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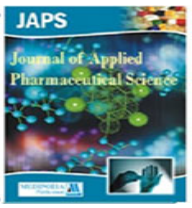

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Enteric coated tablets of novel proton pump inhibitor with super disintegrants design, *in-vitro* evaluation and stability studies

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ABSTRACT

The current work evaluate directly compressible esomeprazole magnesium trihydrate enteric coated tablets were prepared to deliver drug in upper GIT. Different tablets were prepared with super disintegrants like Ac-Di-Sol, Crospovidone, sodium starch glycolate and diluents like Pharmatose DCL11, Mannogem EZ. Tablets were enteric coated using Acryl-EZE. The tablets were evaluated for hardness, disintegration time and *in vitro* drug release. The powder bed showed good rheological properties and enteric coated tablets showed acid uptake value <5 indicates significant protection of acid liable drug. The compressional parameters were within the limits, the drug content in all formulations was found to be uniform and consistent. *In vitro* dissolution studies indicated there is no drug loss during gastric phase. The tablets with Pharmatose DCL11 released higher than Mannogem EZ which colud be due to its hydrophilicity and due to swelling of the super disintegrant. Stability studies indicated that the prepared formulations were stable for a period of four months of all formulations showed comparable dissolution profiles with similarity factor more than fifty at $p<0.05$. From the above findings it can conclude that an Esomeprazole magnesium trihydrate enteric coated tablet could be developed to deliver the drug in to proximal small intestine.

Key words: Esomeprazole, Super disintegrants, Direct compression, Stability studies

INTRODUCTION

Dosage form design of acid liable drugs is a challenge in pharmaceutical research for development of site-specific dosage forms that release active ingredients in the upper part of the small intestine, or in the duodenum through enteric coating to treat duodenal ulcer disease. Duodenal ulcers are a common condition characterized by the presence of a well-demarcated break in the mucosa that may extend into the muscularis propria of the duodenum. More than 95% of duodenal ulcers are found in the first part of the duodenum; most are less than 1 cm in diameter. (Ramakrishnan K et al., 2007). A duodenal ulcer forms when there is an imbalance between aggressive factors, i.e. the digestive power of acid and pepsin and defensive factors, i.e. the ability of the gastric and duodenal mucosa to resist this power. This mucosal resistance constitutes the gastric mucosal barrier. Any process that increases gastric acidity, decreased prostaglandin production due to NSAIDs or by interferes with the mucous layer like *H pylori* infection can cause such an imbalance and lead to peptic ulcer disease (www.mayoclinic.com., 2010, Mallikarjuna Gouda M et al., 2010). Proton pump inhibitors (PPIs) are the most potent inhibitors of gastric acid secretion and are effective for treating all gastric acid-related disorders. Esomeprazole magnesium trihydrate, the S- isomer of omeprazole, inhibits the gastric parietal H^+/K ATPase irreversibly

which involved in hydrochloric acid production in the stomach. It acts as proton pump inhibitor, used to treat gastroesophageal reflux disease (GERD), erosive esophagitis and gastric ulcer (Mucklow , 2002, Putta Rajesh Kumar et al., 2010).

Esomeprazole is a substituted benzimidazole, used for the treatment of NSAIDs-associated gastric ulcer, Helicobacter pylori eradication and control of pathological hypersecretory conditions (Vachhani R., 2009). The stability of esomeprazole magnesium is a function of pH, it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25° C and about 8 hours at 37° C (www.rxlist.com ., 2010). Esomeprazole has a half life of 1.25 ± 0.25 h and has a bioavailability of 48% (www.rxlist.com, 2008, www.dailymed.nlm.nih.gov, 2008). Esomeprazole is combined with antibiotics clarithromycin and amoxicillin or metronidazole in 7-14 days eradication triple therapy of *Helicobacter pylori* infection where majority of peptic and duodenal ulcers were caused by *H. pylori* (www.en.wikipedia.org., 2010, Putta Rajesh Kumar et al., 2011).

The super disintegrants which swell to many times their original size when placed in water with minimal viscosity effects were used for aiding fast disintegration of tablet through swelling, wicking and deformation processes. In the present study Sodium Starch Glycolate (Primogel) which is a chemically treated modified Sodium Carboxymethyl Starch shows its mechanism of action by rapid and extensive swelling with minimal gelling is used. crospovidone (Polyplasdone XL) a water insoluble and strongly hydrophilic Cross-linked polyvinyl pyrrolidone acts by water wicking, swelling and possibly some deformation recovery was also studied. The Modified Cellulose Internally cross-linked form of Sodium carboxymethyl cellulose (Ac-Di-Sol) acts through Wicking due to fibrous structure, swelling with minimal gelling was investigated.

Site-specific, drug delivery of a therapeutic agent to the intestinal region can be readily accomplished by the application of an enteric coating on a solid dosage form (Porter S.C et al., 1995). Enteric coatings are designed to remain intact in the stomach and release the contents of the underlying core in the intestines. (Davis. et al., 1986).

In the present investigation directly compressed tablets of Esomeprazole magnesium trihydrate tablets were developed with various superdisintegrants, directly compressible vehicles like Polyplasdone XL, Mannogem EZ. Preliminary formulation development studies were conducted with varying concentrations of different superdisintegrants followed by rheological evaluation of powder blends. Further these are compressed in to tablets, optimized tablet formulations were enteric coated with Acryl EZE to protect the drug from harsh gastric conditions, to deliver drug in the duodenum which helps in improved bioavailability of Esomeprazole. Further various compression characteristics of the prepared tablets were studied. The acryl EZE enteric coated tablets were subjected for *in vitro* dissolution studies and stability studies for 4 months to study the influence of temperature on drug content and drug release profile.

MATERIAL AND METHODS

Active pharmaceutical ingredient, Polymers and Reagents

Esomeprazole magnesium trihydrate was procured from Aurobindo pharma limited, A.P, India). Crospovidone, Sodium starch glycolate, Croscarmellose sodium obtained from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Lactose DC(Polyplasdone XL) and Mannitol DC (Mannogem EZ) were procured from SD Fine Chemicals Limited, Mumbai. Acryl EZE (Eudragit L 30 D55, Colorcon) was supplied by Medreich Limited, Bangalore. Other polymers, solvents and chemicals used in the research were of LR grade.

Method of preparation of esomeprazole enteric coated tablets by direct compression

The esomeprazole tablets were prepared by direct compression technology. Ingredients containing super disintegrants of various core formulas were accurately weighed, milled and passed through sieve # 100/ 120 and then thoroughly blended. The powder blended was studied for rheological characteristics like Angle of repose (°θ), Bulk density, Tapped density and Compressibility index. (www.pharmacopeia.cn., 2010). Later the uniformly blended powder containing esomeprazole magnesium trihydrate and directly compressible vehicles of various core formulations from Core 1 to Core 6 were compressed into tablets on a 10 station tablet punching machine (PP1D, Chamunda) using 6 mm flat punches at a pressure of 3-6 kg/cm^2. In each batch 500 core tablets were prepared. To protect esomeprazole from gastric acid and to deliver in duodenum the core tablets were film coated with an enteric coating polymer, Acryl EZE. (Anroop B Nair et al., 2010).

Enteric Coating of esomeprazole magnesim trihydrate core tablet formulations with Acryl EZE

The core tablets were film coated with an enteric coating polymer, Acryl EZE. First, seal coat was prepared by dissolving HPMC (6 cps) and PEG 8000 in purified water with continuous stirring. Then slowly methylene chloride was added and the solution was filtered by passing through # 200 mesh. 25 % w/w of acryl EZE (Eudragit L 30 D55, Colorcon) was prepared by dispersing acryl EZE in a beaker containing purified water and stirred slowly for 20 minutes and passed through # 200 mesh. The tablets were enteric coated in a Neocoata coating pan (Neo Machine Manufacturing Company Pvt. Ltd, Kolkata) so as to build up 8 to 10 % weight. Inlet bed temperature was adjusted to 52 º± 1 ºC and the solution was atomized at 1.5 psi/bar. The pan was rotated at a speed of 22 rpm and the total coating time was 90 min.

Compressional parameters of Esomeprazole magnesium tablets

The tablets were studied for their weight variation, Diameter test, Tablet thickness, Determination of drug content (Mina Ibrahim Tadros., 2010, Putta Rajesh Kumar et al., 2011), Hardness test (Yagnesh Bhatt et al., 2009). Friability test (Singh et al., 2009), Density measurement (Streubel et al., 2003),

Disintegration test and Acid uptake testing. (Indian pharmacopoeia., 2007, Charles et al., 2001).

***In vitro* dissolution studies of esomeprazole magnesium trihydrate core tablets (Ramkanth et al., 2010)**

The release of esomeprazole magnesium from enteric coated tablets was determined by using dissolution rate test apparatus (Six Station Electrolab, India). The dissolution test was performed using 900 ml of 0.1 N HCl for 2 h. The medium was stirred at 75 rpm at a temperature of 37 ± 0.5ºC. Samples of 1 ml were withdrawn periodically up to eight hours and the volume was replaced with fresh medium to maintain the sink conditions. The samples were suitably diluted and the absorbances were measured at 203.5 nm for esomeprazole using U.V. 1700 (Pharmaspec Shimadzu. Japan). All studies were carried out in triplicate and the average was considered (n = 3).

Determination of drug content

Tablet of esomeprazole was crushed into powder in a mortar and 100 mg of powder was taken in a volumetric flask containing distilled water and kept aside with constant shaking for 24 hours to extract the total drug present in the tablet. Then the absorbance of the solutions was measured after suitable dilution at 203.5 nm against methanol as blank.

Stability studies (Vidal et al., 2010, Matthews., 1999)

The stability experiments were conducted to investigate the influence of temperature and relative humidity on the drug content and *in vitro* dissolution profile of various core tablets. The tablet formulations were exposed to a temperature of 40 ± 2^0C and also a relative humidity of 75±5 % RH. The samples were removed from the oven at the end of 0, 3, 5, 15, 45, 60, 90 and 120 days and analyzed for drug content. Similarly tablets at the end of 0, 15, 45, 90 and 120 days for each formulation were subjected to *in vitro* dissolution studies in dissolution apparatus. Average of triplicate readings was taken. The observations were tabulated. The dissolution profiles were compared with dissolution profile performed on tablets kept at ambient conditions.

RESULT AND DISCUSSION

Various super disintegrants to disintegrate the tablet in < 2 min, were used and the weight percent of the super disintegrants was optimized at 7.5 % and also two different directly compressible vehicles were used as diluents. Talc and magnesium stearate was included to assist in free flowing of powder blend and smooth ejection of compressed tablet, at 2 %w/w and the tablets were prepared by direct compression technology.

The esomeprazole core tablets were developed using various super disintegrants with directly compressible vehicles by direct compression technique. The powder bed was studied for various rheological parameters and compressed tablets were subjected for compression parameters studies. Later these tablets were enteric coated with methacrylic polymer Acryl EZE for protecting acid liable esomeprazole from gastric acid. Then these coated tablets were subjected for acid uptake studies showed acid uptake values in the range of 3.83 to 4.07 which are less than 5 indicating significant protection of esomeprazole drug by acryl EZE enteric coating in stomach. The results were presented in our previously published article. (Putta Rajesh Kumar et al., 2011). In the present study the developed core formulations were studied for *in vitro* release profile after investigating the pre, post compressional parameters and acid uptake studies.

Esomeprazole magnesium trihydrate C_{20} from C1 to C6 was 21.0 to 102.4 min, with slope ranges from 0.0352 to 0.1054 and showed regression values (r^2) of 0.9049 to 0.9848 (Table 1).

Table 1. Drug release kinetics of enteric tablet formulations of Esomeprazole magnesium Trihydrate.

Formulation	C_{20} (min)	Slope(m)	Regression (r)
C1	59.0	0.0656	0.9323
C2	48.0	0.0406	0.9148
C3	21.0	0.0352	0.9049
C4	100.8	0.0563	0.9848
C5	102.4	0.0774	0.9820
C6	60.9	0.1054	0.9665

In vitro dissolution study showed esomeprazole from C1 core released 20% of drug in 59 min and 18.527 mg (92.63%) in 600 min from 19.79 mg dose. The release followed first order kinetics with slope value 0.0656 and correlation coefficient (r) of 0.9323. *In vitro* dissolution study of esomeprazole from C2 core released 20% of drug in 48 min and 18.762 mg (93.18%) in 600 min from 19.84 mg dose. The release followed first order kinetics with slope value 0.0406 and correlation coefficient (r) of 0.9148. Where esomeprazole from C3 core released 20% of drug in 21 min and 19.550 mg (98.59%) in 600 min from 19.86 mg dose. The release followed first order kinetics with slope value 0.0352 and correlation coefficient (r) of 0.9049. Where esomeprazole from C4 core released 20% of drug in 100 min and 18.024 mg (90.11%) in 600 min from 19.73 mg dose. The release followed zero order kinetics with slope value 0.0563 and correlation coefficient (r) of 0.9848. The *In vitro* dissolution study of C5 core released 20% of drug in 102 min and 18.318 mg (91.58%) in 600 min from 19.94 mg dose. The release followed zero order kinetics with slope value 0.0774 and correlation coefficient (r) of 0.9820. Where esomeprazole from C6 core released 20% of drug in 60.9 min and 19.016 mg (95.07%) in 600 min from 19.74 mg dose. The release followed zero order kinetics with slope value 0.1054 and correlation coefficient (r) of 0.9665 (Figure 1).

The lactose DC containing core tablets showed lag time of 03 min and Mannitol DC containing core tablets showed lag time of 15 min to release esomeprazole in pH 9.0 this is due to time taken for rupturing and solubilization of Acryl EZE enteric coating over core tablets which is also observed during *in vitro* dissolution studies of tablets. The results of disintegration time (sec) of enteric coated tablets showed that the tablets did not disintegrate in 0.1N HCl and the same when continued with phosphate buffer of pH 7.4 the tablets were found to disintegrated within 78.33 to 94.16 sec

which helps the dosage form to disintegrate in < 2 min for immediate drug release and absorption from the upper part of the GIT. The drug content studies of Core tablets in methanol and phosphate buffer showed that almost 98.01% to 99.68 % of Esomeprazole magnesium trihydrate was present which indicates the drug content uniformity in all the formulations before and after stability studies (Table 2).

Table 2. Drug content estimation studies of esomeprazole from enteric coated tablets during Stability studies at 40±0.5^{0}C/75±1%RH.

Day	Percentage drug content (% DC)					
	C1	C2	C3	C4	C5	C6
0	98.82	99.68	99.14	96.88	97.96	97.37
3	98.49	99.73	99.03	96.83	98.01	97.42
5	98.39	99.52	98.82	96.61	97.85	97.26
15	97.96	99.25	98.76	96.45	97.69	97.10
30	97.31	98.87	98.49	96.29	97.47	97.04
45	96.83	98.60	97.15	96.18	97.20	96.77
60	96.29	96.24	96.29	95.81	96.99	96.34
90	95.81	95.86	96.02	95.43	96.34	96.02
120	95.48	95.65	95.59	90.43	96.08	95.81

These tablet formulations were subjected to stability studies conducted according to ICH protocol at 40±2^{0}C/75±5% RH.

The effect of constraints for period of 120 days has been obtained and is presented in tables 03 to 05. It was found that there is 03% deviation in % DC (Figure 2) and 04 % deviation in % release of drug (Figure 3). It was found that the dissolution profiles were comparable and there was no significant difference observed between the means of dissolution profile conducted without stress and with stress at $p<0.05$ with reference to their similarity factor of dissolution profiles up to 120 days.

CONCLUSION

The literature was reviewed from various journals and the recent research articles were updated from various sources on enteric coated tablets, tablet formulation method, various polymers for formulation and development of tablets and also for *in vitro* dissolution method. The tablets did not disintegrate in 0.1 N HCl however; they disintegrated within 94.16 sec when the study was continued in phosphate buffer pH 7.4. The drug content in all core formulations was found to be uniform and consistent. Accuracy and precision studies of esomeprazole in core tablet formulations indicated the accurate and precise drug content uniformity of esomeprazole in tablet core formulations.

Table 3. *In vitro* dissolution studies of esomeprazole from enteric coated tablets C1 and C2 during Stability studies at 40±0.5^{0}C/75±1%RH.

Time min	Percentage drug release (% DR)									
	Day 0		Day 15		Day 45		Day 90		Day120	
	C1	C2	C1	C2	C1	C2	C1	C2	C1	C2
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.05	0.23	0.00	0.07	0.00	0.00	0.00	0.06	0.00	0.00
10	0.27	3.15	0.09	2.73	0.21	2.71	0.00	2.45	0.05	2.68
15	0.68	7.97	0.63	7.01	1.83	7.05	0.39	6.82	0.49	6.94
30	3.45	13.84	3.32	12.48	3.97	12.48	2.80	12.23	2.90	12.28
45	9.36	22.48	8.79	20.63	9.01	20.61	7.97	20.17	7.63	19.88
60	22.82	32.80	21.87	30.38	20.64	30.35	20.21	29.85	20.17	29.12
90	37.21	46.14	35.77	43.50	34.15	43.07	33.74	41.82	33.57	41.73
120	50.17	56.53	48.65	53.19	46.09	53.17	46.26	50.98	47.35	51.62
180	64.82	69.61	63.10	65.50	60.16	65.96	60.32	63.62	60.79	64.37
240	74.21	81.88	71.54	81.12	68.32	78.55	68.14	76.79	68.93	77.77
300	82.91	91.06	79.71	89.84	77.06	88.12	76.91	88.46	77.80	86.12
360	87.17	93.53	84.36	92.21	82.50	90.42	82.46	90.13	83.03	88.84
420	90.67	93.65	88.25	92.26	87.48	90.49	87.32	90.25	86.70	88.96
480	92.53	93.71	90.62	92.30	89.93	90.54	89.79	90.31	88.74	89.02
540	92.61	93.78	90.70	92.35	90.04	90.59	89.86	90.38	88.81	89.10
600	92.64	93.81	90.72	92.38	90.09	90.62	89.89	90.41	88.84	89.13

Table 4. *In vitro* dissolution studies of esomeprazole from enteric coated tablets C3 and C4 during Stability studies at 40±0.5^{0}C/75±1%RH.

Time (min)	Percentage drug release (% DR)									
	Day 0		Day 15		Day 45		Day 90		Day120	
	C3	C4	C3	C4	C3	C4	C3	C4	C3	C4
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	3.37	0.00	2.72	0.00	2.66	0.00	2.39	0.00	2.40	0.00
10	7.42	0.00	6.43	0.00	6.05	0.00	5.10	0.00	5.76	0.00
15	11.90	0.00	10.44	0.00	9.96	0.00	8.86	0.00	9.85	0.00
30	21.97	0.15	19.50	0.12	18.70	0.07	18.41	0.05	18.81	0.18
45	28.29	2.03	25.34	1.73	24.34	2.23	24.06	1.58	24.22	1.98
60	37.76	8.54	34.57	7.28	33.09	9.24	34.16	7.41	32.90	7.40
90	52.57	14.57	49.12	14.02	47.59	14.67	48.53	12.86	47.26	12.56
120	64.41	23.27	60.84	21.96	59.67	22.90	61.99	21.09	60.69	20.87
180	76.92	33.09	73.87	32.16	72.66	31.85	74.70	30.54	71.86	30.09
240	85.62	44.89	83.20	43.30	81.94	45.03	83.60	43.38	81.76	41.07
300	97.86	53.53	97.14	52.24	95.38	53.20	94.98	53.62	94.76	50.62
360	98.21	66.66	97.57	64.82	95.74	65.65	95.33	64.99	94.94	62.01
420	98.38	72.20	97.74	69.98	95.90	71.10	95.45	70.44	95.03	69.05
480	98.48	77.98	97.80	75.31	96.01	77.90	95.51	75.59	95.08	74.53
540	98.55	85.00	97.86	82.96	96.08	83.74	95.57	83.20	95.13	81.27
600	98.59	90.12	97.89	89.67	96.12	89.23	95.60	88.85	95.16	86.02

The acid uptake studies of enteric coated esomeprazole magnesium trihydrate tablets with Acryl EZE showed less than 5% acid uptake for all tablets indicates that the drug could be protected from degradation in gastric environment and successfully delivered to upper part of small intestine. Stability studies were conducted according to ICH guidelines region IV at 40±2^{0}C / 75±5 % RH indicates that there slight decrease in drug content and no significant difference between the means of *in vitro* dissolution profiles without stress and with stress for a period of 4 months at P<0.005 compared by similarity factor analysis. The tablets were found to be stable with respect to drug content, against the influence of temperature and humidity during the stability study period. Therefore it could conclude that esomeprazole enteric coated tablets can be formulated to deliver the acid liable drug with absorption window in proximal intestine for suppression of excess gastric acid for the treatment of peptic and duodenal ulcers.

Table 5. *In vitro* dissolution studies of esomeprazole from enteric coated tablets C5 and C6 during Stability studies at 40±0.5^{0}C/75±1%RH.

Time (min)	Percentage drug release (% DR)									
	Day 0		Day 15		Day 45		Day 90		Day120	
	C5	C6	C5	C6	C5	C6	C5	C6	C5	C6
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
10	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
15	0.00	0.00	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00
30	0.97	1.80	0.82	1.52	0.58	1.17	0.67	1.58	0.97	1.33
45	3.82	5.98	3.50	5.29	3.29	4.92	3.29	4.95	3.82	5.07
60	9.02	15.72	8.28	14.16	8.19	14.22	7.88	14.17	9.02	13.94
90	15.22	29.42	14.74	27.32	13.78	27.58	13.56	28.32	15.22	27.05
120	26.00	39.24	24.80	36.53	24.43	36.94	24.14	36.75	26.00	37.19
180	40.79	52.52	38.22	49.26	38.84	50.04	38.24	49.29	40.79	49.54
240	48.51	60.63	48.24	59.09	46.14	59.37	46.38	57.14	46.34	58.78
300	56.63	67.93	55.19	66.93	55.17	67.13	55.25	63.64	54.46	66.81
360	70.08	75.59	68.29	73.61	67.90	75.36	68.87	71.86	67.91	73.28
420	76.47	81.77	74.00	80.62	73.56	81.28	75.17	79.15	74.29	79.02
480	82.41	86.55	81.94	86.48	79.86	85.95	80.59	84.23	80.23	84.15
540	89.62	93.93	88.89	94.43	88.09	93.41	87.64	91.83	87.44	91.12
600	91.59	95.08	90.94	95.30	18.00	94.46	89.71	93.20	89.41	92.12

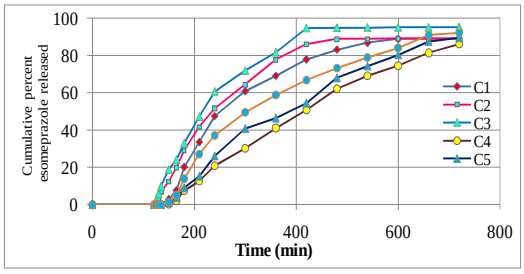

Fig 1. Cumulative percent release of Esomeprazole magnesium trihydrate from enteric coated formulation containing superdisintegrants, Pharmatose DCL11 and Mannogem EZ.

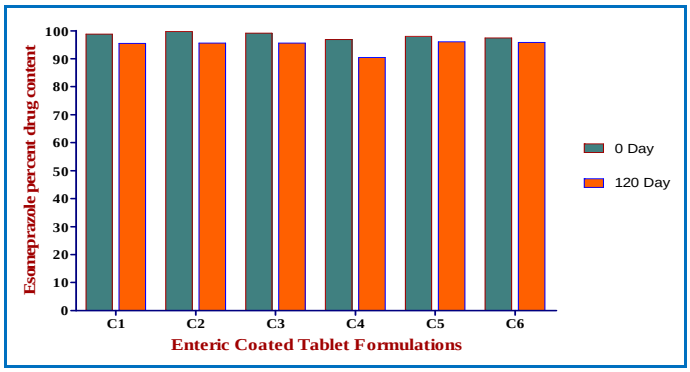

Fig 2. Drug content uniformity of Esomeprazole during stability studies at 40±0.5^{0}C/75±1%RH

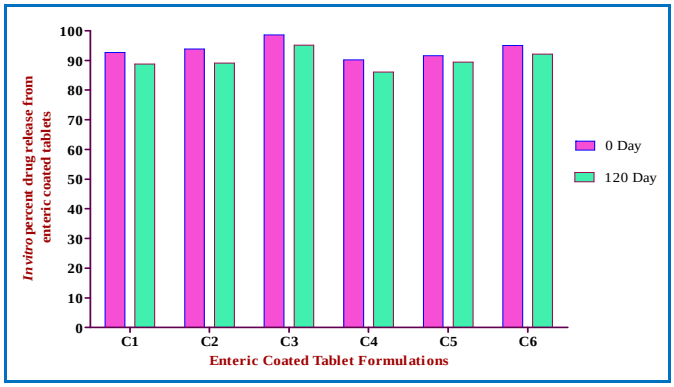

Fig 3. Effect of temperature and humidity on percent drug release from esomeprazole enteric coated tablets before and stability studies at 40±0.5^{0}C/75±1%RH.

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