

Original Article

Formulation and evaluation of delayed release tablets of Omeprazole

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ABSTRACT

The objective of the study was an attempt to formulate and evaluate delayed release tablets for Omeprazole which is a benzimidazoles anti-ulcer agent and is one of the most widely used drugs for treating mild and severe ulcers. The stability of omeprazole a proton pump inhibitor is a function of pH and it rapidly degrades in acidic medium of the stomach, but has acceptable stability in alkaline conditions. The present study demonstrates that the omeprazole enteric coated granules could be successfully intestine targeted by using pH dependent polymers in different concentrations. The drug and excipient compatibility study was performed by FT-IR and study revealed that there was no interaction between drug & excipient. The tablets were evaluated for various parameters like hardness, friability, weight variation, percentage drug content and *in-vitro* disintegration time, *in-vitro* dissolution study, drug release kinetic study and stability study. By observing the dissolution profile for all the formulations, F5c was better formulation of all the formulations with drug release in 0.1 NHCL and pH 6.8 phosphate buffer was found to be 0.88% and 98.91% at the end of 60 min and percentage drug content and *in-vitro* disintegration time 98.8% and 30.16±0.75sec respectively. The kinetic treatment showed that all formulations were followed zero order release kinetics with Fickian diffusion mechanism.

1. INTRODUCTION

Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia [1]. (Difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications [2]. Orally disintegrating tablets are also called as orodisperse, orally disintegrating tablets, quick dissolving tablet, fast melt tablets, rapid disintegrating tablets and freeze dried wafers. These tablets releases the medicament in the mouth for absorption through local oromucosal tissue and through pre-

gastric (Oral cavity, Pharynx, and oesophagus), gastric (stomach) and post-gastric (small and large intestine) segments of Gastro Intestinal Tract (GIT) [3]. Orally disintegrating tablets offer all advantages of solid dosage forms and liquid dosage forms along with special advantages, which include: As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients [4-6]. Bioavailability of drugs that are absorbed from mouth, pharynx, and esophagus is increased [7-9]. Pre gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increase the bioavailability [10].

Oral administration is the main way of delivering controlled release drugs owing to easy delivery, a better adjustment of the doses administered, better acceptance by patients and cost-

effective manufacture, and no need of maintaining sterility. This requires special techniques to avoid contact of drug with gastric acid of the stomach. One technique most commonly used is to coat acid-labile compound, or its granules or pellets, with an enteric coating, which is insoluble in water under acidic conditions and soluble in water under neutral to alkaline conditions. However, the material used in enteric coatings itself is acidic, which can cause the decomposition of the acid-labile compound. Such decomposition occurs even during the enteric coating process, which results in the coloration of the surface of the drug-containing core. In order to avoid such problems, an inert sub coating, which is not acidic, is often required between the core and enteric coating, which increase the complexity and the cost of the formulation manufacture processes involving acid-labile compounds. For substances that are labile in acid media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline reacting inactive constituents in order to increase the stability of the active compound during manufacture and storage.

Enteric coated tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach and release the drug in small intestine [11]. Omeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit ant cholinergic or histamine H₂-receptor antagonist properties, but rather suppress gastric acid secretion by specific inhibition of the (H⁺,K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell [12]. Because this enzyme system is regarded as the acid (proton) pump within the parietal cell, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. Omeoprazole (Fig. 1) chemical name 1H-Benzimidazole, 5-methoxy-2-[[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl] Molecular Weight: 345.42 g/mol and half life 1.5hr.

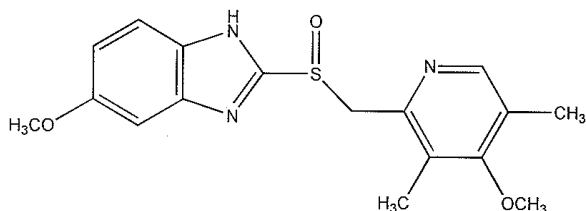


Fig. 1. Structural of Omeprazole

The stability of Omeprazole a proton pump inhibitor is a function of pH and it rapidly degrades in acidic medium of the stomach, but has acceptable stability in alkaline conditions. Hence in order to deliver omeprazole into the intestine, delayed release formulation was developed by enteric coating of the

drug loaded sugar spheres. The aim of proposed work was to formulate and characterize enteric coated tablets omeprazole for delayed release of drug in small intestine for treatment of mild and severe ulcers.

2. MATERIALS AND METHODS

2.1 Chemicals

Omeprazole was a sample from Dr Reddys laboratories, Hyderabad. Hydroxypropyl methylcellulose, E5 was purchased from Colocon Asia Pvt.Ltd., USA. Eudragit L 30 D-55 and Eudragit Ne 30 D were purchased from Rohm GMBH & KG Germany. Hydroxy propyl cellulose was purchased from Asha cellulose Pvt.Ltd. Hyderabad. Crosopovidone was purchased from Colorcon Asia Pvt. Ltd. Goa, India. All other reagents used were of analytical grade.

2.2 Drug-polymers compatibility study

IR spectra were obtained using a FTIR spectrophotometer (FTIR-8300, SHIMADZU, JAPAN). The study was carried out to find out the compatibility among the drug and polymers. A total of 5% w/w of sample with respect to the KBr was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar, pestle and compressed under a hydraulic pressure of 10,000 psi. Each disc was scanned at a speed of 4 mm/sec at a resolution of 400-4500 cm⁻¹. The peaks were recorded and the characteristic peaks were assigned. IR spectra of pure drug, and optimized formulation were done in pellets at moderate scanning speed between 4500-500cm⁻¹.

2.3 Preformulation Studies

2.3.1 Bulk Density: Bulk density was determined (bulk density apparatus, Electrolab instruments, India Model no ETD1020) by taking the dried granules in a measuring cylinder and measures the volume and weights of the total granules.

$$\text{Bulk Density} = \frac{\text{Total Weight}}{\text{Total Bulk Volume}}$$

2.3.2 Tapped Density: Tapped density was determined (bulk density apparatus, Electrolab instruments, India Model no ETD1020) by taking the dried granules in a measuring cylinder and measures the volume of granules after 100 tapping and weight of the total granules.

$$\text{Tapped Density} = \frac{\text{Total Weight}}{\text{Total Tapped Volume}}$$

2.3.3 Compressibility Index: Compressibility index was determined by placing the dried granules in a measuring cylinder and the volume (V₀) was noticed before tapping, after 100 tappings again volume (V) was noticed.

$$\text{Compressibility index} = (1 - V_0/V) * 100$$

Where, V₀ = volume of powder/granules before tapping

V = volume of powder/granules after 100 tappings.

2.3.4 Hausner's Ratio: Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. Hausner's ratio is calculated by the formula:

$$H = \frac{\text{Bulk Density}}{\text{Tapped Density}}$$

Where, H = hausner's ratio

2.4 Formulation of Omeprazole delayed release orally disintegrating tablets

2.4.1 Drug Loading: Sugar pellets (850-1000µm) were sieved through 18 mesh and 33% of pellets were taken for drug loading from total batch size. Required quantity of drug was taken according to the formula shown in (Table 04 and 05) and dispersed in specified ml of purified water and stirred for 10 minutes. The required quantity of HPMC E5 was taken and dispersed in specified ml of purified water and stirred for 10 minutes to obtain a clear solution. Purified water containing drug was mixed with dispersed HPMC E5 solution with stirring. Pellets were loaded using dispersion both into FBC bowl and coated. The operation conditions are shown in the Table 1.

Table 1. Fluidized bed coater operation conditions for drug loading

Parameters	Operation conditions
Air pressure	2lb/in ²
Inlet temperature	48 °C
Bed temperature	42 °C
Spray RPM	3-6
Blower RPM	290

2.4.2 Barrier coating: Required quantity of drug loaded pellets was taken for barrier coating. Required quantity of hydroxy propyl cellulose and mannitol was taken and dissolved in specified ml of purified water and stirred until a clear solution was obtained and coating was done by following the operation parameters shown in Table 2.

Table 2. Spray coater operation conditions for barrier coating

S. No	Name of parameters	Operation parameter
1.	Pump RPM	35
2.	Air pressure	2 Psi
3.	Pan RPM	10-12
4.	Inlet temp	65°C
5.	Outlet temp	38 °C
6.	Gun distance	20

2.4.3 Enteric coating: Specified quantity of Barrier coated pellets were taken for Enteric coating. Required quantity of Eudragit L30 D-55, Eudragit NE 30-D, triethyl citrate, tween 80, talc, glyceryl monosterate, were taken and dispersed in purified water and stirred for 10 minutes until a clear solution was obtained and coating was done according to the operation parameters shown in the Table 3.

Table 3. Spray coater operation parameters for enteric coating

S. No	Name of parameters	Operation parameter
1.	Pump RPM	35
2.	Air pressure	2 Psi
3.	Pan RPM	10-12
4.	Inlet temp	65°C
5.	Outlet temp	38 °C
6.	Gun distance	20

2.5 Preparation of inactive granules

2.5.1 Weighing & sifting: MCC PH 101, Crospovidone were weighed and passed through 40 mesh.

2.5.2 Blending: Materials were mixed in polybag for 3 min.

2.5.3 Granulation: Required quantity of hydroxy propyl cellulose was taken in purified water and stirred until dissolved. This binder solution was added to the MCC PH 101, Crospovidone blend to get a dough mass, which was passed through 12 meshes to give wet granules.

2.5.4 Drying: Wet granules were dried by using tray drier at 60°C.

2.5.5 Screening: The dried granules are passed through 16 mesh to get uniform dried granules.

2.5.6 Mixing: The enteric coated granules and inactive granules were taken in a polybag and mixed properly.

2.5.7 Lubrication: Magnesium stearate and aerosil passed through 60mesh were added to the above granules and mixed in polybag for around 5 min.

2.5.8 Compression: The homogenously mixed blend was compressed using 9 mm Standard concave punch.

Table 4. Formula for preparation of drug loading and barrier coating of pellets

Drug loading	mg/ tablet
Omeprazole	30
Sugar sphere	75
Tween 80	0.25
HPMC E 5	5.50
Dibasic sodium phosphate	0.75
Water	q.s
Barrier coating	
HPC	7.5
Mannitol	26
Water	q.s

q.s = quantity sufficient

Table 5. Formula for the preparation of formulation batch F1-F8

Ingredients	FORMULATIONS CODE												
	F1	F2	F3	F4	F4 a	F4 b	F5	F5 a	F5b	F5c	F6	F7	F8
Barrier Coated Pellets	145	145	145	145	145	145	145	145	145	145	145	145	145
Enteric coated													
Eudragit L30 D-55	15.75	31.15	38.75	46.5	46.5	46.5	41.85	41.85	41.85	41.85	37.2	32.55	23.125
Eudragit NE 30-D	-	-	-	-	-	-	4.65	4.65	4.65	4.65	9.3	13.95	23.375
Triethyl citrate	1.57	3.11	3.87	4.65	6.98	9.32	4.65	6.97	9.32	13.92	4.65	4.65	4.65
Tween 80	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93	0.93
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Glyceryl mono stearate	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Inactive granules													
MCC PH 101	145.15	128.21	119.85	111.32	108.99	106.65	111.32	109	106.65	102.05	111.32	111.32	111.32
HPC	16	16	16	16	16	16	16	16	16	16	16	16	16
Crospovidone	15	15	15	15	15	15	15	15	15	15	15	15	15
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Mg stearate	5	5	5	5	5	5	5	5	5	5	5	5	5
Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	350	350	350	350	350	350	350	350	350	350	350	350	350

*q.s= quantity sufficient

2.6 Evaluation of Omeprazole delayed release oral disintegrating tablets

2.6.1 Hardness Test: The Monsanto hardness tester was used to determine the tablets hardness. The tablets was held between a fixed and moving jaw, the body of the Monsanto hardness tester carrier an adjustable scale which was set zero against an index mark fixed to the compression plunger, when the tablet was held between the jaws. The load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the tablet hardness. Hardness of six tablets was determined and the average result was tabulated.

2.6.2 Friability Test: Another measure of tablet strength is friability. Friability is related to tablets ability to withstand both shock and abrasion without crumbling during the handling of manufacturing, packaging, shipment and consumer use. Friability was evaluated by means of friability test apparatus known as Roche's friabilator. A definite quantity (20 tablets) of weighed tablets was placed in the friabilator and then operated at 25 rpm for 4 minutes. After operation the tablets were dedusted and reweighed. The difference in the two weights is used is calculated as friability - F

$$F = 100 \left(1 - \frac{W}{W_0} \right)$$

Where, W_0 = initial weight

W = final weight

For compressed tablets, the loss less than 0.5-1% in weight is generally considered acceptable.

2.6.3 Weight Variation Test: The USP weight variation test was conducted by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test that there were no more than 2 tablets were outside the percentage limit and no tablet differed by more than 2 times.

$$\% \text{ deviation} = \frac{\text{Difference between average weight and tablet weight}}{\text{Average weight of tablet}} \times 100$$

The above results are shown in Table 08.

2.6.4 Drug Content Determination

Preparation of the mobile phase: Mobile phase selected for this method contained 30 parts of phosphate buffer (Adjusted to pH 3.0 with 0.5% orthophosphoric acid) and 70 parts of acetonitrile. 300ml of phosphate buffer (pH adjusted to 3 with 5% orthophosphoric acid) and 700ml of acetonitrile was transferred into a 1000ml of flask. The mobile phase was filtered through

0.45-micron membrane filter.
 Chromatographic system
 Detector: 284 nm (UV)
 Column: 4.6mm × 25cm × 5.0µm; Symmetry C 18 (Waters)
 Column temperature: 30°C
 Flow: 1.0 ml/minute
 Volume: 10 µl
 Mobile Phase: Phosphate Buffer pH 3: Acetonitrile (3:7)
 Diluent: Mobile phase

Standard solution preparation: Weighed accurately 20mg of omeprazole was transferred into 100ml volumetric flask and 50ml of the mobile was added. The solution prepared was sonicated for 30 minutes. Cooled to room temperature. The volume was made up to mark with mobile phase. Transfer 5ml of the solution into 50ml volumetric flask and volume was made up to mark with mobile phase to produce a concentration of 50µg/ml. The solution was filtered through 0.45-micron membrane filter.

Sample preparation: Twenty tablets of the formulation were weighed and the average weight per tablet was calculated. Twenty tablets were crushed and ground to a fine powder. Powder equivalent to 30mg of omeprazole was weighed and transferred to a 100ml volumetric flask. From this 5ml filtered solution was pipetted out into 50ml volumetric flask. Then 25ml of mobile phase was added, and then the volume was made up to mark with mobile phase. The powder was dissolved in the mobile phase and filtered through a membrane filter (0.45µ).

Assay Calculations

$$\text{Mg/tablet} = \frac{\text{Aspl} \times \text{Wstd} \times 5 \times 100 \times 50 \times \text{POT} \times \text{Aw} \times 100}{\text{Astd} \times 100 \times 50 \times \text{Wspl} \times 5 \times 100}$$

Where in,

Aspl is the peak area for omeprazole obtained from the test solution

Astd is the peak area for omeprazole obtained from the standard solution

Wstd is the weight of omeprazole working standard (mg)

POT is the potency of omeprazole working standard (%)

A W is the average weight of the tablets (mg)

The results are shown in Table 9.

2.6.5 In-vitro disintegration test: *In-vitro* disintegration time was measured using USP disintegration test apparatus. Randomly six tablets were selected from each batch for disintegration test. Disintegration test was performed in 900ml distilled water at 37±0.5 °C temperature and at the rate of 30±2 cycles/min. The results are shown in Table 09.

2.6.6 In-vitro dissolution study: The *In-vitro* dissolution study was conducted as per the United States Pharmacopoeia (USP) XXIV. The rotating paddle method was used to study the drug release from the tablets. The dissolution medium was 0.1N HCL and phosphate buffer pH 6.8. The release was performed at 37°C ± 0.5°C, at a rotation of speed of 50 rpm. 5 ml samples

were withdrawn at predetermined time intervals 60 min for 0.1N HCL and 10,20,30,40,50, and 60 min intervals in phosphate buffer (pH 6.8) and the volume was replaced with fresh medium. The samples were filtered through 0.45-micron membrane filter and analyzed for omeprazole after appropriate dilution by UV spectrophotometer at 284 nm. The percentage drug release was calculated using the calibration curve [13].

The results are shown in Figure. 3-6.

2.7 Drug release kinetics

Data obtained from *in vitro* release studies of all the formulations F1-F8 were fitted to various kinetic equations such as Zero order, First order, Higuchi's model, Korsmeyer-Peppas model and Hixson-Crowell model to explain the release kinetics of omeprazole delayed release orally disintegrating tablets [14 -16].

Zero order equation

$$Q = Q_0 - K_0 t \text{ First order equation}$$

$$\ln Q = \ln Q_0 - K_1 t$$

Higuchi equation

$$Q = K_2 t^{1/2}$$

Korsmeyer-Peppas equation

$$Q/Q_0 = K t^n$$

Hixson-Crowell cube root of law

$$Q_0^{1/3} - Q t^{1/3} = K_{HC} t$$

Where K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug release at time t , Q_t is the amount of drug released in time t , K was constant and n was diffusion constant that indicates general operating release mechanism.

The n value is used to characterize different release mechanisms as given in Table 6 for cylindrical shaped matrices.

Table. 6 n values for cylindrical shaped matrices

Diffusion exponent	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n > 0.89	Super case- II transport

The results are shown in Table 10 and Figure.8-12.

2.8 Stability studies

A study was carried out to assess the stability of the optimized formulation F5 batch. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of the accelerated stability studies are adopted. The tablets were packed in glass container. Stability studies were carried out at temperature 25°C/60% RH and 40°C/75%RH as per ICH guidelines over a period of 2 months and samples were evaluated after 15, 30, 45 and 60 days for various

physicochemical parameters such as physical appearance, hardness, weight variation, drug content and dissolution were evaluated [17]. The results are shown in Table 11 and Figure. 17-18.

2.9 Scanning electron microscopy analysis (SEM)

The drug loaded enteric coated granules were examined by scanning electron microscopy to observe the morphological changes and the particle size changes that occurred due to the formulation variation. The results are shown in Fig. 13-16.

3. RESULTS AND DISCUSSION

3.1 Drug-Polymers Compatibility studies

This study was carried out to find out the possible interaction between selected drug omeprazole and enteric coating polymers. From the FTIR analysis among the drug and enteric polymers showed no unaccountable extra peaks were found. The FT-IR of omeprazole showed the following peaks at 1734.01, 3410.15nm due to S=O and N-H functional groups. The results are shown in Table 07 and Figure 02-03.

Table 7. IR interpretations of pure drug and optimized formulation

Sl. No.	Interpretation	IR absorption bands(cm ⁻¹)	
		Pure drug	Optimized formulation F5c
1	S=O	1734.01	1732.08
2	N-H	3410.15	3402.43

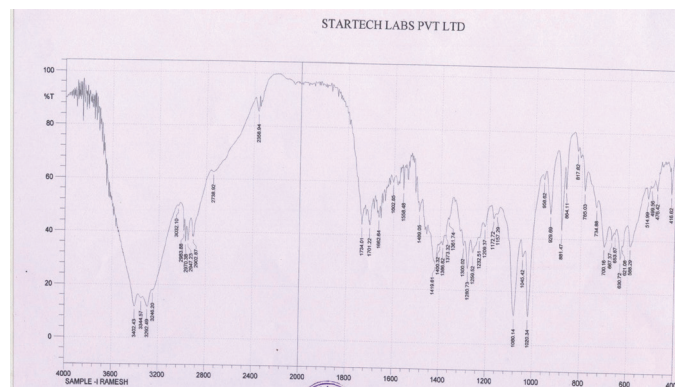


Fig. 2. FTIR spectroscopy of pure drug sample

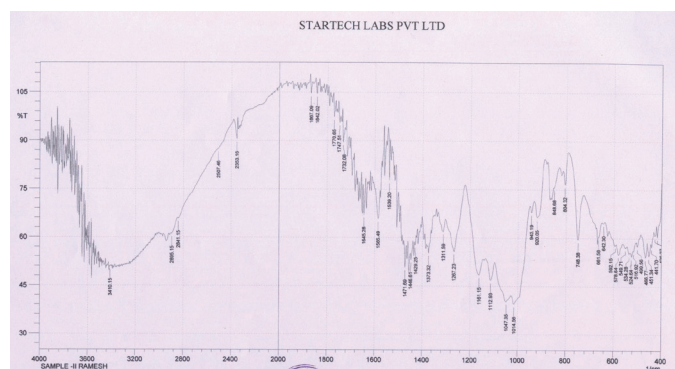


Fig. 3. FTIR spectroscopy of optimized formulation F5c

3.2 Pre compression parameters

The omeprazole enteric coated, inactive granules were mixed and evaluated for pre compression parameters and results are shown in Table 08.

The granules were evaluated for Bulk density, Tapped density, Carr's index and Hausner's ratio. This method was able to produce narrow shaped granular particles with fewer fines. The obtained granules were smooth and almost uniform size.

The bulk densities of the granules were found to be in the range 0.428 to 0.473 gm/ml, while the tapped densities of the granules were found to be in the range 0.453 to 0.529 gm/ml.

The flow properties of the granules were assessed by determining the Carr's index. The low values of the compressibility (5.42 to 10.44%) signify good flowability. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets.

Table 8. Physicochemical evaluations of Omeprazole granules

Formulations code	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	0.428	0.456	5.94	1.063
F2	0.432	0.469	7.90	1.085
F3	0.428	0.453	5.40	1.057
F4	0.438	0.478	8.28	1.090
F4a	0.440	0.469	6.11	1.065
F4b	0.428	0.458	6.48	1.069
F5	0.440	0.486	9.44	1.104
F5a	0.443	0.480	7.82	1.084
F5b	0.453	0.489	7.42	1.080
F5c	0.447	0.486	8.16	1.088
F6	0.443	0.478	7.26	1.078
F7	0.456	0.503	9.48	1.104
F8	0.473	0.529	10.44	1.116

3.3 Evaluation of Omeprazole tablets

The granules, inactive granules were compressed into tablets and tablets were evaluated for their hardness, weight variation, drug content, friability and *in-vitro* disintegration. The results are shown in the Table 09. The hardness test is one of the control parameter during the manufacturing of tablets. Generally the tablet prepared with low compression force was dissolved faster than that with high compression force. Hardness must be controlled to ensure that the product is firm enough to withstand handling without breaking or crumbing and not so hard that the disintegration time is unduly prolonged. The recommended for tablet is 4 to 8 kg/cm². The average hardness of the tablets to be in range was found within 4.16±0.29 to 4.63±0.23 kg/cm². The average weight variation of tablets was found within the limits of 5% (I.P).

Friability value which also affected by the hardness value of tablets should be in the range of 0.5 to 1% limits, which is the usual friability range of tablets. The friability of the prepared tablets was found less than 1% w/w. The uniformity of drug

omeprazole present in tablets formulation ranged from 98.1% to 100.08%. It was found that the physicochemical parameters of the prepared tablets are within standards. Prepared tablets were evaluated for weight variation and percentage deviation from the average weight was found to be within the range of 348.97 to 352.35 mg prescribed official limits. The inactive granules prepared by wet granulation comprise a superdisintegrant (Crospovidone) concentration of 4.28%, which was aided for the tablet to disintegrate in few seconds and the range was found to be 28.16 to 31.66 seconds.

Table 9. Physicochemical evaluations of omeprazole tablets

Formulations code	Weight variation test (%) [*]	Hardness (kg/cm ²) ^{**}	Friability (%)	Drug content (%)	Disintegration time (sec) ^{***}
F1	351.20±1.26	4.20±0.35	0.483	100.6	31.66±1.6
F2	351.07±1.71	4.45±0.32	0.537	99.6	28.66±0.81
F3	348.97±2.14	4.16±0.29	0.424	100.4	28.16±0.75
F4	349.24±1.31	4.56±0.23	0.538	98.7	28.50±1.0
F4a	350.55±1.47	4.30±0.30	0.536	98.4	29.66±1.2
F4b	352.35±2.08	4.16±0.23	0.451	100.02	28.66±1.2
F5	350.57±1.66	4.46±0.24	0.509	99.2	29.33±1.2
F5a	349.34±1.81	4.63±0.23	0.508	98.1	28.83±0.40
F5b	350.78±2.00	4.40±0.28	0.651	98.2	29.50±1.0
F5c	351.11±1.55	4.20±0.17	0.506	98.8	30.16±0.75
F6	350.37±1.85	4.43±0.23	0.594	99.3	28.83±1.4
F7	352.07±1.16	4.60±0.25	0.623	99.5	28.83±0.75
F8	351.08±1.85	4.50±0.20	0.846	100.8	28.16±1.1

* (n = 20±S.D), ** (n = 6±S.D), *** (n = 6±S.D)

3.4 In vitro drug release

Dissolution testing becomes a mandatory requirement for several oral dosage forms. Dissolution testing has been an integral component in pharmaceutical research and development of solid dosage forms. It provides decisive information on formulation selection, the critical processing variables *in vitro/ in vivo* correlation study and quality assurance during manufacturing. In formulation F1 the concentration of Eudragit L30 D-55 was used as 4.28%. The 24.18% drug release was obtained at the end of 1st hour in 0.1 N HCl, with 100% drug release achieved in 40 min in pH 6.8 phosphate buffer.

In formulation F2, in order to prevent the release of drug in 0.1N HCl, the concentration of Eudragit L30 D-55 was increased to 8.9% as a result 16.27% drug release was obtained at the end of 1st hour in 0.1 N HCl and 100% drug release was obtained at the end of 50 min in pH 6.8 phosphate buffer.

In formulation F3, F4, in order to prevent the release of drug in 0.1N HCl, as omeprazole is acid labile the concentration of Eudragit L30 D-55 was increased to 11.07 % and 13.28% as a result 13.56% and 9.76% of drug release was obtained at the end of 1st hour in 0.1 N HCl respectively and 100% and 99.06% of drug release at the end of 60 min in pH 6.8 phosphate buffer respectively.

The drug release profiles of formulations (F1, F2, F3, and F4) were characterized by an initial drug release i.e. 9% in 1st hr in 0.1 N HCl. In order to further prevent the drug release in 0.1 N HCl medium, the formulation trials F4a, F4b were formulated such that the concentration of Eudragit L30 D-55 was kept constant at 13.28% and triethyl citrate (plasticizer) concentration was increased.

In formulation F4a, F4b the concentration of Eudragit L30 D-55 was kept constant at 13.28% and triethyl citrate concentration was included as 2% and 2.6% , so that 8.12 and 6.36% of drug release obtained at the end of 1st hour in 0.1 N HCl respectively.

In formulation F5, in order to further prevent the release in 0.1 N HCl medium, a pH independent rate retarding polymer Eudragit NE 30-D 1.32% was employed and it was used in combination with that of Eudragit L30 D-55 13.28%, triethyl citrate at 1.32% concentration was used as plasticizer as a result 5.20% drug release was observed in 0.1N HCl medium and 100% drug release in pH 6.8 phosphate buffer.

In formulations F6, F7, F8 Eudragit NE 30D and Eudragit L30 D-55 combination was taken in concentration such as (10.6% & 2.65%), (9.3% & 3.98%), (6.6% & 6.67%) with triethyl citrate at 1.32% concentration was kept constant. Formulations F6, F7, F8 controlled the drug release to a greater extent in 0.1 N HCl medium as 2.06%, 1.06% and 0.54% but whereas the drug release in 60 min was found to decrease to a greater extent such as 82.08%, 65.50%, and 43.71% respectively.

In formulation F5, 5.20% drug release was observed in 0.1 N HCl medium and 100% drug release in pH 6.8 buffer. Thus in order to further decrease the drug release in acidic medium, formulations F5a, F5b and F5c were formulated with Eudragit NE 30 D and Eudragit L30 D-55 combination taken in concentration as (10.6% & 2.65%), kept constant and the triethyl citrate concentration was increased as 2%, 2.6%, 4% respectively as a result the release at the end of 1 hr for F5a, F5b and F5c in acidic media was found to be 4.24%, 1.78%, 0.86% drug released and in 6.8 pH buffer the drug release at 60 min was found to be 99.88%, 99.76%, 98.90% drug released respectively. The F5c formulation was the optimized formulation since it has the lowest drug release 0.86% in 1 hr and greater than 95% in 60 minutes. The results are shown in Figure 04-07.

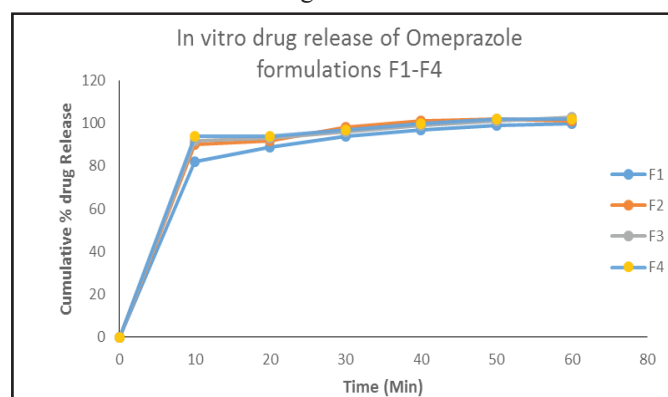


Fig 4. *In vitro* drug release profile of Omeprazole from formulations (F1 to F4)

Values represented are mean±S.D.(n=3)

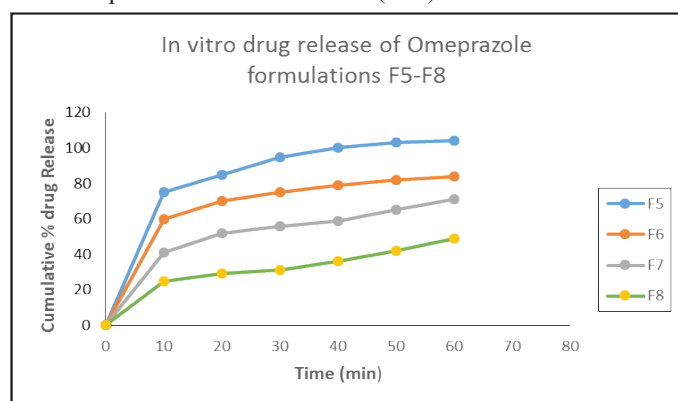


Fig 5. *In vitro* drug release profile of Omeprazole from formulations (F5 to F8)

Values represented are mean ± SD (n=3)

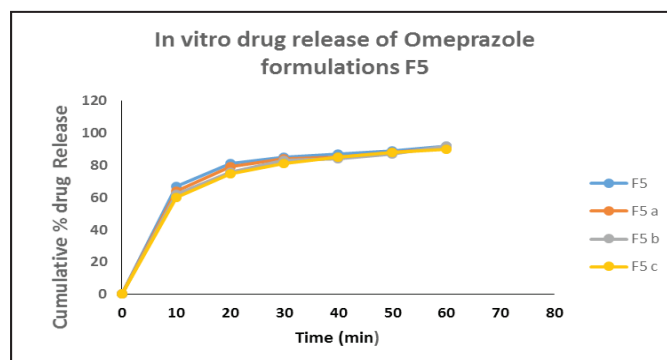


Fig 7. *In vitro* drug release profile of omeprazole from formulations F5 batch

Values represented are mean±S.D.(n=3)

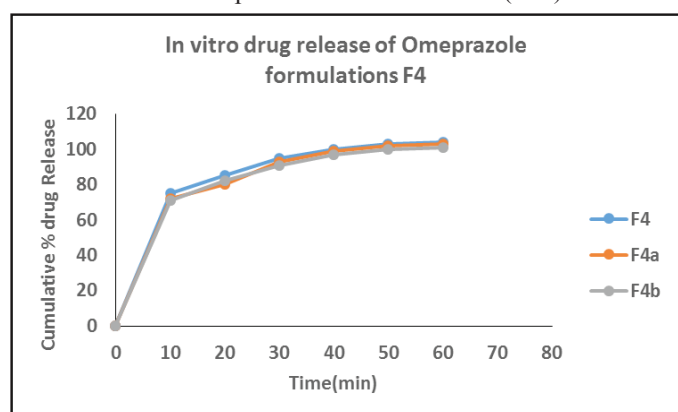


Fig 6. *In vitro* drug release profile of Omeprazole from formulations F4 batch,

Values represented are mean ± SD (n=3)

3.5 Drug release kinetics

The data obtained from *in vitro* release studies of the entire formulations F1-F8 were fitted to various kinetic equations such as Zero order, First order, Higuchi's model, Korsmeyer-Peppas. In case of zero order ($Q = Q_0 - K_0t$) the graph was plotted between cumulative percent of drug dissolved Vs time, and in First order kinetics ($\ln Q = \ln Q_0 - K_1t$) the graph plotted between log cumulative percent of drug remaining Vs time. For Higuchi's model kinetics ($Q = k_2t^{1/2}$) the graph was plotted in cumulative percent of drug dissolved Vs square root of time, and for Korsmeyer-Peppas model ($Q/Q_0 = Kt_n$) the graph was plotted between log cumulative percent of drug dissolved Vs log time, for Hixson-Crowell ($Q_0^{1/3} - Qt^{1/3} = K_{HC}t$) the graph was plotted between cube root of drug % remaining Vs time and resultant values for all the formulations shown in Table 10.

Table 10. Release kinetics profile of formulation (F1-F8)

Formulations Code	Zero order		First order		Higuchi		Korsmeyer -peppas		Hixson -crowell	
	R ²	K	R ²	K	R ²	K	R ²	N	R ²	K
F1	0.957	-0.301	0.920	0.138	0.981	2.897	0.988	0.138	0.935	0.049
F2	0.935	-0.325	0.924	0.0875	0.976	3.419	0.992	0.178	0.977	0.042
F3	0.929	-0.310	0.901	0.0736	0.961	3.527	0.991	0.199	0.996	0.038
F4	0.969	-0.412	0.894	0.0690	0.957	4.698	0.986	0.279	0.995	0.036
F4a	0.977	-0.407	0.903	0.069	0.960	5.336	0.985	0.321	0.883	0.053
F4b	0.987	-0.515	0.920	0.064	0.968	5.817	0.986	0.354	0.896	0.051
F5	0.978	-0.516	0.947	0.0690	0.987	5.804	0.997	0.346	0.996	0.040
F 5a	0.9655	-0.5135	0.8366	0.0898	0.9929	5.7303	0.9949	0.3422	0.9388	0.046
F 5b	0.9678	-0.5707	0.8782	0.0831	0.9961	6.3371	0.9982	0.3872	0.9598	0.0465
F 5c	0.953	-0.591	0.950	0.0644	0.981	6.606	0.982	0.405	0.920	0.052
F6	0.974	-0.511	0.881	0.0230	0.993	5.691	0.995	0.428	0.992	0.018
F7	0.900	-0.378	0.769	0.0138	0.961	4.297	0.986	0.406	0.928	0.010
F8	0.975	-0.273	0.765	0.0069	0.911	2.494	0.938	0.414	0.965	0.005

The value of regression correlation coefficient (R^2) was calculated for all the formulations F1-F8 which values were close to 1. Among regression correlation coefficient (R^2) values of Higuchi's equation, Korsmeyer-Peppas equation and Hixson-Crowell equation, R^2 values of Korsmeyer-Peppas equation was found to be higher and the n values was found to be ($n < 0.45$) release mechanism.

Similarly among Zero order and First order equation, R^2 values of zero order equation was found to be higher. Hence the drug release followed zero order release kinetics with fickian diffusion mechanism. The results are shown in Figure 08-12.

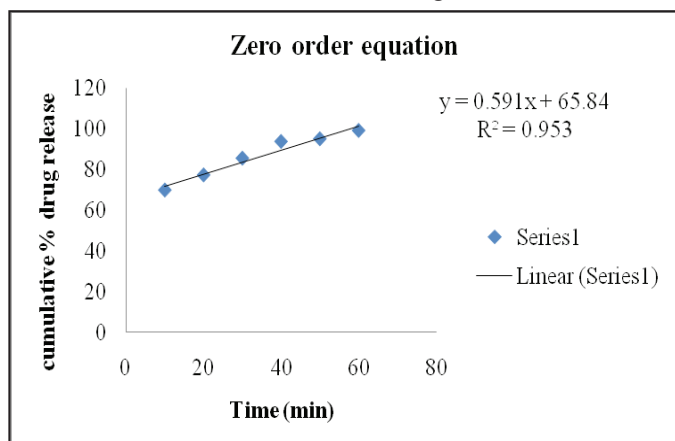


Fig. 8. Zero order release kinetics of formulation F5c

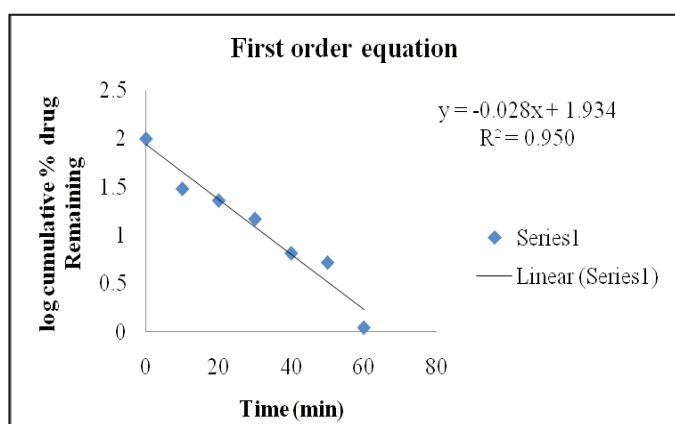


Fig. 9. First order release kinetics of formulation F5c

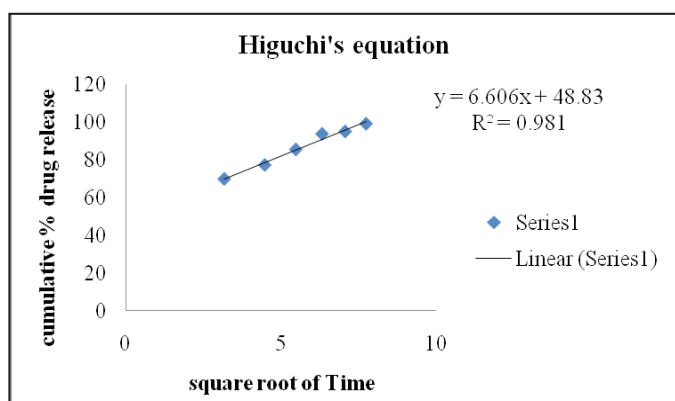


Fig 10. Higuchi model release kinetics of formulation F5c

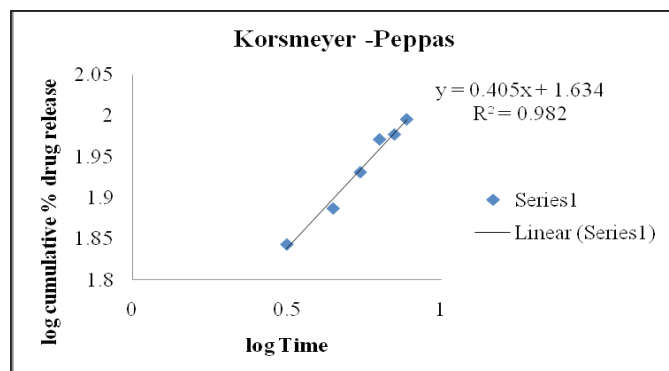


Fig. 11. Korsmeyer-Peppas model release kinetics of formulation F5c

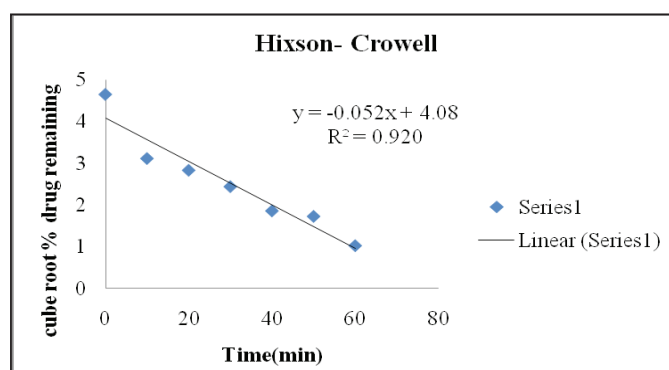


Fig. 12. Hixson-Crowell release kinetics of formulation F5c

3.6 Scanning electron microscopy

3.6.1 Influence coating level of Eudragit L 30 D-55 on properties of pellets

Obtained SEM photographs of pellets coated with Eudragit L30 D-55 and Eudragit NE 30D are shown in Figure 13-16.

The morphology and surface of the pellets is clearly dependable on the type and the amount of applied layer. With the application of the consecutive layers on the surface of sugar pellets, surface became smoother and sphericity was maintained.

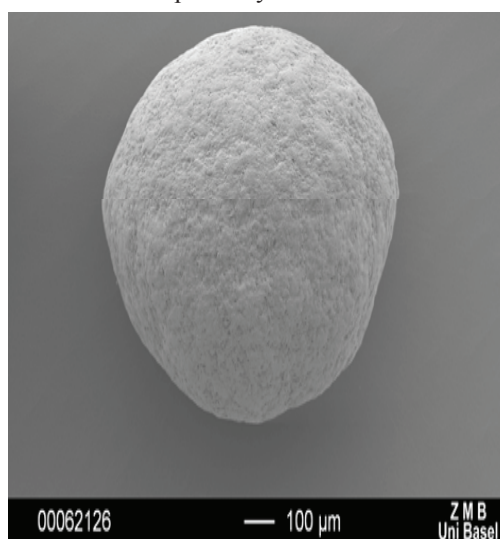


Fig. 13. Surface of neutral sugar pellet magnification × 70

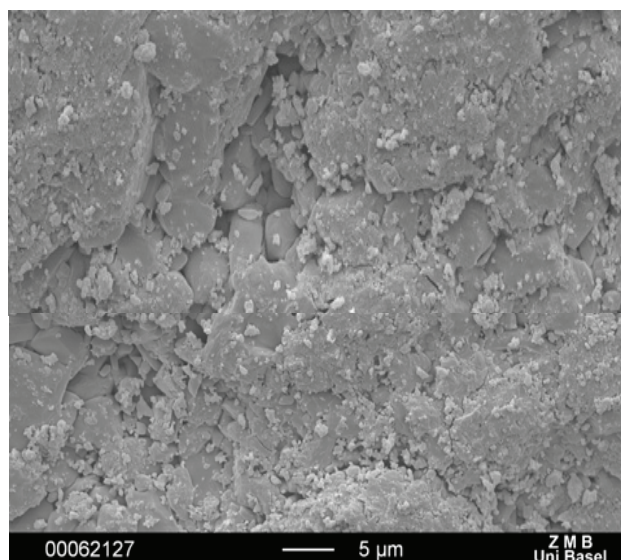


Fig. 14. Surface of neutral sugar pellet magnification × 2000

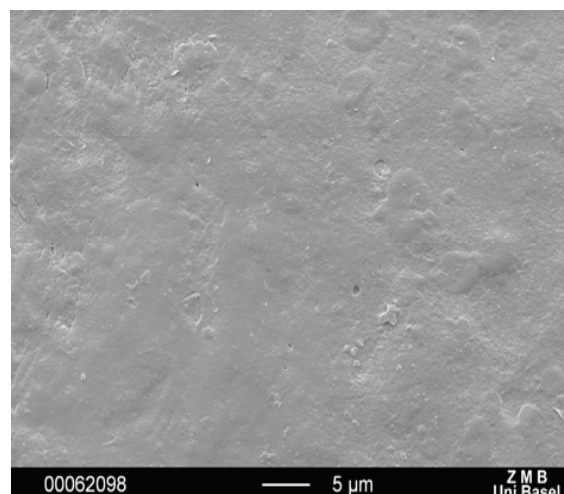


Fig. 16. Surface of omeprazole pellet enteric coated with Eudragit L30 D-55 & Eudragit NE 30D magnification × 2000.

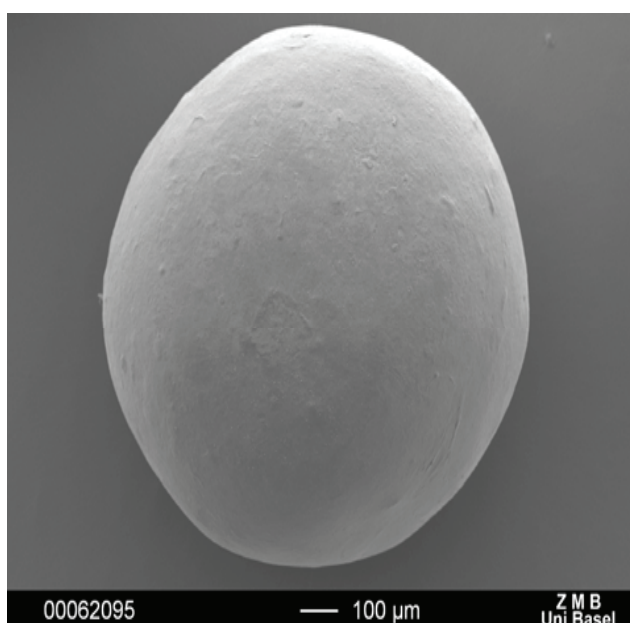


Fig. 15. Surface of omeprazole pellet enteric coated with Eudragit L30 D-55 & Eudragit NE 30D magnification × 70.

3.7 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, odour, taste or texture of the formulation indicate the drug instability. Among the four F5 formulations, optimized formulation F5c was selected for stability studies based on the physicochemical characterization of coating composition and release characteristics.

The stability studies results of prepared formulation F5c tablets were carried out at 25°C/60% RH and 40°C/75%RH as per ICH guidelines over a period of 2 months. There was no significant change in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the sample analyzed after 15, 30, 45 and 60 days of storage were similar. The release profile also not showed any significant changes indicating that there were no 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 2 months. The results are shown in Table 11 and Figure 17-18.

Table 11. Stability studies of optimized formulation F5c

Evaluation Parameters	Initial	Time (days)							
		At 25°C/60% RH				At 40°C/75%RH			
		15	30	45	60	15	30	45	60
Physical appearance	White in color	No change	No change	No change	No change	No change	No change	No change	No change
Average weight of tablet	351.11	351.11	351.11	351.05	351.01	351.11	351.04	351	351
Hardness kg/cm ²	4.20	4.20	4.20	4.05	4.0	4.15	4.10	4.05	4.0
Drug content (% w/w)	98.80	98.60	98.60	98.45	97.64	98.75	98.01	97.89	97.44
% CDR	98.13± 1.7	98.09± 0.52	98.09±0.32	97.56±0.52	97.23±0.37	98.10±0.62	98.04± 0.25	97.68±0.52	96.14±0.33

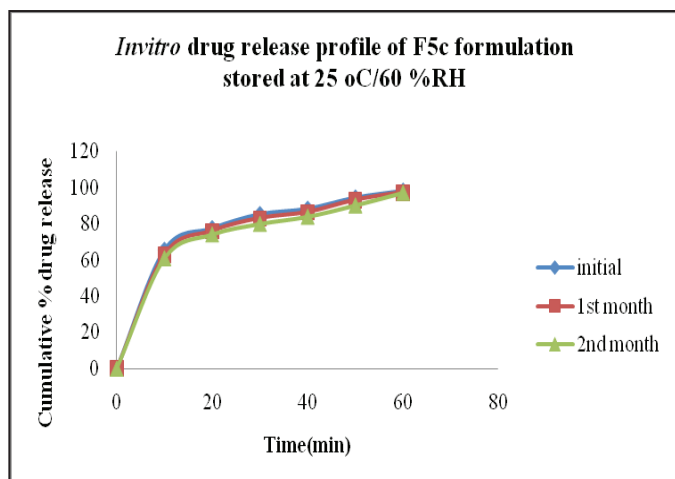


Fig. 17. *In vitro* drug release profile of F5c formulation stored at 25°C/60 %RH

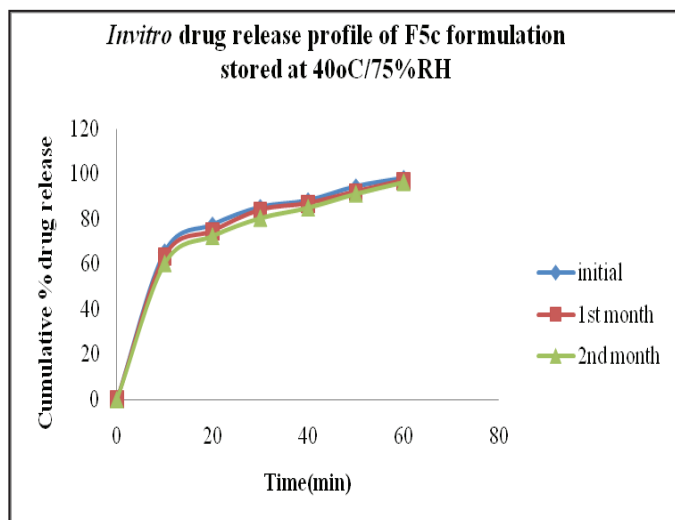


Fig. 18. *In vitro* drug release profile of F5c formulation stored at 40°C/75%RH

4. CONCLUSION

The stability of omeprazole a proton pump inhibitor is a function of pH and it rapidly degrades in acidic medium of the stomach, but has acceptable stability in alkaline conditions. Therefore, omeprazole should be delivered into intestine. Hence, an attempt was made to formulate omeprazole delayed release oral disintegrating tablets, by using different enteric coating polymers, super disintegrates for ODT action. Formulation batches with combination of Eudragit L30 D-55 and Eudragit NE 30D was able to prevent the drug release to a greater extent in 0.1 N HCl medium than Eudragit L30 D-55 alone. Increase in the triethyl citrate concentration had a retarding effect on the drug release. It was also observed that by increasing the concentration of Eudragit NE 30 D, a retarding effect on the drug release from the polymer matrix was observed. From the dissolution profile modeling it was found that the optimized formulation

followed Zero order release kinetics with Fickian diffusion mechanism. Further in-vivo investigations are required to correlate in-vitro drug release studies for the development of delayed release oral disintegrating tablets omeprazole. The formulation, batch was considered to be the best enteric formula and further studies can be carried out and finally ready to be market.

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