Research Article

Formulation and Evaluation of Enteric Coated Tablets of Pantoprazole

Sourav Tribedi[1]*, Mahantesh Ananthapur[1], JS. Sabitha[1], Rinku Mathappan[1] and VV. Prasanth[1]

[1]Faculty of Pharmacy, Department of Pharmaceutics, Gautham College of Pharmacy, Sultanpalya, R.T. Nagar, Bangalore- 560032, Karnataka, India.
[2]Faculty of Pharmacy,, Department of Pharmacognosy, Gautham College of Pharmacy, Sultanpalya, R.T. Nagar, Bangalore- 560032, Karnataka, India.

ABSTRACT

Pantoprazole is a proton pump inhibitor, belongs to group of benzimidazole, Pantoprazole sodium were prepared by direct compression method using different concentration of, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, crosscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. Direct compression is economic compare to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. 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 cellulose acetate phthalate, Eudragit L100 and by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Prepared all batch's C2F9 was found best, with hardness 6.3 ± 0.14 (Kg/cm^2**)**, drug content 98.54 ± 0.12(%), disintegration time 6.02± 0.21(min), and percentage cumulative drug released which started after 120 min and reached 99.72 after 180 min. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40 °C / 75% RH for a period of 3 month.

Keywords: Pantoprazole, Direct compression, Proton pump inhibitor, Cellulose acetate phthalate.

INTRODUCTION

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing[1]. Enteric refers to the small intestine, therefore enteric coatings prevent release of medication before it reaches the small intestine .Most enteric coatings work by presenting a surface that is stable at the highly acidic pH found in the stomach, but breaks down rapidly at a less acidic (relatively more basic) pH[2].

Enteric coated dosage forms, such as coated tablets, sugar-coated tablets, soft and hard gelatin capsules, granulates or pellets, have their firm place in the medical arsenal.The enteric coating of the tablets utilizes the pH differences of gastric pH 1-3 and intestinal pH 6-8. The materials used for enteric coating are acid impermeable polymers[3]. Nowadays, enteric coatings are particularly used to protect active substances destroyed by the acidic gastric juice, improve tolerability of medicaments irritating the stomach by only releasing them in the small intestine, making active substances available after a time delay (sustained release) and achieving targeted release and concentration in the small intestine[4].

Drugs such as pantoprazole which have an irritant effect on the stomach and must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric coated delivery systems are required. Similarly, certain groups of Azoles (Esomeprazole, omeprazole, and all grouped azoles) are acid-unstable . For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH

environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action. The purpose of this study was to prepare and formulae the Entericoated Pantoprazole tablets[2].

Proton pump inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+- ATPase in the gastric parietal cell. This process starts with absorption of the PPI in the parietal cell. PPIs are weak bases, so protonation takes place in the acidic region of the secretory canaliculus of the parietal cell. In the secretory canaliculus, the methylsulfinylgroup shifts to a highly reactive sulfenamide. The final step is covalent binding of the reactive sulfenamide to 2 cysteine moieties of the catalytic subunit of the H+/K+-ATPase of the proton pump. This results in inhibition of the acid secretion, followed by elevation of the intragastric pH. The Bioavailability of pantoprazole is 77%, tmax 2.5 hr, Cmax 2-3 mg/L,Vd 1.5L/kg,CL 7L/h and AUC 4.34 mg*h/L[5].

MATERIALS AND METHODS

MATERIALS

Pantoprazole sodium (Signet Chemical Corporation), Mannitol (Signet Chemical Corporation) Croscarmellose sodium (SD Chemical Corporation), Micro crystalline cellulose (Cipla Pharma, Mumbai, India), Dicalcium phosphate (Fine Chem Industries, India), Magnesium stearate (Spectrochem Pvt. Ltd. Mumbai), Talc (Spectrochem Pvt. Ltd. Mumbai) Eudragit L-100 (Sd fine Chem. Ltd., Mumbai, India), Cellulose acetate phthalate (SD Pharma, Mumbai, India).

METHODS

Preparation of powder blend

Pantoprazole sodium powder blend for tablets were prepared by direct compression method. Required quantity of pantoprazole, croscarmellos sodium, manitol, calcium phosphate, and microcrystalline cellulose were weighed (**Table 1**), transferred in a mortar and pestle and mixed thoroughly. The above prepared powder was passed through sieve no 80 to obtain the granules. Finally,specified quantity of magnesium stearate and talc were added and mixed for the formulation of tablets.

Formulation of pantoprazole sodium tablets

The above mixture of granules were directly punched into tablets (200 mg) containing 40 mg of pantoprazole sodium (**Table 1**), using rotary tablet compression machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India), using 8 mm diameter concave punches. The different batches of pantoprazole sodium tablets were collected and stored in air tight containers.

Table 1: Composition of pantoprazole sodium enteric coated tablets

Compositions	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium (mg)	40	40	40	40	40	40	40	40	40
Croscarmellose sodium (mg)	2	4	6	2	4	6	2	4	6
Microcrystalline cellulose(mg)	27	25	23	27	25	43	34	50	23
Mannitol (mg)	50	75	100	40	85	80	43	50	75
Dicalcium phosphate (mg)	75	50	25	85	40	25	75	50	50
Talc (mg)	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

Coating of compressed pantoprazole sodium tablets

The enteric coating solution was prepared by simple solution method using 6 % w/w and 8% $_{w/w}$ of Eudragit L100 (E1 and E2) or cellulose acetate phthalate (C1 and C2) as an enteric polymer (Table 2). The PEG (1.5% w/w) was used as plasticizer and acetone and isopropyl acetone was used as solvent. This mixture was constantly stirredfor 1h with paddle mechanical stirrer and the stirred coating solution was again filtered through muslin cloth to obtaina coating solution[6,10.]

Table 2: Composition of coating solution

Ingredients	Quantity (%)
Cellulose acetate phthalate / Eudragit L100	6.0 / 8.0
PEG	1.5
Acetone	59.4

Enteric coating of pantoprazole sodium compressed tablets by dipping method

The compressed tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for its weight variation, thickness, uniformity of drug content and *in vitro* dissolution study.[6,10]

Precompression parameters

Bulk density (D_b)

Accurately weighed granules were carefully transferred into graduated measuring cylinder. The granules bed was then made uniform and the volume occupied by the granules was noted as per the graduation marks on the cylinder as mL. It is expressed in gm/mL and is calculated using the following formula[11,12.]

Tapped density (D_t)

It is the ratio of total mass of granule to the tapped volume of granule. The graduated measuring cylinder containing accurately weighed granule was manually tapped for 50 times. Volume occupied by the granule was noted. It is expressed in gram/mL and is calculated by following formula[11,12].

Compressibility index (I) and Hausner's ratio

Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula[11,12].

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Hausner's ratio = D_t / D_b

Where, D_t – Tapped density of the powder

D_b – Bulk density of the powder.

Angle of repose (θ)

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole granules were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula[11,12].

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where, h – Height of the pile in cm

r – Radius of the pile

Post compression parameters

Hardness test and Friability test

The hardness of the prepared tablets were carried out by using hardness tester. . For friability 20 tablets from each batch were weighed separately ($W_{initial}$) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (W_{final}) and the percentage friability (F) was calculated for each batch by using the following formula[13,22.]

$$F = \frac{(W_{initial}) - (W_{final})}{(W_{initial})} \times 100$$

Weight variation test and Drug content

Twenty tablets were selected at randomly from the lot, weighed individually and the average weight was determined using digital balance. For drug content three tablets of each formulation were weighed and finely powdered. About 40 mg equivalent of pantoprazole sodium was accurately weighed and completely dissolved in phosphate buffer (pH 6.8) and the solution was filtered. 1 mL of the filtrate was further diluted to 100 mL with phosphate buffer (pH 6.8) and assayed at 288 nm using UV spectrophotometer[6].

Disintegration time of Pantoprazole sodium core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Servewell Instruments pvt. Ltd., Electrolab ED-2L, India). Phosphate buffer (pH 6.8 was used as the disintegration media at 37 ± 0.5 ºC and the time in second were observed for there completion of disintegration of the tablets.

Physicochemical evaluations of coating films

The same polymer solution was used to prepare the polymeric films and was subjected for

The thickness of the dried films was determined by digital micrometer. The film solubility was studied with phosphate buffer (pH 1.2 and 6.8). The 1×1 cm^2 coating film was selected, weighed and transferred in a beaker containing 20 mL of specified phosphate buffer (pH 1.2 and 6.8) medium, which was mixed in a magnetic stirrer for 1 h at 37 °C and finally film solubility was examined.

***In vitro* drug release studies of pantoprazole sodium core tablets**

USP dissolution apparatus type II (Electrolab TDT-08L,Mumbai,India) was used to determine the *in vitro* release of pantoprazole sodium from the prepared formulations. The dissolution medium was 900 mL of acidic buffer (pH 1.2) for 2 h and phosphate buffer (pH 6.8) for 1 h. The tablet was kept in to the basket at 37 ± 0.5 °C and 100 rpm. Samples (10 mL) were withdrawn at regular time intervals and the dissolution medium was replaced with equal volume fresh dissolution medium. The samples were measured by UV spectrophotometer at 283 nm against a blank[6].

Accelerated stability studies

Accelerated stability studies were performed as per the ICH guidelines. Selected formulations of Pantoprazole sodium tablet were sealed in aluminum foil cover and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3 months and evaluated for physical appearance, hardness and drug content[23].

RESULTS AND DISCUSSION

Precompression parameters

The prepared pantoprazole powder blend were evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index (**Table 3).** The bulk densities of the granules were ranged between 0.286 ± 0.05 and 0.384. ± 0.04 gm/mL and the tapped densities varied from 0.313 ± 0.04 to 0.429 ± 0.05 gm/mL. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility (5.74 ± 0.13 to 10.48 ± 0.20%) signify good flowability. The angle of repose of all formulation was less than 30 º (25.79 ± 0.24 to 29.52 ± 0.14) also indicate the good flowability of the prepared granules.

Table 3: Precompression parameters of pantoprazole sodium blend

Formulation code	Parameters				
	Bulk density (gm/mL) *	Tapped density (gm/mL) *	Carr's Index (%)*	Hausner's ratio*	Angle of repose (Θ)*
F1	0.357±0.03	0.384±0.05	7.03±0.09	1.075±0.04	28.31±0.26
F2	0.312±0.04	0.335±0.02	6.86±0.15	1.073±0.05	27.20±0.14
F3	0.306±0.03	0.326±0.03	6.13±0.12	1.065±0.02	29.13±0.34
F4	0.312±0.03	0.334±0.06	6.58±0.14	1.070±0.06	26.13±0.26
F5	0.306±0.03	0.334±0.05	8.38±0.17	1.091±0.08	26.78±0.18
F6	0.384±0.04	0.429±0.05	10.48±0.20	1.117±0.07	25.79±0.24
F7	0.358±0.05	0.385±0.04	7.01±0.13	1.075±0.03	29.52±0.14
F8	0.286±0.05	0.313±0.04	8.62±0.07	1.094±0.03	26.95 ±0.15
F9	0.348±0.08	0.328±0.05	5.74±0.13	1.06±0.08	26.13±0.26

*Mean ± SD n=3

Post compression parameters of pantoprazole sodium core tablet

The pantoprazole core tablets were prepared by direct compression method and were evaluated for their hardness, weight variation, content uniformity, friability and *in vitro* drug release **(Table 4).** The hardness of the core tablets varied from 4.93 ± 0.15 and 6.20 ± 0.35 Kg / cm^2. Hardness has to be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbling and not so hard that the disintegration time is unduly prolonged. The friability of the prepared tablets was found less than 1% w/w which is indicated that friability was within the range. and this might also affected by the hardness of the tablets. . The drug content of pantoprazole sodium present in tablets

formulation ranged from 96.28 ± 0.15 and 100.34 ± 0.13%. The mass uniformity was found between 198 ± 0.15 and 208 ± 0.20 mg and disintegration time varied between 5.38 ± 0.23 and 11.48 ± 0.15 and all shows favorable results. From the above all nine formulations, F3 and F9 were selected as best formulation depends upon drug content and disintegration time and coated with 6% and 8% with CAP and Eudragit L 100 and renamed as C1F3, C2F3, E1F3,E2F3, C1F9, C2F9, E1F9,E2F9.

Table 4: Post compression parameters of pantoprazole sodium core tablets

Formulation code	Parameters				
	Hardness (Kg/cm^2)*	Friability (%)**	Weight variation (mg) **	Drug content (%)*	Disintegration time(min) *
F1	5.80 ± 0.12	0.69 ± 0.015	199 ± 0.12	96.28 ± 0.15	10.6± 0.62
F2	5.56 ± 0.24	0.51 ± 0.017	206 ± 0.24	97.62 ± 0.27	8.26± 0.56
F3	5.83 ± 0.08	0.48 ± 0.014	201 ± 0.17	99.51 ± 0.36	5.38± 0.23
F4	4.93 ± 0.15	0.64 ± 0.015	208 ± 0.20	98.17 ± 0.16	11.48± 0.15
F5	5.73 ± 0.25	0.71 ± 0.016	203 ± 0.16	98.92 ± 0.42	9.32± 0.18
F6	5.12 ± 0.34	0.68 ± 0.026	206 ± 0.14	100.34 ± 0.13	6.13± 0.25
F7	5.66 ± 0.17	0.54 ± 0.026	199 ± 0.22	98.50 ± 0.48	10.54± 0.43
F8	6.20 ± 0.35	0.49 ± 0.025	204 ± 0.18	98.41 ± 0.34	9.12± 0.71
F9	5.60 ± 0.24	0.42 ± 0.018	198 ± 0.15	99.08 ± 0.35	6.02± 0.21

***** Mean ± SD, n=3, ****** 20

Physicochemical evaluation of coating films

Physicochemical evaluation of cellulose acetate phthalate, Eudragit L100 and were studied for different parameters such as film thickness, and film solubility. The thickness of the films varied between 0.21 ± 0.07 and 0.24 ± 0.08. The enteric polymer cellulose acetate phthalate, Eudragit L100 were found to be completely soluble in phosphate buffer (pH 6.8) and insoluble in phosphate buffer (pH 1.2) (Table 4).

Table 4: Physicochemical evaluation of different polymer coating films

Polymers	Parameters		
	Film solubility		Film thickness (mm) *
	Phosphate buffer (pH 1.2)	Phosphate buffer (pH 6.8)	
Cellulose acetate phthalate	Insoluble	Soluble	0.21 ± 0.07
Eudragit L 100	Insoluble	Soluble	0.24 ± 0.08

*****Mean±SD, *n* = 3

Physicochemical evaluation of pantoprazole sodium enteric coated tablets

The enteric coated tablets of pantoprazole sodium showed almost favorable results in disintegration and drug content (F3 and F9) coated by dip coating method. The weight variation of the formulations (F3 and F9) ranged from 0.210 ± 0.24to 215 ± 0.15 mg and the drug content varied between 93.47 ± 0.23 to 98.45 ± 0.12 %. The hardness was of the selected formulations lies between 5.2 ± 0.11 and 6.5 ± 0.15 Kg/cm2 (Table 5).

Table 5: Physicochemical evaluation parameters of enteric coated tablets

Polymer	Batch Code	Parameter		
		Weight Variation (mg) *	Hardness Kg/cm^2*	Drug content (%)*
Cellulose acetate phthalate	C1F3	217 ± 0.35	6.5 ± 0.15	96.75 ± 0.14
	C2F3	219 ± 0.16	5.9 ± 0.24	93.65 ± 0.35

	C1F9	218 ± 0.06	5.4 ± 0.09	94.45 ± 0.26
	C2F9	219 ± 0.24	6.3 ± 0.14	98.54 ± 0.12
Eudragit L 100	**E1F3**	218 ± 0.21	5.5 ± 0.16	93.47 ± 0.23
	E2F3	216 ± 0.12	6.0 ± 0.06	94.56 ± 0.14
	E1F9	219 ± 0.15	6.5 ± 0.31	98.27 ± 0.45
	E2F9	216 ± 0.24	5.7 ± 0.20	96.35 ± 0.12

*Mean±SD, *n* = 3

***In vitro* drug release of pantoprazole sodium of enteric coated tablets**

The in vitro drug release of pantoprazole sodium core tablets is shown in **Figure 1(a) and (b).**The formulation C2F9 showed most satisfactory results, where drug released after 2 hrs, and maximum release was 99.72% after 3 hrs. The formulation CIF3 started release at 90 min and showed maximum of 96.42% release after 3 hrs, C2F3 started release after 2 hrs and showed maximum release (94.59%) after 3 h, E1F3 started release at 90 min and showed maximum release (98.15%) after 2 h and 45 min, E2F3 started release at 105 min and showed maximum release (97.54%) after 3 h, C1F9 started release at 90 min and showed maximum release (99.79%) after 2 h 45 min, EIF9 started release at 90 min and showed maximum release (97.97%) after 2 h 45 min and E2F9 started release at 2 hrs and showed maximum release (97.39%) after 3 hrs.

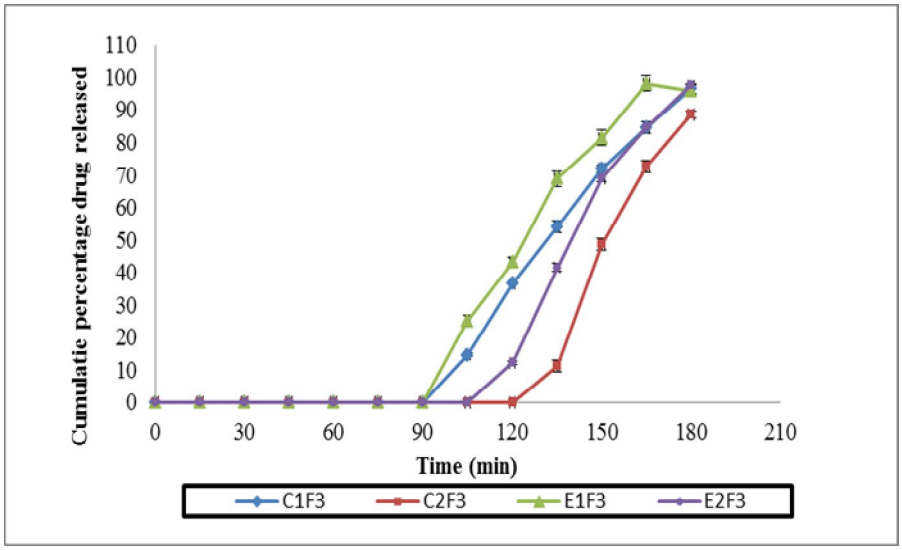

Fig. 1(a): *In vitro* drug release of enteric coated pantoprazole sodium tablets

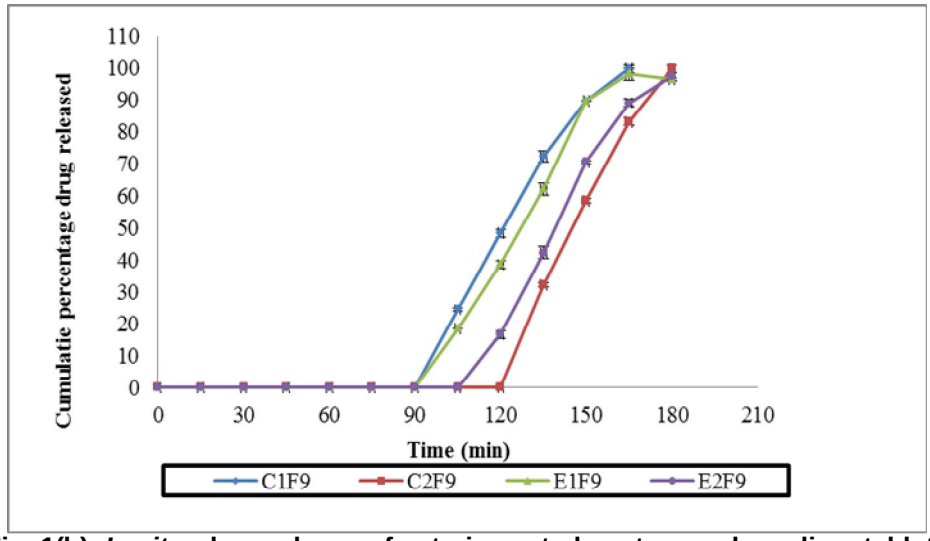

Fig. 1(b)*: In vitro* drug release of enteric coated pantoprazole sodium tablets

Accelerated stability studies

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odor, taste or texture of the formulation indicate the drug instability. Among all the enteric coated formulations, C2F9 was selected for stability studies based on the physicochemical characterization of coating films and release characteristics. The stability studies were carried out at 40 ± 2 °C with 75 ± 5%% RH which shown in **Table 6**. There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the samples analyzed after 1,2,3 month of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of 3 month.

Table 6: Accelerated stability studies of selected formulation C2F9

Evaluation parameters	Observation in month			
	Initial	1st month	2nd month	3rd month
Physical Appearance	white color tablets	No change	No change	No change
Hardness (Kg / cm^2) *	6.3 ± 0.14	6.2 ± 0.56	6.2 ± 0.64	6.2 ± 0.26
Drug Content (%)*	98.54 ± 0.12	98.36 ± 0.52	98.16 ± 0.36	98.07 ± 0.28

*Mean ± SD, n=3

CONCLUSION

Pantoprazole sodium were prepared by direct compression method using different concentration of, MCC as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. The *in vitro* dissolution studies were carried out for compressed and coated tablets using USP dissolution apparatus type II. The cumulative percentage of drug release from the tablets varied and depends on the type of polymer used and its concentration. In this present research work, both the polymer have been used as an enteric coating polymer, with the best formulation. CAP and EudragitL100 have been used 6% and 8% with the best formulation. From the dissolution studies it was observed that, the enteric coated both polymer was intact for 2 hours in pH 1.2 buffer. The formulation which is said to the best formulation is C2F9, which is formulation no. 9 and coated with 8% CAP.

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