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Research Article

FORMULATION AND EVALUATION OF ESOMEPRAZOLE DELAYED RELEASE TABLETS

TUSHAR G. RUKARI[1]*, GANESH V. AHIRE[2]

[1]A.R.A. College of Pharmacy, Nagaon, Dhule, Dist: Dhule,[2]R.C. Patel College of pharmacy, Shirpur, Dhule,Email: tushar.rukari@gmail.com

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ABSTRACT

In the present work emphasize on Esomeprazole magnesium is formulated as delayed release tablets to provide desired effect at certain time in maintained drug concentration without any unwanted effect with patient compliance also to improve it bioavailability by decreasing its expose to gastric acid. A delayed release dosage form is designed to release the drug from the dosage form at a time other than promptly after administration. UV spectrophotometric method has been developed for the estimation of Esomeprazole in pharmaceutical formulations. Then the tablets were prepared by wet granulation method rather than direct compression because of cohesive property of the drug. Optimized core tablet then subjected for enteric coating by selected base coat polymer cellulose derivative for preventing core tablet from moisture. The coated formulations were compared with marketed sample (ESOZ) for optimization. Dissolution results of tablets with enteric coating have shown release of Esomeprazole in simulated gastrointestinal fluid pH 1.2, but most of the drug released in pH 6.8 Phosphate buffer. At the end it was found that prepared formulation gave satisfactory results compared with marketed sample dissolution profile. Hence prepared formulation by-pass the degradation of Esomeprazole by enteric coating approach and can be used as single unit dosage for the treatment of acid-related diseases. Thus a pharmaceutically equivalent, robust formulation of Esomeprazole delayed release tablet was developed.

Keywords: Esomeprazole, UV spectrophotometric method, Enteric coating, Delayed release tablets, In *vitro* drug release.

INTRODUCTION

Delayed release dosage form is the best formulations which are used for drugs that are destroyed in gastric fluids, or cause gastric irritation or absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer.[1] Esomeprazole, the new S-isomer of omeprazole, is introduced to reduce gastric acid secretion more efficiently. esomeprazole exhibits significantly higher bioavailability, leading to the greater inhibition of gastric acid secretion compared to Omeprazole.[2] Esomeprazole, the stereospecific S-isomer of Omeprazole, is the first proton pump inhibitor (PPI) to be developed as a single isomer for use in the treatment of acid-related diseases.[3] The intragastric pH-monitoring data for esomeprazole, 20 mg once daily, show improvement over omeprazole, 20 mg once daily, but the esomeprazole, 40 mg once daily, intragastric pH data show a further convincing gain in control of gastric pH.[1]

Early studies have shown Esomeprazole achieves greater and more sustained acid control than Omeprazole, with a similar tolerability and safety profile. Furthermore, Esomeprazole shows a more rapid onset of acid-suppression effect than Omeprazole, and less inter-individual variation in acid control.

Additionally, a recent crossover study demonstrated that Esomeprazole at a standard dose of 40 mg once daily provides more effective control of gastric acid at steady state than standard doses of Pantoprazole, Lansoprazole and Rabeprazole in patients with symptomatic gastroesophageal reflux disease (GERD).[4]

In addition, Esomeprazole treatment yields higher erosive esophagitis healing rates and provides sustained resolution of heartburn in more patients than any other.[5]

MATERIALS AND METHODS

Materials

Esomeprazole Magnesium, Magnesium oxide, Sodium bicarbonate, Mannitol, Polyvinyl Chloride, Pregelatinised starch, Magnesium stearate, Talc, Colloidal silicon dioxide, Isopropyl alcohol and Purified water.

All the chemicals and solvents used are of analytical reagent grade and were supplied by M/s S. Kant Healthcare Ltd.(Vapi, Gujarat).

Instacoat sol*®, Methylene chloride, Instacoat EN-Super-II*®

* Registered trade mark of Idealcures Ltd.

Methods

Development of Spectroscopic Method

Proton pump inhibitors (PPIs) are the most potent medications available to reduce gastric acid secretion. Since their introduction in the late 1980s, these efficacious acid suppressants have rapidly assumed a major role for the treatment of acid-peptic disorders. They are now among the most widely prescribed drugs worldwide because of their outstanding efficacy and safety.[6]

Esomeprazole is 6-bis(5 methoxy-2-[(S)-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole-1yl) magnesium trihydrate, a compound that inhibits gastric acid secretion. Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Omeprazole is official in I.P 1996.[7] Macek J et al (2007) had estimated omeprazole in human plasma by protein precipitation and liquid chromatography-tandem mass spectrometry. Hultman La et al (2007) had determined Esomeprazole by liquid chromatography with tandem mass spectrometry. I.P (1996) suggests HPLC method for the estimation of omeprazole in bulk drugs. None of the UV Spectrophotometric method reported for the estimation of the Esomeprazole in pharmaceutical dosage forms, and there are number of formulations available in market, which contain these drugs. In this present work a very simple and economic UV spectrophotometric method has been reported.

Preparation of Standard Solutions

Stock solution of Esomeprazole was prepared by dissolving accurately weighed quantity of standard Esomeprazole in 10 ml of 6.8 phosphate buffer. This was further diluted to get a working standard stock solution of 200 µg/ml. Then 1,2,3,4.....10ml of working standard solution were transferred into a series of 10ml volumetric flasks. The volume made up with 6.8 phosphate buffer solution. Then the sample was scan in UV range (200-400), Peak maxima were observed at 300.0 nm by using UV Spectrophometer - 1600 make Shimadzu (Figure 1). The absorbance of the solution was measured at 300.0 nm against blank, and the calibration curve plotted.

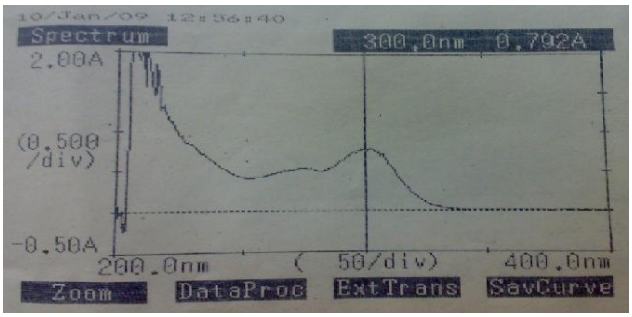

Fig 1:It shows uv spectra of esomeprazole (in 6.8 phosphate buffer for determination of λ_{max})

Calibration Curve

The stock solution of 20 µg/ml was prepared by dissolving 10mg of Esomeprazole in 100ml of phosphate buffer pH 6.8 and then 20ml of this solution was diluted to 100ml with phosphate buffer pH 6.8. The calibration curve was prepared using the aliquot of 2 - 20µg/ml from stock solution.

UV spectra of Esomeprazole (20µg/ml) solution in Phosphate buffer pH 6.8 shows absorbance maxima at wavelength 300.0 nm. This wavelength was considered as λ_{max} in Phosphate buffer pH 6.8. The details are discussed in result and discussion section.

Preparation Of Tablets

Preparation of Core Esomeprazole Tablets

Initially core tablets were formulated by using Wet granulation method rather than Direct compression or Dry granulation due to cohesive nature of Esomeprazole and its poor flowability. In maintained room condition, relative humidity 65 % and with minimum expose to the light all the ingredients were weighed and sieved. Geometrically mixed dry blend was taken in try for granulation and slowly added granulating fluid (Hydro-alcoholic mixture of PVP K-30) in it to form damp like consistent mass, granulating fluid added until suitable strength granules get. Semidried granules and then passed through sieve (18 #). Passed granules dried in tray drier at 45^{0}C for 1 hour. After drying granules were evaluated for moisture content (i.e. not less than 3 % present). Dried granules are then mixed with the lubricating material passed through sieve except Magnesium stearate for 10 minutes. After uniform mixing, mix these granules with sieved Magnesium stearate granules for another 5 minutes. These are the lubricated granules ready for compression. Compression of the dried granules is done on Tablet compression machine with 7 mm standard concave shape at approximately 160 mg weight of core tablets. The detailed compositions of Esomeprazole core tablets are given in Table 1.

Table 1: Shows Core Tablets Composition

Formulations For Esomeprazole Core Tablets					
Sr. No.	**FORMULA**	**F1**	**F2**	**F3**	**F4**
	Ingredients	**Qty.**	**Qty.**	**Qty.**	**Qty.**
1	Esomeprazole	44.50	44.50	44.50	44.50
2	Magnesium oxide	44.50	44.50	44.50	44.50
3	Sodium bicarbonate	10.00	10.00	10.00	10.00
4	Mannitol	50.50	49.00	49.00	48.50
5	PVP (K 30)	0.50	0.50	0.50	1.00
6	Croscarmelose sodium	--	6.00	--	--
7	Pregelatinised starch	--	--	6.00	6.00
8	Mg.stearate	6.00	3.00	3.00	3.00
9	Talc	3.00	1.50	1.50	1.50
10	Coll.silicon dioxide	1.00	1.00	1.00	1.00
11	IPA:Purified water	Q.S.	Q.S.	Q.S.	Q.S.
	Tablet Weight	**160.0**	**160.0**	**160.0**	**160.0**

All quantities are expressed in mg

Coating approach

The optimized formula of core tablets was continued further tablet formulations for application of enteric coat. Seal coating (Instacoat sol) layer is done to protect drug and for increasing the stability of a drug. Also mechanical strength of the tablet is increased. In order to prevent interaction with functional groups contained in the enteric film coat, it is of advantage to combine enteric coatings with sealing coats made up of cellulose derivatives. Colloidal silicon dioxide is used to avoid charging of particles. Application of enteric coating (Instacoat EN-Super-II) was done with varying amount of coating material. The detailed compositions of Esomeprazole enteric coated tablet formulations are given in Table 2.

Table 2 :Shows Coating Approach For Esomeprazole Core Tablets

Coating Approach For Esomeprazole Core Tablets (Formula same as F4)					
Sr. No.	**FORMULA**	**F5**	**F6**	**F7**	**F8**
	Material used	**Seal coat**			
1	Instacoat sol*	1	1	1	1
2	IPA	60	60	60	60
3	Methylene chloride	40	40	40	40
	Weight gain	**1.5**	**2**	**2**	**2**
		Enteric coat			
4	Instacoat EN-Super-II	20	20	20	20
5	Purified water	80	80	80	80
	Weight gain	**15**	**12**	**10**	**9**

All quantities are expressed in percentage (%)
*** Cellulose derivative**

Evalution Of Granules

Angle of repose

Static angle of repose was determined according to the fixed funnel method reported by Patel et al.[1] The mean diameter of the base for the powder cone was measured and the angle of repose (θ) was calculated using the following equation.

$$Tan\theta = H / R$$

Different types of flowabiliaty depending upon angle of repose shown in Table 3.

Table 3: Shows Flowability And Angle Of Repose

Sr. No.	Flowability	Angle of Repose
1	Excellent	25-30 ^{0}
2	Good	30-35^0
3	Passable	35-37^0
4	Poor	37-45^0
5	Very poor	Above 45^0

Bulk density and tapped density

The bulk density and tapped density was determined by the method reported by Patel et al.[1] The tapping was continued until no further change in volume was noted.

Bulk Density = Weight of the powder / Volume of the packing
Tapped Density = Weight of the powder / Tapped volume of the packing

Hausner's factor

Housner found that the ratio of tapped density to bulk density was related to interparticle friction and as such, could be used to predict powder flow properties.[1]

Hausner Ratio = Tapped Density / Bulk density

Values less than 1.25 indicate good flow, whereas greater than 1.25 indicates poor flow property.

Compressibility index

Compressibility index of granules was calculated from the following formula.[1]
It is also known as Carr's index.

$$Compressibility\% = Dt - Db / Dt * 100$$

Where Dt is tapped density and Db is bulk density.
Various values for carr's index are shown in the Table 4.

Table 4: Shows Interpretation Of Carr's Index

Carr's index (%)	Type of flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor*
33-38	Very poor*
>40	Extremely poor*

*** May be improved by glidant**

Characterization of esomeprazole tablets

Characterization of core esomeprazole tablets

Description

Esomeprazole core tablets were evaluated for Shape, Surface, morphology, color of tablet. Results are illustrated in Table 8.

Weight variation test

Twenty tablets were selected randomly and weighed. The average weight was compared with individual tablet weight. The percentage weight variation was calculated.

Friability test:[8]

Weighed amount of 20 dedusted tablets were subjected to rotating drum of friability test apparatus. The drum was rotated at a speed of 25 rpm for 4 minutes and reweighed the tablets. % friability was calculated by the following formula.

% friability = {(Initial weight – final weight) / initial weight} X 100
% friability of tablets less than 1% of their weight are considered acceptable.

Diameter & thickness

Twenty tablets selected randomly and determined its diameter & thickness by using vernier caliper and reading were noted.

Disintegration test

Placed one tablet in each tube of the basket and the apparatus, using purified water maintained at 37^0 C as immersion fluid for 2 hrs. Noted down the time to complete disintegration.

Drug content

Prepared core tablets were subjected for the drug content. Weighed and powder 20 tablets. Weighed a quantity of powdered tablet containing 20 mg of Esomeprazole to 100 ml volumetric flask, add 20 ml of 0.1 M Sodium hydroxide, mix with aid of ultrasound and dilute to volume with 0.1 M Sodium Hydroxide. Centrifuge for 5 minutes and dilute 5.0 ml of the clear supernatant liquid to 50.0 ml with the phosphate buffer pH 6.8. The resultant solution is then analysed by using UV Spectrophotometer at λ_{max} 300.0 nm. Results were tabulated in the Table no. 8.

Characterization Of Enteric Coated Esomeprazole Tablets

Description

Esomeprazole core tablets were evaluated for Shape, Surface, morphology, color of tablet. Results are illustrated in Table 8.

Weight variation test

Twenty tablets were selected randomly and weighed. The average weight was compared with individual tablet weight. The percentage weight variation was calculated.

Diameter & thickness

Twenty tablets selected randomly and determined its diameter & thickness by using vernier caliper and reading were noted.

Disintegration test

Placed one tablet in each tube of the basket and the apparatus, using 0.1 N HCl maintained at 37^0 C as immersion fluid for 2 hrs. Noted were tablet remain intact not Later placed same tablet in each tube of the basket and the apparatus , using 6.8 pH phosphate buffer maintained at 37^0C as immersion fluid for 45 min. Noted down the time to complete disintegration.

Drug content

Prepared core tablets were subjected for the drug content. Weighed and powder 20 tablets. Weighed a quantity of powdered tablet containing 40 mg of Esomeprazole to 100 ml volumetric flask, add 20 ml of 0.1 M Sodium hydroxide, mix with aid of ultrasound and dilute to volume with 0.1 M Sodium Hydroxide. Centrifuge for 5 minutes and dilute 5.0 ml of the clear supernatant liquid to 50.0 ml with the phosphate buffer pH 6.8. The resultant solution is then analyzed by using UV Spectrophotometer at λ_{max} 300.0 nm. Results were tabulated in the Table no. 8.

***In Vitro* Dissolution Study**

Prepared delayed release tablets were evaluated for their integrity in the physiological environment of stomach and small intestine. These study were carried out using USP dissolution test apparatus type-II .The tablets were tested for drug release in 0.1N HCl (900 ml) for first 2 h as average gastric emptying time is 2 h, then dissolution media was replaced with 6.8 pH phosphate buffer (900 ml) for 1 h. At the end of respective time periods, each sample of 10 ml were taken at specified intervals (i.e. 5, 10, 15, 30, 45, 60 minutes) and analysed for Esomeprazole content at 300 nm using UV spectrophometer (Shimadzu UV-1600).

RESULT AND DISCUSSION

Development of Spectroscopic Method

In the present study, UV spectrophotometric method has been developed for the estimation of Esomeprazole in pharmaceutical formulations. Optimum operating conditions used in the procedures were established adopting one variable at a time. The absorption maxima was found to be 300.0 nm. The Beer's law was found in the concentration range of 2-20 µg/ml. The correlation coefficient was found to be 0.9994. The precision and accuracy of the method was established by measuring six replicate samples of the drug in commercial formulations. None of the excipients of the formulation interfered in the analysis of Esomeprazole by this proposed method. The results obtained by the proposed method were in good agreement with the labelled amounts. Performing recovery experiments using standard addition method checked the accuracy of the proposed method. In this, known amount of pure drug was added to the previously analysed samples, and these samples were re-analyzed. The percentage recovery was close to 100% (Table 5). The proposed method is simple, convenient, accurate, sensitive and reproducible. Hence this can be utilized for routine analysis of Esomeprazole in formulations.

Table 5 :Shows Result Of Analysis Of Commercial Formulations

Formulations	Amount labeled mg/tab	Amount found mg/tab	SD*	%RSD*	SE*	't' cal*	% recovery
1	40	40.82	0.121	0.6	0.049	1.324	99.56
2	40	40.67	0.143	0.7	0.058	1.981	99.21
3	40	40.02	0.098	0.4	0.04	1.212	99.79

***Average of six determinations; SD=standard deviation; %RSD= Relative standard deviation; SE= standard error.**

Calibration curve

UV spectra of Esomeprazole (20µg/ml) solution in Phosphate buffer pH 6.8 shows absorbance maxima at wavelength 300.0 nm. This wavelength was considered as λ_{max} in Phosphate buffer pH 6.8. Calibration curve of Eomeprazole in Phosphate buffer pH 6.8 follows Beer-Lambart law in concentration range of 2 to 20 µg/ml with R^2 value of 0.9994 (Figure 2).

Evaluation of Esomeprazole Granules

Esomeprazole powder and the prepared granules were evaluated for angle of repose, poured density, tapped density and compressibility index which was shown in Table 7. The angle of repose of pure Esomeprazole powder could not be measured because the powder was too cohesive to flow through the funnel, where as the value of prepared granules ranged from 27-31. Further, housner factor (HF) measured for pure Esomeprazole was found to be 2.14 which show the cohesiveness of the powder and consequently the very poor flowability. The HF factor for granules ranged from 1.167-1.210, which shows good flow property as a result of increase in particle size owing to granulation. Tapped density of the granules was decreased due to increase in the particle size compared with the pure drug. The % compressibility value for pure Esomeprazole was found to be 53.28, which shows that the pure drug have very poor flowability, where as the values of granules (14.31-17.38) shows good flowability.

Evaluation of core tablets

Prepared tablets are then evaluated by various parameters viz. hardness, diameter and thickness, friability, weight variation and content uniformity.

Results for evaluation of core tablets are summarized in Table no.8.

Table 6: Shows Absorbance Of Esomeprazole At Λ_{max} 300.0 Nm

Sr. No.	Conc.	Absorbance
1	0	0.000
2	2	0.065
3	4	0.114
4	6	0.177
5	8	0.233
6	10	0.290
7	12	0.343
8	14	0.408
9	16	0.465
10	18	0.523
11	20	0.566

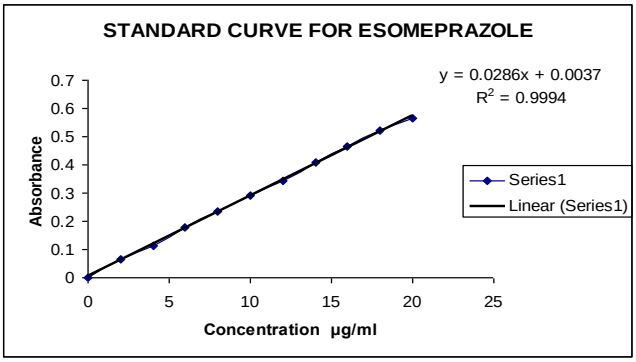

Fig. 2: it shows standard calibration curve for esomeprazole

Table 7 :Shows Physical Properties Of Prepared Granules

Formulations	Angle of repose (θ)	Bulk density (g/cm³)	Tapped density (g/cm³)	Hausner factor	Compressibility (%)
Esomeprazole powder	----	0.256	0.548	2.140	53.28
F1	29	0.423	0.512	1.210	17.38
F2	30	0.397	0.465	1.171	14.56
F3	31	0.425	0.496	1.167	14.31
F4	27	0.274	0.325	1.186	15.61

Table 8 :shows physical properties of delayed release tablets, expressed as mean ± s.d.

Formu-lation no.	Descri-ption	Hardness (Kg)	Friability (%)	Thickness (mm)	Weight (mg)	Disintegration test	Drug content (%)
F1	White coloured, uncoated, bi-convex tablet, plain on both sides	7.00 ± 0.54	0.19	3.8 ± 0.07	160 ± 3.98	Fails	101.32 ± 0.52
F2		6.00 ± 0.26	0.25	3.7 ± 0.08	160 ± 5.21	Passes	99.43 ± 0.43
F3		6.00 ± 0.93	0.37	3.8 ± 0.09	160 ± 4.34	Passes	99.67 ± 0.32
F4		5.00 ± 0.35	0.31	3.6 ± 0.11	160 ± 3.45	Passes	98.69 ± 0.87
DRT1	Slightly brown coloured, enteric coated, bi-convex tablet, plain on both sides	8.00 ± 0.34	NA	4.0 ± 0.08	184 ± 3.98	Passes	101.12 ± 0.89
DRT2		8.00 ± 0.34	NA	3.9 ± 0.06	180± 5.21	Passes	100.12 ± 0.12
DRT3		9.00 ± 0.87	NA	3.8 ± 0.07	175 ± 4.45	Passes	99.65 ± 0.72
DRT4		9.00 ± 0.76	NA	3.6± 0.05	170 ± 3.14	Passes	100.45 ± 0.31

Evaluation of enteric coated tablets

Esomeprazole delayed release tablet were prepared and found to have biconvex surface, circular shape having 7.0 mm diameter. The physical properties such as hardness, friability, thickness, and weight and % drug content of prepared delayed release tablets were presented in. The hardness of tablet range from 5.00 to 8.00 kg/cm². It was also observed that the variation of thickness was minimal. The thickness of prepared tablet ranged from 3.6-4.0 mm; also it was observed that increasing polymer concentration resulted in slight decrease in thickness of the tablet formulation. This result might be due to binding property of polymer. The percentage friability of tablets ranges from 0.19-0.52 % which was in acceptable range. The weight variation (<7.5%) and % drug content (98.69%-101.32%) of the tablet formulations were as per specification.

In *vitro* dissolution of Esomeprazole enteric coated tablets shows that release of drug mostly depends on average weight gain by tablets ultimately amount of polymers that get coated. Coating thickness shows inverse relationship with the release pattern of drug. Initially, after coating (DRT1) average weight gain by tablets was near about 15 % of total weight of tablets gives only near about 75 % release in pH 6.8 phosphate buffer. Hence it was decided to decrease average weight gain of tablets for enteric coating consequently amount of polymers to achieve desirable release pattern of drug and found that approach was positive. In the final formulation (DRT4), average weight gain by tablets was near about 9 % and gives satisfactory release pattern which matches the innovator release profile. Thus, it was observed that near about 9 % (preferably 8-9%) weight gain is sufficient. Thus a pharmaceutically equivalent, robust formulation of Esomeprazole delayed release tablet was developed.

Table 9 :Shows In *Vitro* Dissolution Study Compared With Reference (Innovator)

Sr. No.	Time (minutes)	% Drug Release				
		Rt	DRT1	DRT2	DRT3	DRT4
Acid Resistance Test						
1	**0 -120**	**2.7**	**1.52**	**1.6**	**1.8**	**1.7**
Buffer Stage						
2	05	77.75	13.75	11.53	11.58	78.38
3	10	85.85	23.08	22.18	23.07	92.22
4	15	89.95	41.23	35.88	37.07	95.08
5	30	97.08	52.58	51.88	53.57	98.23
6	45	99.88	65.87	72.02	78.65	100.48
7	60	101.97	75.35	81.47	90.25	100.82

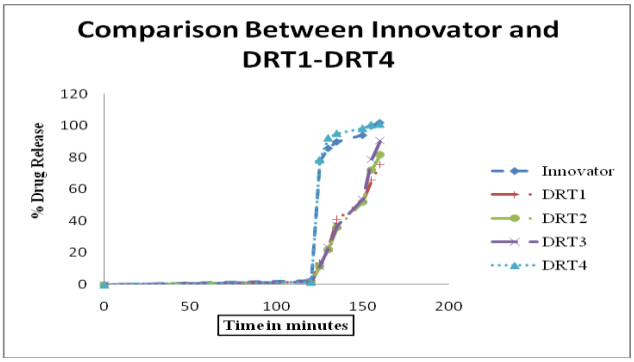

Fig. 3: it shows dissolution profile for innovator and delayed release tablets

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