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Research

Formulation and Evaluation of Nevirapine Tablets 400mg

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Abstract

To develop and evaluate Nevirapine (NVP) Extended release tablets for reducing the dosing frequency using Hypermellose USP and lactose monohydrates USP used as rate retarding polymers and extragrnaular ingredient Magnesium stearate as lubricant.

Methods: Tablets were equipped by using roller compaction technique by using 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 16 the hour.

Results: Obtained results had recommended that focus of polymer had shown a potential consequence over many process parameters and in-vitro drug release studies recommended that formulated tablets had presented a sustained release up to 16h 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.

Keywords: Nevirapine Tablets 400MG, Formulation, Evaluation, QbD, HIV

INTRODUCTION

Modification and improvement of solubility has been attempted with much success for the development of effective drug formulation This is especially true for Biopharmaceutical Classification System (BCS) class II drugs.Compounds exhibiting dissolution rate-limited bioavailability are considered class II according to the BCS classification and these compounds have low and variable bioavailability.The solubility of these drug candidates can be enhanced using suitable conventional formulation strategies, which include cosolvents, milling techniques, super critical processing, solid dispersions, including complexation and precipitation techniques. There still remains an unmet need to equip the pharmaceutical industry with tools to effectively enhance the solubility of BCS class II compounds. With particle engineering technologies, the solubility can be enhanced.

Nanosuspension technology is one such technique. With decrease in size, the surface area increases and thereby improved solubility can be achieved. In this regard, nanoscale formulations have attracted attention of various pharmaceutical scientists and these products especially, nanosuspensions, demonstrated clinical and market success.The reduction of drug particles to nanosize leads to a significant increase in the dissolution rate,

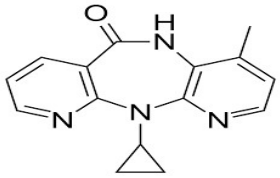
solubility and therefore enhances bioavailability.Nanosuspensions lead to a reduction in the particle size and/or can transform drugs from a crystalline to an amorphous state and thereby enhance the dissolution rate and solubility. Variability of fed-fasted state bioavailability with nanosuspension formulation can be reduced.Increase in saturation solubility is achieved with nanosuspenions by an increase in dissolution rate of the compound.

Acquired immunodeficiency syndrome (AIDS) is a serious disease afflicting several populations of the world. Several classes of the drugsare used in the treatmentofAIDS. Of these, nonnucleoside reverse transcriptase inhibitors (NNRTIs) are a specific class of antiAIDS drugs. Some of the NNRTIs use is limited due to low bioavailability resulting from dissolution rate-limited bioavailability.

In this study we chose nevirapine, a BCS class II NNRTI with undesirable solubility and dissolution kinetics from the dosage form. Its solubility in neutral pH is about 0.1 mg/ml. Although the drug appears to be well absorbed orally, at higher doses, its bioavailability is low and variableOn occasions it is administered as 200 mg twice daily.

Nanosuspensions of nevirapine were prepared using nano-edge technique and then they were subjected to *in vitro* and *in vivo* characterisation.

Drug Profile



Neverapine is a non-nucleoside Reverse transcriptase inhibitor used as part of a management Regimen for HIV-1 virus infection

Drug class:Non-nucleoside Reverse Transcriptase inhibitor. Nevirapine is always used in combination with HIV medicines

Weight:Average-266.2979, monoisotopic-266. 11676109, Chemical formula:-C15H14N4O

Indication:for use in combination with other antiretrovial drugs in the ongoing treatment of the HIV-1 infection

Purpose of study: To develop and evaluate Nevirapine (NVP) Extended release tablets for reducing the dosing frequency using Hypermellose USP and lactose monohydrates USP used as rate retarding polymers and extragrnaular ingredient Magnesium stearate as lubricant.Design of Experimental approach for enhancing assay using Hypermellose USP as a Disintegrants in extended release Nevirapine (NVP) Extended release tablets.The proposed method shall be used for the quantification of active material Nevirapine in Nevirapine 400 mg tabletsThe proposed method shall be validated for Dispensing of raw material, Sifting, Dry mixing, Binder preparation, Wet mixing, Drying, milling, lubrication and CompressionControls of critical process parameters and Critical process attributes.Controls the in process parameters: Blend uniformity, Loss of drying. Water by KF , Bulk density , tapped density, Particle size, description, assay, dissolution, weight of 10 capsules, Disintegration time , hardness, weight variation and Uniformity of the dosage form.

MATERIALS AND METHODS

Materials

NevirapinePolymers: Hypromellose (HPMC)- Excipients: Lactose, Magnesium Stearate, etc.- Analytical Reagents and Solvents, Equipments: Vibratory Sifter, Rapid Mixture granulator 1000 l, Fluid Bed Dryer, Multimill, Octagonal blender,Vernier calliper, Tablet deduster Metal detector Analytical balance Moisture analyzer Bulk density apparatus, Tablet compression Machine

Methods

Preformulation Studies, Solubility analysis, Compatibility studies with excipients, Formulation Development:- Design of Experiments (DoE) to determine critical parameters- Preparation of extended-release tablets using direct compression method- Optimization Using QbD:- Identification of Critical Quality Attributes (CQAs)- Risk assessment and mitigation- Design space establishment

Evaluation of Formulation

Physicochemical Evaluation:Tablet hardness, thickness, friability, and weight variation- In vitro Drug

Release Studies: Dissolution testing under various pH conditions- Release kinetics modeling (e.g., Zero-order, First-order, Higuchi, Korsmeyer-Peppas)- Stability Studies: Conducting stability testing under ICH guidelines- Assessment of drug content and release profile over time.

Representation of the in process test during the formulation and manufacturing of the product

Sr.No	Test	Methods
Granulation :		
1.	Loss of Drying	Performed in moisture analyzer balance
2.	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
3.	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
4.	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
5.	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.
6.	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
Compression		
7.	Weight Variation	Randomly 20 tablets were selected and weighed using a single balance. Standard deviations were calculated and checked with the standard pharmacopeial limits.
8.	Thickness	Tablets were selected randomly from all batches and measurement of thickness was done by using Vernier Calliper.1
9.	Hardness	The strength of tablet is expressed in the form of tensile strength (Kg/cm2). The amount of force required to break the tablets was measured by using a hardness tester
10.	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.

Manufacturing Process

Process Parameters and critical quality attributes

Unit Parameter	Process Parameter	Quality Attributes
Dry Mixing	Order of addition	Particle size distribution , Bulk/tapped density ,flow properties
	RMG amperage	
	Impeller Speed and time	
	Mixing	
Wet Granulations	Binder addition time	Granules size, Granule shape, flow properties
	Impeller Speed	
	Chopper Speed and Run time	
	Binder fluid temperature	
	Post granulation fix time	
Milling	Speed of mill	Blend Uniformity flow, Particle size and distribution , Granules size and distribution, granules strength and uniformity solid form
	Screen size	
	Feeding rate	
Drying	Inlet temperature, inlet air flow, volume	Granule size and distribution , granules strength and uniformity, particle size, bulk/tapped density, moisture content, residual solvents
	Bowl temperature	
	Exhaust temperature	
	Shaking interval	
	Product temperature	
Blending	Blender type	

	Blender RPM	Blend uniformity and flow properties
	Blending time	
Compression	Compression speed	Target weight, weight uniformity, content uniformity, Hardness thickness, friability and DT
	Compression force	
	Force speed frame type and speed	

Experimental Designed for the formulation

Pharmaceutical Assessments:

- **Determination of Bulk and Tapped Density :**

Tapped density: Tapped density of a powder is the ratio of the mass of the powder to the volume occupied by the powder after it has been tapped for a defined period of time. The tapped density of a powder represents its random dense packing. Tapped density can be calculated using equation :

where M=mass in grams, and Vf=the tapped volume in milliliters.

Tapped**Density(g/mL)=M / Vf**

Bulk density: The term bulk density refers to a measure used to describe a packing of particles or granules and the term Tapped density refers to the true density of the particles or granules

- **Determination of Carr,s Compression Index**

Flow Properties according to angle of repose comes under that range 0–90º. Carr Index of any solid is calculated for compressibility of a powder which is based on true density (ρT) and bulk density (ρB), CI=100[(ρT−ρB)/ρB].

- **Determination The Hausner Ratio**

The Hausner Ratio of a material is calculated with the following formula :

H = ρ tapped /ρ bulk

H : Hausner Ratio , ρ tapped : the tapped bulk density of the material(kg/m3) , ρ bulk : the loose bulk density of the material(kg/m3).

Table 1: Different quantity of ingredient were change for the formulation to optimized the formula

Ingredient	**Quantity in batch per kg (mg/Tablets)**						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Nevirapine Anhydrous USP	60.00	60.00	60.00	60.00	60.00	60.00	60.00
Lactose Monohydrates USP	55.00	52.0	54.5	54.5	51.5	52.5	52.5
Hypermellose	45.00	45.00	40.00	43.00	46.0	45.00	45.00
Purified water	450.00	450.00	450.00	450.00	450.00	450.00	450.00
Magnesium stearate USP NF	5.00	2.000	4.500	1.500	1.500	1.500	1.500
Total tablet weight	**159.0.00**	**159.0.00**	**159.0.00**	**159.0.00**	**159.0.00**	**159.0.00**	**159.0.00**
Modification	**NA**	Decrease Lactose Monohydrates USP and Magnes	Increase Lactose Monohydrates USP and Magnesium stearate And DecreaseHypermellose	No change in Lactose Monohydrates Increase in	Decrease in Lactose Monohydrates Increase Hypermellose	No change in Magnesium stearate Increase Lactose Monohydrates USP	Optimized formula

Table 1: Different quantity of ingredient were change for the formulation to optimized the formula

Ingredient	Quantity in batch per kg (mg/Tablets)						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
		ium stearate		Hyper mellose Decrease in Magnesium stearate	No change in Magnesium stearate	And DecreaseHypermellose	
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent

Different Trail were taken for the optimizing the formula.Same has been determined in table 1 Different quantity of ingredient were change for the formulation to optimized the formula.

Granulation control	**Trail 1**	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Total Drying time	20 min	20 min	20 min	20 min	20 min	20 min	20 min
Inlet Granulation Stage temperature of FBD	59-65	60-61	59-65	55-65	56-68	55-62	55-63
Out let temperature of FBD	20-32	29335	29-39	30-45	39-48	27-32	28-35
Impeller Speed (RPM 50)	50	50	50	50	50	50	50
Amperage Impeller	12	13	12	14	14	14	14
Chopper off	Off	Off	Off	Off	Off	Off	Off
Amperage Impeller	12	13	12	14	14	14	14
Chopper ON slow RPM 1500	05	04	04	034	02	02	02
Blender RPM	10	10	10	10	10	10	10
Blending time	10	10	10	10	10	10	10
Loss of Drying	2.0	1.3	0.6	1.4	0.6	1.4	1.4
Bulk density(g/ml)	0.351	0.43	0.625	0.524	0.589	0.458	0.458
Tapped density (g/ml)	0.24	0.316	0.494	0.432	0.401	0.694	0.694
Angle of Repose	8	47	43	38	33	28	28
Carrs Index	33	28	22	17	13	<10	<10
Hausner Ratio	1.46	1.36	1.27	1.21	1.4	0.8	0.8
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent
Compressibility index (%)	31.801	37.995	29.595	67.695	37.995	38.804	38.804
Water Content by KF	4.25	4.85	9.0	3.50	2.01	2.85	2.85

Conclusion : From the above table all in process control and parameter is observed well within criteria for Trail batches Trail 6 and Trail 7.

Blend Uniformity	Trail 1	Trail 2	Trail 3	Trail 4	Trail 5	Trail 6	Trail 7
Granulation Stage : Blend Uniformity Acceptance Criteria Individual values 90-110.0 with the RSD not more than 5.0%							
Location 1	88.0	78.0	88.0	89.0	88.2	99.0	95.8
Location 2	87.0	100.3	70.8	90.0	98.3	99.1	96.1
Location 3	72.0	101.1	86.5	78.0	98.2	99.1	96.0
Location 4	76.0	100	86.2	89.0	98.2	100.3	96.4
Location 5	88.0	89.0	78.0	90.1	89.4	100.3	96.1
Location 6	90.0	90.0	74.8	96.0	99.3	101.1	96.5
Location 7	78.0	78.0	86.1	96.4	99.1	100	96.2
Location8	70.8	70.8	96.1	96.1	88.2	99.1	96.0
Location 9	84.0	93.1	83	98.3	82.2	100.3	96.4
Location10	92.0	84.0	99.1	98.2	99.3	100.3	96.4
RSD %	6.0	5.28	6.18	6.26	4.92	2.85	2.85

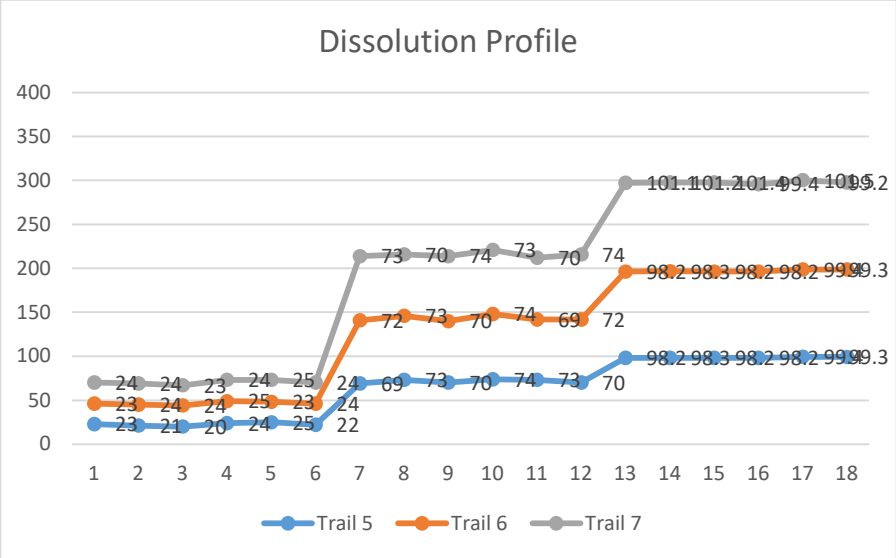
From the above table blend uniformity is observed well within criteria for Trail batches Trail 6 and Trail 7.

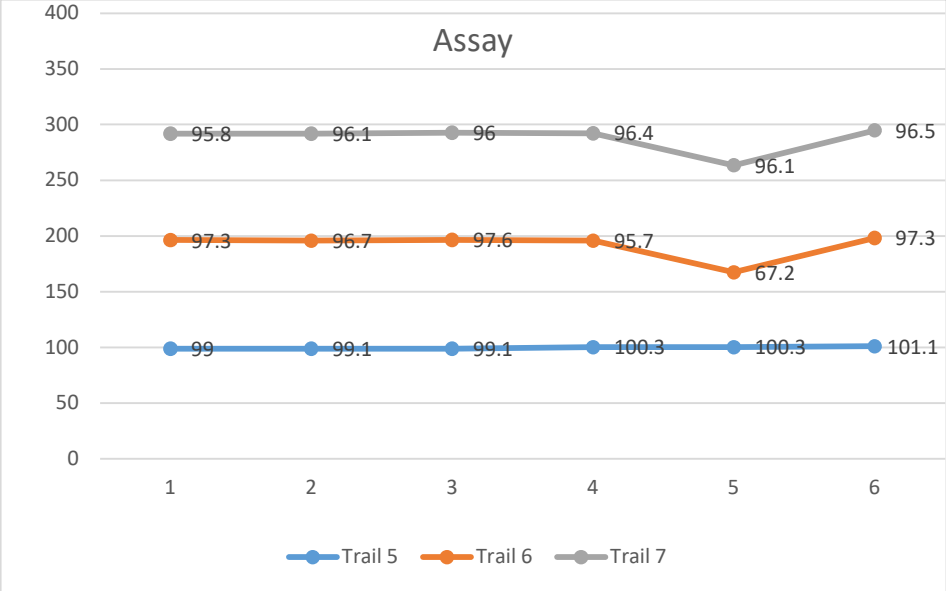
Dissolution Profile of Tablets

Assay	Trail 5	Trail 6	Trail 7
1	99.0	97.3	95.8
2	99.1	96.7	96.1
3	99.1	97.6	96.0
4	100.3	95.7	96.4
5	100.3	67.2	96.1
6	101.1	97.3	96.5
Mean	100	96.7	96.2
SD	1.13	0.84	0.26
%RSD	1.13	0.87	0.27
HPLC	QC-HPLC001	QC-HPLC001	QC-HPLC001
Column	QC-COL-003	QC-COL-002	QC-COL-003

Dissolution:in pH Phosphate buffer and 2% SLS at 75 RPM USP 1

	Time	Specification	Trail 5	Trail 6	Trail 7
1	2nd Hours	NMT 30%	23	23	24
2			21	24	24
3			20	24	23
4			24	25	24
5			25	23	25
6			22	24	24
1	8th hours	Between 60-80%	69	72	73
2			73	73	70
3			70	70	74
4			74	74	73
5			73	69	70
6			70	72	74
1	16th hours	NLT 80 %	98.2	98.2	101.1
2			98.3	98.3	101.2
3			98.2	98.2	101.4
4			98.2	98.2	99.4
5			99.4	99.4	101.5
6			99.3	99.3	99.2





SUMMARY

Nevirapine Extended release 400mg tablets were developed and evaluated using QbD approach by the technology. Summary of the study results states, it was concluded that concentration of polymer had play a possible effect over various process parameters and in-vitro drug release studies (dissolution) suggested that formulated tablets had shown a sustained release up to 16 hrs when compared with marketed product

CONCLUSION

The current research work predicts the applicability of QbD in manufacturing Nevirapine ER Tablets by using rate delaying the polymers. From the outcomes it was clearly apparent that as the polymer concentration increases, there was a decline in the release of drug. Grouping of polymers with other excipients do not interact with drug and vice versa, which informations to sustained delivery of drug for longer periods. The enhanced formulation from factorial design can be used as a single dose per day in the organization of HIV/AIDS.

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