Original Article

Development and Optimization of Naproxen Sodium Controlled Release Tablets: QbD Approach

Atul Phatak[1,*], Dhanashri Joshi[1], Mahesh Bhadgale[2], Pravin Chaudhari[1]

[1]Department of Pharmaceutics, PES's Modern College of Pharmacy, Sector 21, Yamunanagar, Nigdi, Pune, Maharashtra, INDIA.
[2]Department of Formulation Research and Development, Callidus Research Labs, Chakan Industrial Area, Nighoje, Pune, Maharashtra, INDIA.

ABSTRACT

Objectives: The aim of present study was to formulate and optimize Multi-unit Naproxen Sodium controlled release tablet by QbD approach. Controlled release dosage form for naproxen sodium was selected to reduce dosing frequency and gastrointestinal side effects of drug. **Methods:** Naproxen Sodium CR tablets were prepared by using wet granulation method by employing Quality by Design (QbD). This tablet was made by a mixture of a granulate having an immediate release with a granulate having a controlled release, in terms of the active ingredient. Eudragit RSPO and RLPO polymers were used to control the drug release. Optimization of tablet formulation was done using 2^3 factorial design to study the effect of concentration of Eudragit RSPO, Eudragit RLPO polymers and concentration of disintegrating agent i.e. crospovidone on disintegration time and f2 factor of drug released. Tablets were evaluated for thickness, hardness, friability, assay and drug release. **Results:** Optimized formulation shows controlled drug release profile upto 14 hrs. with disintegration time of 88 min. **Conclusion:** It was concluded that tablet formulation of Naproxen Sodium CR tablets employing QbD leads to a single dose per day in the management of rheumatoid arthritis and also concluded that Eudragit RLPO and Eudragit RSPO polymers can be successfully used to controlled drug release profile of tablet.

Key words: Multi-unit-controlled release system, Quality by Design, Design of experiment, Eudragit RLPO, Eudragit RSPO.

INTRODUCTION

Quality by Design (QbD) is a systemic approach to pharmaceutical development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.[1] One of the major parameters in QbD is developing a design space which includes equipment, excipients and manufacturing environment. To ensure better quality of product, the product variables are periodically monitored in design space. Large scale productivity can be improved by applying QbD approach. Hence, this approach is beneficial from market point of view.[2]

Multiple-units composition is used for administration of a therapeutically effective amount of NSAID to obtain both a relatively fast or quick onset of therapeutic effect and maintenance of therapeutically active plasma concentration for a relatively long period of time.[3]

Naproxen Sodium Is Non-steroidal Anti-inflammatory (NSAID) drug which is widely used in the treatment of arthritis and as analgesic and antipyretic in the treatment of mild to moderate pain, such as dysmenorrhea or arthritis. This drug is acting by blocking COX-1 and COX-2 enzymes thereby inhibit prostaglandin synthesis and gives analgesic and anti-inflammatory effect. Inhibition of COX-1 is related with gastrointestinal and renal toxicity, while inhibition of COX-2 gives

Submission Date: 13-08-2019;
Revision Date: 27-09-2019;
Accepted Date: 26-02-2020

DOI: 10.5530/ijper.54.2s.67

Correspondence:
Dr. Atul Phatak,
Department of Pharmaceutics, P.E.S's Modern College of Pharmacy, Nigdi, Pune-411044, Maharashtra, INDIA.
Phone: +91 9822449380
E-mail: atulapin@yahoo.com

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anti−inflammatory activity.[4,5] In these new formulations, drug from IR granules was released in a short time, so that it quickly develop its therapeutic action and reach therapeutic blood levels, while the remaining portion of the drug in CR granules was released in a longer interval of time so as to maintain therapeutic concentration until subsequent administration. These therapeutic concentrations can even last twenty-four hours.[6] The objective of research work was to develop controlled released multi-particulate Naproxen Sodium tablet employing QbD approach to reduce the dosing frequency and adverse GI side effect of drug.

MATERIALS AND METHODS

Materials

Naproxen Sodium was obtained from Divis Laboratories Limited, India. Eudragit RLPO, Eudragit RSPO and Eudragit L100 were supplied by S. Zhaveripharmakem Pvt. Ltd, Dombiveli, Maharashtra. Citric acid was from Merck India Ltd, Mumbai. Crospovidone was from Signet Industries Ltd, Mumbai. Magnesium stearate was obtained from Peter Greven GmbH and Co. KG, Germany. Microcrystalline cellulose was obtained from JRS Pharma GmbH and Co. KG, Germany. Povidone K-30 and all other ingredients used throughout the study were of analytical grade.

Methods

Quality Target Product Profile for Naproxen sodium CR Tablets

QTTP is the prospective summary of the quality characteristics of a drug product that ideally ensure the desired quality, taking into account safety and efficacy of the drug product.[7] Brief explanation about QTTP that affects formulation of Naproxen Sodium CR Tablets shown in Table 1.

Identification of critical and non-critical quality attributes (CQAs) for Naproxen Sodium CR Tablets

CQAs were established based on the QTTP's defined in the above table for the development of Naproxen sodium CR tablets. The attributes which are related to the safety of the formulated product and which have a potential effect on formulation variable during development of process are termed as CQA.[2,8] Brief explanation about CQA's were depicted in Table 2.

Manufacturing process of Naproxen sodium CR Tablets using DOE

Experimental Design

A 2^3 factorial design with 3 center points were employed to optimize the tablet formula.

In this design independent factors were concentration of Eudragit RSPO, Eudragit RLPO polymers and concentration of disintegrating agent i.e. Crospovidone. Disintegration time and F2 factor of drug released were selected as responses. The coded values of design for Naproxen Sodium CR tablets are given in Table 3.

Preparation of Naproxen Sodium CR Tablets

Tablets were formulated by using following procedure.[9,10]

i. **Preparation of CR granules:** Weighed quantity of naproxen sodium, citric acid, Eudragit RLPO, Eudragit RSPO were passed through 30 # sieve and dry mixed for 5 min. Wet granulation was done by using Eudragit L binder solution. Semi-dried granules were passed through 20# Sieve. Granules were dried at 40°C for 20 min.
ii. **Preparation of IR granules:** Weighed quantity of naproxen sodium and MCC pH101 were passed through 30 # sieve and dry mixed for 5 min. Wet granulation was done by using povidone K-30 binder solutions, granules were dried at 60°C for half hour and passed through 30# sieve.
iii. **Blending of CR and IR granules with extra granular part:** CR and IR granules were blended with MCC pH 102, crospovidone for 15 min at 14 rpm. and lubrication was done with magnesium stearate for 10 min. Then blend was compressed into tablets. Composition for all batches of Naproxen sodium CR tablet is shown in Table 4.

Characterization of CR and IR granules[11,12]

Bulk density

Bulk density was measured by pouring 20 g of the granules (W) into a 100 ml measuring cylinder and the initial volume was noted. This volume was considered as bulk volume. From this, the bulk density was calculated by using formula given below.

$$\text{Bulk density} = W / V_b$$

Where W = Weight of the granules and V_b = Bulk volume of the granules.

Tapped density

Tapped density is defined as the ratio of total mass of granules to the tapped volume of powder. Tapped volume was measured by tapping the granules for 100 times. Tapped density was calculated by using formula given below.

$$\text{Tapped density} = W/V_t$$

Where W = Weight of the granules and V_t = Tapped volume of granules.

Table 1: QTTP of Naproxen Sodium CR Tablets.

QTPP Element	Target	Justification
Dosage form	Tablet	ANDA needs same dosage form as that of Reference product
Dosage Design	Controlled Release tablets	Controlled Release design needed to meet label claim.
Route of administration	Oral	Pharmaceutical equivalence requirement: Same route of administration
Dosage strength	Naproxen Sodium CR Tablets 750 mg	Pharmaceutical equivalence requirement: Same strength as that of Reference product.
Pharmacokinetics	Fasted and Fed condition Bioequivalence study.	Bioequivalence requirement Initial plasma concentration through the first two hours that provides a clinically significant therapeutic effect followed by a sustained plasma concentration that maintains the therapeutic effect
Stability	At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes Identification Assay Weight variation Residual Solvents Drug Release Related Substances Water Content	Pharmaceutical equivalence requirement : Meeting the same compendia or other applicable (quality) standards (i.e., identity, assay, purity and quality)
Container Closure System	Suitable container closure system to achieve the target shelf-life and to ensure tablet integrity during shipping.	HDPE bottles with Child Resistant (CR) Caps are selected based on similarity to the RLD packaging. No further special protection is needed due to the stability of drug substance

Table 2: Critical and non-critical quality attributes (CQAs) for Naproxen Sodium CR Tablets.

Drug Product quality attributes		Target	Is this critical?	Justification of Criticality
Physical Attributes	Description and Color	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Commercial requirement.
	Shape			
	Size	Similar to RLD	Yes	Tablet size correlates to swallowability; therefore, it is critical. For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet size and volume is set similar to the RLD.
Water Content		Not more than 2.0% w/w	No	Limited amounts of water in oral solid dosage forms will not impact patient safety or efficacy. Therefore, it is not critical.
Weight Variation		Complies with Pharmacopoeial requirement	Yes	Manufacturing process impact weight variation of drug product.
Dose Uniformity		Complies with Pharmacopoeial requirement for uniformity of dosage units	Yes	Both formulation and process impact the uniformity.
Assay of Naproxen Sodium		90% - 110% of label claim	Yes	Variability in assay will affect safety and efficacy; therefore, assay is critical.
Dissolution Media: pH 7.4 Phosphate buffer, Type: USP-II(Paddle), Media Volume: 900ml, Speed: 50 RPM Time points: 0.5,1,2,3,4,6,8,10,12, 14 hr.		Similar drug release profile as RLD using a predictive dissolution method (as per USP)	Yes	The drug release profile is important for BA and BE; therefore, it is critical. For tablets containing a multi-particulate system, a non-uniform distribution of CR granules may cause different drug release in tablet. Therefore, it is critical.
Related Substances/Impurities		Individual unknown degradation product: NMT 0.2%Total degradation products: NMT 1.0%	Yes	The limit of degradation products is critical to drug product safety. The limit for individual unknown degradation products complies with ICH Q3B. A limit for the total degradation products is set based on analysis of the RLD near expiry.

Compressibility index

It can be calculated by using following formula.

$$\text{DPPH radical scavenging effect (\%)} = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control} \times 100}$$

A material having values of less than 20% has good flow property.

Hauser's Ratio

Hausner's ratio is an indirect way of accessing the ease of granules flow. It was calculated by the ratio of tapped density to the bulk density.

$$\text{\% Moisture content} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}}$$

Table 3: Coded values of design.

Sr. No.	Name	Low (-1)	High (+1)
1	X_1 (Eudragit RL PO)	54.5	94.5
2	X_2 (Eudragit RS PO)	129	169
3	X_3 (Crospovidone)	142.25	182.25

Evaluation of Naproxen Sodium CR Tablets[11,12]

Weight Variation

Weight variation test was done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. Standard deviation were calculated and checked with the standard USP pharmacopoeial limits.

Thickness and Diameter

10 tablets were randomly picked from each batch and their thickness and diameter were measured using a calibrated dial Vernier caliper (Mitutoya Digimatic Caliper, Kanagawa Japan). (± 5% is allowed).

Hardness

The hardness of each batch of tablet was checked by using Erweka hardness tester. The hardness was measured in terms of Newton (N). 5 tablets were chosen randomly and tested for hardness.

Friability

20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friabilator (Model 902, EI product, Panchkula, India) and rotated at the speed of 25 rpm for 100 revolutions. Then

Table 4: Composition of DOE batches.

Sr.no	Name of Ingredient	Quantity in mg/tab										
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
CR granulate part												
1	Naproxen Sodium	577.5	577.5	577.5	577.5	577.5	577.5	577.5	577.5	577.5	577.5	577.5
2	Citric acid	82.5	82.5	82.5	42.5	42.5	82.5	82.5	82.5	122.5	82.5	122.5
4	Eudragit RLPO	94.5	74.5	74.5	94.5	94.5	54.5	54.5	74.5	54.5	94.5	54.5
5	Eudragit RSPO	129	149	149	169	169	169	169	149	129	129	129
Binder												
6	Eudragit L 100	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5	46.5
7	Ethanol	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s	q.s
IR granulate part												
8	Naproxen Sodium	247.5	247.5	247.5	247.5	247.5	247.5	247.5	247.5	247.5	247.5	247.5
9	MCC 101	45.05	45.05	45.05	45.05	45.05	45.05	45.05	45.05	45.05	45.05	45.05
Binder												
10	Povidone K-30	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95	2.95
11	Water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Extra-granular part												
12	Crospovidone	182.2	162.2	162.2	142.2	182.2	142.2	182.2	162.2	142.2	142.2	182.2
13	MCC 102	15.25	35.25	35.25	55.25	15.25	55.25	15.25	35.25	55.25	55.25	15.25
14	Magnesium stearate	10	10	10	10	10	10	10	10	10	10	10

Tablet weight- 1433 mg

tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded. Percentage friability was calculated by using the formula:

$$\text{Tensile strength} = \frac{N}{mm^2} = \frac{\text{Load at failure} \times 100}{\text{Strip thickness} \times \text{Strip width}}$$

Disintegration Test

The disintegration time of tablet was determined by using Disintegration test apparatus. 6 tablets were randomly selected and placed them in the disintegration basket containing 900 ml of water, maintained the temperature at 37± 2°C. Time taken for complete disintegration of tablets was noted.

In vitro dissolution study

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus (Lab India, DS 8000, Mumbai, India) at 50 rpm. Dissolution media was phosphate buffer pH 7.4 for 14 hrs. and temperature was maintained at 37±0.5°C. Sampling time interval set at: 30 min, 1,2,3,4,6,8,10,12 and 14 hr. After each time interval 5ml was withdrawn and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 7.4, filtered and analyzed on UV spectrophotometer (Shimatzu UV 1800) at 332 nm using pH 7.4 as a blank. Percentage drug release was calculated.

Assay of Tablet[13]

Assay of Naproxen Sodium CR tablet was performed by using following procedure.

- **Preparation of standard solution**
  Weighed 23mg of naproxen sodium and transferred into the 50ml volumetric flask, added sufficient water to dissolve the drug. Sonicate this solution for 15min. After sonication volume was make up to 50ml with water. Pipette out 10ml of this solution and diluted up to 50ml with water.
- **Preparation of sample solution**
  20 tablets were weighed and powdered. Weighed quantity of powder equivalent to 600 mg of Naproxen sodium API.Transferred into 100ml volumetric flak and add 50ml water and sonicate this solution for 30 min. Finally make up the volume with water.

Pipette out 3ml of this solution and transferred into 200ml volumetric flask. Add sufficient water and sonicate it for 15 min.

Both the solution was analyzed by UV spectrophotometer. Assay of tablet was calculated by below formula.

$$CI = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

Similarity factor[14]

Similarity factor (f2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in percentage (%) dissolution between two curves. Similarity factor can be found out by using following formula.

$$f_2 = 50 \times \log\left\{\left[1 + 1/N \sum_{i=1}^{N} (R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where N = No. of time points, Rt = Mean % drug release of reference product and Tt = Mean % drug release of test product. Similarity factor f2 in the range of 50 to 100 shows similarity between two dissolution profiles.

RESULTS AND DISCUSSION

Optimization of Naproxen Sodium CR Tablet was done by using 2^3 factorial designs. The summary of data obtained of various responses for Naproxen Sodium CR tablets was shown in Table 5.

Effect of Formulation variables on Disintegration time of tablet[15]

Summary of ANOVA analysis

The Model F-value of 85.16 implies the model was significant. *P*-values less than 0.0500 indicate model terms were significant. In this case AB, AC was significant model terms. The Lack of Fit F-value of 0.72 implies the Lack of Fit was not significant relative to the pure error. Lack of fit was non-significant which was required to fit well with the experimental design.

Model graphs

From the interaction graph (Figure 1), it was clear that AB interaction was significant. This indicates that the impact of factor B i.e. Eudragit RSPO polymer on disintegration time of tablet depends upon the level of A i.e. Eudragit RLPO polymer in the formulation. When factor B (i.e. Eudragit RSPO) is at higher level, Disintegration time of tablet increases with increase in the concentration of Eudragit RLPO. Whereas when the Eudragit RSPO polymer concentration is at lower level, Disintegration time of tablets decreases with increase in the concentration of Eudragit RLPO polymer.

Table 5: DOE design layout and observed responses for Naproxen Sodium CR Tablet.

Run	Factor 1 A: Eudragit RL PO mg	Factor 2 B: Eudragit RS PO mg	Factor 3 C: Crospovidone mg	Response 1 Disintegration time minutes	Response 2 F2 factor of Drug release %
1	94.5	129	182.25	82	36.6
2	74.5	149	162.25	87	53.15
3	74.5	149	162.25	90	53.82
4	94.5	169	142.25	98	45.38
5	94.5	169	182.25	100	62.25
6	54.5	169	142.25	78	50.98
7	54.5	169	182.25	77	44.44
8	74.5	149	162.25	89	54.49
9	54.5	129	142.25	101	74.68
10	94.5	129	142.25	78	61.03
11	54.5	129	182.25	96	54.91

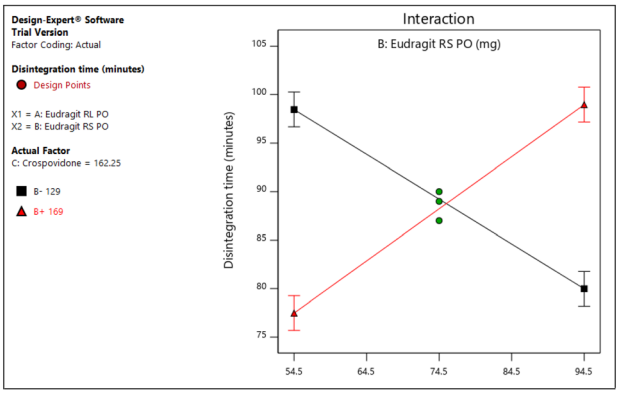

Figure 1: Interaction Plot.

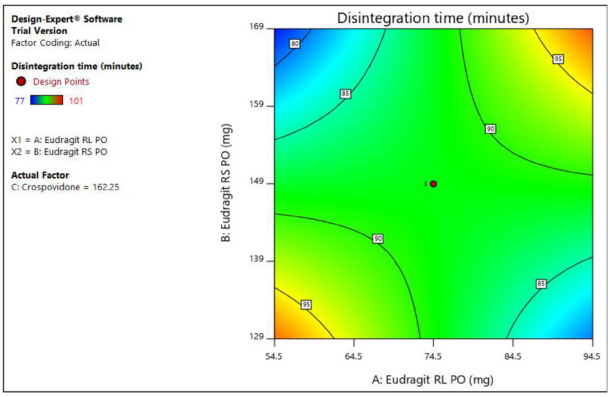

Figure 2: Contour plot.

From the contour plot (Figure 2) it showed that AB interaction was significant. As the contour curves had considerable curvature, it implies that the AB interaction was large and important.

Effect of formulation variables on F2 factor of drug release

Summary of ANOVA analysis

The Model F-value of 486.87 implies the model was significant. *P*-values less than 0.0500 indicate model terms were significant. In this case A, B, C, AB, AC, BC, ABC were significant model terms. The Lack of Fit F-value of 0.01 implies the Lack of Fit was not significant relative to the pure error. Lack of fit was non-significant which was required to fit well with the experimental design.

Model Graphs

From Interaction Graph (Figure 3) it was clear that AB interaction was significant**.** Spread of the points on the right side of the graph (where Eudragit RLPO Concentration is high) was smaller than the spread between the points at the left side of the graph (where Eudragit RLPO conc. was low). In other words, the effect of Eudragit RSPO concentration was less significant at high level of Eudragit RLPO. Therefore, Experiment could run at high Eudragit RLPO polymer concentration and reduce Eudragit RSPO polymer concentration.

From the contour plot (Figure 4) it showed that AB interaction was significant. As the contour curves had considerable curvature that implies the AB interaction was large and important.

Evaluation of optimized batch

From the DOE study F2 batch was found to be optimized batch with f2 factor of drug release was 53%. It was evaluated as follows.

Evaluation of CR and IR granules

The CR and IR granules of tablets were evaluated for all following flow properties as shown in Table 6. Compressibility index of CR and IR granules were

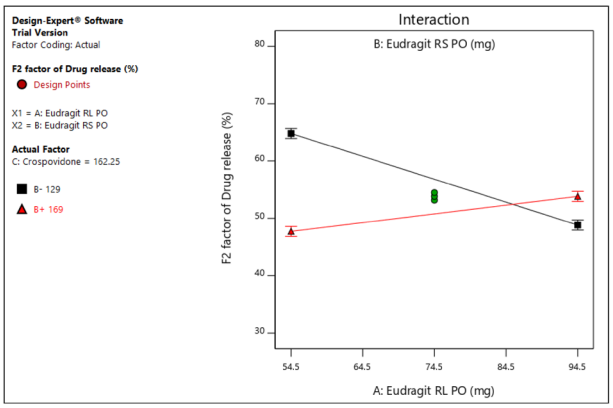

Figure 3: Interaction Plot.

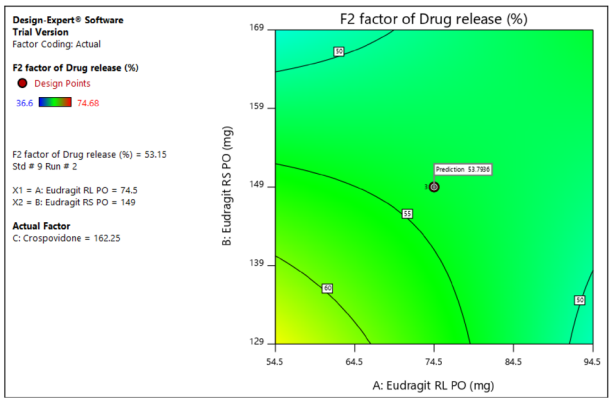

Figure 4: Contour plot.

Table 6: Evaluation of CR and IR granules.

Parameters	Results of F2 Batch	
	CR granules	IR granules
Bulk density (w/v)	0.47	0.59
Tapped density (w/v)	0.54	0.70
Compressibility index (%)	12.9	15.7
Hausner's ratio	1.14	1.18

found to be 12.9 % and 15.7 % respectively. This value was within the range of 12 to 20% which indicated that CR and IR granules had good flow. Hauser's ratios of CR and IR granules were found to be 1.14 and 1.18 respectively. This value was within the range of 1.14 to 1.20 which indicates that CR and IR granules had free flow.

Evaluation of Naproxen Sodium CR Tablets

Tablets of F2 batch were evaluated for appearance, Thickness, Hardness, Friability, Disintegration time, assay and *in-vitro* dissolution study. Results were summarized in below Table 7.

Table 7: Evaluation of Naproxen Sodium CR Tablets.

Sr. No	Parameters	Results
		Optimized batch (F2)
1	Appearance	White
2	Average Wt. (mg)	1433
3	Thickness (mm)	9.05
4	Length (mm)	22.31
5	Hardness (N)	162
6	Friability (%)	0.40
7	Disintegration Time (min)	87

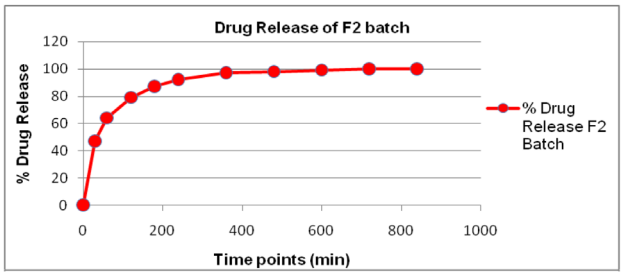

Figure 5: Drug Release profile of F2 batch.

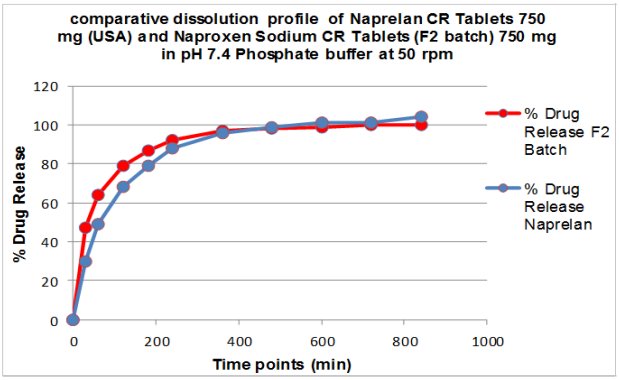

Figure 6: Comparative Dissolution profile.

In vitro dissolution studies

Dissolution studies for controlled release tablets of Naproxen sodium were carried out in 900ml of pH.7.4 phosphate buffer in USP Type-2 dissolution apparatus at 50 rpm and 37± 0.50C for 14 hr. Results Demonstrate that when Eudragit RSPO and Eudragit RLPO polymers used in 1:2 ratio, drug released was followed controlled release profile. Drug release profile of F2 batch shown in Figure 5.

Comparative in vitro drug release of optimized batch with marketed product

Comparative dissolution study (Figure 6) of optimized batch and marketed product were carried out. It was

found that drug release profile of Naproxen sodium CR release tablet shows comparative drug release profile with marketed product.

CONCLUSION

The present research work foresees the applicability of QbD in formulating Naproxen sodium CR tablets by using rate retarding polymers that was Eudragit RLPO and Eudragit RSPO. From the result it was clearly evident that as the Eudragit RSPO polymer concentration increases, there was increase the disintegration time of tablet and drug release was decline. The optimized formulation from 2^3 factorial design can be used as a single dose per day in the management of rheumatoid arthritis.

ACKNOWLEDGEMENT

The authors are grateful to PES Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India and Callidus Research Labs, Chakan Industrial Area, Nighoche, Pune, Maharashtra, India for providing the necessary facilities, assistance and support for carrying out the project.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QbD: Quality by Design; **DOE:** Design of experimentation; **ICH:** International Conference on Harmonisation; **CR:** Controlled Release; **IR:** Immediate Release; **MCC:** Microcrystalline Cellulose; **QTTP:** Quality Target Product Profile; **CQA:** Critical Quality Attribute; **BA:** Bioavailability; **BE:** Bioequivalence; **USP:** United States Pharmacopoeia; **UV:** Ultraviolet; **ANOVA:** Analysis of Variance.

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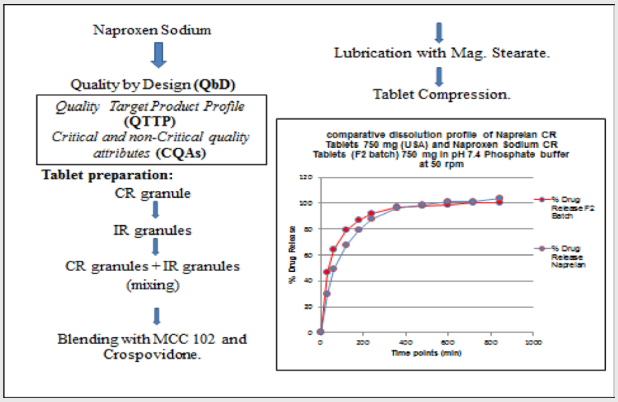
SUMMARY

- In the present study Naproxen sodium Controlled release tablets were developed and evaluated using QbD approach.
- Eudragit RLPO and Eudragit RSPO were used as rate retarding polymers. Crospovidone was used as disintegrating agent and Magnesium stearate was used as lubricant.
- From the obtained results it was inferred that concentration of Eudragit RSPO and Eudragit RLPO had shown potential effect on disintegration time and drug release profile of tablet. *In-vitro* drug release studies suggested that formulated tablets had shown a controlled release up to 14 h when compared with marketed formulation.

PICTORIAL ABSTRACT



Cite this article: Phatak A, Joshi D, Bhadgale M, Chaudhari P. Development and Optimization of Naproxen Sodium Controlled Release Tablets: QbD Approach. Indian J of Pharmaceutical Education and Research. 2020;54(2s):s108-s116.