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FORMULATION AND EVALUATION OF NANOCRYSTALS FOR SOLUBILITY ENHANCEMENT OF LOSARTAN POTASSIUM BY ANTISOLVENT PRECIPITATION TECHNIQUE.

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ABSTARCT

The present research focuses on the formulation and evaluation of nanocrystals of Losartan Potassium to enhance its solubility and bioavailability, utilizing the antisolvent precipitation technique. Losartan Potassium, an antihypertensive agent, belongs to Biopharmaceutical Classification System (BCS) Class II drugs, characterized by low aqueous solubility and high permeability. To overcome its solubility limitations, nanocrystals were prepared using a bottom-up antisolvent precipitation method, employing stabilizers to prevent agglomeration and promote uniform particle size. The prepared nanocrystals were characterized by particle size analysis, zeta potential, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffraction (XRD) to assess their physical and chemical properties. In vitro solubility and dissolution studies demonstrated a significant improvement in the solubility and dissolution rate of the nanocrystals compared to the pure drug. The results indicate that the antisolvent precipitation technique is an effective and scalable approach for enhancing the solubility of poorly water-soluble drugs like Losartan Potassium.

KEYWORDS: Solubility, nanocrystal, antisolvent, bioavailability, antihypertensive.

INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness. However, the therapeutic efficacy of many orally administered drugs is limited by their poor aqueous solubility, leading to low bioavailability. Losartan potassium, an angiotensin II receptor antagonist widely used in the treatment of hypertension, belongs to Biopharmaceutical Classification System (BCS) Class II,

characterized by low solubility and high permeability. Enhancing the solubility and dissolution rate of such compounds is a critical challenge in pharmaceutical formulation development.

Nanocrystal technology has emerged as a promising approach to overcome solubility limitations of poorly water-soluble drugs. Nanocrystals, defined as drug particles in the nanometer range stabilized by surfactants or polymers, exhibit significantly increased surface area and saturation solubility, leading to improved dissolution rates and bioavailability. Among various methods for nanocrystal preparation, the antisolvent precipitation technique is particularly attractive due to its simplicity, cost-effectiveness, and suitability for thermolabile drugs.

This study focuses on the formulation and evaluation of losartan potassium nanocrystals using the antisolvent precipitation technique. The primary objective is to enhance the solubility and dissolution profile of losartan potassium, thereby potentially improving its oral bioavailability. The prepared nanocrystals were characterized for particle size, zeta potential, saturation solubility, drug content, and in vitro dissolution behavior. This research aims to contribute to the growing field of nanotechnology-based drug delivery systems by offering a feasible strategy to address solubility-related challenges in drug formulation.

MATERIAL AND METHOD

Losartan Potassium, used as the pure drug in this study, was procured from Aurochem Pharmaceuticals (India) Pvt. Ltd. Various surfactants employed included PVPK 30, PEG-6000, Pluronic-407, Polyvinyl alcohol, Hydroxypropyl methylcellulose (HPMC), Polyvinyl pyrrolidone, Pluronic-188, and Pluronic-68. These excipients were obtained from Research Lab Fine Chem. Industries, Mumbai, and were used as received without further purification.

Ethanol, serving as the solvent in the formulation process, was also purchased from Research Lab Fine Chem. Industries, Mumbai. Distilled water was used as the antisolvent throughout the experimental procedures, with the quantity adjusted as required for each formulation.

The following Preformulation studies are done for losartan potassium.

The following preformulation studies are carried out:

1) Organoleptic properties
2) Melting point
3) Dissociation constant
4) Solubility studies

5) Estimation of pure drug wavelength by UV-spectroscopy method

6) Estimation of drug by Fourier Infra- Red Spectroscopy (FTIR)

Organoleptic properties: Losartan potassium was, examined for Color, Oduor and nature. These characteristics were evaluated by visual observations.

Melting point: The melting point is fundamental physical property, used to identify the active pharmaceutical ingredient. The melting point of Losartan potassium was determine using digital melting point apparatus. The capillaries filled with the drug were placed in melting point apparatus containing liquid paraffin to check melting point. The temperature at which drug starts melting was recorded.

LogP: LogP is most commonly referred as lipophilicity. It is the log of partition coefficient of solute between octanol and water, at near infinite dilutions. It should be between 0 to 5. Log P value for Losartan potassium found to be 4.48.

pKa: pKa value is an acid-base dissociation constant of a drug. It indicates the strength of an acid. Fluorescence spectroscopy is used to determine pKa values and depends on difference in the fluorescence spectrum between a free acid and base to pKa value for losartan potassium was found to be 3.89 and 14.22±0.10 respectively.[37][43]

Solubility study: According to Biopharmaceutical classification system (BCS) losartan potassium falls under BCS class III, means it has high solubility and low permeability. The solubility of drug was tested in methanol, ethanol, acetone, ether and water.

Estimation of Losartan potassium by UV-spectroscopy method:

✓ Preparation 0.1NHCl:

8.3ml of concentrated hydrochloric acid was weighed and transfer to volumetric flask containing 1000 ml of distilled water.

✓ Preparation of standard calibration curves:

Accurately weighed 10 mg of losartan potassium and transfer to volumetric flask containing 100ml 0.1N HCl, dissolved with magnetic stirrer to form clear primary stock solution. From stock solution 5, 10, 15, 20, 25 and 30 µg/ml was pipetted out and further diluted up to 10 ml. All the solutions were scanned and absorbance was measured at observed χ max234 nm against 0.1 N HCl was used to run blank. Scanning was done in range of 400 to 200nm. Standard calibration curve was plotted for Losartan potassium in 0.1N HCl using UV spectrophotometer at χ max234 nm.

Estimation of drug by Fourier Infra-Red Spectroscopy (FTIR): To determine purity and to confirm the structure of drug. FTIR spectrum of the pure Losartan potassium recorded on

FTIR spectrophotometer. The scanning was performed between 4000- 600 cm-1 range and the peaks were recorded.[38][42]

Method of Preparation

Initially, a weighed quantity of Losartan Potassium was dissolved in ethanol to form the organic phase. Separately, the aqueous phase was prepared by dissolving PVPK-30 in distilled water, followed by continuous stirring on a magnetic stirrer for 30 minutes to ensure complete dissolution.

The organic phase was then added dropwise into the aqueous phase using a syringe, under continuous stirring with a magnetic stirrer. The resulting mixture was stirred at a speed of 1000–1500 rpm for a duration of 2 hours to facilitate uniform mixing and formulation development.

Following stirring, the mixture was subjected to centrifugation for 5 minutes. The obtained residue was collected carefully and dried under sunlight to yield the final product.

Table no. 1: Formulation Table.

Formu ation	Losart an*(mg)*	Ethanol (mL)	Water (ml)	PVPK 30(mg)	PEG 6000 (mg)	Pluronic 407 (mg)	Polyvinyl alcohol (mg)	HPMC (mg)	Polyviny pyrrolidone (mg)	Pluronic 188 (mg)	Pluronic 68(mg)
B1	50	10	50	40	-	-	-	-	-	-	-
B2	50	10	50	-	40	-	-	-	-	-	-
B3	50	10	50	-	-	40	-	-	-	-	-
B4	50	10	50	-	-	-	40	-	-	-	-
B5	50	10	50	-	-	-	-	40	-	-	-
B6	50	10	50	-	-	-	-	-	40	-	-
B7	50	10	50	-	-	-	-	-	-	40	-
B8	50	10	50	-	-	-	-	-	-	-	40

Evolution of losartan potassium nanocrystal

1. Appearance

The Appearance of the nanocrystal was observed visually.

2. In-Vitro Release Studies

The *In-Vitro* drug release studies performed using diffusion technique. The membrane was soaked before use in 0.1 N HCL solution for 4 hours. The nanosuspension was transferred into dialysis membrane bag, tied and placed in beaker containing 250ml dissolution medium. The entire system was kept at 37 ± 1^0C with magnetic stirring at 100rpm. At appropriate interval 5ml of aliquot was taken and 5ml fresh medium was added to maintain sink condition. The amount of drug in the release medium was evaluated by UV

Spectrophotometer at 234 nm.[41]

3. Zeta potential

Zeta potential of the nanocrystal is measured by HORIBA SZ-100. The zeta sizer mainly consists of laser which is used to provide a light source to illuminate the particles within the sample. For zetapotential measurements this light split to provide an incident and reference beam. The incident laser beam passes through the center of the sample cell, and the scattered light at an angle of about 130 is detected. Zeta sizer software produces a 65-frequency spectrum from which the electrophoretic mobility hence the zeta potential is calculated.[39]

4. Percentage (%) drug content

The 1 ml formulation was taken and dissolved in 9 ml methanol. From this solution, 1 ml withdrawn and diluted with 0.1N HCl to make up volume 10 ml. Then this solution was sonicated for 1 to2 hrs by using Sonicator. Then filter through Whatman's filter paper (No.41). Analysed at237 nm by using UV double beam spectrometry [125]. The % drug content calculated by formula: -

$$\% \text{ Drug Content} = \frac{\text{Actual concentration of drug in the formulation}}{\text{Theoretical concentration of drug}} \times 100$$

5. Drug Entrapment Efficiency

Take 2 ml of formulation in Nessler's tube (10 ml). This solution was centrifuged in centrifuge machine at 2000 – 3000 rpm for 4 to hrs. Then supernatant liquid was filtered through Whatman's filter paper (No.41) and diluted with 0.1N HCl solution Up to 10 ml. This solution was analyzed at 237 nm using UV double beam spectrometry [125]. The % entrapment efficiency was calculated by following formula: -

$$\text{Entrapment Efficiency} = \frac{\text{Total drug concentration - Free drug concentration}}{\text{Total drug concentration}} \times 100$$

6. Determination of Particle Size

Particle size of Nanocrystal was determined using particle size analyzer (HORIBA SZ-100). It Is a laser diffraction particle size analyzer and suitable for measuring particle sizes 0.1µm to 3mm works on the principle that when beam of light is scattered by a group of particles, the angle of light scattering is inversely proportional to particle size (i.e. smaller the particle size, larger the angle of light scattering).

7. Scanning Electron microscopy (SEM)Analysis:

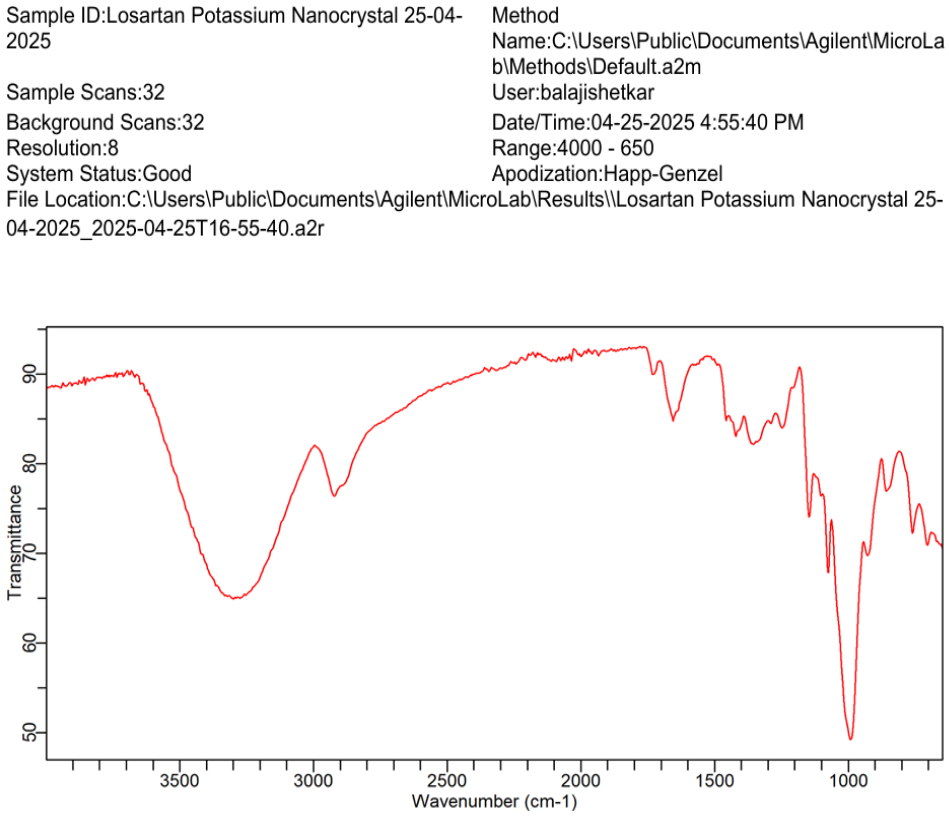
Scanning electron microscopy analysis provides high resolution imaging. The surface characteristics of nanocrystal formulation were determined by scanning electron microscopy. Sample was deposited on a glass slide and was kept under vacuum. The sample were coated with thin gold layer of thickness 200nm under reduced pressure using sputter coater unit of SEM. Images were taken at suitable magnification.[40]

RESULT AND DISCUSSION

CHARACTERIZATION OF PURE DRUG

Estimation of drug by Fourier Transform Infrared Spectroscopy (FTIR)

The IR spectrum of the pure Losartan potassium sample recorded by FTIR spectrometer is shown in graph no. 2. This was compared with standard functional group frequencies of Losartan potassium as shown in Table No.9. Table showed that frequencies of functional group of losartan potassium in the reported range which indicates that the obtained sample of losartan potassium was pure.



Graph 2: FTIR spectrum of losartan potassium.

Table 9: FTIR spectrum of Losartan potassium.

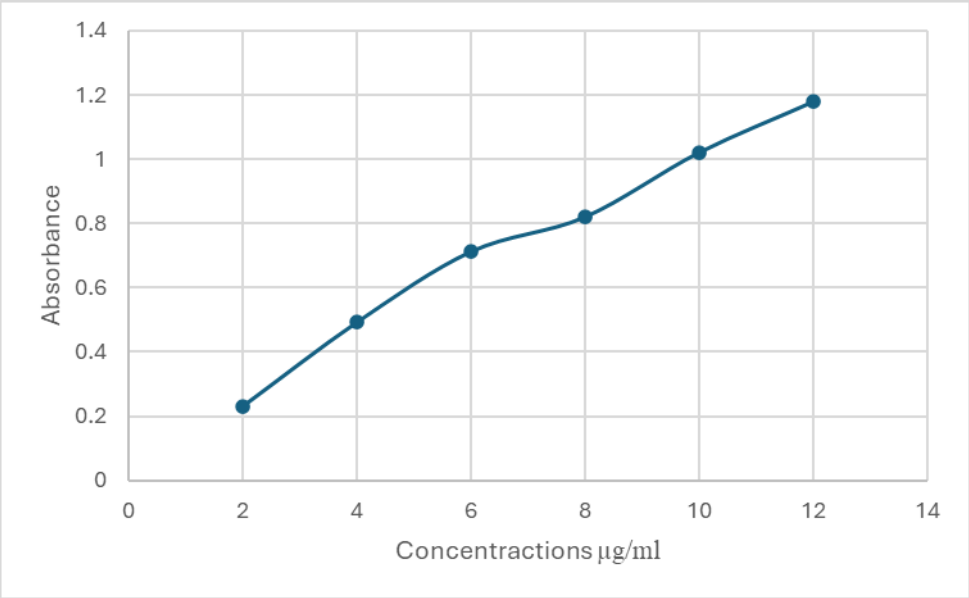
Wavenumber	Functional group
670.92	C–S stretch (thiol or thioether), C–Cl (alkyl halide), or aromatic C–H out-of-plane bend
711.92	C–Cl stretch (alkyl halide), or C–H out-of-plane bend in aromatic rings
764.10	C–H out-of-plane bend in mono- or disubstituted aromatics
991.47	=C–H out-of-plane bend (alkenes), or ring breathing mode in aromatics

Standard calibration curve using UV spectrophotometer:

Losartan potassium shows maximum absorption at wavelength 234 nm in 0.1N HCl, standard curve was plotted by taking absorption of diluted stock solutions (5, 10, 15, 20, 25 and 30) µg/ml at wavelength 269 nm. The calibration curve of losartan potassium is given below

Table 8: Estimation of standard calibration curve of Losartan potassium.

Sr. No	Concentration((µg/ml)	Absorbance
1	2	0.231
2	4	0.493
3	6	0.713
4	8	0.821
5	10	1.022
6	12	1.180



Graph1: Standard calibration curve of losartan potassium.

Estimation of drug by Fourier Transform Infrared Spectroscopy (FTIR)

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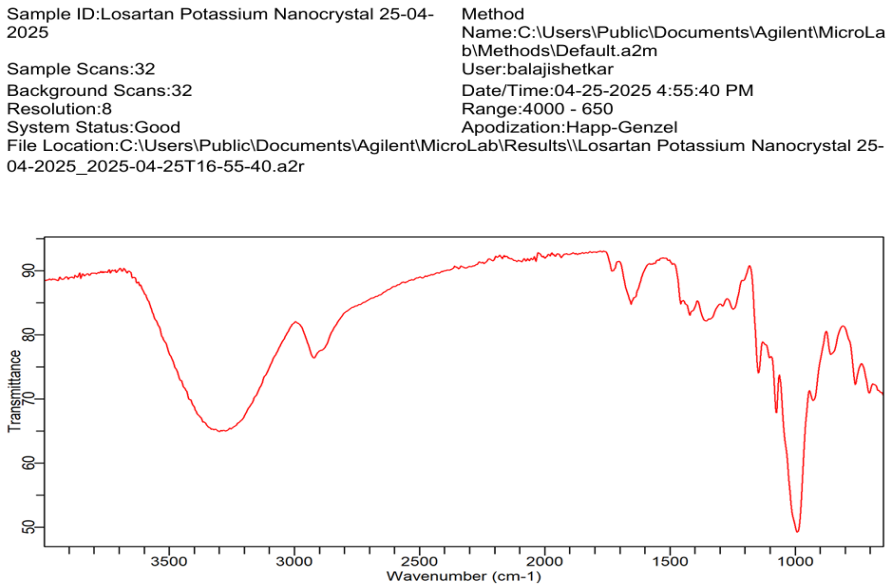

Graph 2: FTIR spectrum of losartan potassium.

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Wavenumber	Functional group
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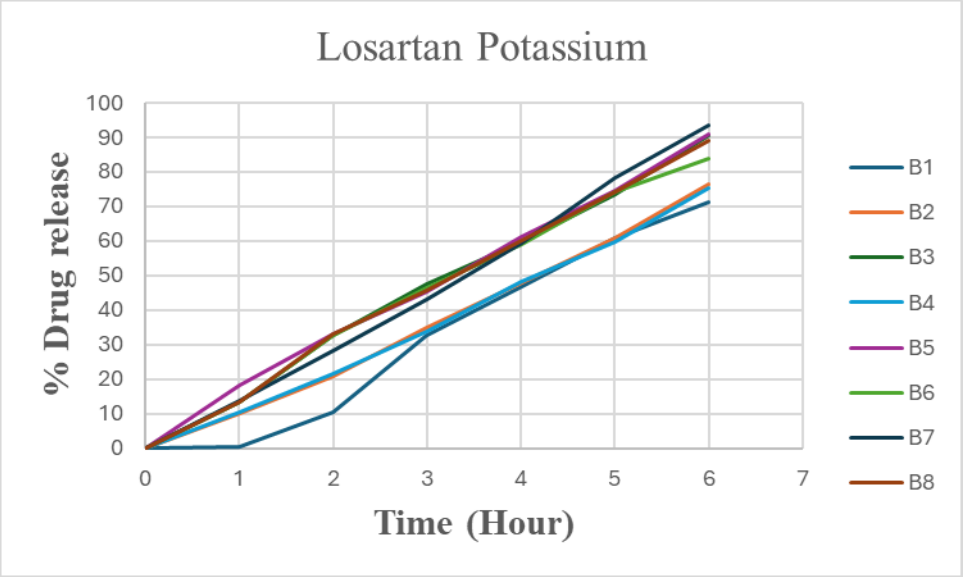
711.92	C–Cl stretch (alkyl halide), or C–H out-of-plane bend in aromatic rings
764.10	C–H out-of-plane bend in mono- or disubstituted aromatics
991.47	=C–H out-of-plane bend (alkenes), or ring breathing mode in aromatics

EVALUATION OF LOSARTAN POTASSIUM NANOCRYSTAL

In vitro drug release

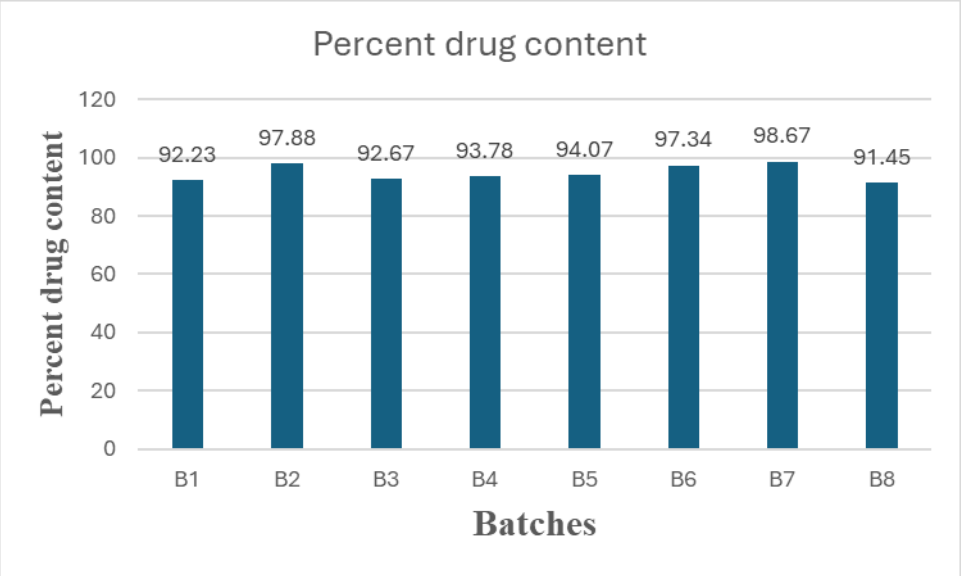
The in vitro diffusion of Losartan Potassium from the nanocrystal was varied in amount according to different surfactants of PVPK-30, PEG-6000, Pluronic-407, Polyvinyl alcohol, HPMC, Polyvinyl pyrrolidone, Pluronic-188 and Pluronic-68 used in formulation. The formulation B7 highest shows 93.48 % of drug release. From the study it was concluded that nanocrystal showed better diffusion than conventional formulation of losartan potassium within 6 hr. In vitro drug release data shows that drug release from nanocrystal formulation was highest in comparison with conventional formulations of losartan potassium (batch B0). This is because of nanocrystal plays major role in drug targeting and drug delivery.



Graph 3: In vitro drug release of nanocrystal formulation.

Percent Drug Content

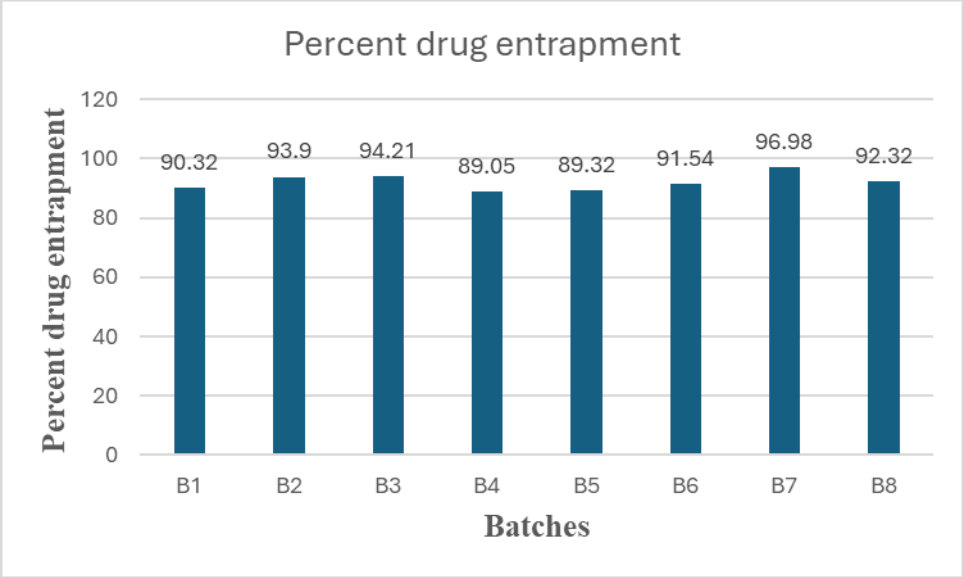
The % drug content of all formulations was found between 91-98%. Among all formulations, B7 shows 98.67 % drug content.



Graph 3: Percent Drug Content.

Percent Entrapment Efficiency

The percent entrapment efficiency of all formulations was found between 89-96 %. Among all formulations, B7 shows 96.98 % drug entrapment efficiency.



Graph 4: Percent Entrapment Efficiency.

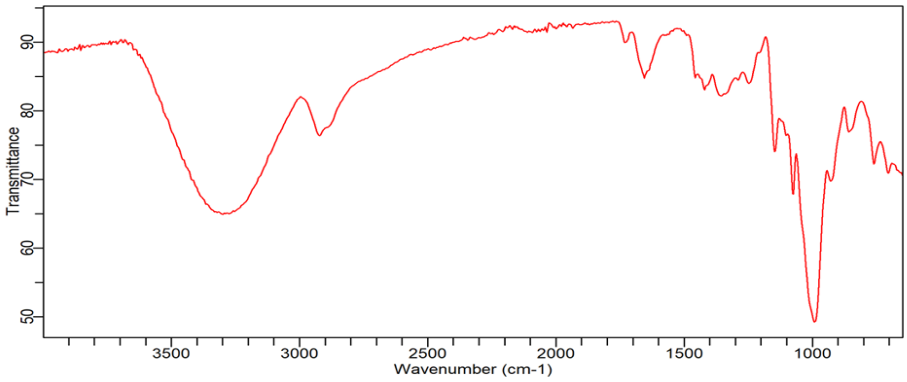
Table 10: Evaluation of nanocrystal.

Surfactant	% Drug release	% Drug content	% Drug entrapment
PVPK-30	71.22	92.23	90.32
PEG-6000	76.39	97.88	93.90
Pluronic-407	90.52	92.67	94.21
Polyvinyl alcohol	75.47	93.78	89.05
HPMC	90.79	94.07	89.32
Polyvinyl pyrrolidone	89.25	97.34	91.54
Pluronic-188	93.48	98.67	96.98
Pluronic-68	88.90	91.45	92.32

Identification of Nanocrystal formulation by FTIR Spectroscopy and compatibility study:

in graph No. 6:

Sample ID:Losartan Potassium Nanocrystal 25-04-2025
Method Name:C:\Users\Public\Documents\Agilent\MicroLab\Methods\Default.a2m
Sample Scans:32
User:balajishetkar
Background Scans:32
Date/Time:04-25-2025 4:55:40 PM
Resolution:8
Range:4000 - 650
System Status:Good
Apodization:Happ-Genzel
File Location:C:\Users\Public\Documents\Agilent\MicroLab\Results\\Losartan Potassium Nanocrystal 25-04-2025_2025-04-25T16-55-40.a2r

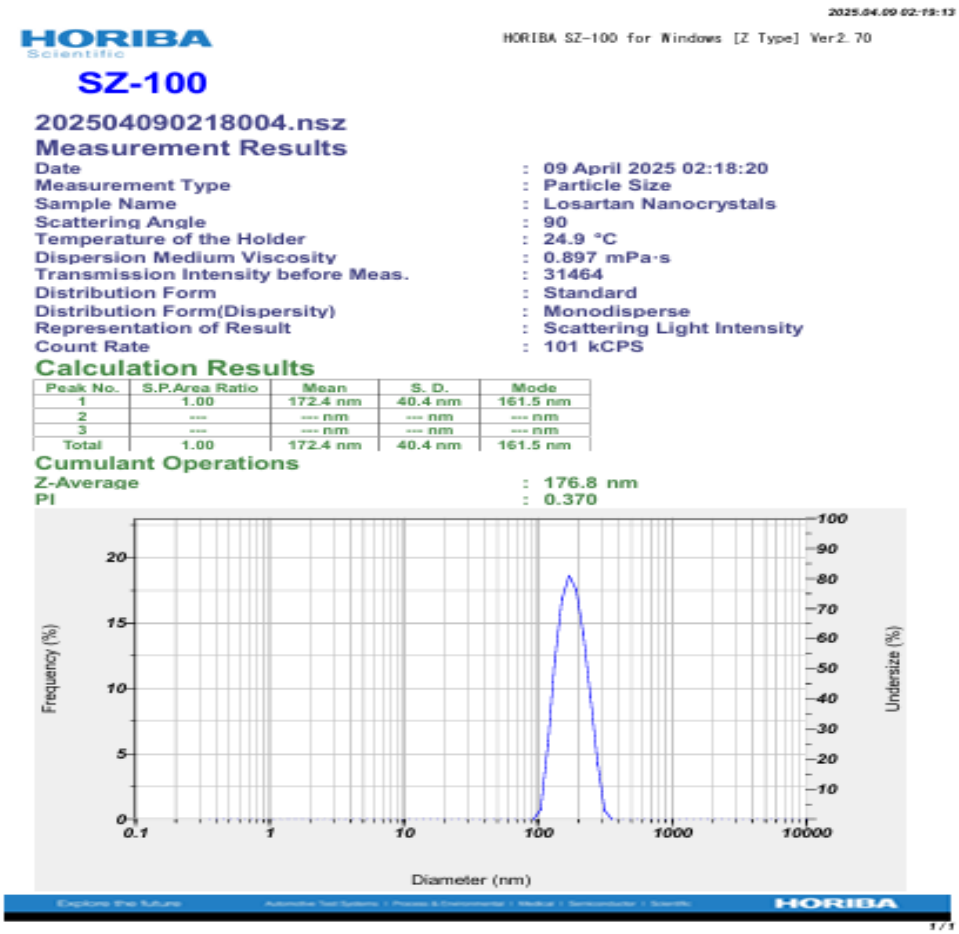


Graph 6: FTIR spectrum of nanocrystal formulation.

Table 11: FTIR spectrum of nanocrystal formulation.

Wavenumber	Functional group
704.47	Likely C–Cl stretch or ring deformation in aromatics
760.38	C–H out-of-plane bend (aromatic)
857.29	C–H out-of-plane bend, possibly para-substituted benzene
928.11	C–O–C or C–C stretching (ethers or alkanes)

Particle size analysis



Graph 3: Particle Size Analysis.

The particle size distribution studies showed that the formulation particle size was 176.8 nm.

Zeta potential

Zeta potential is a term related to the stability of samples for molecules and particles that are small enough, high zeta potential will confer stability i.e. it resists aggregation. Here zeta potential of nanocrystal was found to be -14.7 mV, which would not allow aggregation.

Graph 4: Zeta potential of nanocrystals.

SEM

Formulated nanocrystal surface morphology and shape were visualized using SEM (Nova Nano SEM NPE303). The SEM image shows the surface morphology of the Losartan Potassium nanocrystals. The average particle size is approximately 25nm. The nanocrystals were found to be oval with smooth surface.

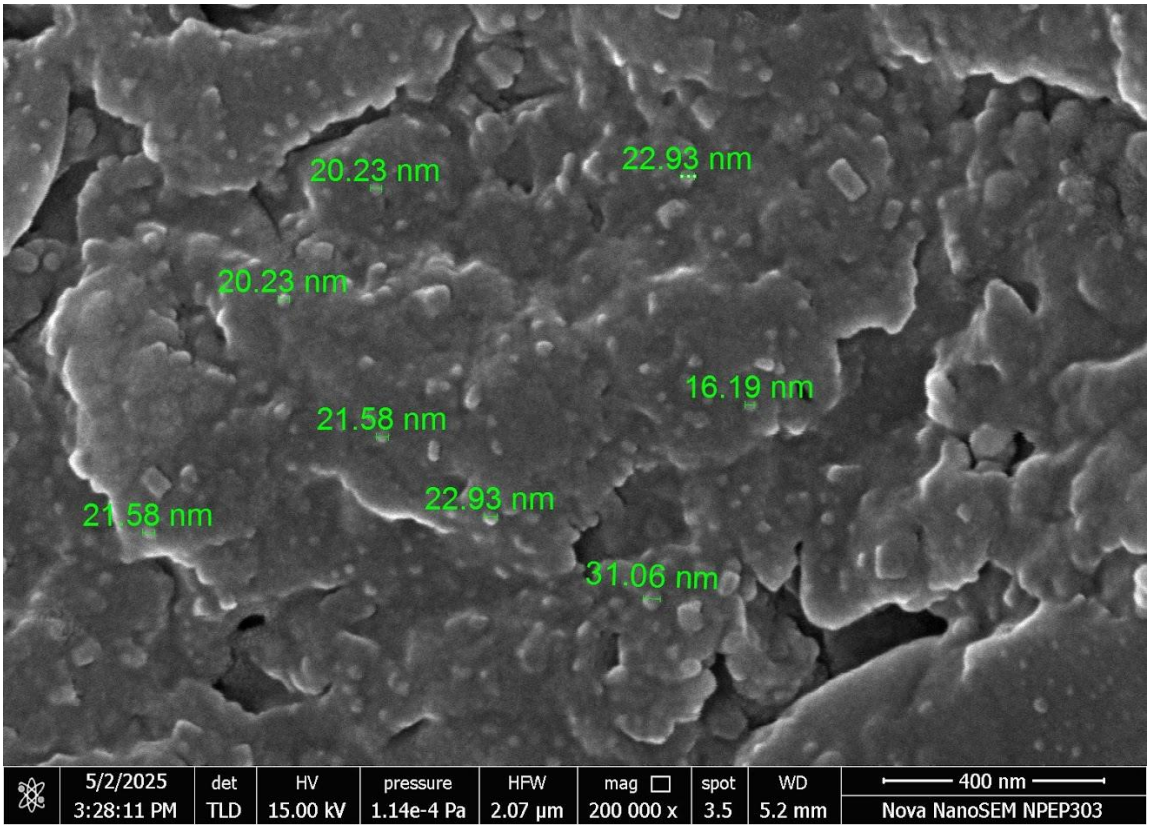


Fig. 5: SEM analysis of nanocrystal formulation.

SUMMARY & CONCLUSION

Losartan has poor solubility and poor bioavailability compound. By using nanocrystals, drugs that are poorly soluble in lipid and aqueous mediums can become more soluble, hence were selected for the formulation of Nanocrystal. The Losartan potassium was Procured from Aurochem Pharmaceutical (INDIA) Pvt. Ltd.

In Preformulation studies, the obtained drug sample of Losartan potassium was authenticated by FT-IR and melting point. FTIR study indicates that frequencies of functional group of Losartan potassium were in the reported range which indicates that the obtained sample of Losartan potassium were pure. Melting point of Losartan potassium was found to be 183°C which is similar to melting point mentioned in Indian pharmacopoeia.

After authentication, the Losartan potassium sample was subjected to wavelength determination and standard calibration curve was constructed using UV-Visible Spectrophotometer, wavelength was found to be 234nm.

The Losartan potassium Nanocrystals were prepared by using losartan potassium, PVPK-30, PEG-6000, Pluronic-407, Polyvinyl alcohol, HPMC, Polyvinyl pyrrolidone, Pluronic-188, Pluronic-68, were used as surfactant, ethanol as solvent and distilled water as antisolvent. The

Nanocrystals were formulated using Antisolvent precipitation technique, total 8 batches were prepared.

The Prepared Nanosuspensions was evaluated for different parameters like, entrapment efficiency, Drug content. The Drug content and % EE of batch B7 showed 98% and 96%. Other physicochemical evaluation parameters of nanosuspension were found within acceptable limits.

Further, these formulations were subjected to evaluations like Particle size, Zeta Potential and In- vitro drug release. The particle size distribution studies showed that all the formulations particle size was in the range of 176-714nm. Particle Size of the B7 batch was found to be 176 nm and zeta potential was found to be -14.7Mv. The Drug release of batch B7 was found to be 93.48 % of drug release.

From all the physiochemical evaluation parameters, batch B7 was considered as optimized formulation. Therefore, it can be concluded that Nanocrystal can be a potential candidate for the delivery of Losartan potassium for the treatment of Hypertension.

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The completion of this research is not only the fulfillment of my dreams but also the fulfillment of the dreams of my parents. No research is ever the outcome of a single individual’s talent or efforts. I have seen and experienced the countless blessings showered upon me by my parents, all my family members, teachers, friends, and well-wishers. Knowing that God’s hand is always there, guiding me and leading me towards greater heights, gives me immense strength and confidence.

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FUTURE PROSPECTIVE

To conduct in-vitro bioequivalence study.

To formulate nanocrystals in suitable dosage form.

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