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Research articles

Fabrication and characterization of β-cyclodextrin-based nano sponges for delivery of abiraterone acetate

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ABSTRACT

Abiraterone acetate is a steroidal progesterone derivative that inhibits the enzymes CYP17A1, CYP11B1, and the androgen receptor antagonist. It is clinically used in adrenal, testicular, and prostatic cancer. Abiraterone has limited use, due to poor water solubility and low oral bioavailability (<10%). The current study focused on the enhancement of water solubility of abiraterone using β-cyclodextrin nano sponges, which are a hyper cross-linked novel nano-drug delivery system. Design and optimization of β-cyclodextrin nano sponges were carried out, using the modified solvent method. Polymer to cross-linker ratio, solvent volume, and reaction time were defined as critical parameters for optimization. Fourier-transform Infrared spectroscopy, differential scanning calorimetry, scanning electron microscopy, Zeta sizer, and powdered X-ray diffraction technique were used for characterization. Drug entrapment and In-vitro dissolution studies were performed and samples were analysed using reverse phase high performance liquid chromatography. Optimized β-cyclodextrin nano sponges were porous para-crystalline particles (25.3%) with an average particle size of 463.4 nm. High drug entrapment leads to enhancement of solubility by 17.33 folds and a 3-fold increase in drug dissolution profile. The present approach offers the best way to increase the solubility of abiraterone by formulating a nano-size hyper cross-linked β-cyclodextrin nano sponges which can tend to the improvement of abiraterone oral bioavailability.

Keywords: Abiraterone acetate, β-cyclodextrin nano sponges, Solubility, bioavailability.

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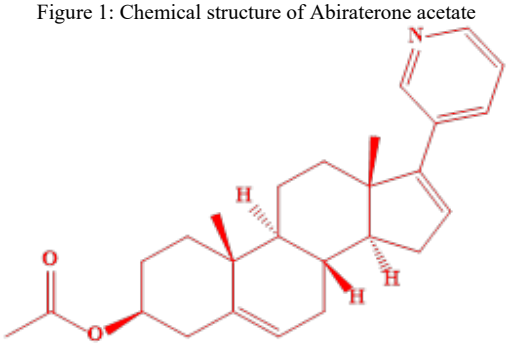
INTRODUCTION

Chronic and genetic level influenced diseases are now the major challenge for the global medical sciences, especially different types of cancers like prostate, blood, breast, lung, rectum, cervix, liver is the major concern for human beings. [1]. Globally, the second most common type of cancer is prostate cancer (PC). In a lifetime, one-sixth of men will eventually be diagnosed with PC, with the prevalence increasing with advancing age. It represents a major health concern, especially in western countries, with a greater proportion of elderly in the general population. PC is universally acknowledged as a complex disease, with multi-factorial etiology involving multiple genetic and environmental factors. [2].

Abiraterone Acetate (ABT)

is used in the treatment of PC. ABT is a steroidal progesterone derivative used to treat hormone-refractory PC. It works by preventing the synthesis of androgen in man. This is done by inhibiting CYP17A1 specifically 17α-hydroxylase, and 17, 20-lyase that is responsible for the production of androgen. ABT is also capable of reduction of serum testosterone levels to less than 1 ng/dL and decreases the weights of the seminal vesicles, prostate gland, and testes under its anti-androgen action. [3]. Because of low bioavailability and high susceptibility to hydrolysis abiraterone is administered as a prodrug (acetate salt of Abiraterone). Chemically ABT acetate is (3β)-17-(3-pyridinyl) androsta5, 16-dien-3c-yl acetate (Figure 1). [4].

Figure 1: Chemical structure of Abiraterone acetate



The three-dimensional novel hyper cross-linked polymeric nano-structures are called nano sponges (NS). Cyclodextrin-based

nano sponges (CDNS) are highly porous crystalline, spherical structures with swelling properties. The shape, geometry, dimension, polarity, and release pattern of the entrapped drug can be tuned by using different categories of cross-linkers at various molar ratios. NS are the most encouraging nano-sized drug delivery system as it offers high drug carrier capacity with greater stability, and provides feasibility for the inclusion of both hydrophobic and hydrophilic drug substances. Controlled drug release is also a unique advantage offered by NS. They are biodegradable and bio-safe. Various ligands can be conjugated on the surface of NS to achieve site-specific drug targeting. NS can also be utilised to improve the lipophilic drug's aqueous solubility, chemical stability, and bioavailability, as well as in cosmetics, protein/peptide delivery, and other applications. NS can be synthesized using the solvent method, melt method, ultrasound-assisted method, and Microwave-assisted method, etc. [5]. NS can be obtained by cross-linking CD with different types of cross-linkers like carbonyl or dicarboxylate compounds. To optimise drug loading and release profile, the ratio of βCD to cross-linker can be varied [6].

Advantages of Nano sponges

Novel nanomaterials are currently being researched to improve the properties of current materials such as greater size control, enhanced drug loading, homogeneity, predictable and controlled drug release. [7]. NS has great potential because of the attractive features such as amphiphilic nature, Simplicity in chemistry, tunability, ability to produce predictable/controlled drug release, [8], formulation flexibility, [9], biodegradable nature. [10]. NS can improve stability [11] and elegance of formulation. [7]. NS can be tagged with specific markers to target diseased cells hence achieving greater efficacy, decreasing dose, and dosing frequency, reducing side-effects, and in turn increasing patient compliance. [12].

MATERIAL AND METHOD

ABT was supplied by Glenmark Pharmaceuticals Ltd, Mumbai (India), as a gift sample and was used as such without any auxiliary treatment. Carbonylimidazole and dimethylsulphoxide (DMSO) were procured from Spectrohem, India. All other chemicals and reagents were purchased from Dodal enterprises Aurangabad (India) and are of analytical grade.

Complexation of abt with βcd

A physical mixture of βCD and ABT was kneaded using ethanol: water (15: 85) mixture by the wetting method. The kneaded mass was then passed through sieve number 80, dried, and stored in a desiccator over fused $CaCl_2$.[13].

Synthesis and optimization of nano sponges

The β-CDNS were synthesized by adopting a previously established method, with some modification using IKA®RCT basics parallel reaction synthesizer [14]. Briefly, anhydrous β-CD was dissolved in dimethyl sulphoxide (DMSO) and allowed to react with carbonyldimidazole (CDI) at 500rpm. Temperature and time were optimized (Table 01). Once the reaction completes, the NS was collected, and grounded in a mortar, extensively washed with deionized water and ethanol. In the end, NS were Soxhlet-extracted with ethanol for 24hr to remove all possible by-products. All studies were performed in triplicate to assure the results. The synthesis of β-CDNS is depicted schematically in Figure 2.

Figure 2: A schematic representation for the synthesis of ABT-loaded β-CDNS

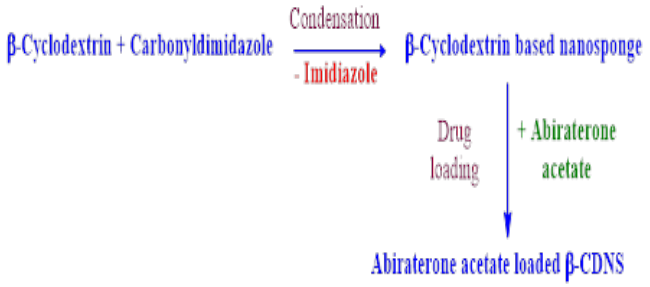


Table 1. Optimization parameters of CDI β-CDNS

Variable	Units	Low	Middle	Upper
β-CD: Crosslinker ratio	Ratio	1:2	**1:4**	1:8
Reaction time	min	75	**90**	105
Temperature	°C	90	**100**	110
Solvent volume	Ml	6	**8**	10

*The bold values indicate the optimized conditions

Preparation of drug-loaded ns

Abiraterone-loaded nano sponges were prepared by slight modification in the already established freeze-drying method. [15]. Briefly, the 1:1 (w/w) ratio of nano sponges and ABT was suspended in distilled water and stirred for 24 h. The resultant is centrifuged at 10000rpm for 10min at room temperature to separate the uncomplexed drug. The supernatant was separated and lyophilized to obtain the ABT-loaded nano sponges as a powder, which was stored in a desiccator till further studies.

Rp-hplc method for estimation of abt

The chromatographic method with reverse-phase isocratic mode, C-18 column, 69: 31(% v/v) acetonitrile, and ammonium acetate buffer (pH 3.5) as a mobile phase with a flow rate of 0.75 ml/min and 235nm detection wavelength was developed and used for estimation of ABT in bulk and ABT-loaded β-CDNS [5].

Solubility study

The saturated solubility method was employed to estimate the increase in solubility of ABT in distilled water using β-CDNS. Briefly, an excess amount of drug-loaded β-CDNS was added to 10ml of distilled water and agitated for 24h using a thermostatic rotary shaker (Remi Inst. Division, Rajendra electrical Ind. Ltd.) maintained at 25°C and 100rpm. After 24hr, the dispersions were allowed to equilibrate, the supernatant was separated by filtering through 0.45µm filter paper, and analysed by the RP-HPLC method for calculating the solubility of ABT [5].

Physicochemical characterization [16]

Evaluation of micrometric properties of nano sponges

Bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio were chosen to test the flowability of the

prepared NS powder.[17].

Percentage yield determination

The percentage yield was calculated accurately by comparing the weight of the end product after drying to the original weight of the drug and polymer used to prepare NS. [18].

$$\% \text{ yield} = \frac{\text{Practical weight of nanosponges obtained}}{\text{Theoretical weight (drug + polymers)}}$$

Determination of loading efficiency

A weighed amount of ABT-loaded NS was dispersed in 100ml Distilled water. The suspension was sonicated for 10min to break the complex and centrifuge at 5000rpm for 15mins. The supernatant was filtered using 0.45µm filter paper, and analysed by RP-HPLC method at 235nm. [19]. The drug loading efficiency (%) of the NS was calculated thus:

$$\text{Drug loading efficiency (\%)} = \frac{\text{Concentration of drug encapsulated}}{\text{Concentration of total drug}} \times 100$$

Fourier transform infrared spectroscopy (ftir)

To understand the existence of any interactions between ABT and NS, IR spectroscopy was performed, using JASCO FTIR IRT-4100. The spectra were obtained using the KBr mixture technique. Dried samples were mixed with IR grade KBr and scanned in the range of 4000 cm^{-1}–400 cm^{-1}.

X-ray powder diffraction (xrpd)

X-ray powder diffraction patterns of ABT, β-CDNS and ABT-loaded β-CDNS were recorded by using Bruker AXS D8 Advance with DAVINCI design X-ray diffractometer. The sample was bombarded with monochromatized Cu K radiation and evaluated at temperatures ranging from 5-80º (2θ). 40kV and 30mA were employed as the voltage and current, respectively.

differential scanning calorimetry (dsc)

DSC was performed using a SHIMADZU DSC 60 PLUS equipped with TA 60 WS collection Monitor software. Accurately weighed samples (2–5 mg) were kept in a crimped aluminium pan and heated at the scanning rate of 10ºC/min over a temperature range of 10-450 ºC under nitrogen purging.

Size, polydispersity index, and zeta potential values

ABT-loaded NS were analysed for particle size and polydispersity index (PDI), and zeta potential by dynamic light scattering using Malvern pananlyticals (zetasizer nano ZS UK) principled on photon correlation spectroscopy (PCS). The measurements were made at 24ºC. The samples were suitably diluted and filtered with HPLC-grade water for each measurement.

In-vitro dissolution study

In-vitro release studies of ABT from ABT-loaded β-CDNS was examined in phosphate buffer (pH 7.4) containing 1% w/v of Tween 80. [20]. Tween 80 was utilized to raise the solubility of ABT in buffer and to prevent its binding to the tube wall. Briefly, 30mg of dried ABT-loaded β-CDNS was placed in the tube, which was suspended in 60mL of release buffer. The samples were incubated at 37ºC with continuous agitation at about 100rpm. The sink condition was maintained by withdrawing 1mL of the release medium at regular time intervals. The withdrawn release medium was centrifuged at 3000rpm for 15min. The amount of ABT in withdrawn samples was determined by the RP-HPLC method, [5].

Stability study of β-cdns

The short-term accelerated stability studies as per ICH were carried out. The β-CDNS were charged in the stability chamber and stored at 40°C±0.2 / 75% ±5 RH (ICH Q1B) for 3 months. [21,22]. The CDNS were periodically tested and evaluated for their IR spectra and physical appearance.

RESULT

For the last two decades, oral delivery of cyclodextrin-based nano sponges has been studied. API loaded β-CDNSs reduces the undesired effects of a drug or formulation and enhances its efficacy by improving solubility and bioavailability. ABT is a potent androgen receptor antagonist but has limited use, due to its poor water solubility and low oral bioavailability (<10%). Keeping this in mind, β-CDNS were designed and optimized to enhance the aqueous solubility and in-vitro dissolution profile of ABT.

A series of NS with varying degrees of cross-linking and crystallinity were synthesized and characterized. The optimized batch was selected for drug loading. The synthesis β-CDNS was optimized for various process parameters like polymer: crosslinker ratio, reaction time, and solvent volume. After optimization, ABT-loaded β-CDNS were characterized for % yield. % drug encapsulation efficiency, saturated solubility, and various physiochemical characterization by FTIR, DSC, XRPD, etc.

Shiladhatri Yoga prepared here is not mentioned in any classics. Although for the processing of different ingredients the classical guidelines were followed where they comply. At places where they comply the process repeated until the desired results were obtained as in the case of Swarnamakshik Maran [13-14]. It takes 38 cycles of puta to get converted in the desired quality bhasma. In case of Yasada the method used for the Samanya Shodhana[6] is that mentioned by Rasaratnasammucchya i.e., for the all the metals 7 times quenching in Taila, Takra, Gomutra, Kanji and Kullatha Kwatha. The method followed for the aqueous extraction[18] is that mentioned by Sharangdhara Samhita i.e., Kwathana\Ghana. [15-16]. The method followed for the extraction of karvellaka juice[2] extraction is that mentioned by Charaka and Sharangdhara Samhita i.e. Nishpidan.

Physicochemical characterization

Ftir spectroscopy

The FTIR spectra of the β-CDNS showed a shift of the carbonate peak from 1775±5 cm^{-1} to 1750±5 cm^{-1} which is characteristic for confirmation of formation of NS. The characteristic peaks of ABT are exhibited at around 1106, 1733, 2857, 2942, 3046, and 3529 cm^{-1}. These characteristic peaks of ABT broadened or disappeared in the nanocarrier which suggests weak interactions of ABT and NS (Figure 4).

Figure 3: ABT-loaded β-CDNS

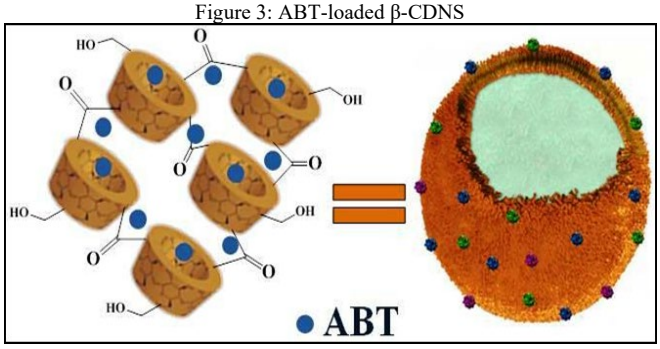
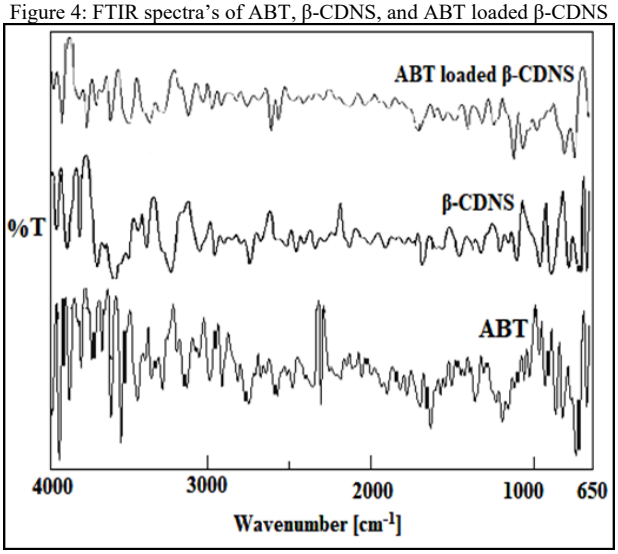


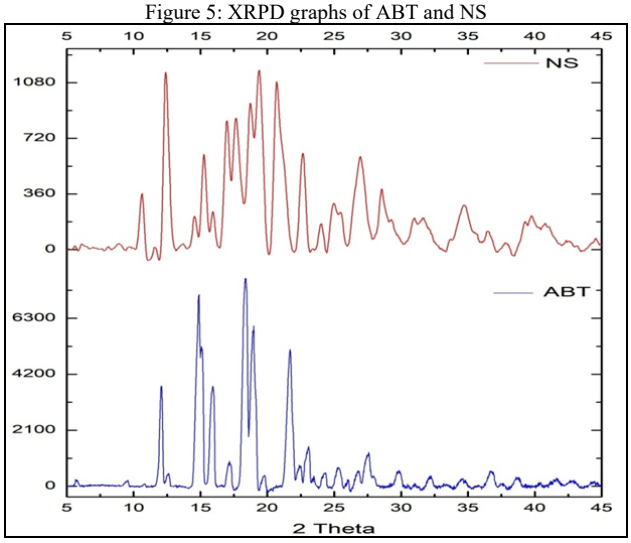
Figure 4: FTIR spectra's of ABT, β-CDNS, and ABT loaded β-CDNS



Powder x-ray diffraction

PXRD analysis was used to determine the % crystallinity of the compound. Both β-CDNS and ABT showed a crystalline structure (Figure 5). XRPD spectra of ABT show sharp peaks with 44.7% crystallinity, while β-CDNS shows paracrytallanity (25.3%). The XRPD pattern of ABT-loaded β-CDNS was similar to blank NS except for a few shifted peaks with reduced intensity.

Figure 5: XRPD graphs of ABT and NS



Particle size, polydispersity, and zeta potential

The micromeritic properties of β-CDNS reveal good flow properties. SEM and Zeta size analysis provided particle size and porosity of β-CDNS. β-CDNS (1:4) showed Zeta sizer analysis with an average particle size of 463.4nm (Figure 6). The polydispersity index was found to be 0.367. The topography of Scanning Electron Microscopy of β-CDNS showed crystalline spherical porous structures (Figure 7).

Figure 6: Particle size distribution of NS by zeta sizer

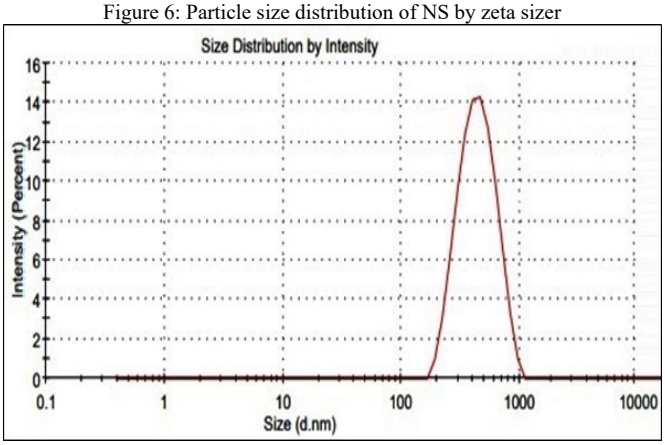
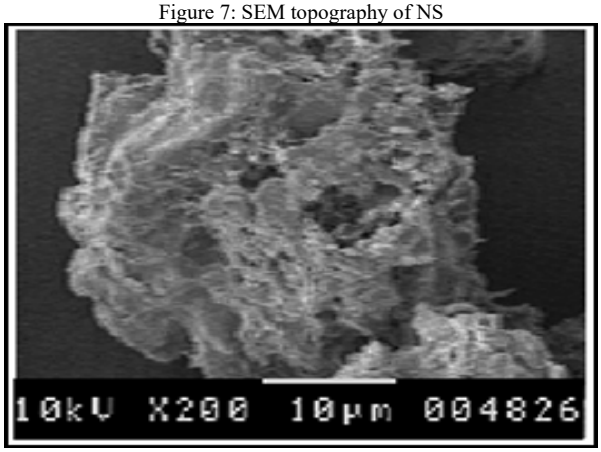


Figure 7: SEM topography of NS



differential scanning calorimetry (dsc) studies

DSC thermogram of ABT shows a sharp endothermic peak at 145.8ºC (Figure 8) signifying its purity and its crystalline nature. While the endothermic peak of ABT diminishes in the DSC thermogram of the ABT-loaded β-CDNS (Figure 9) which confirms the formation of the drug and NS inclusion complex.

Figure 8: DSC thermogram of ABT

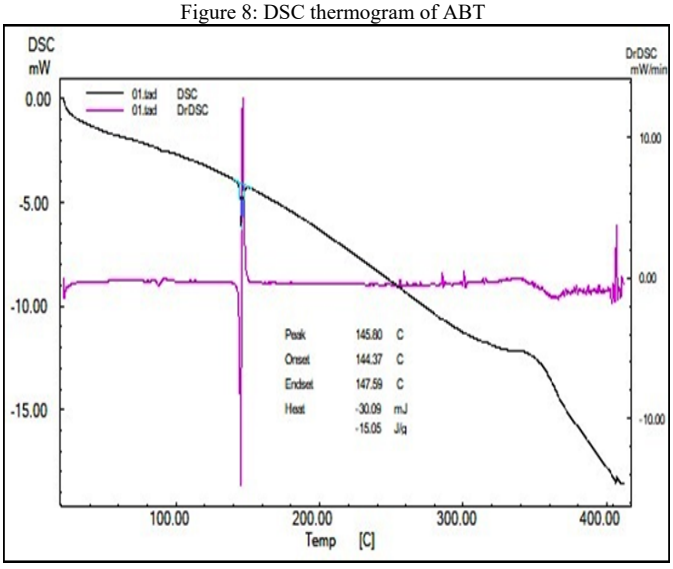
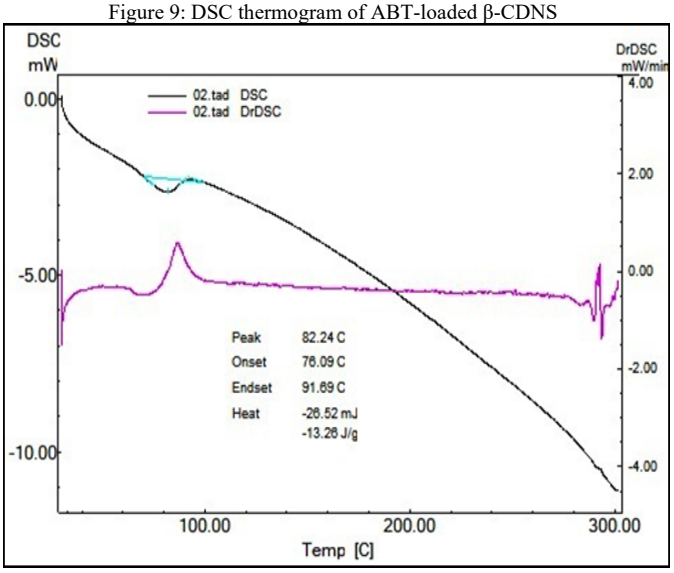


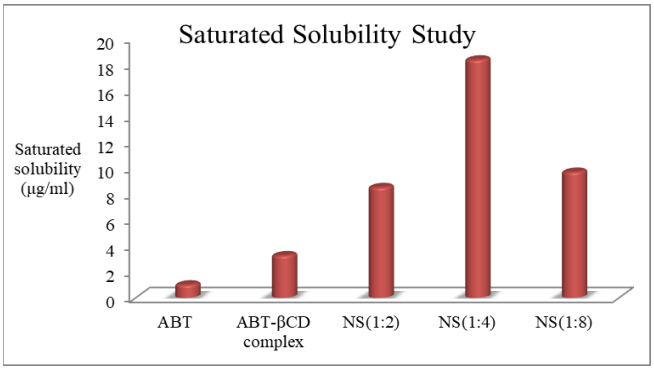
Figure 9: DSC thermogram of ABT-loaded β-CDNS



Solubilization efficiency of the prepared nano sponges

Saturated solubility studies reveal that incorporation of ABT into β-CDNS increases drugs solubility. Drug complexes with βCD showed an increase in solubility by 2.25 folds in distilled water. The 1:4 ratio of β-CDNS showed the maximum enhancement in aqueous drugs solubility by 17.33 folds (Figure 10). The solubility enhancement could be due to the crystalline nature, the formation of inclusion of ABT within the NS cavities, and the masking of hydrophobic groups of ABT by CDNS.

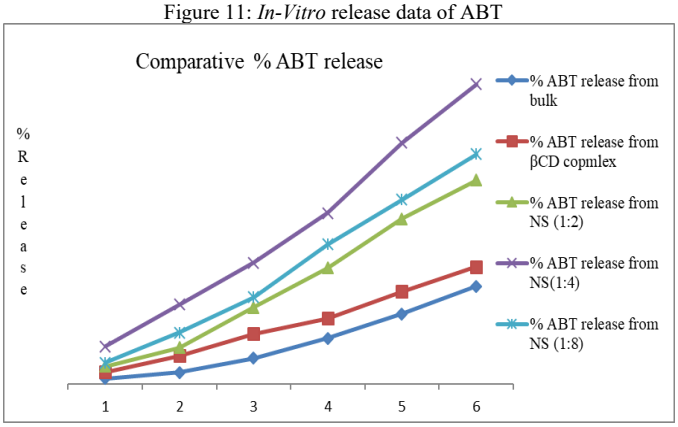
Figure 10: Saturated solubility study of ABT, ABT-βCD complex, and various ratios of NS



In-Vitro RELEASE STUDY

Due to differences in the solubilities of ABT, ABT-βCD complex, and ABT-loaded β-CDNS, the release pattern also varies. The % drug release goes on increasing as the solubility of the drug increases; hence the best % drug release was observed in ABT-loaded β-CDNS (Figure 11). Comparative % release data showed that the maximum drug release was achieved with β-CDNS of molar ratio of 1:4 with 87.31%. Due to the lower aqueous solubility of ABT, only 28.50% drug release was achieved after 75min in phosphate buffer pH 7.4. The complexation of ABT with βCD enhances the aqueous solubility due to inclusion complexation, which furthermore helps to increase the % drug release rate by 34.15%. This problem of low % drug release is overcome by encapsulating ABT in the β-CDNS carrier. Hence it was found that NS prepared modified solvent method using a Parallel Reaction synthesizer, enhances the % ABT release to 59.46%, 87.31%, and 66.97% respectively in 1:2, 1:4, and 1:8 molar ratios.

Figure 11: *In-Vitro* release data of ABT



Stability study

The accelerated stability studies (as per ICH guidelines) for CDNS were carried out at 40 ± 0.2°C/ 75 ±5% RH in the stability chamber for 3 months. The results showed no changes in the physical appearance and IR characteristics of CDNS after the 1st, 45th, and 90th days.

DISCUSSION

Abiraterone acetate (ABT) is a prodrug of abiraterone, a steroidal progesterone derivative. It is approved for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in combination therapy with prednisone or prednisolone. Co-administration of prednisone is recommended as a glucocorticoid replacement therapy. ABT is an inhibitor of the enzymes CYP17A1, CYP11B1, and blocks the androgen biosynthesis. It is clinically used in adrenal, testicular, and prostatic cancer. ABT has limited use, due to poor water solubility and low oral bioavailability (<10%). The current work focused on the enhancement of water solubility of ABT using β–cyclodextrin-based nano sponges (β-CDNS), a hyper cross-linked novel nano-drug delivery system.

In the current work, we have prepared and optimized nano sponges using βCD (polymer) and carbonyldimidazole as a crosslinker. Preparation and optimization of β-CDNS were carried out for modified solvent method for some dependent variables like the molar ratio of polymer and crosslinker, solvent volume, time, and reaction temperature. The optimized batches were selected based on IR peaks and yield of NS.

The optimized β-CDNS using parallel reaction synthesizer was characterized for their micromeritic properties, crystallinity, particle size, particle size distribution, % drug loading, and % drug release. From all the batches 1:4 molar ratio of β-CDNS showed the best micromeritic properties (good flowability and particle size distribution) along with good loading efficiency, and Para crystallinity (25.3%).

Due to high Para crystallinity, 1:4 β-CDNS showed better physicochemical properties and the best drug release pattern. The optimized β-CDNS showed enhancement in solubility by 17 folds and enhances % drug release from 28.5 to 87.31%.

CONCLUSION

Abiraterone acetate, a steroidal androgen receptor antagonist has a restricted therapeutic utility because of its low aqueous solubility and low bioavailability (<10%). β-Cyclodextrin based nano sponges are the novel nano-drug delivery system that can enhance the solubility and bioavailability of the drug by encapsulating it. Different molar ratios of β-CDNS are prepared and optimized for various dependent variables. The Synthesis was carried out by a modified solvent method using a parallel synthesizer. From all the batches 1:4 molar ratio was able to encapsulate ABT efficiently with the Para crystallinity of 25.3%, and enhancement in the aqueous solubility by 17 folds. The β-CDNS have a spherical shape and colloidal sizes. The % release profiles for ABT in bulk, βCD inclusion complex, and β-CDNS (molar ratios 1:2, 1:4, and 1:8) were evaluated within an efficient time of 75min. The β-CDNS in 1:4 molar ratio was found to be most efficient with the maximum enhancement of solubility and % release along with the stability over 3 months (as per ICH guidelines). Hence it can be concluded that Para crystalline β-CDNS show better physical and pharmaceutical properties in terms of drug loading, drug stability, and drug release.

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DECLARATIONS

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CONFLICT OF INTEREST

All the authors have no conflict of interest.

ETHICAL APPROVAL

Not required

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