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ORIGINAL ARTICLE

Formulation, Optimization and *In-vitro* Characterization of Abiraterone-Loaded Cubosomes for Sustained Drug Delivery

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ABSTRACT
Though abiraterone, an androgen production inhibitor, is widely used in the treatment of prostate cancer, its oral dosage form is challenged by its low solubility in water and poor permeability, hence the need to administer high doses daily. The purpose of the study was to develop and optimize abiraterone-loaded cubosomes as a lipid nanocarrier formulation to provide prolonged drug release and improve the formulation efficiency. Cubosomal dispersions were prepared by the emulsification and sonications methods using glyceryl monooleate as the lipophilic component and Poloxamer 407 as the triblock polymer which act as copymer which is often used in combination with PEG. 3^2 full factorial design was used to study the effects of the formulation variables on the key quality parameters, namely size, zeta potential, and entrapment efficiency. The optimized formulations had high entrapment efficiency, nanometer-sized particles with suitable polydispersity, and appropriate surface charge for colloidal stability. Results from the Fourier transform infrared spectroscopy study confirmed that there were no chemical incompatibilities between abiraterone and its formulation excipients. Drug release studies carried out using the Franz diffusion cell indicated that the cubosomal formulations had a sustained release compared to abiraterone solution. From this study, there is evidence to show that abiraterone-loaded cubosomes, formulated from lipid nanocarriers, are feasible and warrant further testing for their therapeutic use.
Keywords: *Abiraterone, Cubosomes, Lipid nanocarriers, Glyceryl monooleate, Formulation optimization and In vitro drug release.*

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INTRODUCTION

Additionally, prostatic cancer represents one of the most frequent forms of cancer in men all over the world and is considered a primary cause of cancer-related morbidity and mortality [1]. Moreover, in the context of the treatment of metastatic prostatic cancer [2], an essential role is played in the administration of androgen deprivation therapy due to the great importance of androgen signaling in its progression [3]. However, in regard to the administration of treatments, chronic disease is a challenge due to limitations in the pharmacological approach and the need for a considerable systemic exposure [4]. Abiraterone is a specific inhibitor of cytochrome P450 17A1 (CYP17)[5], which inhibits the production of androgen in multiple regions, including the testes, adrenal glands, and tumor tissue, among others [6]. The effectiveness of abiraterone has been observed in patients with hormone-sensitive and castration-resistant prostatic cancer [7]. However, in terms of formulation, abiraterone has poor water solubility, in addition to low permeability [8]. These two factors can be used to define abiraterone as a Class IV drug[9], based on the Biopharmaceutics Classification System (BCS)[10]. The two factors can also cause poor oral absorption, hence the high oral doses required [11]. In order to address the problems of poorly water-soluble compounds with limited solubility and dissolution in their oral absorption, lipid drug-delivery systems have received considerable attention as a new class of drug-delivery systems [12]. Within this category, nanostructured lipid carriers have advantages such as large drug carrying capacity, protection of the drug against degradation, and controlled drug release rate. In this regard, cubosomes, which are nanostructured dispersions formed from bicontinuous cubic liquid crystals, have been

recognized as promising lipid nanocarriers [13]. Cubosomes may usually be prepared with amphiphilic lipids, such as glyceryl monooleate, and stabilized with suitable surfactants. Because of their peculiar internal structure, consisting of interwoven aqueous channels divided by a lipid bilayer, they have a very large interior surface area that can accommodate both hydrophilic and lipophilic medicinal agents [14]. Their structure provides for a high efficiency of drug encapsulation and the possibility to control or prolong the release of drugs, making cubosomes of interest for oral drug delivery [15]. Though the advantages of cubosomes are well realized, working towards achieving efficient performance and stability as a formulation requires careful optimization of the formulation as well as its physicochemical characterization. By applying the concepts of experimental design, as in the case of factorial design, formulation optimization is accomplished [16]. The proposed work is concerned with the preparation of abiraterone-loaded cubosomes through the lipid nanocarrier method. The impact of various factors in the proposed work is examined through the 3^2 complete factorial design. The modified abiraterone-loaded cubosomes are analyzed through the use of FTIR. Furthermore, the abiraterone release study is done through the Franz diffusion cell. The purpose of this study is to establish a groundwork in terms of the physicochemical characteristics and release properties of abiraterone-loaded cubosomes[17].

MATERIAL AND METHODS

Materials

Abiraterone sample was received as a gift, as documented in the original file. Lipid component used was glyceryl monooleate (GMO) and for surfactant stabilizer use of Poloxamer 407 as a copolymer was made [18]. All other solvents and reagents utilized within this experiment were of analytical grade and did not require any additional purification steps for use. Throughout the experiment process, double-distilled water was used[19].

Preparation of abiraterone-loaded cubosomes

Abiraterone-loaded cubosomes were prepared by emulsification and sonication methods. Known levels of abiraterone were dissolved in melted glyceryl monooleate to form a homogeneous lipid phase. The aqueous phase, comprising Poloxamer 407, was separately made and heated to the same temperature as the lipid phase. The aqueous phase was slowly poured into the homogeneous lipid phase to form a crude emulsion, which was further subjected to probe sonication for a predefined time to prepare cubosomal dispersions. The dispersions reduced the size of the cubosomes. Before proceeding to further characterization, the preparations were allowed to reach stabilization at room temperature [20].

Experimental design and formulation optimization

To optimize the variables of formulation, a 3^2 complete factorial design was performed using the Design-Expert software. Two independent variables were selected for formulation, namely the concentration of glyceryl monooleate (X_1) and Poloxamer 407 (X_2), and were designed at three levels [17]. The responses were the particle size of cubosomes (Y_1), zeta potential of cubosomes (Y_2), and entrapment efficacy of cubosomes (Y_3)[21]. Results were generated by the software, and cubosomal formulation was developed according to the design matrix. ANOVA test was conducted for analysis of the variables of formulation on responses [17].

Particle size, polydispersity index, and zeta potential

Cubosomal suspensions were analyzed for average particle size, polydispersity index, and zeta potential by dynamic light scattering. The samples were made to be free from effects of multiple scattering by being diluted with distilled water. The measurements were carried out at room temperatures, and the average values of the data obtained were noted [22].

Fourier transform infrared (FT-IR) spectroscopy

For assessing the possible chemical reactions between abiraterone and excipients in the formulation, we employed an FT-IR spectroscopy technique. The spectra for both abiraterone and the optimized cubosomal formulation under the specified scan range for spectra in the original research paper were assessed by an FT-IR spectrophotometer. The obtained spectra were evaluated for any distinctive changes or the disappearance of distinctive peaks [23].

Determination of entrapment efficiency

The indirect approach was utilized to determine the efficiency of abiraterone encapsulation within cubosomal preparations. To remove unentrapped active substances and determine the amount of entrapped active substances, a cubosomal dispersion was subjected to a centrifugation process. The quantity of unentrapped abiraterone within a cubosomal dispersion was determined by UV-VIS spectrophotometry at a predetermined wavelength [24].

Entrapment efficiency was calculated using the following equation:

$$\text{Entrapment efficiency (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100 [25]$$

In vitro drug release study

Franz diffusion cells were used to perform in vitro drug release studies. It was filled with the correct amount of the cubosomal formulation needed to provide the required content of medication. Phosphate buffer, pH 7.4, was applied as the receptor media. This buffer had been stirred and maintained at a temperature of 37 ± 0.2 °C constantly. Samples removed from the receptor compartment at periodic time intervals were replaced with fresh buffer to maintain the principle of the sink conditions. The amount of abiraterone released was measured by UV-visible spectrophotometry [26].

Statistical analysis

All the experimental data were analyzed by Design-Expert® software. The effects of formulation factors on the specific output were investigated by using analysis of variance. The confidence level from the original dataset was used as the level at which the results were considered statistically significant [27].

RESULT AND DISCUSSION

Optimization of abiraterone-loaded cubosomes using factorial design

The influence of the formulation variables on the abiraterone-loaded cubosomes' physical and chemical characteristics was evaluated using the 3^2 complete factorial design. Particle size, zeta potential, and entrapment efficiency were the response variables. Glyceryl monooleate and Poloxamer 407 concentrations were the other variables. This experimental method enabled the investigation of the combined and individual effects of the variables in the formulation. Selected formulations were found to be very effective, thus selected based on the set criteria. In Table 1, the abiraterone-loaded cubosome particle size, zeta potential, and the details of the various formulations can be found [20].

Table 1. Formulation composition and physicochemical characteristics of abiraterone-loaded cubosomes.

Formulation	Abiraterone (mg)	Glyceryl monooleate (% v/v)	Poloxamer 407 (% w/v)	Particle size (nm)	Zeta potential (mV)
A	200	1.0	0.5	96.9	−76.6
B	300	1.0	0.5	121.8	−32.6
C	400	1.0	0.5	110.0	−35.0
D	200	1.5	0.5	131.3	−30.2
E	300	1.5	0.5	115.0	−32.8
F	400	1.5	0.5	143.5	+56.0
G	200	2.0	0.5	174.4	−58.6
H	300	2.0	0.5	121.7	−45.2
I	400	2.0	0.5	120.0	−79.0

Particle size and polydispersity index

The cubosomal formulations prepared exhibited nanometric size ranges, confirming the successful preparation of cubosomes by the emulsification and sonication technique, as evidenced from the particle size analysis. Various formulations differed in their particle sizes depending on the levels of stabilizer and fat applied. Low to moderate polydispersity index values reflected acceptable uniformity in the cubosomal dispersions. A nanometric size range is desirable for lipid-based nanocarriers because it enhances physical stability and offers reproducible performance from the formulation [28]. Figure 1 illustrates the particle size distribution profile of the enhanced cubosomal formulation (Batch G) as determined by dynamic light scattering.

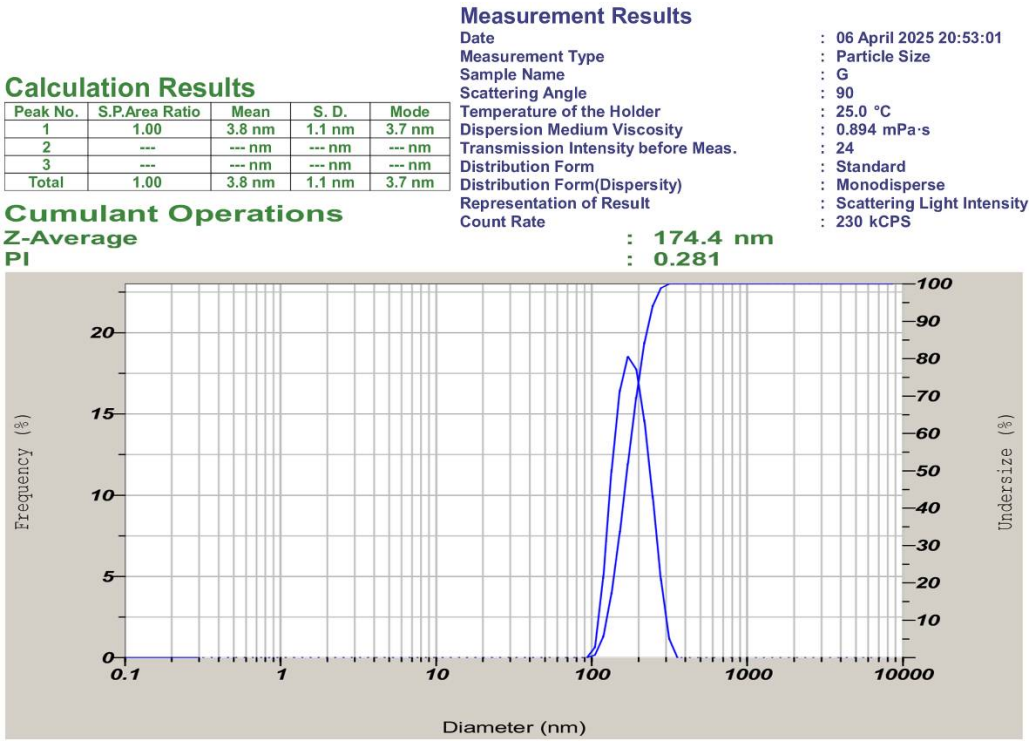

Figure 1: Particle size distribution profile of the optimized abiraterone-loaded cubosomal formulation (Batch G) determined by dynamic light scattering.

Batch G of the cubosomal formulation had a Z-average particle size of 174.4 nm and a polydispersity index of 0.281. This suggests that the particle size distribution profile was narrow and unimodal in nature. The PDI value was low, indicating that the nanosized cubosomes were successfully prepared using the emulsification-sonication technique. It is also an indication of good size uniformity of the cubosomal dispersion. This nanometric particle size range is considered optimum for a lipid-based nanocarrier system because it can help maintain the physical stability of the formulation.

Zeta potential analysis

Zeta potential results indicated that the cubosomal dispersion had a high surface charge value that indicated the electrostatic stabilization of the dispersion. The concentration of Poloxamer 407 co polymer and the amount of lipid influenced the difference in the zeta potential. It is important to consider a high surface charge to avoid particle aggregation during storage. It can be noted that the optimized abiraterone loaded in the cubosomes had a high value of the zeta potential [29]. Figure 2 illustrates the effect of the amount of drug substances and the concentration of glyceryl monooleate on the value of the zeta potential of abiraterone loaded into the cubosomes.

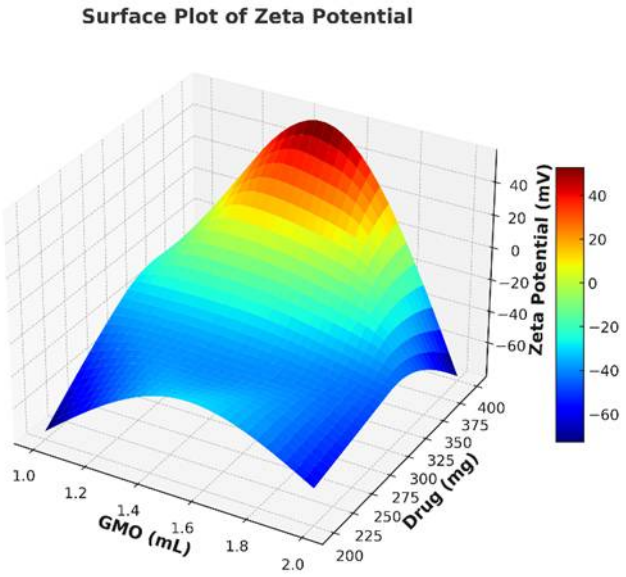

Figure 2. Response surface plot showing the effect of glyceryl monooleate concentration and drug content on the zeta potential of abiraterone-loaded cubosomes.

The surface response plot reveals the influence of the amount of drug and glyceryl monooleate concentration on the zeta potential of the cubosomal systems. The surface charge was greatly altered due to the increased amount of lipid; further variations in drug also contributed to the variations in the values of zeta potentials. The zeta potentials around the various formulations validate the fact that electrostatic stabilization is sufficient in the cubosomal dispersites.

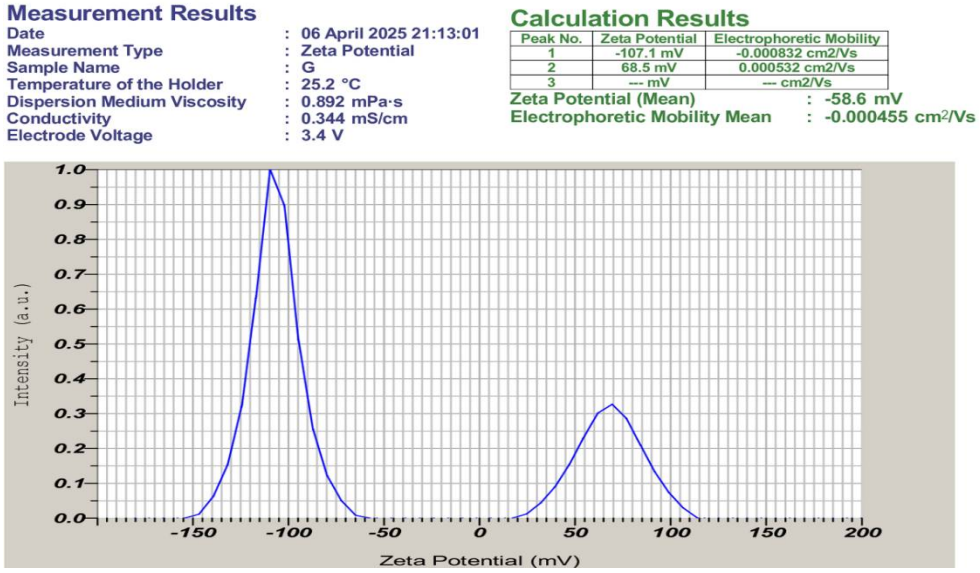

Figure 3: Zeta potential distribution profile of the optimized abiraterone-loaded cubosomal formulation (Batch G).

The enhanced cubosomal formulation, Batch G, exhibited a remarkable surface charge, represented by the mean value of zeta potential, −58.6 mV within its zeta potential distribution profile. This type of distribution pattern indicates the effectiveness of electrostatic stabilization of the cubosomal dispersion and illustrates a main charged population. On the other hand, the level of the zeta potential value reflects another degree of the level of improvement in colloidal stability for the improved formulation with a lower possibility of particle aggregation.

Entrapment efficiency

Entrapment efficacy studies revealed that abiraterone was efficiently entrapped in the cubosomal lipid matrix. The lipophilic nature of the drug enhanced its solubility in the lipid cubic phase, which improved the entrapment efficiency by increasing the concentration of the lipid[28]. Table 2 depicts the entrapment efficiency of various formulation batches of cubosomes with abiraterone. The high entrapment efficiency

observed in the optimized formulations assured efficient drug loading and justified the use of cubosomes for poorly water-soluble drugs like abiraterone.

Table 2: Entrapment efficiency of abiraterone-loaded cubosomes.

Formulation	Entrapment efficiency (%)
A	96.23 ± 0.50
B	92.50 ± 0.75
C	90.50 ± 0.90
D	89.20 ± 0.50
E	90.00 ± 0.57
F	98.99 ± 0.75
G	99.26 ± 0.75
H	98.00 ± 0.40
I	94.50 ± 0.55

Values are expressed as mean ± SD (n = as per experimental data).

Fourier transform infrared (FT-IR) spectroscopy

To assess if there is any interaction between the drug and excipients, we analyzed the FT-IR spectra of abiraterone alone in comparison to the FT-IR spectra of the cubosomal formulation. The FT-IR spectra of abiraterone remained unchanged with no shift in peaks in the cubosomal formulation. The lack of new peaks in this analysis reveals no chemical incompatibility between abiraterone and other excipients in the formulation[30]. The results suggest that abiraterone is physically entrapped in its lipid phase without any chemical change. The FT-IR overlay spectra of abiraterone alone, the FT-IR spectra of optimizéd cubosomal formulation (Batch G), FT-IR spectra of physical mix, FT-IR spectra of formulation excipients, are shown in fig.4.

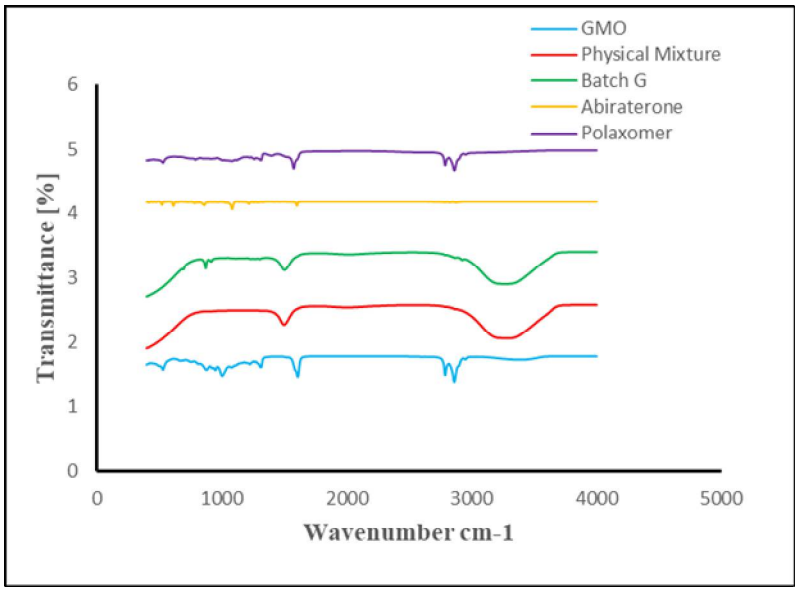

Figure 4. FT-IR overlay spectra of glyceryl monooleate (GMO), Poloxamer 407, pure abiraterone, physical mixture, and optimized abiraterone-loaded cubosomal formulation (Batch G).

The FT-IR spectroscopy of pure abiraterone depicted significant peaks corresponding to its functional groups. These same peaks were observed in the spectroscopy of both the physical mixture and the optimized cubosomal preparation of abiraterone. The absence of new peaks and major shifts within the cubosomal preparation indicates that abiraterone underwent no chemical reactions during the preparation of the formulation. This indicates compatibility of the drug with the excipients as well as its entrapment within the lipid matrix in a physical sense.

In vitro drug release study

An in vitro diffusion study was conducted by using a Franz diffusion cell to test the release of abiraterone from cubosomal dispersions. Compared to the abiraterone solution, abiraterone-loaded cubosomes demonstrated an extended release of the drug throughout the study. Due to their bicontinuous cubic structure, cubosomes form a diffusion-controlled release channel within the lipid domains, making their controlled release properties easier. On detecting the longer release characteristics of cubosomes, these

could act as potential carriers for orally administering drugs to patients[28]. Figure 5 illustrates an in vitro release study of abiraterone solution and abiraterone-loaded cubosomes.

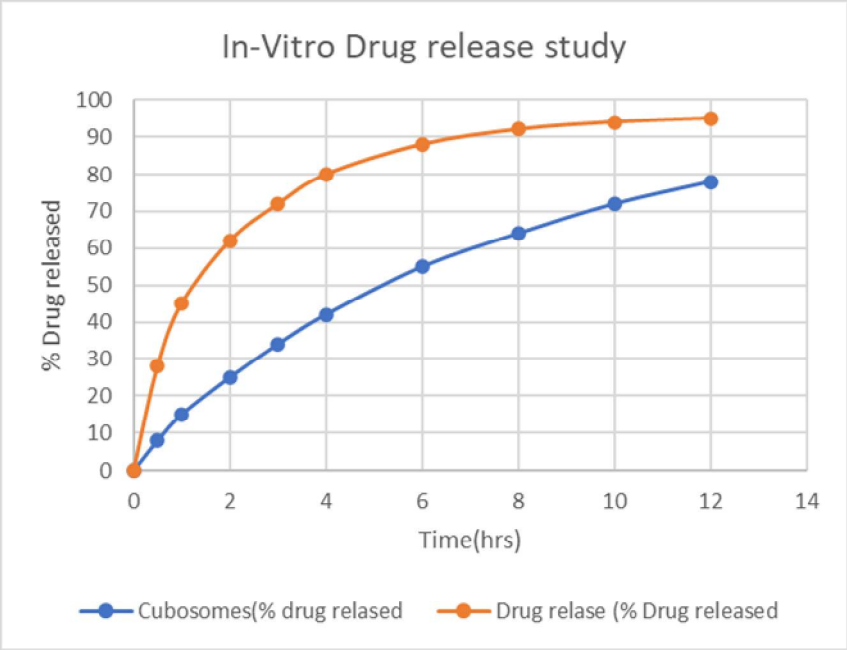

Figure 5: Comparative in vitro drug release profiles of abiraterone-loaded cubosomes and abiraterone suspension.

In vitro drug release studies have revealed the distinct difference in the release patterns of abiraterone from the cubosomal formulation and the drug dispersion. During the in vitro studies, the cumulative amount of the drug liberated from the cubosomal formulation bearing abiraterone was found to increase steadily, signifying sustained-release characteristics. However, the cumulative amount of the drug liberated from the suspension preparation increased rapidly, and a substantial amount of the drug was liberated in the initial time points. The sustained-release mechanism from the cubosomal formulation can be ascribed to the entrapment of abiraterone in the bicontinuous cubic lipid structure, facilitating diffusional release.

Overall discussion perspective

From the results, there are significant formulation factors that influence the physicochemical characteristics and release profiles of abiraterone-loaded cubosomes. By utilizing the factorial design approach, we were able to distinguish appropriate formulations that possess desirable size, stability, and drug loading qualities. Additionally, the longer in vitro release further confirms that cubosomes could act as potent lipid-based nanocarriers for abiraterone.

CONCLUSION

In this research work, lipid nanocarriers have been employed for the formulation and optimization of cubosomes encapsulating abiraterone using a combination of the 3^2 complete factorial design technique and the emulsification and sonication method for a comprehensive assessment of the variables involved in the formulation of the cubosomes and their influence upon the significant physicochemical characteristics of the cubosomes. The successful formulation of abiraterone into the lipid matrix is evident from the nanosize of the optimized cubosomes, polydispersity index, surface charge, and entrapment efficiency. The FT-IR analysis confirmed no chemical incompatibility between the medication and the excipients. In this regard, the drug is encapsulated physically without degradation. In comparison with the abiraterone solution, cubosomal formulations, through in vitro drug release studies, exhibited a sustained release profile. This shows how the cubic lipid structure can alter drug release characteristics. In general, the results indicate that cubosomes are appropriate for abiraterone formulation using lipid nanocarrier technology. This forms the basis for further biological testing to establish their therapeutic relevance. Polymer cubosomes have several advantages over other nanostructures like micelles and vesicles as they are quite uniform and porous structures. Due to the large specific surface area of the

interior and bicontinuous nature, they have the capacity to load significant amounts of hydrophobic and hydrophilic substances.

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