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Research Article

Preparation Optimization And Evaluation Of Lenvatinib As A Nanocochleats

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ABSTRACT

The objective of developing nanocochleates was to enhance drug bioavailability by improving solubility. Preformulation studies identified the drug and excipients through physical analysis methods. The drug's maximum wavelength was 254 nm in phosphate buffer pH 6.8, and 249 nm in methanol. Initially, liposomes were formed using the thin film hydration method, adjusting the cholesterol and lipid ratio. Subsequently, nanocochleates were produced using a trapping method. The formulation was optimized by considering the rotary evaporator speed, solvent system ratio and volume, hydration media pH, production yield, entrapment efficiency, and in-vitro drug release. Batch M5 met all these criteria and was selected as the optimal liposome formulation. FTIR and DSC tests confirmed drug-excipient compatibility, showing no chemical interactions. SEM analysis revealed the nanocochleates to be small and rod-shaped, with a particle size of 114.9 nm. The optimized batch had a drug release rate of 89.50% after 4.5 hours. This trapping method effectively incorporated the poorly water-soluble drug lenvatinib into liposomal formulations.

INTRODUCTION

Oral Drug Delivery System

Oral administration is favored for its simplicity of ingestion, avoidance of pain, versatility in handling different types of drugs, and, most importantly, high patient compliance. Additionally, solid oral delivery systems do not need sterile conditions, making them more cost-effective to produce.

Noval Drug Delivery System

Several new technologies for oral drug delivery have emerged recently, aimed at addressing the physicochemical and pharmacokinetic properties of drugs while enhancing patient compliance. Innovations like electrostatic drug deposition and coating, along with computer-assisted 3D printing for tablet manufacturing, have also been introduced. The development of oral modified drug delivery systems has allowed for extended drug release over several hours, reducing dosing

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frequency, minimizing side effects, improving therapeutic outcomes, and increasing bioavailability, making it more favorable than conventional dosage forms.

Challenging Oral Drug Delivery Via Nano-Carriers

The Vesicular drug delivery systems offer several benefits over conventional and prolonged-release dosage forms, such as:

- Enhanced drug permeation into cells.
- Extended presence of drugs in systemic circulation.
- Reduced toxicity due to selective uptake.
- Lower therapy costs.
- Improved bioavailability
- Ability to incorporate hydrophilic and lipophilic drugs.
- Function as a sustained-release system.
- Delayed elimination of drugs that are rapidly metabolized.
- Overcoming issues related to drug insolubility, instability, and rapid degradation.

Conventional chemotherapy for treating intracellular infections is often ineffective due to limited drug permeation into cells. Vesicular drug delivery systems improve bioavailability at the disease site, minimize harmful side effects associated with conventional and controlled-release systems, and address issues of drug degradation and loss.

Liposome

Liposomes are composed of one or more concentric lipid bilayers that enclose internal aqueous compartments. For drug delivery purposes, liposomes are typically unilamellar and have diameters ranging from approximately 50 to 150 nm. Larger liposomes are quickly removed from the bloodstream. Liposomes are distinctive in their capacity to encapsulate drugs with varying physicochemical characteristics, including polarity, charge, and size. Drugs can localize in different regions within liposomes: the hydrophobic hydrocarbon chain core of the bilayer, the large polar surface (which can be neutral or charged), and the internal aqueous space. Liposomes offer selective passive targeting to tumor tissues (e.g., liposomal doxorubicin), enhanced drug efficacy and therapeutic index (e.g., Actinomycin-D), stability through encapsulation, biocompatibility, complete biodegradability, non-toxicity, flexibility, and lack of immunogenicity for both systemic and non-systemic administrations. They also reduce the toxicity of encapsulated agents (e.g., Amphotericin B, Taxol) and limit the exposure of sensitive tissues to toxic drugs. Additionally, liposomes provide a site-avoidance effect and the flexibility to be coupled with site-specific ligands for active targeting.

Cochleate And Nano-Cochleats

Various modifications to liposome formulations have led to the creation of a new class of drug carriers known as "cochleates." Cochleates are solid particles composed of large, continuous lipid bilayer sheets rolled into a spiral structure without an internal aqueous phase. This technology addresses the challenges of orally delivering various biological molecules, particularly hydrophobic ones. Unlike liposomes, cochleates have a water-free interior, rod-like shape, and rigid, stable structure. Cochleates and nanocochleates are spiral rolls formed from negatively charged phospholipid bilayers, rolled through interactions with multivalent counter ions (Ca^{2+} or Zn^{2+}) that act as bridging agents between the bilayers. Nanocochleates feature both hydrophilic and hydrophobic surfaces, making them suitable for encapsulating hydrophobic drugs like amphotericin B and clofazimine, as well as amphipathic drugs like doxorubicin. This technology excels at encapsulating drugs within the nanocochleate structure, which remains intact

even when exposed to harsh environmental conditions or enzymes.

Components Of Nano-Cochleate Drug Delivery System

The three primary components used to prepare nano cochleates are atmospheric pressure ionization (API), lipids, and cations.

1. Lipids: Phosphatidyl serine (PS), phosphatidic acid (PA), dioleoyl PS, phosphatidylinositol (PI), phosphatidyl glycerol (PG), phosphatidyl choline (PC), dimyristoyl PS, phosphatidyl ethanolamine (PE), diphosphatidyl glycerol (DPG), dioleoyl phosphatidic acid, distearoyl phosphatidyl serine, and dipalmitoyl PG.

2. Cations: Zn^{2+}, Ca^{2+}, Mg^{2+}, or Ba^{2+}.

Objective

- Conduct preformulation studies of lenvatinib.
- Enhance the solubility of lenvatinib.
- Target cancer cells by improving drug delivery.
- Increase entrapment efficiency.
- Utilize drug and polymer carriers.
- Improve the stability of the drug.

Nano cochleates encapsulate anticancer drugs and deliver them directly to the target site. This enhances the solubility and permeability of BCS Class II drugs, thereby increasing drug efficacy.

MATERIAL AND EQUIPMENTS

List Of Materials

Sr. No	Name of the ingredient	Name of the supplier
01	Lenvatinib	Lab
02	Soy lecithin	Lab
03	Cholesterol	Lab
04	Ethanol	Lab
05	Calcium chloride	Lab

List Of Equipment

Sr. No	Name of equipment and instrument	Make and model
1	Single pan electronic balance	Shimadzu, AX 120, Japan
2	UV-Visible Double Beam spectrophotometer	UV-1800, Xhimadzu, Japan
3	FTIR Spectrophotometer	JASCO FTIR-410, Japan
4	Rotary evaporator	Super fit (model PBU6D)
5	Bath sonicator	Remi Instrument, LTD

EXPERIMENTAL WORK

Preformulation Study

The primary objectives of preformulation studies are to identify the physicochemical properties of the new drug entity and to determine its compatibility with common excipients[19].

Organoleptic Properties:

The visual assessment included examining the physical appearance, color, and odor of the Lenvatinib sample[20].

Melting Point Determination:

The condition refers to its melting point. Moreover, the purity of the substance influences its melting point, which provides insights into its characteristics. This method identifies the temperature at which the medication begins to melt. The experiment was to ensure accuracy. The observed melting point was recorded and documented for reference.

Fourier Transforms Infrared Analysis:

To identify potential structural changes, the atorvastatin sample was analyzed using Fourier Transform infrared spectroscopy (Agilent Technologies Cary 630 FTIR)[21].

Preparation of Phosphate buffer pH 6.8

To prepare the solution, sodium hydroxide (28.80 g) and potassium dihydrogen ortho phosphate (11.45 g) were dissolved in a sufficient amount of distilled water, then diluted to a total volume of 100 ml in a volumetric flask.

Preparation of lenvatinib loaded liposomes

Multi-lamellar vesicle (MLV) liposomes were created using the thin film hydration method. The lipid phase comprised mixtures of cholesterol and phosphatidylcholine in various molar ratios (refer to the table). In brief, the lipid mixture and 50 mg of lenvatinib were dissolved in a 3:3 v/v chloroform solution, then evaporated under vacuum at 45°C. This resulted in a thin, dry lipid layer on the flask wall, produced using a rotary flash evaporator. The film was hydrated by adding phosphate buffer (pH 7.4) and vigorously shaking with a vortex mixer until vesicles formed after all solvent traces were removed. The liposomes were further reduced in size using a sonicator to create small unilamellar vesicles[21].

Preparation of lenvatinib loaded nanocochleates

Lenvatinib-loaded nanocochleates were prepared using the trapping technique. The resulting liposomes were vortexed, and 50 microliters of a 0.1 M calcium chloride solution was added drop by drop. This immediately caused the lenvatinib liposomal phase to become turbid, indicating the formation of nano cochleates. These nano cochleates were then evaluated for drug content, encapsulation efficiency, zeta potential, and particle size.

In efforts to improve nano cochleate formulations, researchers have tried creating dry powder using lyophilization technology. Dry powder formulations offer several advantages over liquid forms, including improved physicochemical stability and reduced risk of microbial contamination. The lyophilized powder was analysed using FTIR, PXRD, and DSC techniques[22].

Optimization of Liposome Preparation:

A thin, uniform coating is crucial for determining the final product of the liposomal preparation. During the hydration and film formation processes, the rotational speed was maintained between 60 and 100 rpm.

Table.no.3: Batch made on basic of different concentration of drug

Formulation Code	Ratio SL:CH	Amount of soya lecithin (mg)	Amount of cholesterol
L1	8:0	200	0
L2	7:1	175	25
L3	6:1	150	50
L4	5:3	125	75
L5	4:4	100	100
L6	3:5	75	125
L7	2:6	50	150
L8	1:7	25	175

Speed of the rotary evaporator

The ratio and volume of solvent system

The solvent system was adjusted by mixing varying amounts of methanol and chloroform, the two organic solvents. The film was tested at ratios of 3:1, 3:2, and 3:3, and its homogeneity was evaluated.

pH of the hydrating media

The effect of the phosphate buffer's pH on the formulation was studied, as pH influences drug entrapment in liposomes. Entrapment efficiency was measured by adjusting the hydration buffer's pH to levels near the drug's pKa. Distilled water and phosphate buffer with pH values of 5.2, 6.8,

and 7.4 were used as hydrating media. The entrapment efficiency of each formulation was then analyzed[23].

Optimization of nanocochleates preparation by change in molarity of calcium chloride solution:

The influence of the calcium chloride solution's concentration on the batches of nanocochleates was investigated. Prior to evaluating how calcium ions affect entrapment efficiency, practical yield, and in vitro drug release within the nanocochleates, the synthesis of these liposomes was optimized using multiple criteria.

RESULTS AND DISCUSSION:

Preformulation study:

The preformulation studies of the medication produced the following results, based on spectral and melting point analyses.

Organoleptic properties:

The powder was found to be without odor and had a color ranging from white to off-white.

Table No. 5: Result of organoleptic properties of Lenvatinib

Sr. No.	Parameter	Observation
01	Physical state	Solid
02	Colour	White to off white
02	Odour	Odourless

Melting Point Determination:

The documented melting point of Lenvatinib ranged from 216 to 231°C, with the observed melting point specifically noted at 226°C. This confirms the purity of the powdered drug and verifies its identity as Lenvatinib.

Table No.06 Melting point of drug

Drug	Melting point	Observed Melting point
Lenvatinib	216-231°C	226°C

Cholesterol:

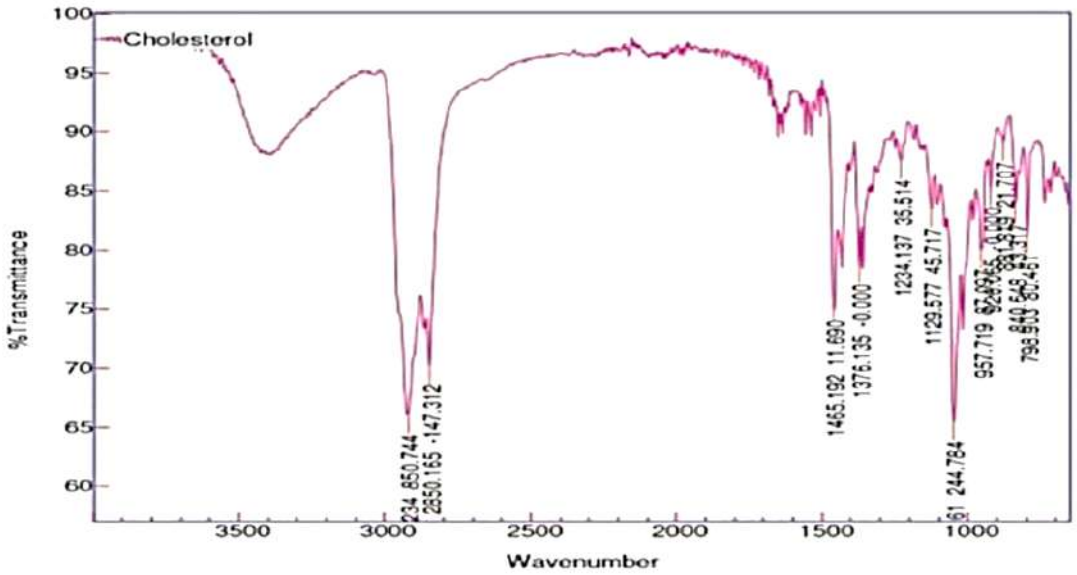

Fig no 2: FTIR Spectra of Cholesterol

Table no7: Major Observed IR Peaks of Cholesterol

Sr. No	Functional Groups	Wavenumber (cm-1)	Peak Position (cm-1)	Indication
1.	Alkanes	3000-2850	2924.234	C-H
2.	Alkene	1680-1400	1465.192	C=C
3.	Alkene	3600-2800	2850.165	O-H

Soya Lecithin

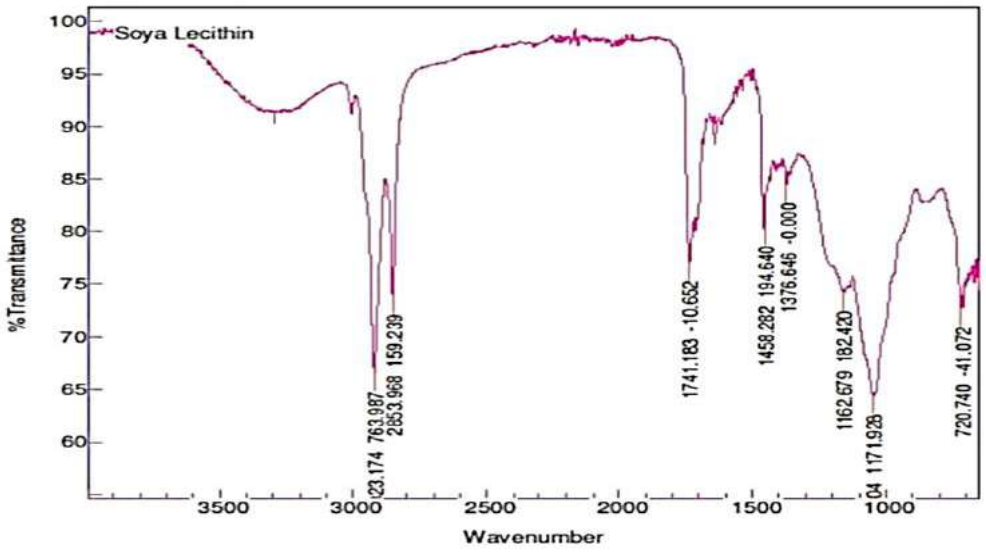

Fig no 3: FTIR Spectra of Soya Lecithin

Table No 8: Major Observed IR Peaks of Soya Lecithin

Sr. No	Functional Groups	Wavenumber (cm^{21})	Peak Position (cm)	Indication
1.	Aldehyde	1750-1720	1741.183	C=o
2.	Amide	3500-3100	3339.347	N-H (Stretch)
3.	Alkane	3000-2850	2923.174	C-H
4.	Alkene	1680-1400	1458.282	C=C

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