Review Article

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Naproxen Delayed Release Drug Delivery Systems

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Abstract

Delayed release drug delivery systems are a major advance towards solving problems concerning the stability and solubility of drug in gastrointestinal tract and thereby release the drug in the small intestine. Naproxen is a non-selective Cyclo-oxygenase (COX) inhibitor, which is insoluble in acidic environment and cause gastric distress or irritation. In order to prevent the gastric irritation, Naproxen is designed to formulate as Enteric coated tablet which is more soluble in pH 6.8 at small intestine.

Keywords: Naproxen; Cyclo-oxygenase (COX) inhibitor; Delayed release drug delivery systems.

Aim of the Present Study

Delayed release drug delivery systems are a major advance towards solving problems concerning the stability and solubility of drug in gastrointestinal tract and thereby release the drug in the small intestine. Naproxen is a non-selective Cyclo-oxygenase (COX) inhibitor, which is insoluble in acidic environment and cause gastric distress or irritation. In order to prevent the gastric irritation, Naproxen is designed to formulate as Enteric coated tablet which is more soluble in pH 6.8 at small intestine.

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The aim of present study is to develop a pharmaceutically, equivalent, low cost quality improved formulation of 500 mg Naproxen Enteric coated tablets comparable to the innovator product (Naprosyn).

Objective

The objective of present study was to develop Naproxen delayed release tablets of which will meet the standards to that of the innovator product with the subsequent achievement of in-vitro correlation with the innovator product. The Innovator product of the Naproxen Hcl is Naprosyn.

The Major Objectives of this Investigation are as Follows-

- To prepare Naproxen delayed release tablets by wet granulation method by using enteric polymers.
- To evaluate the Micromeritic properties of API as per standard specifications.
- To perform the drug-excipient compatibility studies by physical observation.
- To evaluate the Micromeritic properties of prepared granules as per standard specifications.
- To evaluate the physicochemical properties of the formulated tablets as per specifications.
- To perform the in vitro dissolution studies for the formulated tablets as per specifications.
- To compare the in-vitro dissolution profiles of formulated tablets
- To evaluate the drug release kinetics from the

delayed release matrix tablets.

- To compare the dissolution data (similarity factor) for the optimized formulation with marketed product.
- To conduct the stability studies for the optimized formulation as per ICH guidelines.

Plan of Work

- Collection of the relevant literature.
- Selection of drug and excipients.
- Pre-formulation studies, like
  - a) Bulk density
  - b) Tapped density
  - c) Compressibility index
  - d) Angle of repose
  - e) Hausner's ratio
- Drug- Excipient Compatibility studies.
- Preparation of the Naproxen delayed release tablets.
- To evaluate the different formulations of Naproxen delayed release tablets for following parameters
  - a) Appearance
  - b) Hardness
  - c) Weight variation test
  - d) Friability
  - e) Thickness
  - f) Percentage of drug content
- Study of *in-vitro* drug release profile for Naproxen delayed release tablets
- Selection of best formulation on the basis of *in-vitro* drug release and Similarity factor (f2).

Stability studies according to the ICH guidelines.

Drug - Excipient Compatibility Study

The objective of drug/excipient compatibility considerations and practical studies is to delineate, as quickly as possible, real and possible interactions between potential formulation excipients and the API. This is an important risk reduction exercise early in formulation development. Homogenous mixtures of drug and excipients were prepared and filled in glass vials and self-seal LDPE (Low Density Poly Ethylene) bags.

Conditions

a. Samples packed in glass vials were maintained at 60 2°C for 2 weeks.

b. Those packed in LDPE bags were maintained at 40 ± 2°C/75 ± 5% RH for 1 month.

c. Samples packed in glass vials are kept in controlled conditions (2-8°C) for comparison purpose. All the samples mentioned above were compared for physical characteristics with those of the initial samples.

Preparation of Calibration Curve for Naproxen

A. Standard Curve in Methanol

1. Stock Sample Preparation

Accurately weighed 100 mg of drug (Naproxen) was first dissolved in100 mL of Methanol in 100 mL of volumetric flask to make a concentration of 1000 µg/mL (primary stock solution). 5 mL of primary stock solution was pipetted out into 50 mL of volumetric flask and volume was adjusted with Methanol to make a concentration of 100µg/mL (sondary stock solution).

Sample Preparation

From the sondary stock solution various concentrations such as 5, 10, 15, 20, 25, 30, 35, 40 µg/mL were prepared for calibration curve. Standard curve was plotted by taking absorbance of sondary stock solutions in UV double beam spectrophotometer at 271 nm.

B. Standard Curve in Phosphate Buffer (pH 6.8)

1. Stock Sample Preparation

Accurately weighed 100 mg of drug (Naproxen) was first dissolved in 100 mL of phosphate buffer (pH 6.8) in 100 mL of volumetric flask to make a concentration of 1000 µg/mL. (primary stock solution) 5 mL of primary stock solution was pipetted out into 50 mL of volumetric flask and volume was adjusted with phosphate buffer (pH 6.8) to make a concentration of 100 µg/mL (sondary stock solution).

Sample Preparation

From sondary stock solution various concentrations such as 5, 10, 15, 20, 25, 30, 35, 40 µg/mL were prepared for calibration curve. Standard curve was plotted by taking absorbance of sondary stock solutions in UV double beam spectrophotometer (at 332 nm).

Formulation and Development of Naproxen Delayed Release Tablets

Steps involved in the preparation of Naproxen delayed release tablets

1. Preparation of core tablets
2. Enteric coating of optimized core tablets

Preparation of Naproxen Core Tablets

Core Tablets has been Prepared by

1. Direct Compression method
2. Wet Granulation method

Direct Compression Method

Step 1: All the ingredients-Naproxen and Sodium Starch Glycolate (SSG), L-HPC have been weighed individually into separate poly bags.

Step 2: These ingredients are then sifted though sieve no. 40 and blended together in a poly bag for 10 min.

Step 3: Lubrication-Weighed amount Stearic Acid sieved though mesh sieve no. 60 are added to the above blend and blending is carried out for 5 more min.

Step 4: Compression-The lubricated blend is compressed using 16×8 mm Oblong deep concave punch toolings.

Upper punch: Plain

Lower punch: Plain.

Step 5: Description of core tablets:

White and Oblong biconvex tablet plain on both sides.

Table 1: Formula for the preparation of core tablets by Direct Compression method

S No	Ingredients	F1 (mg / tab)
1.	Naproxen	500
2.	L-HPC LH-11	10
3.	Crospovidone	20
4.	Stearic acid	5
	Total weight of core tablet (mg)	535

Wet Granulation Method

Trial batches have also been formulated using Wet Granulation method for the purpose of Comparison between the two granulation methods (Direct compression method and Wet granulation method).

Steps Involved in Wet-Granulation

1. Weighing and Sifting: Naproxen and Sodium Starch Glycolate (SSG) were weighed and sieved though sieve number 40 and collected and mixed in a poly bag.
2. Preparation of Binder: Binder was prepared by dissolving L-HPC in the purified water under stirring and it was continued until clear solution was obtained.
3. Dry Mixing: Dry mix Naproxen, SSG in rapid mixing granulator for 10 min.
4. Granulation: Binder was added at slow speed to granulate the mixture.
5. Wet Milling: The wet mass was milled though multi mill though sieve number 12.
6. Drying and Dry Milling: The wet granules were

Table 2: Optimization of core tablets by Aqueous Wet Granulation

S. No.	Ingredients	Trial Batches (mg/Tablet)								
		F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Naproxen	500	500	500	500	500	500	500	500	500
2.	L – HPC	0.5	1	4	8	12	16	20	16	16
3.	Crospovidone	15	-	-	-	-	-	-	-	-
4.	SSG	-	14	14	14	14	14	14	14	14
4.	Purified water*	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Pre-Lubrication									
5.	SSG	-	2.5	2.5	2.5	2.5	2.5	2.5	5	5
	Lubrication									
6.	Stearic Acid	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	5
	Total weight of the core	518	520	523	527	531	535	539	537.5	535

* Purified water was evaporated during drying of granules

dried in fluid bed drier at a temperature of 60°C and the dried granules were sieved though sieve number 18.

7. Pre-Lubrication: SSG was sieved though sieve number 40, blended with the above dried granules for 3 min.
8. Lubrication: Stearic acid was added to pre-lubricated granules and lubricated for 2 min.
9. Compression: The lubricated granules were compressed with 16 mm concave punches with a tablet weight of 500 mg, respectively on a 12 stationary compression machine.
   i. Upper punch: Plain
   ii. Lower punch: Plain.

Description of Core Tablets: White and Oblong biconvex tablet plain on both sides.

Evaluation of Naproxen Core Tablets

Weight Variation

This test is not applicable to coated tablets other than film coated tablets and to tablets that are required to comply with the test for uniformity of content for all active ingredients. USP and NF provide limits for the permissible variations in the weights of individual tablets expressed as a percentage of the average weight of the sample.

Individually weighed 20 tablets and calculated the average weight not more than two of the individual weights deviate from the average weight ore than the percentage deviation shown in Table 3 and more deviated by more than twice that percentage.

$$\text{Percentage deviation} = \frac{[\text{Weight of tablet (mg)} - \text{Average weight of tablet (mg)}]}{\text{Average weight of tablet (mg)}} \times 100$$

Table 3: Limits for weight variation

Average weight of Tablets (mg)		Maximum Percentage deviation (%)
USP	**IP**	
130 or less	80 or less	10
130-324	80-250	7.5
324 or more	250 or more	5.0

Thickness

Thickness mainly depends up on die filling, physical properties of material to be compressed under compression force. The thickness of the tablets was measured by using Digital Vernier Calipers.

Desired thickness: **3.6 – 4.0 mm**

Hardness

Hardness of the tablet is defined as the force required in breaking a tablet in a diametric compression test. In this test, a tablet was placed between two anvils, force was applied to the anvils and the crushing strength that just causes the tablet to break is recorded. Hence hardness is sometimes referred to as Crushing Strength. Tablets require certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of a tablet, like its thickness, is a function of the die fill and compression force. At a constant die fill, the hardness value increases and thickness decreases as additional compressional force is applied. At a constant compression force (fixed distance between upper and lower punches), hardness increases with increasing die fills and decreases with lower die fills.

Desired hardness: **8-15 kp**

Friability

Friability is defined as the loss in weight of tablet in the container due to removal of fine particle from their surface. It is expressed in percentage (%). A preweighed tablet sample (20 tablets) was placed in the friabilator chamber and rotated for 10 revolutions. In each revolution the tablets are carried up and are allowed to freely fall from a height of 6

inches. After 100 revolutions the tablets are removed from the chamber, dusted and reweighed. When capping is observed during friability test, tablets should not be considered acceptable, regardless of percentage weight loss.

% Friability was then calculated using the following formula:

Friability = [(Initial wt – Final wt)/ Initial wt] X 100

Limit: Friability should be less than **1%**

Table 4: Coating Formula

S. No.	Ingredients	For mg/tablet
	Dispersion	
1.	Eudragit L 100-55	54.4
2.	1 N NaOH	18.4
3.	Water	111.2
	Total Weight	184
	Redispersion	
1.	Dispersion	184
2.	Talc	27.2
3.	Tri ethyl citrate	5.44
4.	Water	218

Disintegration

Disintegration is breakdown of the tablet into smaller particles and granules. The time i.e. taken by a tablet to disintegrate is measured in a device described by USPNF. 6 tablets of each formulation were taken and placed in 6 tubes of disintegration apparatus. Purified water was used as the medium for disintegration. The results of evaluation of Naproxen un-coated tablets were tabulated in Tables 4 & 5 respectively

Enteric Coating of the Selected Core Tablets

Preparation of Enteric Coating Dispersion

Eudragit L 100-55 was added to water under continuous stirring. To that freshly prepared 1N NaoH (4% Solution) was added and stirred continuously for 10 min and then kept aside. To the water, talc was added under stirring and then Tri ethyl citrate was added slowly. Stirring was continued for 10 min. To the final dispersion, talc dispersion was added slowly under continuous stirring. Stirring was continued for 30 min. The final dispersion was passed though Nylon cloth and collected into a stainless steel container.

Table 5: Enteric Coating Parameters

Inlet Temperature	50 – 55°C
Exhaust Temperature	35 – 40°C
Atomization	1.5 - 2.0 kg/cm^2
Pan Rotation	4 - 5 rpm
Pump rpm	20 – 25
Spray rate	5 rpm

Table 6: Different enteric coating percentages applied to the selected formulation

Parameters	E2	E3	E4	E5
Weight of tablets (gm)	134.94	107.54	80.04	51.64
Initial weight (gm)	131.2	104.32	76.82	48.82
Weight after coating (gm)	137.02	110.01	76.82	48.82
% Coating (%)	4	6	8	10
Weight of 50 tablets (gm)	27.40	27.5	28.2	28.65
Average weight (mg)	548	555	564	573

pH of the final dispersion = 5.52

Procedure for Enteric Coating of Core Tablets

The Optimized core tablets were loaded into coating pan and the tablet bed was warmed till the temperature reaches to 50°C-55°C. The enteric coating dispersion should be kept under continuous stirring during the coating process. The coating was

continued till target weight build has been achieved. More than 2% build up of enteric coating has been given to the core tablets. After target build up has been achieved, the pan speed was reduced and spray gun was turned off. Then the tablets were warmed at the temperature of 38°C-40°C for 10 minutes. The enteric coated tablets were then collected into a container.

The following were the pan parameters to be maintained during the process of enteric coating.

Weight of 300 tablets = 170.924 gm (Average weight = 534.8 mg)

Weight of tablets after warming = 158.7 gm (Average weight = 533.6 mg)

Weight after Coating = 161.92 gm

% Coated = 2 % (**E1**)

Weight of 50 tablets = 26.98 gm

Remaining tablets were further coated.

Among the various trial batches of core tablet formulations prepared by Wet granulation method, one formulation was optimized and different percentages of enteric coating have been applied. These coated formulations were labeled as E1, E2, E3, E4 and E5.

Evaluation of Naproxen Delayed Release Tablets

Coating Uniformity (CU) [14]

CU is generally defined as the variation in weight gain of coated tablets within a coating trial. The reported standard deviation (SD) was calculated as

Standard deviation (SD) = $\{\Sigma [(W_{ta} - W_{tb}) - x] 2/ (n-1)\} 1/2$

Where, W_{ta} and W_{tb} are the weights of tablet after and before coating, corrected for moisture content by drying to final weight, n is the number of tablets measured, x is the average weight gain of the n measured tablets from the coating trial.

Note that the equation is simply the first standard deviation (SD) of the variation in weight gain within a trial. As SD decreased the coating uniformity increased and as SD increased the coating uniformity decreased.

Coating Process Efficiency (CPE)

Coating process efficiency (CPE) is a measure of the actual amount of coating applied to the tablets relative to the theoretical quantity of coating applied. It can therefore be another indicator of over wetting or over drying. When over wetting occurs, material can potentially be transferred from the surface of the tablets to the walls of the coating pan, thus reducing CPE. Conversely, when over drying occurs, coating solution can dry prematurely in the air stream and be lost into the exhaust air stream instead of being transferred to the tablets.

Coating process efficiency was determined by the following equation.

CPE = (%Wga / %Wgt) ×100%

Where, Wgt is the theoretical percent weight gain, which in this experiment was 3% in every coating trial, and Wga is the actual percent weight gain, which is computed as,

Processing % Wga = [(Wta – Wtb) Wtb] ×100%

Where, Wtb and Wta are the total batch weights before and after coating, respectively.

% LOD

% LOD is the moisture content of the coated tablet expressed as percent weight. The tablets were weighed, dried at 60 °C for 24 h, and then reweighed. All uncoated tablet cores used in this study had an initial moisture content of 3%. %LOD was determined by the following equation.

% LOD = [(Wtb – Wta) / Wtb] ×100%

Weight Variation Test

To study weight variation twenty tablets of the formulation were weighed using electronic balance and the test was performed according to the official method.

Dimensional Changes

Dimensional changes were included both diameter and thickness changes of coated tablets. Both diameter and thickness changes were measured by vernier calipers.

Hardness

The hardness of five tablets was determined using the Monsanto type hardness tester and the average values were calculated.

Friability

The friability of ten tablets was measured by Roche friabilator and average values were calculated.

Uniformity of Content

The enteric coated tablets of Naproxen were tested for their drug content. Ten tablets were finely

powdered; quantities of the powder equivalent to 20 mg of Naproxen were accurately weighed and transferred to a 100 mL of volumetric flask. The flask was filled with Methanol and mixed thoroughly. Volume was made up to mark with Methanol and filtered. The absorbance of the resulting solution was measured at the 271 nm using a UV double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was use for estimation of Naproxen in the tablets formulations.

Disintegration Time

Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP Disintegration Apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing 0.1N HCL (pH 1.2) maintained at 37°C±2°C and operated the apparatus for 2 h. After 2 h 0.1N HCL was replaced with phosphate buffer pH 6.8. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

In-Vitro Drug Release Studies

Preparation of 0.1 N HCl

8.5 mL of HCl was diluted to 1000 mL with water.

Preparation of 0.5 N NaOH

Table 7: Dissolution Studies of Enteric Coated Tablets

	ACID STAGE	BUFFER STAGE
Dissolution apparatus	USP XXIV dissolution testing apparatus II (paddle method)	USP XXIV dissolution testing apparatus II (paddle method)
Dissolution medium	0.1N HCl	pH 6.8 phosphate buffer
Volume of receptor fluid	1000 mL	1000 mL
Temperature	37±0.5°C	37±0.5°C
Rpm	50	50
Total dissolution time	2 h	60 min
Sampling time (min)	30,60,90,120	10,20,30,45,60
Sampling volume	10 mL	10 mL
Analysis	Spectrophotometer at 332 nm	Spectrophotometer at 332 nm

20 gms of NaOH pellets were weighed and transferred into a 1000 mL volumetric flask. Dissolve and dilute to volume with water.

Preparation of pH 6.8 Phosphate Buffer

6.8 gms of Potassium dihydrogen phosphate was weighed and transferred into a beaker containing 1000 mL of water and sonicated to dissolve and adjusted the pH by using 0.5 N NaOH solutions.

Procedure

Drug release studies were carried out using a USP type II dissolution test apparatus at 50 rpm (without discs) for 2 h in 0.1 N HCl (1000 mL) maintained at 37°C ± 0.5°C. 10 mL of sample was taken and sample was analyzed using UV spectrophotometer at 332 nm. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (1000 mL) and tested for drug release for 1 h at same temperature and same rotation speed (with discs). After 10, 20, 30, 45 and 60 minutes, 10 mL of the samples were taken out and 10 mL volume of fresh phosphate buffer pH 6.8 was added to kept volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 332 nm. All dissolution studies were performed in 6 times.

a. Assay

b. Dissolution study (acid followed by buffer)

Values of t_{50}, t_{90} and the percentage dissolved in 30 min are used as guides in industry. The value for t_{50} is the length of the time required for 50% of the drug to go into solution. A value for t_{90} of 30 min is often considered satisfactory and is an excellent goal since a common dissolution tolerance in the USP/NF is not less than 80% dissolved in 45 min. The results of

Table 8: Significance of similarity factor value

Similarity Factor	Significance
<50	Test and reference profiles are dissimilar
50-100	Test and reference profiles are similar
100	Test and reference release profiles are identical
>100	The equation yields a negative value

Naproxen Enteric coated tablets were tabulated in Table 7.

Kinetics of Drug Release

Kinetics of drug release was studied by plotting the data obtained from in-vitro release in various kinetic models.

Comparision of Dissolution Profiles

Model Independent Approach

According to US FDA guidance for dissolution data equivalence, model independent approach is recommended. This involves the use of similarity (f_2) and dissimilar factor (f_1) which provides simple means to compare the dissolution data.

Similarity Factor (f_2)

The similarity factor f_2 was defined as a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves. This was calculated to compare the test product and reference product with respect to the drug release or dissolution profiles.

The method is more adequate to compare the dissolution profiles when more than thee or four dissolution time points are available and can be applied if average difference between Rt and Tt is >100.

Dissimilarity Factor (f_1)

It is also called as Difference factor. It describes the relative percentage error between two dissolution profiles. The percent error is zero when the test and reference profiles are identical and increases the proportionality with the dissimilarity between the two profiles.

$$f_1 = \{[\Sigma_{t=1} n (Rt-Tt)] / \Sigma_{t=1} n Rt]\} \times 100$$

Stability Studies

Stability is defined as the capacity of a drug substance or drug product to remain within the established specifications to maintain its identity, strength, quality and purity thoughout the retest or expiration dating period.

Objective of the Study

The objective of stability study is to determine the shelf life, namely the time period of storage at a specified condition within which the drug product still meets its established specifications. Stability is an essential factor of quality, safety and efficacy of a drug product. A drug product, which is not of sufficient stability, can result in changes in physical (like hardness, dissolution rate, phase separation etc) as well as chemical characteristics (formation of high risk decomposition substances).

The Chemical stability of drug is of great importance since it becomes less effective as it undergoes degradation. Also drug decomposition may yield toxic byproducts that are harmful to the patient. Microbiological instability of a sterile drug product could also be hazardous.

Stability testing provides evidence that the quality of drug substance or drug product changes with time under the influence of various environmental conditions such as temperature, relative humidity etc.

The stability study consists of a series of tests in order to obtain an assurance of stability of a drug product, namely maintenance of the drug product packed in it specified packaging material and stored in the established storage condition within the determined time period.

The International Conference on Harmonization (ICH) Guidelines describes the following stability test storage conditions:

Long-term Testing : 25°C ± 2°C / 60% RH ±5% RH for 12 Months.

Intermediate Testing : 30°C ± 2°C / 65% RH ± 5% RH for 12 months.

Accelerated Testing : 40°C ± 2°C / 75% RH ± 5% RH for 6 Months.

Procedure

Selected batch tablets were packed in thee individual 40°C LDPE containers along with 4 gm of silica gel canisters, which serves as desiccant, with 30 counts in each container. The bottles were loaded at accelerated conditions i.e. 40°C/ 75% RH and at long term conditions i.e. 25°C/60% for 2 month periods. The results were tabulated in Tables 7 respectively.

Summary and Conclusion

The Present study was undertaken with an aim to formulate and evaluate Naproxen delayed release tablets, mainly used for the treatment of musculo-

skeletal and joint disorders such as ankylosing spondylitis, osteoarthritis, rheumatoid arthitis and acute gout. Preformulation studies were carried and results were found to be satisfactory. Experiment was started with physical parameters such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose of the Active Pharmaceutical Ingredient. The compatible excipients were selected for the formulation development. Experiment was performed by using both dry and wet granulation techniques based on the flow properties of API. In order to increase the flow property of the tablets, wet granulation was chosen for further formulation and found to be satisfactory. During development of formula, in-process tests such as bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose were evaluated for granules and hardness, friability, weight variation, thickness and disintegration were evaluated for the core tablets. Core tablets were coated with coating suspension. Materials used for coating were shown in the Table 6. Finished products were evaluated for hardness, friability, weight variation, thickness, disintegration, dissolution and drug content. The developed trials were tested for in-vitro dissolution profile and compared with the reference product Naprosyn. The *in-vitro* dissolution of E3 was nearest to the reference product (f_2 = 85.17).The coated tablets of E3 formulations were packed in HDPE containers and stability studies performed at 45°C /75% RH, 25°C / 60% RH for 2 months. Stability samples were evaluated initially and after 2 months. The results were compared with the pre-determined specifications. All the results were found to be satisfactory. It may be concluded from the present study that Naproxen delayed release tablets showed acid resistance and the release was comparable with that the innovator. It was evident from the results that 6% Eudragit L 100-55 coated tablets followed first order release and formulation E3 was found to be an optimized formulation.

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