPMC) or Carbapol or Xanthan gum) and Avicel pH 102 were weighed according to the formula (Table 1) and transferred in a mortar and pestle and mixed thoroughly. The powder mass was mixed with 5% starch paste to obtain a sluggy mass and this was passed through sieve no. 12 to obtain the granules. The granules prepared were dried at 50◦C for 4 h. The dried granules were screened through sieve no. 22 & 44 and stored for further studies. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets. Ideal mixtures of granules were directly punched into tablets weighing about 100 mg containing 10 mg of Rabeprazole sodium, using rotary tablet

compression machine. The different batches of Rabeprazole tablets were collected and stored in air tight containers.

Table.1. Formulation Chart

INGREDIENTS	FORMULATIONS								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
RABEPRAZOLE	10	10	10	10	10	10	10	10	10
HPMC	20	40	60	-	-	-	-	-	-
XANTHAN GUM	-	-	-	20	40	60	-	-	-
CARBOPOL	-	-	-	-	-	-	20	40	60
AVICIL pH 102 (mg)	66	44	24	66	44	24	66	44	24
STACH PASTE 5%	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs
TALC (mg)	2	2	2	2	2	2	2	2	2
MAGNESIUM STEARATE (mg)	4	4	4	4	4	4	4	4	4

Qs= quantity sufficient

Table.2. Composition of coating solution

Ingredients	Quantity (%w/w)
Cellulose acetate phthalate	6.0
Titanium dioxide	2.6
Diethyl phthalate	2.0
Acetone	59.4
Isopropyl alcohol	30.0

2.2.4 Preparation of spraying dispersion for coating The enteric coating solution was prepared by simple solution method. It was prepared by 6% w/w of HPMC-P, 2.6% w/w of titanium dioxide as opacifier, diethyl phthalate 1.2% w/w as plasticizer and acetone and isopropyl alcohol mixture was used as solvent. Titanium dioxide was triturated in a glass motor with small amount of solvent mixture and filtered with muslin cloth into the polymer solution already prepared with one half of solvent mixture. Diethyl phthalate was added and made up the volume with rest of the solvent mixture; this mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a coating solution was obtained.

2.2.5 Enteric coating of Rabeprazole sodium compressed tablets by Spray dried method

For the coat, the tablets were coated by Pan coating apparatus, and in-process samples were taken to check if the target polymer weight gain was achieved. Coating was continued until complete polymer weight gain was achieved. After the coating, the tablets kept a side for 10 min after which they were cured at 40 ◦C for 24 h.

Table.3. PROCESSING PARAMETER USED FOR COATING[9]

Sl.No	Parameter	Set at value
1	Bed temperature	30-40 C
2	Suspension spray rate(gm/min)	5-7
3	Suspension spray time (min)	45-55
4	Spray nozzle (mm)	1
5	Spray pressure (kg/cm²)	4
6	Pan speed(rpm)	6
7	Drying in equipment(min)	10

3. STUDY OF DIFFERENT PARAMETERS [10, 11, 12]

3.1 Drug content

Five tablets were powdered in a mortar. Weighed accurately the quantity equivalent to 10 mg of Rabeprazole sodium and transferred to a 100ml volumetric flask containing few ml of phosphate buffer and mixed well, made up the volume up to 100ml with phosphate buffer. Pipette out 10 ml from this solution into another 100 ml volumetric flask and made up the volume with phosphate buffer 7.2 to produce stock solution of concentration 100 mcg/ml.

The above stock solution of drug was subsequently diluted with phosphate buffer 7.2 to get 2 mcg, 4 mcg, 6 mcg, 8 mcg and 10 mcg, of drug per ml. Then the absorbance of these dilute solutions was measured at a λ max of 287 nm by using double beam U.V.spectrophotometer against a blank of phosphate buffer 7.2

3.2-*In-vitro* release studies

The *in-vitro* dissolution profile of the designed formulations was carried out using USP type I apparatus under conditions specified (Temp 37± 0.5°C, at 100 rpm).As artificial gastric fluid, 0.1N Hcl (pH 1.2) was used. The artificial intestinal fluid was prepared phosphate buffer (pH 7.2).

4. RESULTS & DISCUSSION:

4.1 Compatibility studies

In order to investigate the possible interactions between Rabeprazole sodium and distinct polymers, FT-IR studies were carried out. FT-IR results proved that the drug was found to be compatible with excipients as wave numbers are almost similar for pure drug and also drug excipients mixture.

4.2 Evaluation of pre-compression parameters

The Rabeprazole sodium granules were prepared by wet granulation method. The granules were evaluated for percentage yield, granules particle size, angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index, and the results are shown in Table 5.3. The percentage yield was ranged between 91.68 to 97.82%. The particle size of the granules was ranged between 0.498 ± 0.05 mm to 0.548 ± 0.11 mm. The bulk densities of the granules were

found to be in the range of 0.306 ± 0.03 to 0.384 ± 0.04 gm/ml. The angle of repose varied from 25.79 ± 0.24 to 30.27 ± 0.34. The tapped densities were ranged between 0.313 ± 0.04 to 0.429 ± 0.05 gm/ml. Hausner's ratio was ranged between 1.065 ± 0.02 to 1.117 ± 0.07, while the compressibility index was in the range of 6.13 ± 0.12 to 10.48 ± 0.20.

4.3 EVALUATION OF POST-COMPRESSION PARAMETERS:

The Rabeprazole sodium tablets were prepared by wet granulation method. The results of physicochemical evaluation of prepared tablets are shown in Table 5.4 and Figures 5.11 to 5.13. The tablets were evaluated for Average weight, hardness, friability and drug content. The drug content was found to be between 96.85 ± 0.16% to 99.42 ± 0.26%. The hardness was found to be from 4.73 ± 0.42 to 8.40 ± 0.002 kg/cm2 and in all the cases the friability was less than 1%.

4.5- *IN-VITRO* RELEASE STUDIES:

The *in vitro* release of Rabeprazole sodium from the prepared tablets was studied in pH 1.2 for 2 h and in phosphate buffer pH 7.2 for 12 h. The different Rabeprazole sodium enteric coated tablets have showed marked difference on their drug release by USP dissolution method. The varying concentration of HPMC in tablets formulation F1 to F3, Xanthan gum in tablets formulation F4 to F6 and Carbapol in tablets formulation F7 to F9 showed the marked difference on their drug release pattern (Tables 6.5 to 6.7 and Figures 6.7 to 6.9). The higher concentration of Carbapol showed better sustained release properties than the HPMC and Xanthan gum as polymer. The cumulative percentage releases of Rabeprazole sodium from the tablets were varied from to 69.96 ± 0.28% to 91.87 ± 0.12% depends on the polymer and drug polymer ratio for 12 h.

Table. 4 . Physicochemical evaluations of Rabeprazole sodium granules

Batch Code	Parameter						
	Yield (%)	Mean particle size(mm)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's atio	Angle of repose (θ)
F1	97.82	0.498 ±0.05	0.306 ±0.03	0.326 ±0.03	6.13 ±0.12	1.065 ±0.02	25.79 ±0.24
F2	94.85	0.545 ±0.12	0.312 ±0.04	0.335 ±0.02	6.86 ±0.15	1.073 ±0.05	26.95 ±0.15
F3	95.37	0.527 ±0.06	0.358 ±0.05	0.385 ±0.04	7.01 ±0.13	1.075 ±0.03	26.33 ±0.17
F4	94.12	0.542 ±0.05	0.357 ±0.03	0.384 ±0.05	7.03 ±0.09	1.075 ±0.04	28.31 ±0.26
F5	93.43	0.533 ±0.21	0.359 ±0.04	0.394 ±0.03	8.88 ±0. 24	1.097 ±0.09	27.20 ±0.14
F6	91.68	0.535 ±0.06	0.384 ±0.04	0.429 ±0.05	10.48 ±0.20	1.117 ±0.07	30.27 ±0.34
F7	94.23	0.512 ±0.04	0.312 ±0.03	0.334 ±0.06	6.58 ±0.14	1.070 ±0.06	29.52 ±0.14
F8	95.89	0.548 ±0.11	0.286 ±0.05	0.313 ±0.04	8.62 ±0.07	1.094 ±0.03	26.13 ±0.26
F9	97.14	0.536 ±0.05	0.306 ±0.03	0.334 ±0.05	8.38 ±0.17	1.091 ±0.08	26.78 ±0.18

(n=3 ± S.D)

Table. 5 . Physicochemical evaluations of Rabeprazole sodium tablets

Batch Code	Parameters			
	Hardness (kg/cm^2)*	Friability (%)**	Average weight (g)**	Drug content (%)***
F1	8.40 ± 0.02	0.011 ± 0.021	0.201 ± 0.02	98.85 ± 0.21
F2	5.80 ± 0.12	0.012 ± 0.015	0.199 ± 0.12	97.71 ± 0.15
F3	6.20 ± 0.35	0.016 ± 0.025	0.204 ± 0.009	98.85 ± 0.34
F4	4.90 ± 0.21	0.005 ± 0.034	0.203 ± 0.024	97.42 ± 0.42
F5	4.93 ± 0.15	0.023 ± 0.015	0.208 ± 0.031	96.85 ± 0.16
F6	4.73 ± 0.42	0.024 ± 0.017	0.205 ± 0.015	97.14 ± 0.09
F7	5.66 ± 0.17	0.240 ± 0.026	0.199 ± 0.019	98.55 ± 0.48
F8	8.20 ± 0.16	0.017 ± 0.035	0.209 ± 0.008	99.42 ± 0.26
F9	5.60 ± 0.24	0.110 ± 0.018	0.198 ± 0.007	96.85 ± 0.35

*** (n=5 ± S.D) ** (n=2 ± S.D) *** (n=3 ± S.D)**

Table.6. In-vitro drug release of formulations F1-F9

TIME (hr)		FORMULATIONS							
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0.5	11.31	10.34	10.52	4.52	20.56	9.64	15.47	13.39	9.29
1	20.76	15.99	17.16	15.38	28.04	17.22	21.86	19.41	16.23
1.5	30.21	31.99	24.52	25.32	43.98	28.87	23.7	21.26	22.1
2	43.45	38.61	38.99	37.89	50.57	39.07	28.45	32.98	35.04
3	51.97	48.7	44.44	53.6	59.04	49.68	15.47	40.78	41.83
4	57.3	54.34	51.14	61.25	69.39	56.96	42.9	50.66	48.5
6	68.58	64.94	58.7	72.46	73.99	66.38	53.87	55.09	55.24
8	74.43	71.48	64.47	77.25	81.69	73.68	67.59	69.11	61.51
10	82.09	78.09	70.3	84.15	87.4	80.26	74.33	74.21	66.32
12	90.25	82.14	75.48	91.87	91.24	85.2	87.71	79.52	69.96

Figure.1 . In vitro drug release profile of formulations F1-F3

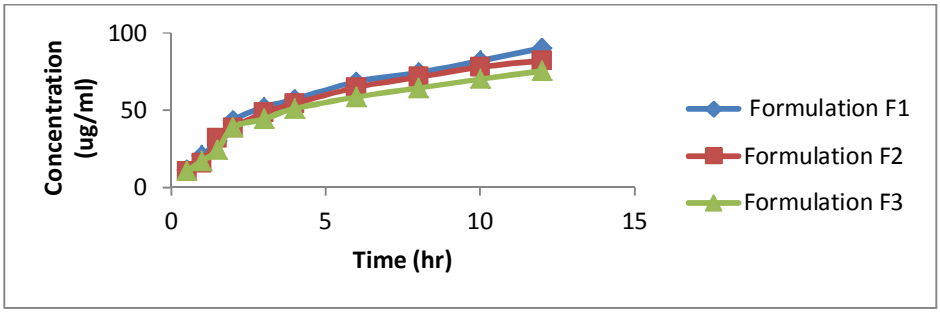


Figure. 2. In vitro drug release profile of formulations F4-F6

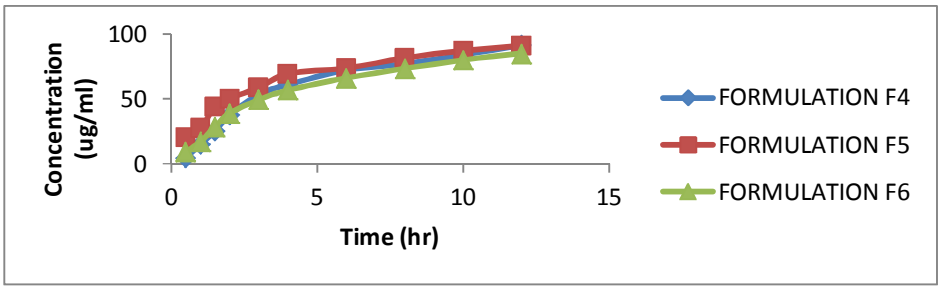


Figure. 3. In vitro drug release profile of formulation F7-F9

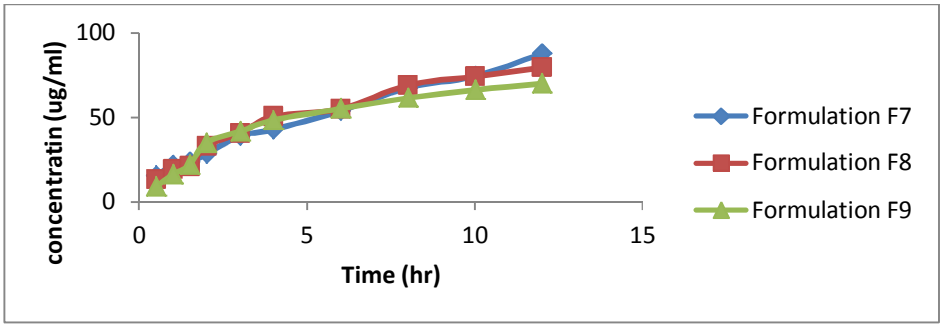
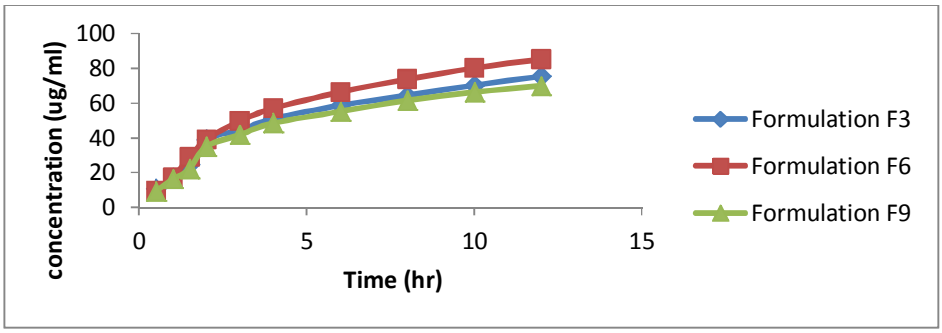


Figure. 4. In vitro drug release profile of formulation F3-F6-F9



5. CONCLUSION:

Based on the observations, it can be concluded that the formulated Modified release tablets of Rabeprazole using widely accepted and physiologically safe polymers and other excipients was capable of exhibiting sustained release properties for a period of at least 12 h. The enteric coated tablets, did not release the drug in the acidic pH 1.2 for a period of 2 h. They are thus may be reducing the dose intake, prevent the degradation of drug in acidic pH 1.2, minimize the blood level oscillations, dose related adverse effects and cost and ultimately improve the patient compliance and drug efficiency.

REFERENCE:

1. Gupta P.K. and Robinson J.R., Oral Controlled-Release Delivery, in Treatise on Controlled Drug Delivery, A. Kydonieus, Eds., Marcel Dekker, New Jersey, 1992, 255-310
2. Park K. and Robinson J.R., Bioadhesive Polymers as Platforms for Oral-Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 19 (1), 1984, 107-127.
3. Andrew G P, Laverty T P and Jones D S. Mucoadhesive polymeric for controlled drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 71 (3), 2009, pp.505-518.
4. S. Ganga, mucosal drug delivery – a review, Vol. 5 issue 6, 2007 http//www.pharmainfo.net. Accesed on 08/07/2010.
5. Gupta P.K. and Robinson J.R., Oral Controlled-Release Delivery, in Treatise on Controlled Drug Delivery, A. Kydonieus, Eds., Marcel Dekker, New Jersey, 1992, 255-310
6. Park K. and Robinson J.R., Bioadhesive Polymers as Platforms for Oral- Controlled Drug Delivery: Method to Study Bioadhesion, Int. J. Pharm. 19 (1), 1984, 107-127.
7. Chowdary K.P.R., Srinivas L., Mucoadhesive drug delivery systems: A review of current status. *Indian Drugs*, 37(9): 400-406, (2000).
8. http://en.wikipedia.org/wiki/Enteric_coating. (Accessed on 24/07/2012)
9. Kro¨gel, R. Bodmeier, Evaluation of an enzyme-containing capsular shaped pulsatile drug delivery system, Pharm. Res. 16 (9) (1999) 1424– 1429.
10. Cooper J, Gunn C. Powder flow and compaction. IN: Carter SJ, eds. Tutorial pharmacy, New Delhi: CBS publishers and distributors; 1986; 211-33.
11. Lachman L, Liberman HA, Nicholas Gl. Sustained release dosage forms, in; 2nd ed, Varghese publishing house, Mumbai, 1987; 439-40.
12. Levin M. Changing Tabletting Machines in Scale-Up and Production: Ramifications for SUPAC Background Notes for FDA CDER DPQR Seminar April 3, 2000.
13. Chowdary K.P.R., Srinivas L., Mucoadhesive drug delivery systems: A review of current status. *Indian Drugs*, 37(9): 400-406, (2000).
14. Gandhi R.B., Robinson J.R., Bioadhesion in drug delivery. *Ind. J. Pharm. Sci*., 50(3):145-152, (1988).
15. Yang X, Robinson JR. In: Okano T, ed. Biorelated functional polymers and gels: controlled release and applications in biomedical engineering, San Diego: Academic Press, 1998, 135.
16. Smart J D. The basics and underlying mechanisms of mucoadhesion. Adv.Drug Del. Rev., 57, 2005, pp. 1556- 1568.
17. Hubbell J A. Biomaterials in tissue engineering. Biotechnology, 13, 1995, pp. 565-576.
18. Peppas N A and Sahlin J J. Hydrogels as mucoadhesive and bioadhesive materials: a review. Biomaterials, 17, 1996, pp. 1553–1561.
19. Wu S. Formation of adhesive bond; Polymer Interface and Adhesion. Marcel Dekker Inc, New York, 1982, pp. 359-447
20. Smart J D. The role of water movement and polymer hydration in mucoadhesion, in Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches and Development, Mathiowitz E, Chickering D E and Lehr M Eds, Marcel Decker, New York, 1999, pp. 11-23.
21. Chen J.L., Cyr. G.N., Composition producing adhesion through hydration, in mainly R.S., ed., Adhesion in biological system. New York; Academic Press, 163-181.
22. Squier, C.A.and Wertz, P.W., Structure and Function of the Oral Mucosa and Implications

for Drug Delivery, in, M.J. Rathbone, Eds; Oral Mucosal Drug Delivery, (1996), Marcel Dekker, Inc., New York, 1-26.

23. Harris, D. and Robinson, J.R., Drug Delivery via the Mucous Membranes of The Oral Cavity, J. Pharm. Sci., 81, 1992, 1-10.
24. Khar, R.K., Ahuja, A. and Ali, J., In; Jain, N.K., Eds , Controlled and Novel Drug Delivery, CBS Publishers & Distributors, New Delhi, 2002, 353-55.
25. Gandhi, R.B. and Robinson, J.R., Oral cavity as a Site for Bioadhesive Drug Delivery, Adv. Drug Del. Rev., 13, 1994, 43-74.
26. A.G. Mikos, N.A. Peppas, Measurement of the surface tension of mucin solutions. Int J Pharm, 53: 1-5, (1989).
27. A. Baszkin, J.E. Proust, P. Monsengo, M.M. Boissonnade, Wettability of polymers by mucion aqueous solutions. Biorheology, 27: 503-514, (1990).
28. C.M. Lehr, H.E. Bodde, J.A. Bowstra, H.E. Junginger, A surface energy analysis of mucoadhesion. II: Prediction of mucoadhesive performance by spreading coefficients. Eur J Pharm Sci, 1: 19-30, (1993).
29. C.M. Lehr, J.A. Bowstra, H.E. Bodde, H.E. Junginger. A surface energy analysis of mucoadhesion: Contact angle measurements on polycarbophil and pig intestinal mucosa in physiology relevant fluids. Pharm Res, 9: 70-75, (1992).
30. R.T. Spychal, J.M. Marrero, S.H. Saverymuttu, T.C. Northfield. Measurement of the surface hydrophobicity of human gastrointestinal mucosa. Gastroenterology, 97: 104-111, (1989).
31. D.H. Kaelble, J. Moacanin. A surfaceenergy analysis of bioadhesion. Polymer, 18: 475-482, (1977).