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Research

Formulation and Evaluation of Indinavir Sulfate Capsules by novel technology using QbD approach

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Abstract

The formulation the drug release up to 45 minutes. The formulation prepared with lactose monohydrates Crospovidone and magnesium stearates.G granulation procedure was the chosen technology for the preparation of Indinavir Sulfate capsule. Based on the preliminary studies, different formulation trials (F1-F7) were carried out with different concentrations of Disintegrants, diluents. From the various formulations it was decided that the formulation batch of F7 was finalized as the optimized formula.. Formulation F7 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when matched with that of the marketed product. The stability studies at all conditions, indicates that the formulated capsules were found to be stable. Hence, it is finally concluded that, Indinavir Sulfate capsules are pharmaceutically comparable, low cost, quality improved and stable formulation. This study has potential commercial and industrial applications after establishing the real-time stability, safety and efficacy.

Key words: Indinavir Sulfate, Capsules Formulation, Evaluation, QbD approach

INTRODUCTION

Indinavir sulfate, a potent protease inhibitor, has emerged as a pivotal component in the treatment of HIV/AIDS. Initially approved by the FDA in 1996, it has played a crucial role in improving the quality of life and extending the lifespan of HIV patients worldwide. Despite its established efficacy, challenges such as bioavailability and formulation have spurred ongoing research aimed at enhancing its therapeutic profile.Indinavir sulfate aims to address these challenges through innovative approaches in formulation and delivery systems. By optimizing its bioavailability and exploring novel formulations, the project seeks to improve patient compliance and treatment outcomes.This introduction sets the stage for a detailed exploration of the objectives, methodologies, and anticipated outcomes of the indinavir sulfate.

Indinavir sulfate is a medication primarily used in the treatment of HIV/AIDS. It belongs to a class of drugs known as protease inhibitors, which work by inhibiting the protease enzyme that HIV needs to replicate. By blocking this enzyme, indinavir helps reduce the viral load in the body, slowing down the progression of HIV infection to AIDS.

Mechanism of Action: Indinavir sulfate inhibits the HIV protease enzyme, which is essential for the virus to replicate and mature. By blocking this enzyme, it prevents the formation of mature viral particles.

In summary, indinavir sulfate played a pivotal role in the history of HIV/AIDS treatment, contributing to the development of combination therapies that have transformed the disease from a fatal condition to a manageable chronic illness for many patients worldwide.

Formulation of Indinavir sulfate: The formulation of indinavir sulfate, an antiretroviral medication used in the treatment of HIV/AIDS, involves several components and considerations to ensure its effectiveness, stability, and patient compliance. Here's a comprehensive look at the formulation of indinavir sulfate:

Active Pharmaceutical Ingredient (API):Indinavir Sulfate: This is the main active ingredient, belonging to the class of protease inhibitors. Indinavir works by inhibiting the HIV protease enzyme, essential for the maturation of infectious viral particles.

Excipients (Inactive Ingredients): Excipients are substances added to the formulation alongside the active ingredient to enhance its stability, bioavailability, and manufacturing process. Common excipients in indinavir sulfate formulations include:

Manufacturing Process:Granulation: The active ingredient (indinavir sulfate) and selected excipients are mixed and granulated to ensure uniform distribution and improve flow properties.

Tablet Compression or Capsule Filling: The granulated mixture is then compressed into tablets or filled into capsules using specialized equipment under controlled conditions.

Quality Control: Rigorous quality control measures are implemented throughout the manufacturing process to ensure the formulation meets regulatory standards for potency, purity, dissolution, and uniformity.

Stability Considerations: Indinavir sulfate formulations must be designed to maintain stability under various storage conditions (e.g., temperature, humidity) to ensure the drug remains effective until the expiration date.

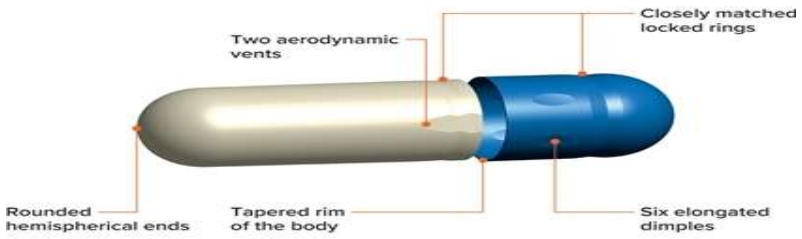
Formulation of indinavir sulfate is a complex process involving careful selection and combination of excipients to optimize drug delivery, stability, and patient acceptability. These formulations undergo thorough testing and quality assurance to ensure they meet the required standards for safety and efficacy in the treatment of HIV/AIDS.

Capsules formulation by using novel technology: Formulating capsules using novel technologies involves innovative approaches to enhance drug delivery, bioavailability, stability, and patient compliance. While specific details can vary based on the drug and intended outcomes, here are some novel technologies and considerations that can be applied to capsule formulations, including for drugs like indinavir sulfate:

Considerations for Development:

- **Regulatory Approval:** Novel technologies may require additional regulatory considerations and approvals.
- **Compatibility:** Ensure compatibility of novel excipients and technologies with the active ingredient and manufacturing processes.
- **Scalability:** Evaluate the scalability and cost-effectiveness of novel technologies for large-scale production.

In summary, applying novel technologies to capsule formulations of drugs like indinavir sulfate offers exciting possibilities for enhancing therapeutic outcomes, patient compliance, and overall treatment efficacy in conditions such as HIV/AIDS. Each technology brings unique advantages that can be tailored to meet specific formulation challenges and clinical needs.



Introduction to QbD: QbD, or Quality by Design, is a systematic approach to pharmaceutical development and manufacturing that emphasizes predefined objectives and understanding of product and process variability. It is a concept endorsed by regulatory agencies such as the FDA (Food and Drug Administration) and EMA (European Medicines Agency) to ensure the quality of pharmaceutical products throughout their lifecycle.

Key Principles of Quality by Design (QbD):Defining Quality Objectives: QbD starts with clearly defining the desired product quality attributes (e.g., potency, stability, safety) based on patient needs and regulatory requirements.

Real-Time Monitoring and Control: Continuous monitoring of CPPs and real-time release testing (RTRT) are employed to ensure consistency and reliability of product quality throughout manufacturing.
Continuous Improvement: QbD promotes a culture of continuous improvement through feedback loops, data analysis, and process optimization. This leads to enhanced process understanding and better control over product quality.





Elements of Quality by Design (QbD)

Quality by Design (QbD) in pharmaceutical development and manufacturing encompasses several key elements that collectively aim to ensure the quality and consistency of pharmaceutical products. These elements are systematically integrated into the product development process to enhance understanding, control, and optimization of both product and process. Here are the fundamental elements of QbD:

Implementation of QbD

Implementing QbD involves collaborative efforts across multidisciplinary teams, including scientists, engineers, regulatory affairs professionals, and quality experts. It requires effective communication, data-driven decision-making, and adherence to regulatory requirements. By incorporating these elements, pharmaceutical companies can enhance product development efficiency, reduce variability, and deliver high-quality medicines that meet patient needs and regulatory expectations.

Study of Objective

Development and optimization of Indinavir Sulfate 400mg Capsules formulation by novel technology using QbD approach.

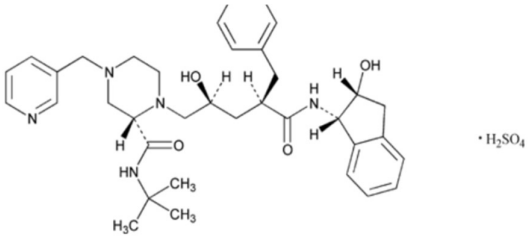
Scope of Study

The present scope is to:Design of Experimental approach for enhancing dissolution using anhydrous lactose, magnesium state for the formulation of the capsule. The proposed method shall be used for the quantification of active material Indinair Sulfate in Indinavir Sulfate 400mg Capsules.Strength of the capsule Indinavir Sulfate 150 mg Capsules, storage at 20-25 ºC.The proposed method shall be validated for Dispensing of raw material, Sifting, Dry mixing, Drying, milling, lubrication and Capsule filling.Controls of critical process parameters and Critical process attributes.Control on 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 , locking length, weight variation and Uniformity of the dosage form.

Drug Profile

Indinavir Sulfate comes in different oral dosage forms: capsules and oral powder.Indinavir Sulfate is a synthetic antiviral agent medicine. Indinavir binds to the active site of human immunodeficiency virus (HIV) protease and inhibits its activity, preventing the protease-mediated cleavage of gag-pol viral polyproteins ; as a result immature, noninfectious visions are produced. Indinavir (Sulphate) is a protease inhibitor with antiretroviral activity. Indinavir (Sulphate) is used in combination with other antiretroviral agents for the treatment of HIV infection and with advanced ae progressive immune-deficiency.BCS Classes, indinavir is BCS class II (low solubility, high permeability) or a BCS class IV (low solubility, low permeability) drug.

- Molecular Formula: $C_{36}H_{49}N_5O_8S$, Molecular Weight : 711.9 g/mol
- Chemical Structure:



Biological Activity: Indinavir sulfate is a potent and selective HIV protease inhibitor

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 Capsule 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.	Disintegration these	With 6 capsule in basket of disintegration
10.	Locking length	by using Vernier Calliper.1

Manufacturing Process

Steps involves in manufacturing process

Following steps are involves in the manufacturing process involving usage appropriate equipment: Dispensing of the raw material, Dry mixing and granulation, Blending Lubrication, Filling

I. blending sample is tested from 10 different location for the blend uniformity
II. Capsule filling : Fill the blend in the capsule cap and body

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	
	Bowl temperature	
	Exhaust temperature	
	Shaking interval	
	Product temperature	
Blending	Blender type	Blend uniformity and flow properties

Unit Parameter	Process Parameter	Quality Attributes
	Blender RPM	
	Blending time	
Capsulation	speed	Target weight, weight uniformity, content uniformity, locking length
	Tamping pin position	
	Force speed frame type and speed	

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

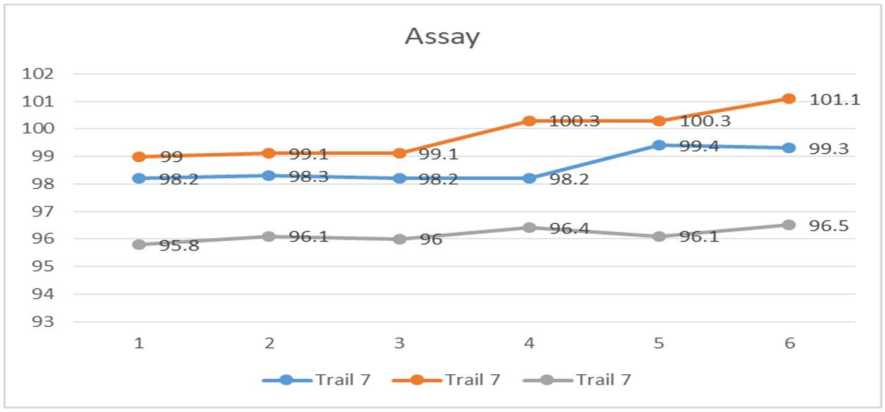
Ingredient	Quantity in batch per kg (mg/Tablets)						
	Trail 1	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Indinavir Sulfates USP	500.00	500.00	500.00	500.00	500.00	500.00	500.00
Lactose Monohydrates USP	117	117.5	117.5	118	118.5	119	120
Lubrication							
Magnesium stearate	15	14.5	14.5	14	13.5	13	12
	632.0	**632.0**	**632.0**	**632.0**	**632.0**	**632.0**	**632.0**
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent

Granulation control	**Trail 1**	**Trail 2**	**Trail 3**	**Trail 4**	**Trail 5**	**Trail 6**	**Trail 7**
Blender RPM	15	15	15	15	15	15	15
Blending time	5	5	5	5	5	5	5
Bulk density(g/ml)	0.354	0.434	0.523	0.529	0.583	0.456	0.447
Tapped density (g/ml)	0.242	0.313	0.495	0.437	0.419	0.694	0.685
Angle of Repose	31	47	46	34	31	28	27
Carrs Index	32	29	24	16	12	<10	<10
Hausner Ratio	1.46	1.34	1.27	1.21	1.30	0.8	0.7
Flow Properties	Very Poor	Poor	Passable	Fair	Good	Excellent	Excellent
Compressibility index (%)	31.809	37.987	29.597	67.694	37.981	38.815	38.701
Water Content by KF	2.24	2.46	2.17	2.53	2.2	2.17	2.13

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

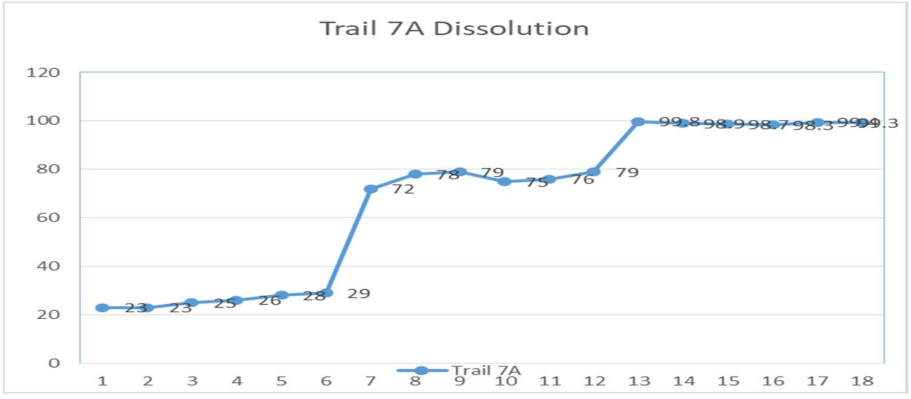
Assay of capsule

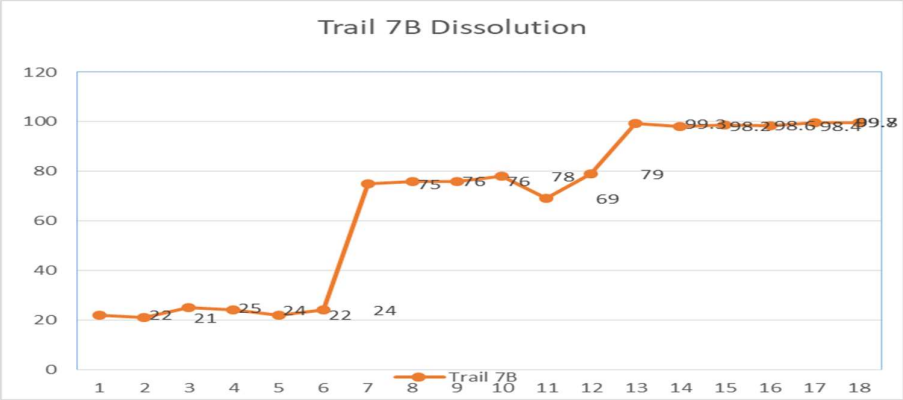
Assay	Trail 7	Trail 7	Trail 7
1	98.2	99.0	95.8
2	98.3	99.1	96.1
3	98.2	99.1	96.0
4	98.2	100.3	96.4
5	99.4	100.3	96.1
6	99.3	101.1	96.5
Mean	99.1	100	96.2
SD	1.24	1.13	0.26
%RSD	1.25	1.13	0.27
HPLC	QC-HPLC001	QC-HPLC001	QC-HPLC001
Column	QC-COL-011	QC-COL-011	QC-COL-011



Dissolution Profile:in pH 6.8 Phosphate buffer and 2% SLS at 75 RPM USP 1

	Time	Specification	Trail 7	Trail 7	Trail 7
1	10nd min	NMT 30%	23	22	28
2			23	21	29
3			25	25	27
4			26	24	26
5			28	22	25
6			29	24	22
1	20 th min	Between 60-80%	72	75	79
2			78	76	73
3			79	76	75
4			75	78	76
5			76	69	79
6			79	79	75
1	45th min	NLT 80 %	99.8	99.3	100.5
2			98.9	98.2	100.5
3			98.7	98.6	100.4
4			98.3	98.4	99.5
5			99.4	99.7	101.6
6			99.3	99.8	99.6





CONCLUSION

The formulation the drug release up to 45 minutes.The formulation prepared with lactose monohydrates Crospovidone and magnesium stearates.Granulation procedure was the chosen technology for the preparation of Indinavir Sulfate capsule. Based on the preliminary studies, different formulation trials (F1-F7) were carried out with different concentrations of Disintegrants, diluents. From the various formulations it was decided that the formulation batch of F7 was finalized as the optimized formula.Formulation F7 showed satisfactory results with various physicochemical evaluation parameters like Disintegration time, Dissolution profile, Assay when matched with that of the marketed product. The stability studies at all condition, indicates that the formulated capsules were found to be stable. Hence, it is finally concluded that, Indinavir Sulfate capsules are pharmaceutically comparable, low cost, quality improved and stable formulation. This study has potential commercial and industrial applications after establishing the real-time stability, safety and efficacy.

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