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Formulation, Design and In-vitro Evaluation of Terbutaline Colon Targeted Delivery

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Abstract

Colon targeting drug delivery system was prepared by direct compression to prepare rapid release core formulation. It shows it action directly on colon. The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture. The post-compression parameters of all formulations were determined and the values were found to be satisfactory. From the *in-vitro* dissolution studies of the rapid release core formulations, it was concluded that the formulation F3 i.e. the formulation containing Cross Povidone, MCC and Magnesium stearate is the best formulation. For the above F3 rapid release core formulation press coat was done by using 300mg Xanthum Gum 100mg Guar gum.So Finally based on all Parameters P3F3 was optimized an showed delayed release pattern in a very customized manner. As a result of this study it may be concluded that the colon targeted drug delivery tablets using a combination of two polymers in optimized concentrations can be used to increase the delayed action of drug release to deliver the drug in a delayed manner. The concept of formulating colon specific drug delivery of Terbutaline offers a suitable and practical approach in serving desired objectives of colon specific tablets.

Keywords: Terbutaline, colon targeting delivery, direct compression.

Introduction

Drug candidates for colon drug delivery

Drug delivery selectively to the colon through oral route is becoming increasingly popular for the treatment of large bowel diseases and for systemic absorption of protein and peptide drugs. Inflammatory bowel diseases (IBD) such as ulcerative colitis and crohn's disease require selective local delivery of drugs to the colon. Sulfasalazine is the most commonly prescribed medication for such diseases. The other drugs used in IBD are steroids such as dexamethazone, prednisolone and hydrocortisone. When these steroids are specifically delivered to the colon, they produce fewer and less intense side effects than when administered orally or intravenously [1-3]. Nicotine is currently under investigation for its therapeutic role in the treatment of ulcerative colitis. *Pinaverium bromide* is a drug for the local treatment of irritable syndrome. Advanced ulcerative colitis if not treated may lead to colon cancer. In such cases, anti-cancer drug like 5-fluorouracil, doxorubicin and nimustine are to be delivered specifically to the colon for the effective and safe therapy.

For the treatment of infectious diseases such as amoebiasis (e.g. metronidazole) would be very much useful in reducing the relapse of these diseases and for minimizing the side effects associated with the

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systemic absorption of these drugs [4]. A variety of protein and peptide drugs like calcitonin, interferon, interleukins, erythropoietin, growth hormone and even insulin are being investigated for systemic absorption using colon specific delivery [1,5].

Beside peptides and protein drugs, the colon is also a good site for the absorption of drugs that are not stable in the acidic environment of the stomach cause gastric irritation (e. g. aspirin, iron supplements) or those degraded by small intestine enzymes [6,7]. The different categories of drugs that are available in this form are anti-inflammatory drugs etc. unless these drugs have good absorption characteristic in the colon, their intended use in the management of respective disorders through sustained release or timed release formulations will be questionable. This is due to the fact that most of these formulations are supposed to release their drug load slowly over a period of 12 hours, sometimes, even 24 hours. The total residence time of formulation in the stomach and small intestine will be not more than 5-6 hours. If the drug is not having inherent absorption properties in the colon it will be eliminated in the faeces as it is.

Approaches to colon specific drug delivery

The targeting of orally administered drug to the colon is accomplished.

Coating with pH dependent polymers: In such systems, drugs are formulated into solid dosage forms such as tablets, capsules, and pellets and coated with pH sensitive polymers. Widely used polymers for this purpose are methacrylic resins (Eudragits) which are available in water soluble and water insoluble forms. Eudragit L and S are copolymers of methacrylic acid and methyl methacrylate. Eudragit L is soluble at pH 6 or above and is used as an enteric coating polymer. The coating weight gain was approximately 8%, 2%, and 6% respectively. The disadvantage of this technique is the lack of consistency in the dissolution of the polymer at the desired site.

Timed release dosage forms: Small intestine transit time is relatively constant and is hardly influenced by the nature of the formulation administered. Studies have shown that, once having left the stomach, the formulation arrives at the ileocaecal junction about 3-4 hrs after dosing. This delivery system consists of a capsule, half of which is non-disintegrating and other half enteric coated. After predetermined time (e. g. 5 hrs), The hydrogel plug swells so much that it becomes ejected from the non-disintegrating bottom half of the capsule thereby releasing the drug. It must be noted that the swelling of the hydrogel plug is pH independent. Other reports also appear in the literature on the use of pH dependent timed release system for site specific drug release in the colon [1,3].

Timed-controlled formulations have also been prepared using water insoluble ethyl cellulose and swellable polymer (Hydroxypropyl Cellulose). Each of the formulations consisted of a core, drug, swelling agent and water insoluble membrane. The swelling agent absorbs liquid and ethylcellulose coat disintegrated as the core swells. A lag time of 4±0.5 hrs in relation to absorption was found for this formulation in a human bioavailability study and it was not influenced by food. However, the site-specific of timed release dosage form is considered poor because of large variation in gastric emptying times and passage across the ileo-caecal junction.

Delivery based on the metabolic activity of colonic bacteria: The colonic bacteria carry out a variety of metabolic reaction and hydrolysis. Different strategies were used to target drugs to the colon based on the actions. The main feature of these systems is the site- specificity.

Methodology

Preformulation Studies

Analytical methods for the estimation of Terbutaline

Determination of λ max for Terbutaline

Preparation of standard calibration curve of Terbutaline

Flow Properties

Angle of Repose

Bulk density

Tapped density

Compressibility index and Hausner ratio

Angle of repose

Drug – excipient compatibility study

Formulation of core tablets by direct compression: The inner core tablets were prepared by using direct compression method. As shown in table 1 powder mixtures of Terbutaline, microcrystalline cellulose (MCC, Avicel PH-102), cross-carmellose sodium (Ac-Di-Sol), SSG, crospovidone, mannitol ingredients were dry blended for 20 min. followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 180 mg of resultant powder blend was, punched to obtain the core tablet.

Formulation of mixed blend for barrier layer: The various formulation compositions containing Xanthum gum and Guar gum as shown in table 2. Different compositions were weighed dry blended at about 10 min. and used as

Table 1: Formulation of core tablets (RRCT) of Terbutaline.

Ingredients (%)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug(mg)	50	50	50	50	50	50	50	50	50
MCC	qs	qs	qs	qs	qs	qs	qs	qs	qs
PVP K30	5	5	5	5	5	5	5	5	5
Crospovidone	5	7.5	10	-	-	-	-	-	-
SSG	-	-	-	5	7.5	10	-	-	-
CCS	-	-	-	-	-	-	5	7.5	10
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total weight	180	180	180	180	180	180	180	180	180

Table 2: Polymer ratio for press coated tablets.

Polymers	C1F*	C2F*	C3F*	C4F*	C5F*
Xanthum gum	400mg	200mg	300mg	100mg	0mg
Guargum	0mg	200mg	100mg	300mg	400mg
*optimized core tablet formulation					

press-coating material to prepare press-coated tablets respectively by direct compression method.

Preparation of press-coated tablets:

The core tablets were press-coated with 400 mg of mixed blend/granules. Different proportions of barrier layer material was weighed and transferred into the die then the core tablet was placed manually at the center. The remaining mg of the barrier layer materiel was added into the die and punched in to a 12mm die at a pressure of 5tons for 3min using hydraulic press.

Preparation of enteric coating solution:

Polymer solution was prepared with HPMC phthalate, myvacet and colour in ethanol as solvent as shown in table 3.

Evaluation of Tablets

- Physical Appearance
- Size & Shape
- Weight variation test
- Content Uniformity
- Thickness and diameter
- Hardness
- Friability
- Disintegration test (RRCT)
- In-vitro release studies for RRCTs [6,8,9]

Dissolution parameters for RRCTs

Apparatus	-- USP-II, Paddle Method
Dissolution Medium	-- pH6.8 Phosphate buffer
RPM	-- 50
Sampling intervals (min)	-- 5, 10, 15, 20, 30, 45, 60min.
Temperature	-- 37±0.5°C

Dissolution parameters for enteric press coated tablets [9]

Apparatus	-- USP-II, Paddle Method
Dissolution Medium	-- first 2 hours 0.1 N HCl Next 6.8pH Phosphate buffer
RPM	-- 50
Sampling intervals (hrs)	-- 1, 2, 3, 4, 5, 6, 7 and 8
Temperature	-- 3±0.5°C

Results and Discussion

Standard calibration curve of Terbutaline

Preparation of standard calibration curve of Terbutaline was shown in figure 1. Drug Excipient Compatibility Studies is explained in figures 2,3.

Pre-compression parameters

From the pre-compression parameters discussed in table 4 it was clear evidence that drug and excipients has good flow properties and suitable for direct compression.

Post compression parameters

For all core formulations, post compression parameters are good and core tablet was optimized based on dissolution profile of core tablet as shown in table 5 and 6.

Dissolution studies of core tablet

Dissolution of core tablet based on the drug release pattern with in required time period F3 was optimized and further formulated for press coating as shown in table 7 and figures 4-6.

Dissolution studies of enteric press coat tablets

Dissolution of Enteric Press Coat Tablets From the above core formulations C3F3 was selected for Enteric press coat by using different natural polymers (xanthum and guar gum) in different ratios (1:0, 0:1, 1:1, 3:1, 1:3) among which 3parts of xanthum and 1 part of guar gum was optimized based on the percent of drug release up to 8hr as shown in table 8 and figures 7-9.

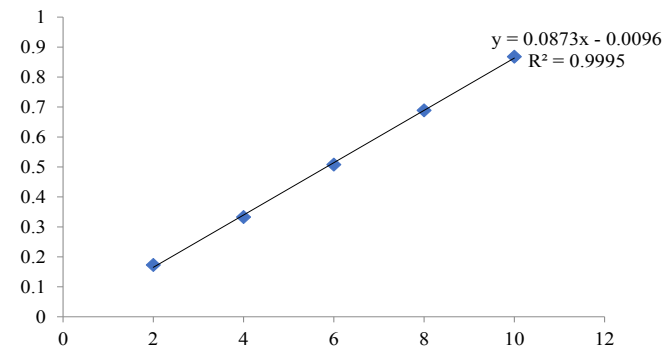

Figure 1: Calibration curve of Terbutaline.

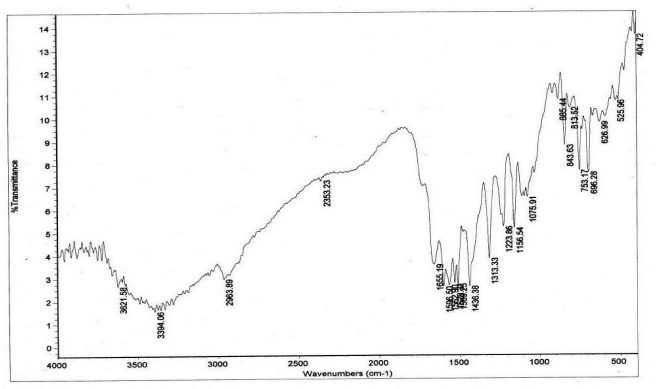

Figure 2: FTIR Spectra of Terbutaline.

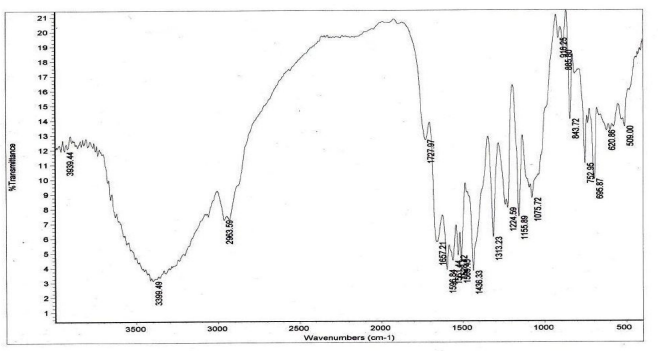

Figure 3: FTIR Spectra of Terbutaline optimized formulation.

Table 3: Formula for enteric coating solution.

Solvents	Weight (mg)
HPMC phthalate 55	17.17mg
Myvacet	1.72mg
Ferric oxide (red)	2.58mg
Ethanol	q.s

Table 4: Pre-compression parameters.

Formulations	B.D(gm/ml)	T.D(gm/ml)	C.I (%)	H.R	Angle of repose (⁰)
F1	0.32	0.37	13.51	1.16	27.36±0.19
F2	0.36	0.44	18.18	1.22	25.49±0.09
F3	0.34	0.39	12.31	1.14	26.03±0.06
F4	0.31	0.35	12.43	1.14	28.10±0.21
F5	0.36	0.41	13.59	1.16	27.05±0.16
F6	0.37	0.43	12.65	1.14	26.19±0.11
F7	0.36	0.42	13.22	1.15	25.49±0.12
F8	0.33	0.37	12.40	1.14	27.18±0.20
F9	0.33	0.39	14.25	1.17	26.19±0.12

Table 5: Characterization of core tablets of Terbutaline.

S. No	Physical parameter	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8	F 9
1	Weight variation	180±1.527	179±1.527	177±1.527	179±3.214	179±1.527	181±1.527	178±1.527	181±3.214	179±2.018
2	Hardness (Kg/cm^2)	4.6±0.1	4.66±0.05	4.26±0.05	4.63±0.05	4.5±0.05	4.66±0.05	4.86±0.05	4.73±0.05	4.9±0.1
3	Thickness (mm)	2.5±0.1	2.56±0.05	2.2±0.1	2.5±0.1	2.43±0.05	2.56±0.05	2.76±0.05	2.66±0.11	2.86±0.05
4	Friability %	0.35	0.34	0.35	0.35	0.35	0.34	0.34	0.35	0.35

Table 6: Evaluation parameters for enteric press coated tablets.

S. No	Physical parameters	C1F3	C2F3	C3F3	C4F3	C5F3
1	Weight variation (%)	605±0.108	606±0.076	609±0.091	610±0.112	606±0.081
2	Hardness (Kg/cm$^{2)}$	7.5±0.04	7.7±0.011	7.6±0.09	7.8±0.04	7.6±0.07
3	Thickness (mm)	4.2±0.012	3.9±0.08	4.0±0.015	3.8±0.013	4.1±0.07
4	Friability (%)	0.49±0.001	0.45±0.004	0.62±0.003	0.74±0.004	0.42±0.005

Table 7: Dissolution profile of core tablet.

Dissolution time (Min)	Core formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	36	34	32	25	27	30	22	24	27
10	42	39	41	36	40	42	37	36	41
15	58	61	66	49	52	50	49	51	48
20	59	64	73	55	59	58	59	62	57
30	78	76	82	68	73	67	67	71	72
45	81	80	90	80	78	74	78	82	78
60	90	89	102	90	91	89	86	92	86

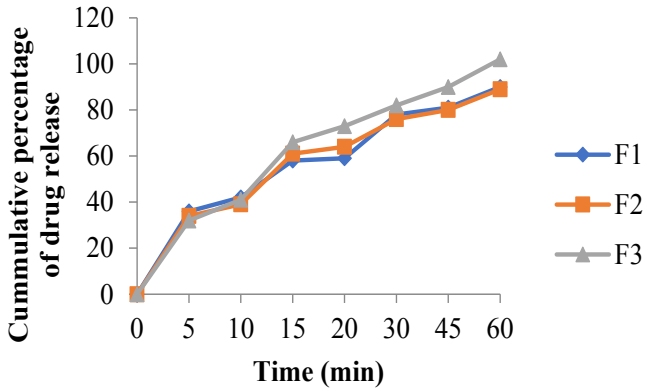

Figure 4: Dissolution graph for formulation F1-F3.

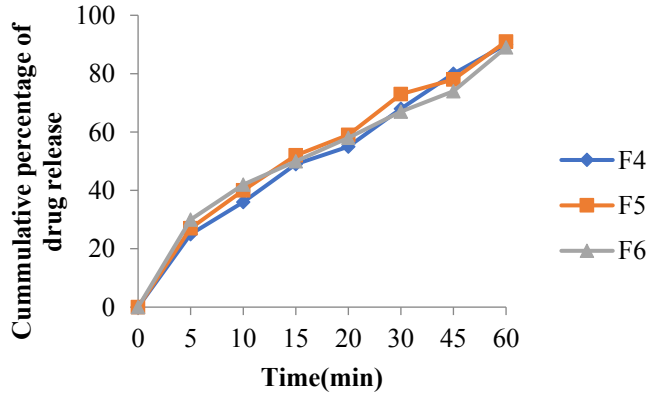

Figure 5: Dissolution graph for Fformulation F4-F6.

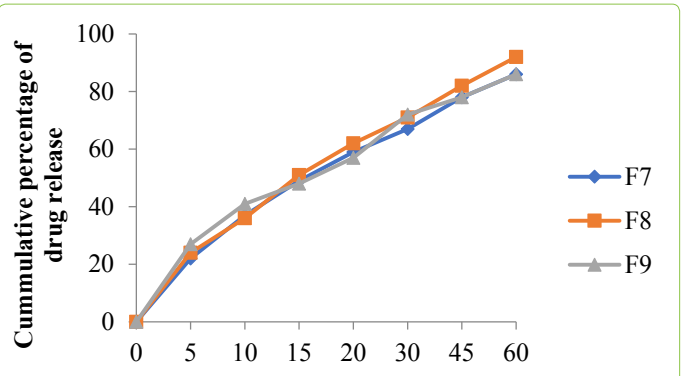

Figure 6: Dissolution graph for formulation F7-F9.

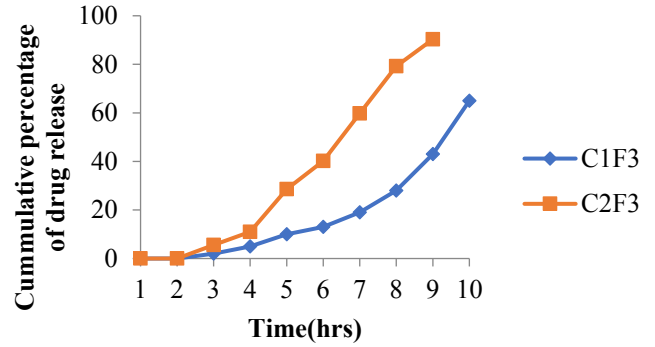

Figure 7: Dissolution Graph for Formulations C1F3 and C2F3.

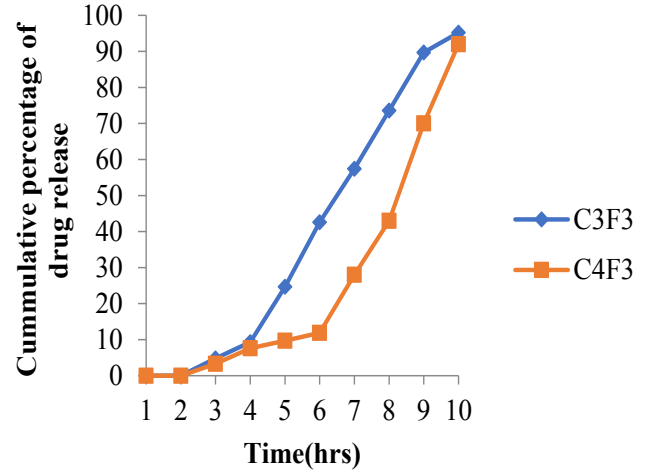

Figure 8: Dissolution graph for formulations C3F3 and C4F3.

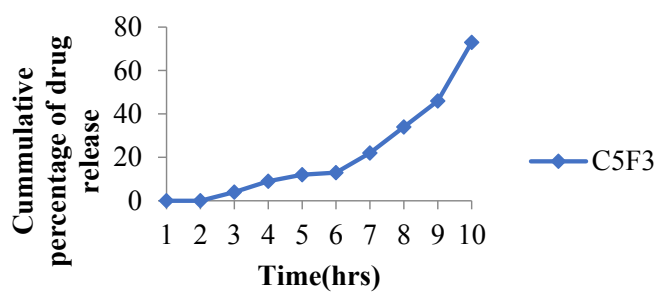

Figure 9: Dissolution graph for formulation C5F3.

Table 8: Dissolution profile of enteric press coated tablets of Terbutaline.

Time in hrs	Press coat Formulation code				
	C1F3	C2F3	C3F3	C4F3	C5F3
pH 0.1NHCl					
1	0	0	0	0	0
2	0	0	0	0	0
Ph6.8 Phosphate Buffer					
3	2	5.6	4.8	3.3	4
4	5	11	9.3	7.6	9
5	10	28.6	24.7	9.7	12
6	13	40.2	42.6	11.9	13
7	19	59.8	57.4	28	22
8	28	79.2	73.6	43	34
9	43	90.3	89.7	70	46
10	65	-	95.2	92	73

Summary and Conclusion

The major problem in oral drug formulations is low and erratic bioavailability, which mainly results from poor aqueous solubility. Colon specific drug delivery thereby targeting site-specific drug release in the colon for local or systemic effects.

All the formulations were prepared by direct compression method. The prepared tablets of all the formulations were evaluated for physical characters, density, hardness and friability, drug content and *in-vitro* drug release. The main aim was to optimize the formulation for 10 hrs in-vitro release with the use of polymers.

Optimized formulation containing Xanthum Gum and Guar Gum polymers in order to delay the release and enteric over this press coat tablet to avoid drug release in stomach region show exactly release of drug at targeted site with longer action.

The following conclusions were drawn from the study:

• Colon targeting drug delivery system was prepared by direct compression to prepare rapid release core formulation. It shows it action directly on colon.

• The pre-compression parameters of all formulations showed good flow properties and these can be used for tablet manufacture.

• The post-compression parameters of all formulations were determined and the values were found to be satisfactory.

• From the in-vitro dissolution studies of the rapid release

core formulations, it was concluded that the formulation F3 i.e. the formulation containing Cross Povidone, MCC and Magnesium stearate is the best formulation.

• For the above F3 rapid release core formulation press coat was done by using 300mg Xanthum Gum, 100mg Guar gum and enteric coat to avoid drug release in stomach.

• So Finally based on all Parameters C3F3 was optimized an showed delayed release pattern in a very customized manner.

As a result of this study it may be concluded that the colon targeted drug delivery tablets using a combination of two polymers in optimized concentrations can be used to increase the delayed action of drug release to deliver the drug in a delayed manner. The concept of formulating colon specific drug delivery of Terbutaline offers a suitable and practical approach in serving desired objectives of colon specific tablets.

References

1. Paharia A, Yadav AK, Rai G, Jain SK, Pancholi SS et al. (2007) Eudragit-coated Chondroitin sulphate Microspheres of 5-Fluorouracil for Colon Targeting. AAPS Pharm Sci Tech 8: 135-146.
2. Sarasija S, Hota A (2000) Colon-specific drug delivery systems. Ind J Pharm Sci 62: 1-8.
3. Vaidya A, Jain A, Khare P Agrawal RK and Jain SK (2009) Metronidazole loaded pectin microspheres for colon targeting. J Pharm Sci 98: 4229-36.
4. Nitesh SC, Roopa K, Firdous BG, Sajal KJ, Uday RS (2009) Studies on Colon Targeted Drug Delivery System for Tinidazole in the Treatment of Amoebiasis. Journal of Pharmacy Research 2: 862-867.
5. Salunkhe KS, Raosaheb SS, Kulkarni MV (2009) Formulation and in-vitro Evaluation of Dextrin Matrix Tablet of Albendazole for Colon Specific Drug Delivery. Journal of Pharmacy Research 2: 429-431.
6. Sunil KJ, Gopal R, Saraf DK, Agrawa GP (2004) The Preparation and Evaluation of Albendazole Microspheres for Colonic Delivery. Pharmaceutical Technology.
7. Vikas J, Ranjit S (2010) Dicyclomine-loaded Eudragit®-based Microsponge with Potential For Colonic Delivery: Preparation And Characterization. Tropical Journal of Pharmaceutical Research 9: 67-72.
8. Mei-Juan Z, Gang C, Hirokazu, Okamoto, Xiu-Hua H, et al. (2005) Colon-Specific Drug Delivery Systems based on Cyclodextrin prodrugs, in vivo Evaluation of 5-Aminosalicylic Acid from its Cyclodextrin Conjugates. World Journal of Gastroenterology 11: 7457-7460.
9. Mohanad NS, Shaymaa AA, Alaa AAR (2006) Design and in vitro Evaluation of Prednisolone Tablets as a Potential Colon Delivery System. Asian Journal of Pharmaceutical and Clinical Research 2: 84-91.

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