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Design and Characterization of Nanosponges Drug Delivery System for Water soluble and insoluble actives

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Abstract

Nanotechnology revolutionized drug delivery systems by maximizing the solubility, stability, and bioavailability of drug molecules. Of all the various nanocarriers, nano sponges have emerged as a very efficient drug delivery system due to the sponge-like porous structure that favors effective encapsulation and controlled delivery of water-soluble as well as water-insoluble actives. This study aims at the synthesis, design, and characterization of β-cyclodextrin-based nano sponges for the targeted and sustained delivery of Acelofenac (ACE), an insoluble water nonsteroidal anti-inflammatory drug (NSAID). The study aims to optimize the nano sponge formulation for better drug solubility, release duration, and therapeutic response.

Keywords: Nanosponges, Design, Evaluation

Introduction

Targeting medication distribution has historically posed challenges for medical researchers, specifically in directing pharmaceuticals to the appropriate location within the body and regulating their release to avert overdosing. The emergence of novel and intricate molecules known as nanosponges may address these issues. Nanosponges are a novel category of materials composed of minuscule particles featuring cavities measuring a few nanometres in width, capable of encapsulating a diverse array of chemicals. These particles may transport both lipophilic and hydrophilic compounds and enhance the solubility of weakly water-soluble molecules. Nanosponges are diminutive mesh-like constructs that have the potential to transform the treatment of several diseases, with preliminary experiments indicating that this technology may be up to five times more efficacious in delivering medications for breast cancer compared to traditional approaches.

The nanosponge measures approximately the size of a virus and features a 'backbone' composed of a naturally degradable polyester scaffold structure. The elongated polyester fibres are combined in a solution with small molecules known as cross-linkers, which exhibit an affinity for specific segments of the polyester. They "cross-link" polyester segments to create a spherical structure containing several pockets for medication storage. The polyester is reliably biodegradable, indicating that when it degrades within the body, the medicine can be released according to a predetermined schedule.

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Table 1: Chemicals used for the synthesis of nanosponges

Crosslinkers	Diphenyl Carbonate, Diarylcarbonates, Diisocyanates, Pyromellitic anhydride, Carbonyldiimidazoles, Epichloridrine, Glutarldehyde, Carboxylic acid dianhydrides, 2,2-bis(acrylamido) Acetic acid and Dichloromethane.
Polymers	Hyper cross-linked Polystyrenes, Cyclodextrines and its derivatives like Methyl β-Cyclodextrin, Alkyloxycarbonyl Cyclodextrins, 2-Hydroxy Propyl β-Cyclodextrins and Copolymers like Poly(valerolactone-allylvalerolactone) & Poly(valerolactone-allylvalerolactoneoxepanedione) and Ethyl Cellulose & PVA

Nanosponges are a form of nanoparticle that encapsulate medicinal molecules within its core. Nanoparticles can be categorised into encapsulating nanoparticles, complexing nanoparticles, and conjugating nanoparticles based on their association with pharmaceuticals. The initial category is exemplified by nanosponges and nanocapsules. Nanosponges, such as alginate nanosponges, are sponge-like nanoparticles characterised by many pores that encapsulate medicinal molecules. Nanocapsules, including poly(isobutyl-cyanoacrylate) (IBCA), encapsulate nanoparticles. They can encapsulate medicinal compounds within their watery core. The second group is complexing nanoparticles, which attract molecules by electrostatic charges. The third type is conjugated nanoparticles, which are attached to pharmaceuticals via covalent bonds. These nanosponges constitute a novel category of nanoparticles often derived from natural sources. In comparison to other nanoparticles, they are insoluble in both aqueous and organic solvents, porous, non-toxic, and stable at elevated temperatures up to 300°C.

Characterization of Nanosponges

Thin Layer Chromatography: The Rf values of a drug molecule significantly decrease in thin layer chromatography, which aids in recognising the complex formation between the drug and nanosponge.

- **Zeta potential:** Surface charge is measured by adding an electrode. Equipment for measuring particle size can be used (Zeta Sizer).
- **Single Crystal X-ray Structure Analysis:** Additionally, the inclusion structure and its interactions may be studied using this method. A precise relationship can be established by determining how host and outside molecules interact.
- **Infra-Red spectroscopy:** Infrared spectroscopy can be used to evaluate how medicinal molecules interact with nano sponges in the solid state. When a compound is formed, nano sponge bands frequently only change significantly. The presence of hydrogen in different functional groups is shown by infrared spectral investigations.
- **Thermo-analytical methods:** It can be determined using thermo-analytical techniques whether the drug substance changes as a result of the heat breakdown of the Nano sponge. It is possible to see changes in the thermogram produced by DTA and DSC, such as broadening, shifting, the development of additional peaks, or the elimination of particular peaks. The creation of inclusion complexes can also be supported by changes in weight loss.
- **X-ray Diffractometry:** Utilizing powder X-ray diffractometry, inclusion complexes in solid state are found. If we take liquid into consideration, it has no unique diffraction pattern and completely varies from a complex Nano sponge. A physical mixture's diffraction pattern is produced by the fusion of two elements. They result in various peaks for a mixture and are helpful in figuring out chemical breakdown and complicated creation.
- **Particle Size Determination and polydispersity:** A key factor in the optimization process is the Nano sponge's particle size. Zeta sizing or laser light diffractometry are two methods for measuring particle size. To evaluate the impact of particle size on drug release, cumulative percentage drug release from Nano sponges of various particle sizes can be plotted against time. Three measurements were made on each sample. This allows one to calculate the mean diameter polydispersity index.
- **Swelling and water uptake:** By soaking the generated Nano sponges in an aqueous solution,

water uptake can be assessed for swellable polymers such polyamido amine nanosponges.

Compatibility Studies: Thin Layer Chromatography (TLC) and Fourier Transform Infrared Spectroscopy can be used to test the drug and polymer compatibility that are utilised to create nano sponges (FT-IR). Differential Scanning Colorimetry (DSC) and powder X-ray diffraction (XRD) are methods for analysing crystallinity (DSC).

In- vitro release studies: Franz Diffusion cells with a diffusional area of 2.26 cm2 and a multi-compartment rotating cell with dialysis membrane can be used to study the drug release from the improved Nano sponge formulation. The drug-loaded nanosponge complex in distilled water makes up the donor phase. The same medium is present in the receptor phase as well. After certain intervals, the receptor phase is entirely removed, appropriately diluted with distilled water, and then subjected to UV spectrophotometer analysis. Utilizing graph pad prism software, the mechanism of drug release from nanosponge was examined. The software estimates the parameters of a non-linear function that gives the closest fit between experimental findings and non-linear function.

Porosity: To determine the extent of produced nanochannels and nanocavities, a porosity analysis is conducted. A helium pycnometer is used to measure the porosity of Nano sponges because helium gas may pass through both inter- and intra-specific channels in materials. "The helium displacement method is used to calculate the material's actual volume."

Optimization of Drug-Loaded Nanosponges:

- To develop the nanosponge formulation based on Quality by Design (QbD) and Design of Experiment (DOE) approaches.
- To study the effects of polymer concentration, crosslinker concentration, and reaction time on drug entrapment and drug release behavior.

Evaluation of Drug Release Profile:

- To conduct in-vitro drug release experiments for an assessment of the sustained and controlled release behavior of drug-loaded nanosponges.
- To compare the drug release profile of nanosponges with that of pure drug.

Improvement of Bioavailability and Solubility:

- To investigate the role of nanosponges on enhancing solubility of hydrophobic drugs.
- To determine the influence of drug permeation and bioavailability through ex-vivo diffusion studies because of entrapment of nanosponges.

Formulation of a Topical Drug Delivery System:

- To formulate ACE-loaded gel nanosponge for topical treatment with enhanced delivery of the drug through the skin.
- For a physicochemical evaluation of developed gel for analysis of physical nature, drug composition, spread ability, viscosity, and pH stability.

Stability and Scalability Study

- For the conductance of accelerated stability studies as per ICH guidelines to establish the long-term stability of nanosponge formulation.
- For assessment of scalability and reproducibility of the optimized formulation of nanosponge for feasible application in a pharmaceutical formulation.

The ultimate aim of this study is to recognize nanosponges as a potential drug delivery system to improve the therapeutic effect of drugs by eliminating restrictions in bioavailability, stability, and solubility and thereby opening the path for drug delivery systems in nanotechnology.

Material & Methods

Material and Methods

The principal drug employed in this research study was Aceclofenac (ACE), which was provided as a sample by Umedica Labs Pvt. Ltd., Mumbai, India. Excipients and chemicals such as the following were employed to formulate nanosponges:

- β-Cyclodextrin
- Hydroxypropyl-β-Cyclodextrin
- Carbonyl Diimidazole
- Dimethyl Carbonate
- Diphenyl Carbonate

In addition to the above excipients and chemicals, solvents such as methanol, acetone, dichloromethane, dimethyl sulfoxide, and ethanol were also procured from SD Fine Chemicals Ltd and Finar Ltd.

Preformulation Studies

API (Aceclofenac) Confirmation

Aceclofenac was confirmed using melting point determination method, UV spectroscopy, FTIR spectroscopy, and differential scanning calorimetry (DSC).

Melting Point Determination:

Melting point of Aceclofenac was studied on Veego Model – VMP-D melting point equipment. Capillary method was followed, and range of melting was approximated for checking purity.

UV-Visible Spectrophotometric Characterization:

Aceclofenac standard solution in methanol was diluted and was scanned from 200-400 nm using Shimadzu UV 1800 spectrophotometer.

Fourier Transform Infrared Spectroscopy (FTIR):

FTIR was done with the help of IR Spirit FTIR, Shimadzu spectrophotometer to establish functional groups present in Aceclofenac.

Differential Scanning Calorimetry (DSC):

DSC was performed on the DSC7020 Thermal Analysis System to determine the thermal stability of Aceclofenac.

Stability Studies

Stability studies were performed according to ICH Q1A (R2) guidelines at accelerated conditions (40°C, 75% RH) for 6 months.

Parameters studied were:
Physical appearance
Drug content
pH stability

This scientific method gives scientific and systematic approach in nanosponge development for water-soluble and insoluble actives drug delivery. "The study employs optimized formulation techniques, advanced characterization equipment, and stability testing to give confidence in the efficacy of nanosponges for drugs."

Results and Discussion

Pre-Formulation Studies

Authentication of API

Organoleptic properties: White to off white colored powder confirms its official characteristics reported in the Certificate of Analysis.

Melting point: The melting point of ACE was found to be 153 ± 1.2 °C. The reported value of melting point for ACE is in the range of 149 to 153 °C (235). The observed value is in the range of melting point reported in the literature which confirms the purity of the sample.

Ultraviolet (UV)-visible spectrophotometric characterization:

By UV- visible spectrophotometric characterization, λmax of ACE was determined. The UV- visible spectra of the standard solution of ACE in methanol was found to exhibit an absorption maximum at 211 nm, after scanning in the UV range from 200-400 nm. This value was confirmed with the reported λmax value (209,210). Figures 4.1 and 4.2 show the standard and experimentally determined spectra of ACE in methanol, respectively.

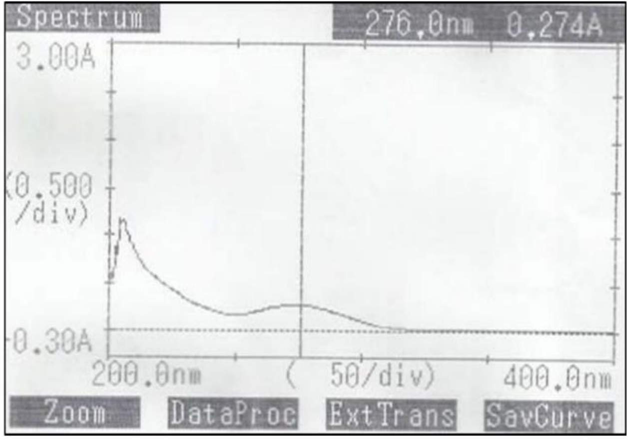


Figure 4.1: Reported UV absorption spectra of ACE

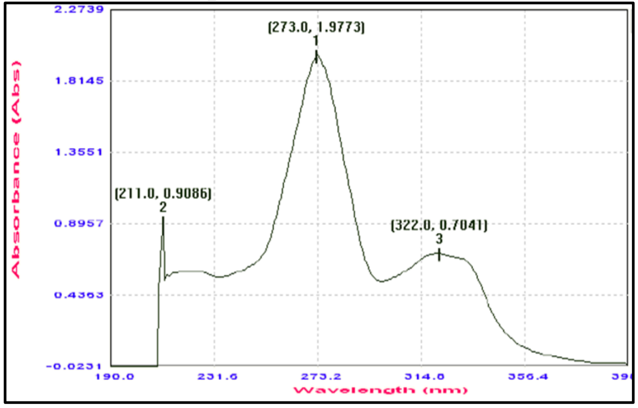


Figure 4.2: UV absorption spectra of aceclofenac

Fourier transform infrared spectroscopy (FTIR):

The reported spectrum of the drug and the FTIR spectra obtained for the pure drug were compared. The FTIR spectrum of ACE (Figure 4.3) showed characteristic peaks as reported in the literature (236) which confirms the authentication of the drug. The characteristics peaks with the wavenumbers (cm^{-1}) are given in Table 4.1.

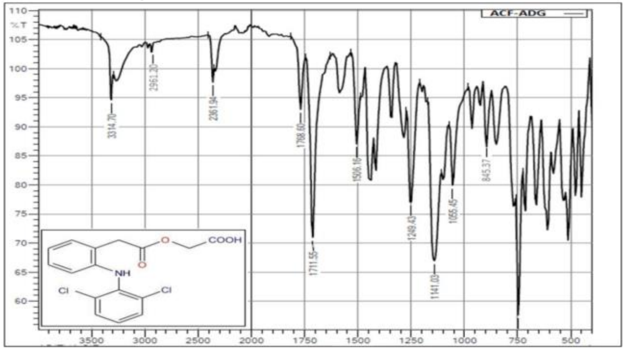


Figure 4.3: FTIR spectrum of ACE

Table 4.1: Characteristic peaks of FTIR spectrum of ACE

Literature value(cm^{-1})	Observed value(cm^{-1})	Assignments of bands
852-550	845.37	C-Clstretching
1510-1400	1506.16	C-Cstretching
1850-1650	1768.6	C=Ostretching
2963-2669	2961.2	C-Hstretching
3400-3250	3314.7	N-Hstretching

Differential Scanning Calorimetry (DSC):

DSC thermogram of ACE (Figure 4.4) showed a pronounced endothermic spike at 153.4 °C, indicating the purity of the drug sample and the absence of any traces of impurities.

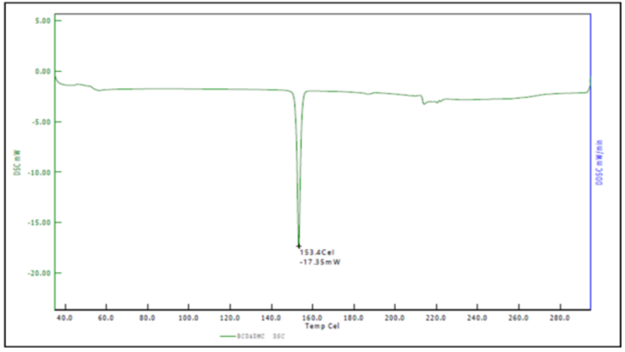
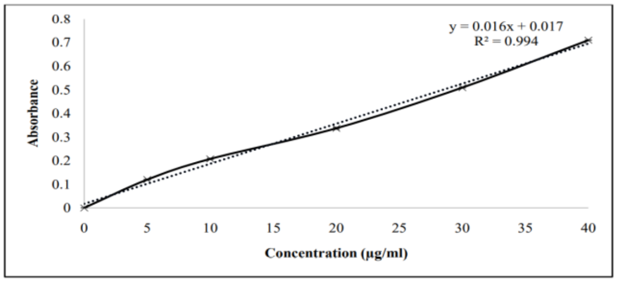


Figure 4.4: DSC thermogram for ACE

Construction of calibration curve

In methanol and pH 7.4 phosphate buffer, the calibration curve of ACE was estimated by UV-visible spectrophotometry. Within a concentration range of 10-40 micrograms per ml, it obeyed Beer-Lambert's law. Figures 7.5 and 7.6 illustrate the calibration curves obtained.



Calibration curve of ACE in methanol

Conclusion

The synthesis and characterization of nanosponges as a water-soluble and insoluble active drug delivery system have offered useful information regarding the potential for enhancing the drug solubility, stability, and controlled release. The porous nature of nanosponges was synthesized and characterized for their physicochemical property, entrapment efficiency, drug loading, and release kinetics efficiently. The research proved that nanosponges could efficiently encapsulate hydrophobic and hydrophilic drugs, an ongoing challenge with drug delivery formulations. Polymer and crosslinker content control was in effect needed in modulating the nanosponge property design to its highest performance.

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