Research Article

Development and Evaluation of Nevirapine Extended Release Tablets using QbD Approach

Vasantakumar Pai Karkala[1], Harsha Jinadatharaya[1], Devagowda Vishakante Gowda[2,*], Praveen Sivadasu[2]

[1]Department of Industrial Chemistry, Kuvempu University Shankaraghatta, B. R. Project, Shimoga-577451, Karnataka, INDIA.
[2]Department of Pharmaceutics, JSS Academy for Higher Education and Research, JSS College of Pharmacy, SS Nagara, Mysore -570015, Karnataka, INDIA.

ABSTRACT

Objective: To develop and evaluate Nevirapine (NVP) Extended release tablets for reducing the dosing frequency using Methylcellulose USP Methocel A15-LV and Hypromellose USP Methocel K4M Premium CR used as rate retarding polymers and Magnesium stearate as lubricant. **Methods:** Tablets were prepared by using roller compaction technique by employing Quality by Design (QbD) and Design of Experimentation (DoE) to study the effect of various process related parameters like Bulk density, Tapped density, Compressibility index, mesh size and *in-vitro* release data at 20th hour. **Results:** Obtained results had suggested that concentration of polymer had shown a potential effect over various process parameters and *in-vitro* drug release studies suggested that formulated tablets had shown a sustained release up to 24h when compared with marketed formulations. **Conclusion:** From the obtained results it can be concluded that formulation of Nevirapine ER Tablets employing QbD lead to a single dose per day in the management of HIV/AIDS.

Key words: Quality by design, Nevirapine, Design of experimentation, Extended release, HIV/AIDS, Tablets.

INTRODUCTION

The basic concept of employing QbD approach in preparing any formulation is "Quality cannot be tested but should be built into it".[1] As per ICH, QbD can be defined as a systematic approach to develop a formulation with predefined objectives and special highlighting on process designing and quality risk management.[2] One of the major parameter in QbD is developing a design which includes, Equipment, excipients and manufacturing environments, any design space should get prior approval from regulatory bodies. In this design space various product variables are monitored in periodic manner for better quality of product. All these parameters will be assessed and conclusions will be reported.[3] Studies suggested that by employing QbD approach large scale productivity of the formulation can be improved, so that they can be released into the market.[4]

Controlled or extended release is a system which provides a continuous release of the medicament for a pre-determined time interval. This infers that release of the medicament from a controlled system proceeds at a rate which is not only predictable but also reproducible.[5] Administration of these systems through oral route will be considered based on the disease, patient, duration of therapy and properties of the drug. Extended release systems controls the delivery of the medicament temporarily, it also makes an attempt to deliver the drug constantly at the deliver site.[6] It was reported that by formulating this controlled release systems the polymers obtained enhanced chain mobility and increased free macromolecular chains

Submission Date: 15-02-2018;
Revision Date: 17-05-2018;
Accepted Date: 14-08-2018

DOI: 10.5530/ijper.52.4s.101

Correspondence:
Dr. Devagowda Vishakante Gowda,
Professor and Head,
Department of Pharmaceutics,
JSS Academy of Higher Education and Research,
Mysore-15, Karnataka,
INDIA.
Phone: +91 9663162455
E-mail: dvgowdajssuni@gmail.com

www.ijper.org

to diffuse through oral mucus layers and sustaining the release of drug from the formulation.[7]

Nevirapine (NVP) is a Non-nucleoside reverse transcriptase inhibitor (NNRTI) of human immune deficiency virus Type-1, which terminates the polymerase activity by getting attached to HIV-1 reverse transcriptase which results in disturbance of enzyme's catalytic site. In recent years research works demonstrated that NVP has shown prominent activity in HIV infected patients in combination of other drugs in therapy. NNRTI's acts by binding and blocking HIV reverse transcriptase and avoids HIV from replicating and resulting in the amount of HIV in blood. NVP reduces the risk of transmitting HIV to non-infected people as it binds to Reverse transcriptase (RT) and blocks RNA and DNA dependent polymerase activities by creating disturbances at enzymes catalytic site.[8] It was reported that in spite of its benefits treatment with NVP can cause severe hepatotoxicity and rashes. Studies suggested that NVP undergoes hepatic metabolism by cytochrome p450 and transformed into several hydroxylated metabolites and these metabolites are responsible to adverse effects when compared with parent molecule.[9-10] The objective of present research was to develop an extended release tablet loaded with NVP employing QbD approach to reduce the dosing frequency and adverse effects caused by the metabolites in managing HIV/AIDS.

MATERIALS AND METHODS

Materials

Nevirapine was obtained as a gift sample from Apotex Research Pvt Ltd, Bengaluru. The other chemicals and excipients used in the study were of analytical grade.

Methods

Quality Target Product Profile for Nevirapine ER Tablets

In combination with other antiretroviral agents Nevirapine ER Tablets are indicated as an alternative for treatment of HIV-1 infection. A brief explanation about quality characteristics that affects formulation of Nevirapine ER Tablets is given in Table 1.

Table 1: Quality Target Product Profile for Nevirapine ER Tablets.

QTPP Element		Target	Justification
Dosage form		Tablet	ANDA needs same dosage form as that of Reference product
Dosage design		Extended release tablet	Extended Release design Needed to meet label claim.
Route of Administration		Oral	Required to match the Reference product
Dosage strength		Nevirapine ER Tablets 400 mg	Pharmaceutical equivalence requirement: Same strength as that of the Reference product
Container closure system		HDPE bottles with Caps	Needed for safety and commercial requirements
Pharmacokinetics		Extended release Bioequivalent (BE) to Reference Product.	Maximum plasma concentration (Cmax) and the area under the curve (AUC) are bioequivalence requirements. Tmax ensures rapid onset of action. Bioequivalence requirement. Needed to ensure rapid onset and efficacy.
Drug Product quality attributes	Physical attributes	Pharmaceutical equivalence requirement: Meeting the same or Compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content uniformity (CU)		
	Degradation products / Impurities		
	Residual solvents		
	Dissolution		
	Microbial Limits		
Patient compliance to the product		Organoleptic properties – shape, size and colour	Shape, size and colour similar to the reference product for patient acceptability
Stability		At least 24-month shelf-life at room temperature.	Needed for commercialization

Identification of critical and non-critical quality attributes (CQAs) for Nevirapine ER Tablets

CQA's were established based on the QTPP's defined in the above table for the development of Nevirapine Extended-Release Tablets. The attributes which have a potential effect on formulation variables during development of process which are related to the safety of the product formulated are termed as CQA. A brief explanation about CQA's are depicted in Table 2.

CMAs of Excipient

The critical material attributes of all the excipients which have impact on the final formulation are listed and discussed below in Table 3.

Table 2: Critical and non-critical quality attributes (CQAs) for Nevirapine ER Tablets.

Drug Product quality attributes		Target	Is this Critical?	Justification of criticality
Physical attributes	Appearance (Colour)	Colour suggested by marketing group	Yes	Pharmaceutical requirement, process and stability may have an impact on appearance
	Size	Similar to Reference Product	No	Formulation impacts size.
	Score configuration	Unscored	No	Not critical because tablet is Unscored.
	Friability	NMT 0.8% w/w	Yes	Both formulation and Process impact friability.
Identification		Positive for Nevirapine	No	Both formulation and Process unlikely to impact the identity.
Assay		90 - 110% of label claim	Yes	Needed for clinical Effectiveness and safety. Process variables may affect the assay value of the Drug product.
Content uniformity (CU)		Complies with harmonized requirements for uniformity of dosage units	Yes	Needed for clinical effectiveness and both formulation and process impact the uniformity
Degradation products / Impurities		Each Individual unidentified impurity: NMT 0.1% Total Impurities: NMT 0.2%	Yes	As per ICH guideline and needed to ensure safety
Dissolution		As per USP 02 H: NMT 25% 08 H: 50-70% 20 H: NLT 80%	Yes	Needed for clinical Effectiveness and both formulation and process affect drug release profile.
Microbial Limits		Meet relevant pharmacopoeia criteria	No	Formulation and process Unlikely have any impact.

Table 3: CMAs of Excipient.

Material Attribute	CMA	
Excipients Name and Functional use	Excipients Name	Functional use
	Hydroxypropyl méthyl cellulose premium	Release controlling polymer
	Methyl cellulose	Diluent
	Magnesium stearate	Lubricant
	Iron Oxide	Colourant
Compendial Requirements	Complies	
Interaction with drug substance	The results of the study confirmed that when these excipients, representing different functional uses in formulation, are combined with Nevirapine and were exposed to solid state stress conditions, no significant difference in impurity levels and (%) Assay was observed. Hence above mentioned.	

Manufacturing process of Nevirapine ER Tablets using DoE

Experimental Design

A 2^3 2-Level factorial design was employed to evaluate the existing curvature effects one centre point. Force, gap and speed of the roller compactor were considered as independent variables. Granule bulk density, tap density, Carr's index and Dissolution at 20 h were used as dependent variables. Best fit model for statistical analysis was considered significant when *P* value was less than 0.05.

Preparation of Nevirapine ER Tablets

Based on the physico-chemical properties of NVP, roller compaction was selected as the most appropriate manufacturing process. In addition, the NVP physical properties (flow) suggested precluded direct compression as the method for formulating tablets. Hypromellose (Methocel K4M Premium) and Methylcellulose (Methocel A15-LV) were separately weighed, sieved and then mixed with NVP. The mixture was then lubricated by intragranular Magnesium stearate and roller compacted to yield active granules by milling the formed ribbon. Prior to compression one more step of lubrication was done by adding extra-granular (Magnesium stearate) and the mixture was forwarded to compression. Formulation chart for formulating NVP Tablets is shown in Table 4.

Table 4: Composition of Nevirapine ER Tablets 400 mg.

Sl. No.	Ingredient	mg/ tablet
		NEVIXAG-081
1.	Nevirapine Anhydrous USP*	400.0
2.	Methylcellulose USP Methocel A15-LV**	82.5
3.	Hypromellose USP Methocel K4M Premium CR	108.0
4.	Yellow Iron Oxide NF	2.0
5.	Magnesium stearate (Intragranular)	1.5
	Magnesium stearate (Extragranular)	6.0
	Tablet weight	600.0

Characterization of Granules

Bulk density

Measurement of Bulk density was done by pouring powder into a measuring cylinder through sieve # 20 and the initial weight was noted. The initial volume was termed as bulk volume.[11]

Tapped density

Tapped density is defined as the ratio between aggregate weights of granules to the tapped volume of powder. Measurement of the volume was done by tapping the granules 750 times. If the variance in volume exceeds 2%, further tapping should be done for 1250 times. It was conveyed in g/ml.[12]

Angle of Repose

Angle of repose was done by using powder flow tester. Angle of repose can be calculated by measuring the height and radius of the pile of granules.[13]

Compressibility index

It demonstrates the flow properties of the granules. It is conveyed in the form of % and can be calculated using bulk density and tapped density.[13]

Hausner Ratio

Hausner ratio is an indirect way of accessing the ease of granules flow. It can be calculated by using bulk density and tapped density.[13]

Evaluation of compressed Nevirapine ER Tablets 400 mg

Weight Variation

Randomly 20 tablets were selected and weighed using a single balance. Standard deviations were calculated and checked with the standard pharmacopeial limits.[14]

Thickness

Tablets were selected randomly from all batches and measurement of thickness was done by using Vernier Calliper.[14]

Hardness

The strength of tablet is expressed in the form of tensile strength (Kg/cm^2). The amount of force required to break the tablets was measured by using a hardness tester.[15]

Friability

Randomly 20 tablets were selected and weighed from all the batches. The weighed tablets then placed in friabilator and then ran for 100 revolutions. After completion of 100 revolutions tablets were de-dusted, re-weighed and %friability was calculated.[16]

In vitro dissolution studies

Dissolution studies for extended release of NVP from the formulated tablets were done by USP type-2 dissolution apparatus using 6.8 pH. Phosphate buffer at 75 rpm and 37±0.5°C for 24 h. Quantity of drug dissolved in the selected buffer was estimated periodically by using ultra violet (UV) spectrophotometer (UV–1601 PC Shimadzu, Japan) at 244nm.[17]

RESULTS AND DISCUSSION

Optimization of Nevirapine ER Tablets

Optimization of Nevirapine ER Tablets was done by employing 2^3 2-Level factorial design. Force, gap and speed of the roller compactor were considered as independent variables. Granule bulk density, tap density, Carr's index, Granule size distribution (retains on #60 mesh ASTM) and Dissolution at 20 h were used as dependent variables, whereas levels -1, 0, +1 were used as ranges of variables respectively which is depicted in Table 5 and 6.

Experimental Design

The summary of data obtained of various responses for Nevirapine ER Tablets is presented in Table 7.

Summary of results of regression analysis for responses

The summary of ANOVA analysis was given in Table 8a and 8b.

Effect of formulation variables on Bulk density of granules

As depicted in the Pareto chart (Figure 1a), the significant factors affecting Bulk density of granules was roll pressure and roll gap. The contour plot for roll gap and roll pressure versus Bulk density of granules presented in the (Figure 1b), showed that bulk density of granules increased with increasing roll pressure (positive effect) and decreases with increasing roller gap (Negative effect).

Effect of formulation variables on Tap density of granules

As depicted in the Pareto chart Figure 2a and Counter plot Figure 2b, no parameter had significant effect on the granules Tap density.

Table 5: Variables in 2^3 2-Level factorial design for Nevirapine ER Tablets.

Independent variable Levels			
	Low	Medium	High
A: Force (KN/cm)	6	10	14
B:Gap (mm)	2	3	4
C: Speed (rpm)	2	3	4

Table 6: 2^3 2-Level factorial design layout for Nevirapine ER Tablets.

Run No.	A: Force (KN/cm)	B:Gap (mm)	C: Speed (rpm)
1	6	4	4
2	6	2	2
3	14	2	2
4	14	4	2
5	10	3	3
6	14	4	4
7	6	4	2
8	14	2	4
9	6	2	4

Effect of formulation variables on Compressibility Index of granules

As depicted in the Pareto chart Figure 3a, the formulation variables which had shown a significant effect on Carr's index of granules was pressure applied on roll and gap between the roll. The contour plot for roll gap and roll pressure versus Carr's index of granules presented in the Figure 3b, showed that Carr's index of granules decreased with increasing pressure on the roll which can be termed as Negative effect and increases with enancing

Table 7: Observed response in 2^3 2-Level factorial design for Nevirapine ER Tablets.

Run	Bulk density (g/ml)	Tapped density (g/ml)	Compressibility Index (%)	Granules PSD Above #60 mesh (%)	*In vitro* release at 20h
1	0.481	0.786	38.804	59.00	88
2	0.520	0.782	33.504	47.60	89
3	0.581	0.799	27.284	51.10	91
4	0.540	0.793	31.904	64.80	99
5	0.530	0.776	31.701	65.64	92
6	0.547	0.771	29.053	63.02	89
7	0.499	0.792	36.995	57.18	93
8	0.572	0.787	27.319	48.52	89
9	0.510	0781	34.669	51.48	90

Table 8a: Summary of ANOVA analysis.

ANOVA Analysis	Granule Bulk density		Granule Tapped Density		Granules Compressibility Index (%)	
	p- values	SR	p- values	SR	p- values	SR
Model	0.001	Yes	0.4693	No	0.0046	Yes
Roller Force	0.003	Yes	0.7291	No	0.0014	Yes
Roller Gap	0.0043	Yes	0.7870	No	0.0185	Yes
Roller Speed	0.2048	No	0.1659	No	0.9612	No

Table 8b: Summary of ANOVA analysis.

ANOVA Analysis	PSD #60 mesh Retained		Dissolution at 20 h	
	p- values	SR	p- values	SR
Model	0.0071	Yes	0.2760	No
Roller Force	0.0017	Yes	0.4079	No
Roller Gap	0.1981	No	0.3125	No
Roller Speed	0.2911	No	0.1384	No

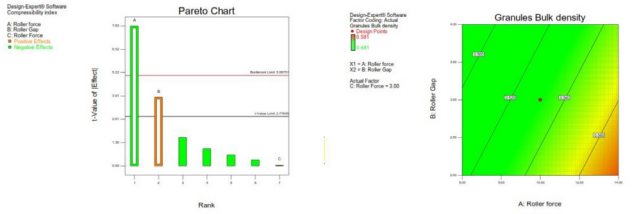

Figure 1a and 1b: Pareto chart and counterplot for Effect of Bulk Density of Granules.

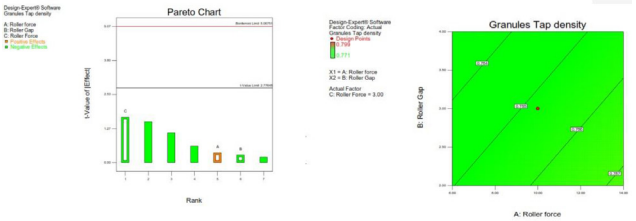

Figure 2a and 2b: Pareto chart and counterplot for Effect of Granules Tap Density.

Figure 3a and 3b: Pareto chart and counterplot for Effect of Compressibility index.

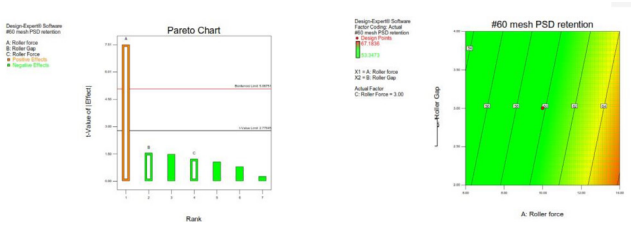

Figure 4a and 4b: Pareto chart and counterplot for Effect of PSD on granules.

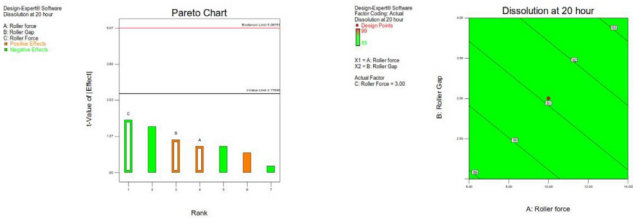

Figure 5a and 5b: Pareto chart and counterplot for Effect of dissolution at 20 h.

the gap between roll which can be termed as Positive effect.

Effect of formulation variables on granules PSD Above #60 ASTM mesh

As depicted in the Pareto chart Figure 4a, the important formulation variables afecting PSD Above #60 ASTM mesh was Roller force. The contour plot for PSD Above #60 ASTM mesh versus roll force and roll gap versus is presented in the Figure 4b, showed that. PSD Above #60 ASTM mesh increased with increasing roll force (positive effect).

Effect of formulation variables on Tablet dissolution at 20 H

Dissolution is one of CQAs of the drug product. Roller compaction process may affect the dissolution of the drug product. But form the Pareto chart and counterplot Figure 5a and 5b; it can be observed that, no parameter

Table 9: Characterization of Granules.

Sl. No	Bulk density	Tapped density	Angle of repose	Compressibility index	Hausner ratio
1	0.481	0.786	29.18	38.804	1.63
2	0.520	0.782	28.39	33.504	1.50
3	0.581	0.799	26.54	27.284	1.37
4	0.540	0.793	26.24	31.904	1.46
5	0.530	0.776	27.14	31.701	1.46
6	0.547	0.771	27.88	29.053	1.40
7	0.499	0.792	28.65	36.995	1.58
8	0.572	0.787	26.89	27.319	1.37
9	0.510	0781	29.85	34.669	1.53

Table 10: Evaluation of Tablets.

Sl. No	Weight (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
1	596-608	6.09-6.23	12.4-16.4	0.094
2	586-615	6.15-6.28	11.4-15.3	0.03
3	595-607	6.09-6.18	14.2-15.5	0.015
4	595-612	6.19-6.30	11.6-14.1	0.06
5	600-608	6.23-6.29	11.9-14.6	0.085
6	598-613	6.19-6.27	11-15.3	0.06
7	586-616	6.11-6.27	11.8-17.3	0.09
8	599-606	6.10-6.22	11.0-13.7	0.045
9	586-608	6.10-6.24	11.2-15.0	0.058

had significant impact on the amount of drug dissolved from the tablet at 20 h.

Characterization of Granules

Tablets were formulated by direct compression method and physicochemical properties of the granules were evaluated prior to compression. The granules of all the batches had shown good flow properties which is evident from the results depicted in Table 9. Bulk and tap density were used to calculate compressability index where bulk density ranged from 0.481 to 0.581 and tapped density ranged from 0.771 to 0.799. The angle of repose value ranged from 25.09º to 29.82º, as the angle of repose was found below 30º it can be inferred that blend have good flow ability. The Hausner ratio ranged from 1.37 to 1.63. Form the reults it can be inferred that the granules posses free flowing property.

Evaluation of Tablets

Formulated tablets were evaluated for variation in weight, thickness, hardness and % friability. The results obtained from these tests were found to be satisfactory which are depicted in Table 10. Results obtained from weight variation demonstrated that all the formulations

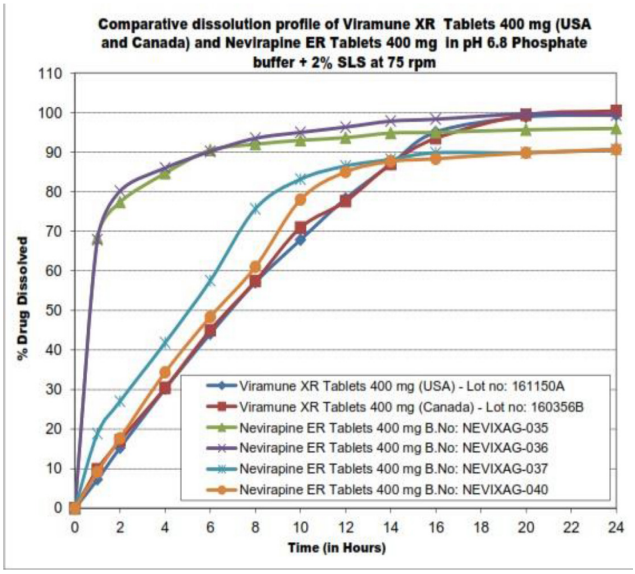

Figure 6: *In vitro* drug release in comparison with marketed products.

are within the limit of 7.5%. Thickness of the tablets from all the batches was uniform and within the range of 6.09 to 6.30 mm. Hardness of tablets of all batches ranged from 11 to 17.3 Kg/cm^2. Friability of tablets from all batches ranged from 0.03 to 0.135, which was well under limit.

In vitro dissolution studies

Dissolution studies for extended release of NVP were carried out in 900 ml of Ph. 6.8 phosphate buffer in USP Type-2 dissolution apparatus at 75 rpm and 37±0.5°C for 24 h. Results demonstrated that concentration of polymer had shown a potential influence over drug release from tablets. Tablets with low polymer concentration exhibited a immediate release when compared with reference product. With increase in concentration of polymer release of Nevirapine was in a controlled manner when compared to reference product which is depicted in Figure 6.

CONCLUSION

The present research work foresees the applicability of QbD in formulating Nevirapine ER Tablets by using rate retarding polymers. From the results it was clearly evident that as the polymer concentration increases, there was a decline in the release of drug. Combination of polymers with other excipients do not interact with drug, which leads to sustained delivery of drug for longer periods. The optimized formulation from 2^3 2-Level factorial design can be used as a single dose per day in the management of HIV/AIDS.

ACKNOWLEDGEMENT

The authors express their gratitude to the JSS University and JSS College of Pharmacy for providing necessary support in due course of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

Nevirapine: NVP; **QbD:** Quality by Design; **DoE:** Design of experimentatio; **ICH:** International Conference on Harmonisation; **HIV/AIDS:** Human immunodeficiency virus infection and acquired immune deficiency syndrome; **NNRTI:** Non-nucleoside reverse transcriptase inhibitor; **RT:** Reverse transcriptase; **RNA:** Ribonucleic acid; **DNA:** Deoxyribonucleic acid; **ER:** Extended Release; **QTPP:** Quality Target Product Profile; **BE:** Bioequivalent; **CU:** Content uniformity; **CQA:** Critical Quality Attribute; **CMA:** Critical material attributes; **USP:** United States Pharmacopeia; **UV:** Ultraviolet; **ANOVA:** Analysis of variance; **PSD:** Particle size diameter.

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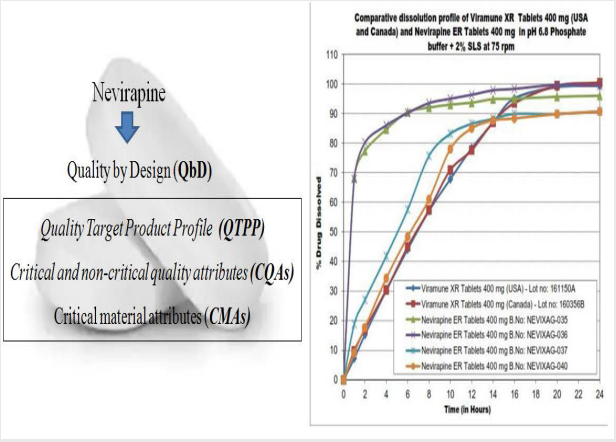
PICTORIAL ABSTRACT



SUMMARY

- In the present study Nevirapine Extended release tablets were developed and evaluated using QbD approach.
- Methylcellulose USP Methocel A15-LV and Hypromellose USP Methocel K4M Premium CR were used as rate retarding polymers and Magnesium stearate was used as lubricant.
- From the obtained results it was inferred that concentration of polymer had shown a potential effect over various process parameters and *in-vitro* drug release studies suggested that formulated tablets had shown a sustained release up to 24h when compared with marketed formulations

About Authors

Dr. Vasantakumar Pai Karkala is working as a Professor in Department of Industrial Chemistry, Jana Sahyadri Campus at Shankaraghatta. His research area is chemistry and various novel drug delivery systems

Mr. Harsha Jinadatharaya is working as a Research Scholar in Department of Industrial Chemistry, Jana Sahyadri Campus at Shankaraghatta. His research area is Tablets and Novel drug delivery systems.

Dr. Devagowda Vishakante Gowda is working as Professor and Head for Department of Pharmaceutics at JSS College of Pharmacy, JSS Academy for Higher Education and Research, Mysuru. His research area is Tablets, Oral vaccines, Nano particles, Nasal delivery.

Mr Praveen Sivadasu is working as a Research Scholar at JSS College of Pharmacy, JSS Academy for Higher Education and Research, Mysuru. His research area is Nasal drug delivery

Cite this article: Karkala VP, Harsha J, Gowda DV, Praveen S. Development and Evaluation of Nevirapine Extended Release Tablets Using QbD Approach. Indian J of Pharmaceutical Education and Research. 2018;52(4 Suppl 2):s220-s228.