



International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Preparation and *In-Vitro* Evaluation of Prednisolone Mucoadhesive Tablets for Colon Targeted Drug Delivery System

Ramesh Reddy K^{*1}, Rubeena Begum H¹, Sai Sri Harsha G¹, Srikar N² and Anil K³

¹Krishna Teja Pharmacy College, Chadalawada Nagar, Tirupati, Andhra Pradesh, India.

²Associate Researcher, Bufna Pharma, Chennai, Tamil Nadu, India.

³OTRI-JNTUA, Anantapuram, Andhra Pradesh, India.

ABSTRACT

The study was designed to develop mucoadhesive tablets of using PVP and Pectin inter polymer complexes and to systematically evaluate their in-vitro and ex-vivo performances. Prednisolone is a synthetic glucocorticoid, a derivative of cortisol, which is used to treat a variety of inflammatory and auto-immune conditions. Colon targeted drug delivery is an active area of research for local diseases affecting the colon, as it improves the efficacy of therapeutics and enables localized treatment, which reduces systemic toxicity. Targeted delivery of therapeutics to the colon is particularly advantageous for the treatment of inflammatory bowel disease (IBD), which includes ulcerative colitis and Crohn's disease. Mucoadhesive tables were prepared by direct compression method. The physicochemical interaction between PVP and Pectin was investigated by FTIR studies. Tablets were evaluated their compatibility studies by using FT-IR, micrometrics properties, post formulation characters such as hardness, thickness, friability, content uniformity, *Ex vivo* mucoadhesive strength and *in-vitro* dissolution studies.

Keywords: Prednisolone, Mucoadhesive, PVP, Pectin, *Ex-vivo*, *In-vitro*.

INTRODUCTION

Colon is being extensively investigated as a drug delivery site. Colon targeted drug delivery system (CTDDS) has been developed by means of one or more controlled released mechanisms (Munjeri O *et al.*, 1997). It is convenient for treating localized colonic diseases, i.e. Ulcerative colitis, Crohn's diseases and constipation etc.

Its potential applications include Chronotherapy, Prophylaxis of colon cancer and treatment of Nicotine addiction. The treatment of Inflammatory Bowel Disease (IBD) with anti-inflammatory drugs is particularly improved by local delivery to bowel by using CTDDS. For successful colon specific drug delivery, many physiological barriers must be overcome; the major one is being absorption or degradation of the active drug in the upper part of the GIT. The minor is disease state, which can potentially alter the delivery and absorption characteristics of drugs from the colon (Sayeh F. Ahrabia *et al.*, 2000; Purushothama Rao K and CC Patil, 2005).

The CTDDS should protect the drug from the absorption and degradation in the stomach and small

intestine, the drug should be absorbed only at the colonic site. The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery (Salunkhe KS *et al.*, 2007). The colon is a suitable absorption site for peptides and protein drugs.

1. Diffusion
2. Polymer erosion
3. Microbial degradation
4. Enzymatic degradation (mammalian and/or bacterial)

In addition, drug solubility and formulation of polymer mixes play important roles in determining the extent of drug delivery and release in the colon (Ravi V *et al.*, 2008; Nath BS *et al.*, 2000). Two broad categories of biopolymers have been employed for formulating colonic systems: Biodegradable and Non-biodegradable polymers (Mastiholimath VS *et al.*, 2007; Ahmed FJ and Khar RK, 2000; Kiran S, 2007). Considerations for designing of Colon Targeting formulations:

To achieve a desired therapeutic action of dosage form, it is necessary to design a suitable formulation with suitable qualities (Aswar PB, 2009). In general, delayed release dosage forms are designed to

***Corresponding author**

Ramesh Reddy K

Email id: k.rameshreddy88@gmail.com

provide a burst release or a sustained/ prolonged release once they reach colon. Various factors includes are

- Pathology and pattern of diseases, especially the affected parts of lower GIT or, Physiology and physiological composition of the healthy colon if the formulation is not intended for localized treatment.
- Physicochemical properties and biopharmaceutical properties of the drug such as solubility , stability and permeability at the intended site of delivery, and
- The desired release profile of the active ingredient.

Prednisolone is a glucocorticoid that prevents or suppresses inflammation and immune responses when administered at pharmacological doses (Irit Gliko-Kabir *et al.*, 1998). At a molecular level, unbound glucocorticoids readily cross cell membranes and bind with high affinity to specific cytoplasmic receptors. This binding induces a response by modifying transcription and, ultimately protein synthesis to achieve the steroid's intended action. Such actions may include: inhibition of leukocyte infiltration at the site of inflammation, interference in the function of mediators of inflammatory response, and suppression of humeral immune responses (Vikas Kumar *et al.*, 2010). In many tissues, the overall effect is catabolic, i.e. some of the net effects include reduction in edema or scar tissue, as well as a general suppression in immune response.

MATERIALS AND METHODS

Prednisolone (Bufna Pharmaceutical Ltd. Chennai), Pectin, Chitosan (SD fine chemicals, Boisar), Potassium hydrogen phosphate (SD fine chemicals, Boisar), Sodium dihydrogen phosphate (SD fine chemicals, Boisar), Magnesium stearate (SD fine chemicals, Boisar), Lactose (SD fine chemicals, Boisar).

Drug – polymer compatibility studies by FTIR

Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy)⁶⁰. FTIR absorption spectra of drug and all the polymers pectin, eudragit, PVP, Carbopol were taken individually and in the combinations. Two mg of sample mixed with 200mg of IR grade KBR in a silicon mortar and this mixture pressed into a disk. Disk was carefully kept in a position of FTIR. Infrared (IR) spectra were obtained in the scanning range of 400 to 4000 cm⁻¹.

Preparation of mucoadhesive bilayer tablets

Accurately weighed 250mg dried granules were compressed using an 8 mm diameter die in a 8 station rotary punching machine (KAMBET). The upper punch was raised and exactly weighed 50mg of carbapol was placed and spreaded evenly above the compressed tablet. The carbopol is used as a mucoadhesive layer. Compression machine was rotated again to make a bilayer tablet.

Pre formulation studies

Determination of bulk density and tap density

Apparent bulk density (ρ_b) was determined by pouring the blend into a graduated cylinder. The bulk

volume (V_b) and weight of powder (M) was determined. The bulk density was calculated using the formula.

$$\rho_b = M/V_b$$

The measuring cylinder containing a known mass of powder or granules was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density (ρ_t) was calculated using the formula

$$\rho_t = M/V_t$$

Compressibility index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by compressibility index (I) which is calculated as

$$I = (\rho_t - \rho_b) / \rho_t \times 100$$

Where,

ρ_t = Tapped density ρ_b = Initial bulk density

The value below 15 % indicates a powder which usually give rise to good flow characteristics whereas above 25 % indicate poor flow ability.

Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose (θ). It was determined using funnel method. The powder or granules were poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose (q) was calculated as

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

Evaluation of prepared bilayer tablets

The prepared bilayer tablets were evaluated for following physicochemical properties.

Thickness

The thickness of the each tablet was measured by using vernier caliper and the average thickness was calculated.

Weight variation

Formulated tablets were tested for weight uniformity. Twenty tablets were weighed collectively and individually. From the collective weight, average weight was calculated. The percent weight variation was calculated by using the following formula.

$$\%Wt \text{ Variation} = \frac{\text{Avg. Wt} - \text{Individual Wt}}{\text{Avg Wt}} \times 100$$

Avg Wt

Hardness

The hardness of Tablets was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm².

Friability

The Roche friability test apparatus was used to determine the friability of the Tablets. Twenty pre-weighed tablets were placed in the apparatus and

operated for 100 revolutions and then the tablets were reweighed. The percentage friability was calculated according to the following formula.

$$\% \text{ Friability} = \frac{\text{Initial Wt} - \text{Final Wt}}{\text{Initial Wt}} \times 100$$

Initial Wt

Drug Content

Drug content uniformity was determined as triplicate by dissolving the tablets in DMSO (Dimethyl sulfoxide) and filtering with Whatman filter paper (0.45 μm , Whatman, Maidstone, UK). The filtrate was evaporated and the drug residue dissolved in 100 ml of phosphate buffer (pH 6.8). The 5 ml solution was then diluted with phosphate buffer up to 20 ml, filtered through Whatman filter paper and analyzed at 240 nm using a UV spectrophotometer.

Ex vivo mucoadhesive strength

A modified physical balance method was used for determining the *ex vivo* mucoadhesive strength. Fresh sheep colon mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer. The two sides of the balance were made equal before the study, by keeping a buffer solution at 37°C. The Sheep colon mucosa was cut into pieces and washed with phosphate buffer. A piece of colon mucosa was tied to the glass vial, which was filled with phosphate buffer.

The glass vial was tightly fitted into a glass beaker so that it just touched the mucosal surface. The mucoadhesive Tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive and adds

weight on the right-hand pan. A weight of 5 g was removed from the right hand pan. This lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min). To the right-hand pan until the Tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of then Mucoadhesive Tablet in grams.

$$\text{Force of adhesion (N)} = \frac{\text{Mucoadhesive strength (g)} \times 9.8}{1000}$$

$$\text{Bond strength (N m}^{-2}\text{)} = \frac{\text{Force of adhesion}}{\text{surface area}}$$

In-vitro drug release study

The dissolution test was performed for all the prepared formulations. The slightly modified USP type II rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 900 ml of phosphate buffer having pH 7.4. The release study was performed at $37 \pm 0.5^\circ \text{C}$, with a rotation speed of 50 rpm. Then samples were collected at regular intervals of time and absorbance was measured at 250 nm.

The backing layer of the mucoadhesive Tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots (5ml each) were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were diluted with phosphate buffer pH 7.4 and were analyzed spectrophotometrically at 250 nm. The release rates of Prednisolone from all the prepared formulations were calculated.

Table.1 Formulations of Fabricated Prednisolone Mucoadhesive Tablets

S. No.	Ingredient	Formulations Code (Weights in 'mg')							
		F1	F2	F3	F4	F5	F6	F7	F8
1	Prednisolone	15	15	15	15	15	15	15	15
2	PVP	15	25	35	45	55	65	75	-
3	Pectin	85	75	65	55	45	35	25	100
4	Lactose	80	80	80	80	80	80	80	80
5	Talk Powder	2	2	2	2	2	2	2	2
6	Starch Mucilage	2	2	2	2	2	2	2	2
7	Mg. Stearate	1	1	1	1	1	1	1	1
8	Carbopol	50	50	50	50	50	50	50	50

RESULTS AND DISCUSSION

Evaluation of granules

Table.2 Results for Derived and Flow properties

Formulation Code	Derived properties (mean \pm SD)		Flow properties (mean \pm SD)		
	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner's ratio
F1	0.337 \pm 0.01	0.393 \pm 0.015	25.45 \pm 0.30	10.44 \pm 1.97	1.119 \pm 0.02
F2	0.347 \pm 0.015	0.403 \pm 0.02	26.21 \pm 0.39	10.22 \pm 1.96	1.116 \pm 0.03
F3	0.393 \pm 0.015	0.46 \pm 0.01	25.97 \pm 0.68	10.86 \pm 3.97	1.125 \pm 0.05
F4	0.366 \pm 0.015	0.426 \pm 0.015	23.21 \pm 0.96	8.48 \pm 1.81	1.115 \pm 0.02
F5	0.333 \pm 0.02	0.496 \pm 0.03	22.94 \pm 0.73	11.65 \pm 2.25	1.135 \pm 0.03
F6	0.32 \pm 0.01	0.363 \pm 0.006	23.25 \pm 0.36	10.32 \pm 3.16	1.113 \pm 0.04

F7	0.353±0.025	0.436±0.025	22.21±0.29	13.54±1.19	1.114±0.02
F8	0.35±0.01	0.41±0.017	24.87±0.40	14.69±3.61	1.116±0.05

Ex vivo mucoadhesive strength:

Table.3 Measurement of Mucoadhesive

Formulation code	Mucoadhesive Strength in g
F1	30.1
F2	24.3
F3	20.2
F4	18.4
F5	15.4
F6	14.2
F7	16.5
F8	32.4

Evaluation of tablets

Table: 4 Physico chemical evaluation of bilayer Mucoadhesive Tablets of Prednisolone

Formulation Code	Thickness (mm)	Weight variation (mg)	Hardness (Kg/cm ²)	Friability (%)	Drug content (mg)
F1	2.92 ±0.01	279±1.45	5.2±0.14	0.43±0.01	27.57±0.21
F2	2.93±0.03	267±0.84	4.2±0.22	0.52±0.02	27.85±0.29
F3	2.92±0.01	299±0.82	4.6±0.33	0.50±0.04	27.32±0.38
F4	2.92±0.02	295±0.62	4.9±0.11	0.46±0.03	27.26±0.21
F5	2.92±0.01	293±0.21	4.5±0.12	0.43±0.01	27.45±0.25
F6	2.93±0.02	287±0.92	4.3±0.16	0.49±0.02	28.19±0.01
F7	2.92±0.01	293±0.28	4.4±0.11	0.41±0.03	27.21±0.03
F8	2.92±0.01	292±0.42	4.3±0.23	0.44±0.02	28.15±0.45

Figure.1 FTIR spectra of Prednisolone

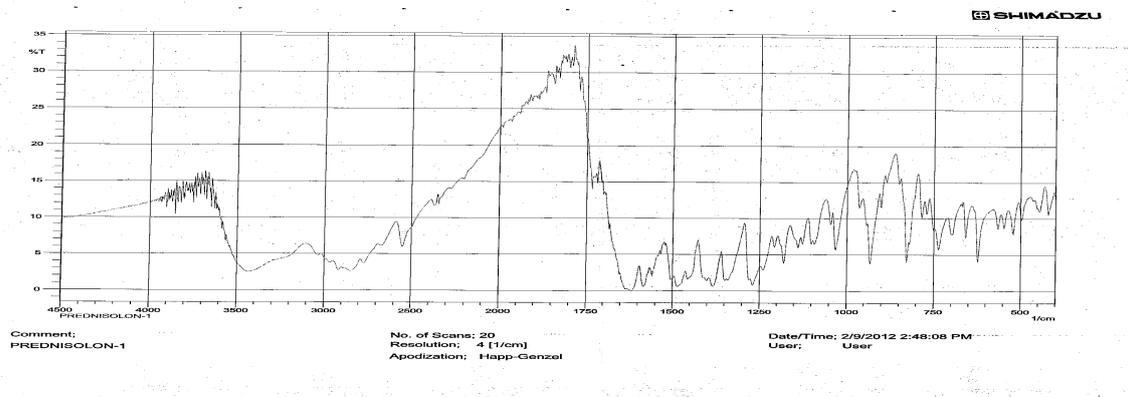


Figure.2 FTIR spectra of Eudragit

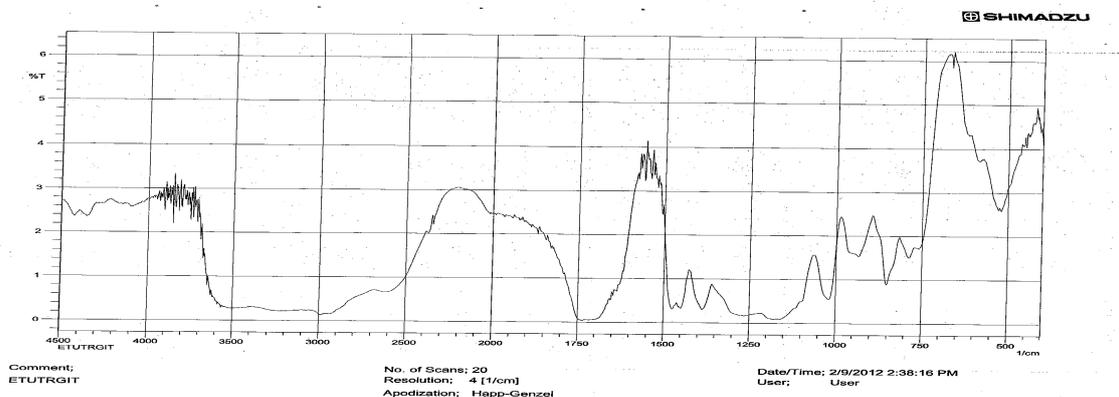


Figure.3 FTIR spectra of Pectin

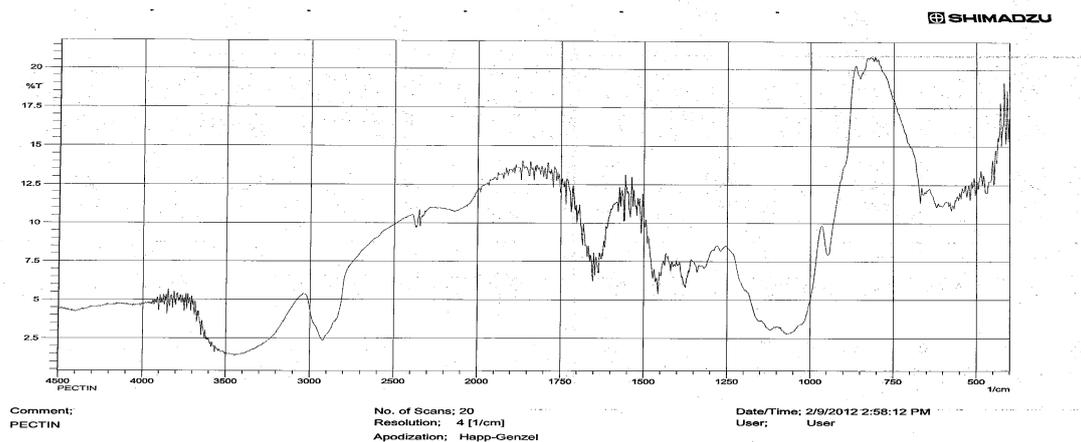
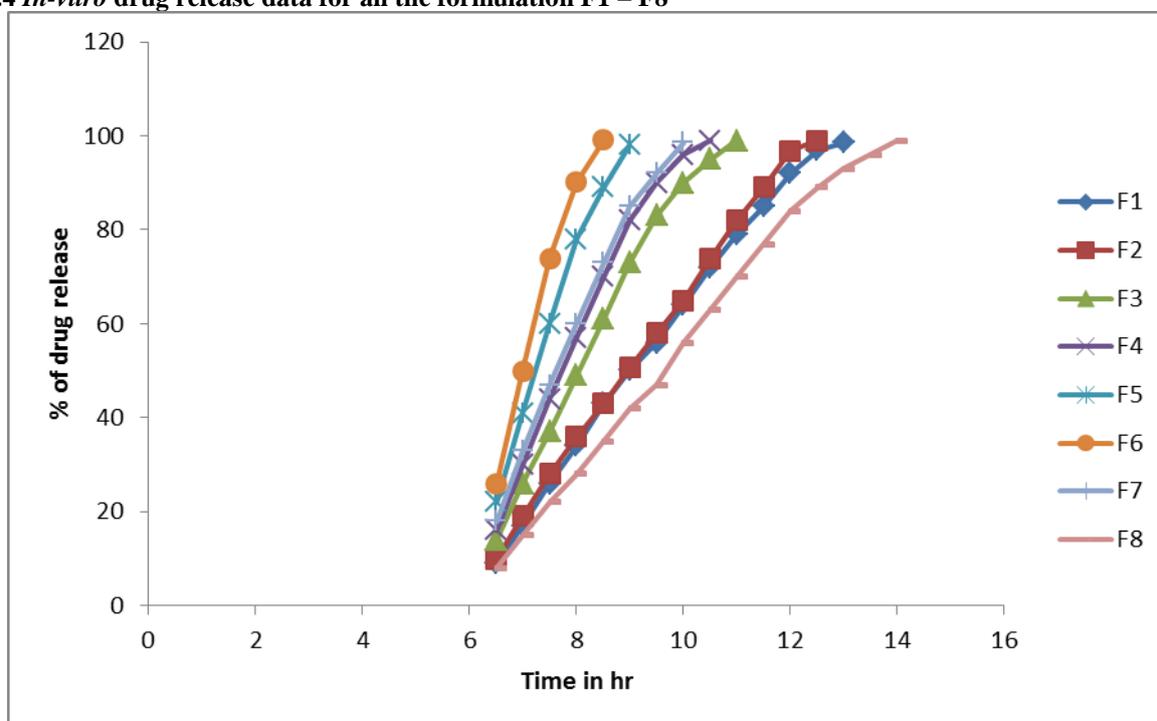


Figure.4 In-vitro drug release data for all the formulation F1 – F8



CONCLUSION

The prednisolone sustained release bilayer tablets were prepared by wet granulation method using different mucoadhesive polymers such as Pectin, PVP along with Carbopol 934P as a mucoadhesive layer. Drug-polymer compatibility studies by FTIR indicates there is no possible interactions between the drug and polymer and prepared tablets were characterized for their physico-chemical characteristics pH resistant, mucoadhesive strength, *in-vitro* drug release shows reproducible results.

Among all, formulations F8 consists of prednisolone (15 mg), pectin (100mg), lactose (80mg), Carbopol (50mg) was selected as best formulation. Various physiochemical parameters tested for this formulation showed good results. Formulation F8 was stable and non-significant from P value obtained by one way ANOVA. Hence prednisolone sustained release mucoadhesive tablets could be maintain and treat such local infections to develop a mucoadhesive bilayer tablet which adhere at the colon to release the Prednisolone for a longer time, minimize the dosing intervals.

REFERENCE

Ahmed FJ and Khar RK. Development of colon specific drug delivery system of 5-Amino salicylic acid. *Indian Journal of Pharmaceutical Sciences*. 2000;527.
 Aswar PB. Development and in-vitro evaluation of colon-specific formulations for orally administered diclofenac sodium. *Arch Pharm Sci & Res*. 2009;1(1):48-53.

- Irit Gliko-Kabir, Boris Yagen, Adel Penhasi, Abraham Rubinstein. Low swelling, cross linked Guar and Its Potential Use as Colon-Specific Drug Carrier. *Pharmaceutical research*. 1998;15:7.
- Kiran S. Effect of Oppositely Charged Polymer and Dissolution Medium Swelling, Erosion and Drug Release From Chitosan Matrices. *AAPS pharm sci tech*. 2007;8(2).
- Mastiholmath VS, Dandagi PM, Samata Jain S, Gadad AP, Kulakarni AR. Time and PH dependent colon specific, pulsatile delivery of theophylline for nocturnal asthma. *International Journal of Pharmaceutics*. 2007;328:49-56.
- Munjeri O, Collett JH, Fell JT. Hydrogel beads based on amidated pectins for colon specific drug delivery: the role of chitosan in modifying drug release", *Journal of Controlled Release*. 1997;46:273-278.
- Nath BS, Venkatesh, Hiremath D. Formulation and evaluation of Sustained Release Dosage form of Theophylline Using combined Hydrophobic and Hydrophilic Matrix. *Ind. J. Pharma. Sci*. 2000;62(1):33.
- Purushothama Rao K and CC Patil. Development of colon specific drug delivery system of Naproxen. *The Indian pharmacist*. March 2005;70-72.
- Ravi V, Pramod Kumar TM, Siddaramaiah. *Indian Journal of Pharmaceutical Sciences*. 2008;70(1):111-113.
- Salunkhe KS, Kulakarni MV. *Journal of Pharmaceutical Research*. 2007;6.
- Sayeh F. Ahrabia, Jyrki Heina Makib, Sverre A. Sandea, Christina Graffnerc. Influence of neutron activation factors on matrix tablets for site specific delivery to the colon. *European Journal of Pharmaceutical Sciences*. 2000;10:225-235.
- Vikas Kumar, Tiwary AK. Investigations on chitosan-carboxymethyl guar gum complexes interpolymer complexes for colon delivery of fluticasone. *International Journal of Drug Delivery*. 2010;2:242-250.