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Design, formulation and invitro evaluation - solid lipid nanoparticles of enzalutamide

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ABSTRCT

The Enzalutamide has low solubility and permeability which give rise to limited and variable bioavailability; its low stability makes it difficult to develop stable aqueous liquid formulations, the aim of this study was to investigate the effectiveness of a strategy based on the development of solid lipid Nanoparticles as an innovative formulation of enzalutamide with improved therapeutic efficacy. The Enzalutamide solid lipid nanoparticles were prepared by emulsification solvent evaporation technique by applying ultrasonic energy through Sonicator, the different formulations with various ratios of drug-lipid and surfactant were evaluated and optimised. The method used for the formulation of Enzalutamide containing soya lecithin solid lipid nanoparticles was solvent evaporation method followed by sonication to reduce the particle size. The prepared nanosuspensions were characterized for particle size, surface morphology by SEM, drug excipient compatibility by FTIR and *in-vitro* drug release studies. Formulation (F-8) showed the highest encapsulation efficiency. In this research, a drug encapsulation efficiency as high as 92.68 % has been achieved. It was found that as the concentration of soya lecithin increased, the encapsulation efficiency was also increased. The present study revealed that solvent evaporation technique followed by sonication can be used as an effective tool for preparation of Enzalutamide solid lipid nanoparticles.

Keywords: Enzalutamide drug, solid lipid Nano Particles, Solvent Evaporation, lipid, FTIR, invitro drug release.

INTRODUCTION

Nanoparticles made from solid lipids are attracting major attention as novel colloidal drug carrier for intravenous applications as they have been proposed as an alternative particulate carrier system.[1] SLN are sub-micron colloidal carriers ranging from 50 to 1000 nm, which are composed of physiological lipid dispersed in water or in aqueous surfactant solution. SLN offer unique properties such as small size, large surface area, high drug loading and the interaction of phases at the interface and are attractive for their potential to improve performance of pharmaceuticals.[2]

In order to overcome the disadvantages associated with the liquid state of the oil droplets, the liquid lipid was replaced by a solid lipid, which eventually transformed into solid lipid nanoparticles. The reasons for the increasing interest in lipid based system are many – fold and include[3].

1. Lipids enhance oral bioavailability and reduce plasma profile variability.
2. Better characterization of lipoid excipients.
3. An improved ability to address the key issues of technology transfer and manufacture scale-up[4].

Solid lipid nanoparticles are one of the novel potential colloidal carrier systems as alternative materials to polymers which is identical to oil in water emulsion for parenteral nutrition, but the liquid lipid of the emulsion has been replaced by a solid lipid. [5] They have many advantages such as good biocompatibility, low toxicity and lipophilic drugs are better delivered by solid lipid nanoparticles and the system is physically stable. Solid lipid nanoparticles (SLNs)

are considered to be the most effective lipid based colloidal carriers, introduced in early nineties. This is the one of the most popular approaches to improve the oral bioavailability of the poorly water-soluble drugs. SLNs are in the submicron size range of 50-1000 nm and are composed of physiologically tolerated lipid components which are in solid state at room temperature[6]. Enzalutamide is clinically effective in the treatment of metastatic castration - resistant prostate cancer. An up-to 89% decrease in serum prostate specific antigen (PSA) levels have been reported after a month taking it. It can be used as an Anti - androgen in feminizing hormone therapy for transgender women[7]. The Enzalutamide has low solubility and permeability which give rise to limited and variable bioavailability; and its low stability makes it difficult to develop stable aqueous liquid formulations Enzalutamide is poorly water-soluble drug with poor oral bioavailability due to extensive first-pass metabolism, The aim of this study was to investigate the effectiveness of a strategy based on the development of solid lipid Nanoparticles as an innovative formulation of enzalutamide with improved therapeutic efficacy. So to increase the bioavailability enzalutamide is prepared by using solid lipid nano particles.

MATERIALS AND METHOD

MATERIALS

Enzalutamide was collected as a gift sample from Aurobindo labs, Hyd, polymers and other excipients were purchased from AR Chemicals, Hyd.

METHODODOLOGY

Compatibility studies

The drug-polymer compatibility was ascertained by subjecting the drug and homogenates of drug and polymer to Infrared spectrophotometric study.

Fourier Transform Infrared Spectroscopy (FTIR)

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in high density polyethylene bags and low density poly ethylene bags. Glass vials were exposed to 60^0C and 40^0C/75 % relative humidity for 4 weeks and low-density polyethylene bags were exposed to 40^0C±75 % relative humidity for 4 weeks. Samples were observed periodically for any physical change.[8]

Method of preparation of Enzalutamide loaded nanoparticles

Enzalutamide loaded SLN were prepared by solvent emulsification/evaporation method. The composition of all the formulations 20 mg of drug was dissolved in 5 mL methanol, and Phosphatidylcholine was dissolved in 20 mL chloroform separately; drug and lipid solutions were mixed together. The organic solvent mixture was completely evaporated at 70°C using rotary evaporator to remove the of organic solvent. Drug embedded lipid layer was then poured into 100 mL of aqueous solution containing poloxamer 407 surfactant and the mixture was Sonicated for 15 minutes by using Sonicator followed by homogenized for 15 minutes at different homogenization speed using high speed homogenizer. The suspension was then allowed to cool at room temperature. The suspension was filtered through membrane filter. The filtrate was centrifuged (1000 rpm for 10 minutes) and nano particles was collected. [9]

Table 1: Composition of Enzalutamide for preparation of solid lipid nanoparticles

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Enzalutamide	10	10	10	10	10	10	10	10
Phosphatidylcholine	25	50	75	100	125	150	175	200
Poloxamer 407	5	10	15	20	25	30	35	40
Solvent(Methanol)	5	5	5	5	5	5	5	5
Chloroform	20	20	20	20	20	20	20	20

Evaluation of Enzalutamide loaded nanoparticles[10,11,12]

Particlesize

All the prepared batches of nanoparticles were viewed under microscope to study their size. Size of Nano particles from each batch was measured at different location on slide by taking a small drop of nanoparticle dispersion on it and average size of nanoparticles were determined.

SEM analysis

The morphology of NPs was studied by a scanning electron microscope. For this purpose, the sample was lyophilized and placed on aluminum stubs and the surface was coated with a layer of gold particles using a sputter coater. The shape of the NPs was determined by scanning electron microscopy (SEM) (XL30, Philips, the Netherlands) at 15 kV and 750 mA.

Drug encapsulation efficiency

Lyophilized nanoparticles 50mg were dissolved in 100ml of phosphate buffer and the drug amount was determined by UV analysis. The encapsulation efficiency was determined as the mass ratio of entrapped Enzalutamide in nanoparticles to the theoretical amount of the drug used in the preparation. The entrapment of the Enzalutamide nanoparticles was expressed as loading capacity.

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Amount entrapped}}{\text{Total drug loaded}} \times 100$$

In-vitro drug release studies

The release studies were carried out by franz diffusion cell. It containing 10 ml Phosphate buffer. Phosphate buffer pH 7.4 (100 ml) was placed in a 10 ml of beaker. The beaker was assembled on a magnetic stirrer and the medium was equilibrated at 37±5^{0}C. Dialysis membrane was taken and one end of the membrane was sealed. After separation of non-entrapped Enzalutamide dispersion was filled in the dialysis membrane and other end was closed. The dialysis membrane containing the sample was suspended in the medium. 1ml of aliquots were withdrawn at specific intervals, filtered after withdrawal and the apparatus was immediately replenished with same quantity of fresh buffer medium.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{Da}{Dt} \times 100$$

Where, Dt = Total amount of the drug, Da = The amount of drug released

Stability studies

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 25^{0}C/60% RH analysed every month for period of three months.
2. 30^{0}C/75% RH analysed every month for period of three months.
3. 40^{0}C/75% RH analysed every month for period of three months[13].

RESULTS AND DISCUSSION

Drug - excipient compatibility studies (FT-IR)

The compatibility between the drug and the selected lipid and other excipients was evaluated using FTIR peak matching method. There was no appearance or disappearance of peaks in the drug-lipid mixture, which confirmed the absence of any chemical interaction between the drug, lipid and other chemicals.

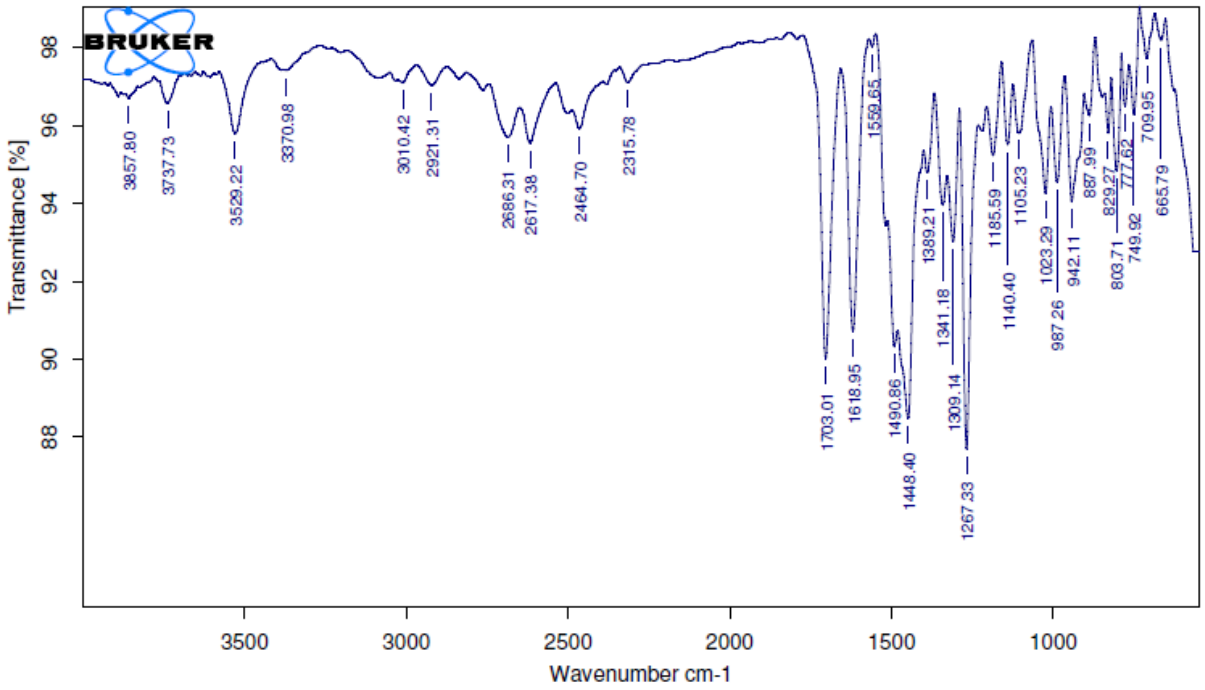

Fig 1: FT-IR Sample for Enzalutamide

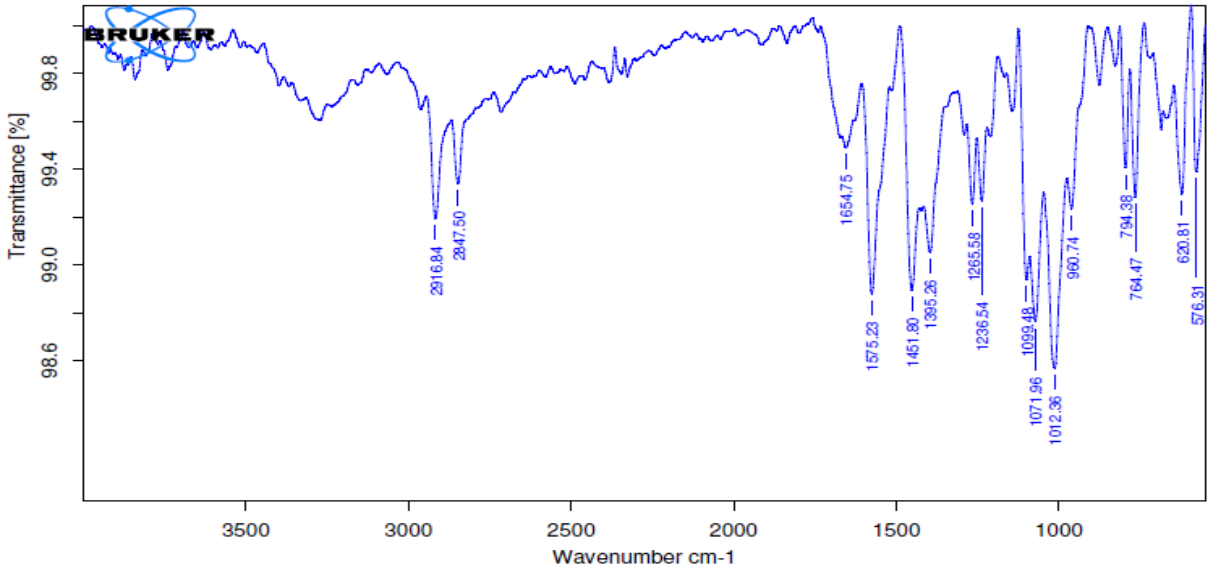

Fig 2: FT-IR Sample for Optimized Formulation

EVALUATION PARAMETERS

The solid lipid nanoparticles prepared were evaluated as per the following parameters-

- Particle size and SEM analysis
- Entrapment efficiency
- In vitro release study
- Stability studies

Particle size

The particle size increased with increasing of lipid concentration. Based on particle size distribution and entrapment efficiency.

Surface morphology

Scanning electron microscopy (SEM) SEM revealed that the solid lipid nanoparticles were smooth and spherical without any aggregation.

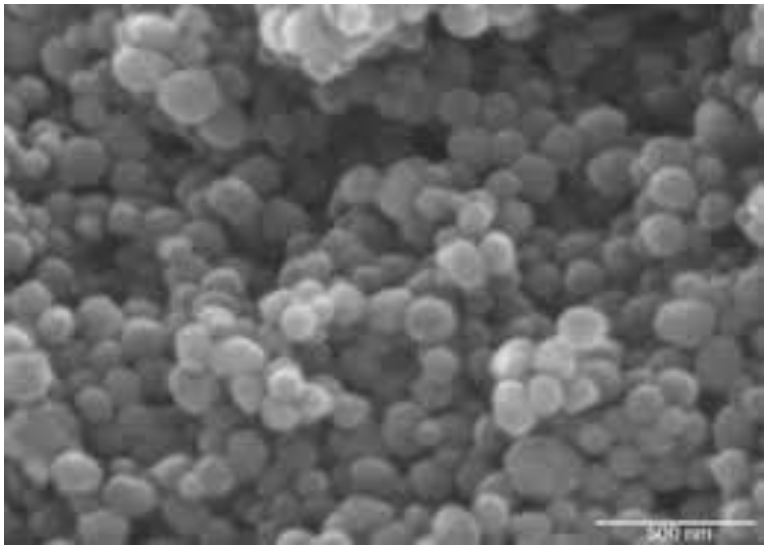

Fig 3: SEM analysis of Optimized solid lipid nanoparticle

Drug entrapment efficiency

The first part of the plan of work was to optimize the concentration of Lipid to be used in the formulation of solid lipid nanoparticles. The optimization of lipid concentration was done on the basis of particle size and entrapment efficiency of solid lipid nanoparticles obtained.

Table: 2 Evaluation Studies of Prepared solid lipid nanoparticles: Entrapment Efficiency and Particle size

Batch No	Particle size (nm)	Entrapment Efficiency (%)
F1	223	72.3
F2	248	74.1
F3	257	76.5
F4	264	78.4
F5	275	81.6
F6	282	84.2
F7	289	88.4
F8	296	92.68

In vitro drug release studies

The in vitro drug release results revealed that the prepared Enzalutamide solid lipid nanoparticles would be able to control drug release for extended period of time.

Table 3: Drug release study profiles for all formulations

Time (hrs)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	26.55	25.45	28.55	27.55	24.56	27.24	23.14	24.62
2	33.25	31.26	34.6	33.52	35.64	36.62	35.42	36.48
3	42.82	36.74	41.56	47.21	42.56	44.62	42.16	43.74
4	53.52	54.46	56.57	57.65	58.24	54.62	57.72	58.52
5	62.28	64.85	66.58	67.55	62.52	66.74	63.74	67.82
6	68.25	71.85	73.92	74.42	73.12	72.19	71.28	73.56
7	76.52	82.34	85.12	88.75	84.62	89.32	88.82	90.42
8	84.14	85.63	87.26	89.72	89.56	91.55	92.29	96.55

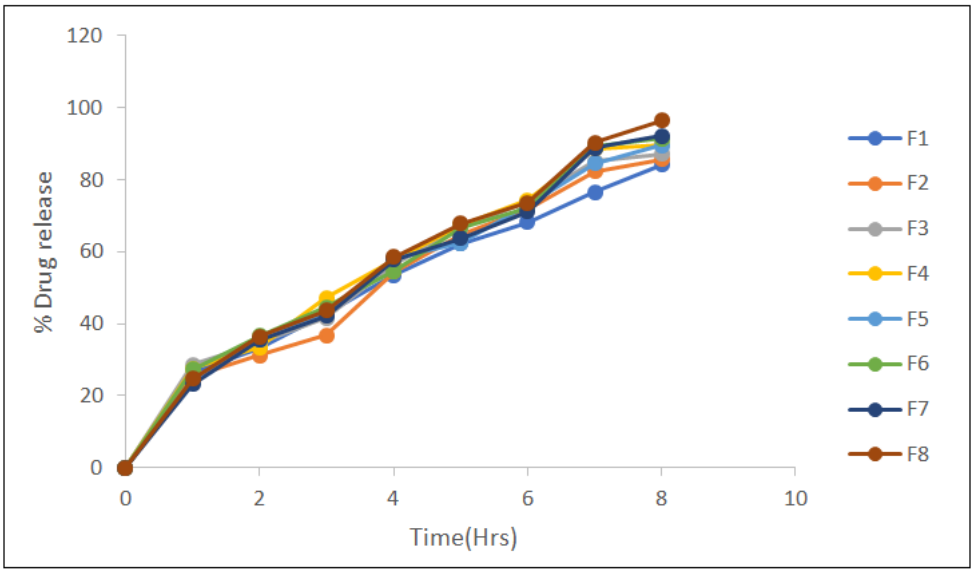

Fig 4: In vitro drug release studies for all formulations

The in vitro diffusion studies were performed in pH 7.4 buffer using Dialysis membrane for 8 hours. Initially the release of drug from all the three batches was found to be about 25-30% in 8 hours. This was due to the release of adsorbed drug from the surface of Solid lipid solid lipid nanoparticles. Later on, a constant and slow drug release was observed for 8hrs. F4 formulation which had lipid and surfactant ratio was decided to be the optimized formulation.

Stability studies

There was no significant change in physical and chemical properties of the nanoparticles of formulation F-8 after 3 months. Parameters quantified at various time intervals were shown

Table 4: Results of stability studies of optimized formulation F-8

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-8	25^0C/60%RH % Release	96.55	95.41	95.38	95.34	Not less than 85 %
F-8	30^0C/75% RH % Release	96.55	95.45	95.37	95.32	Not less than 85 %
F-8	40^0C/75% RH % Release	96.55	95.50	95.35	95.30	Not less than 85 %

CONCLUSION

The present research proposed a novel formulation Enzalutamide solid lipid nanoparticles for controlled release. Investigation of the preparation, characterization and in-vitro release of the solid lipid nanoparticles was carried out. The different formulations of with various ratios of drug-lipid and surfactant were evaluated and optimised. In this research, a drug encapsulation efficiency as high as 92.68 % has been achieved. The method used for the formulation of Enzalutamide containing soya lecithin solid lipid nanoparticles was solvent evaporation method followed by sonication to reduce the particle size. Solid lipid nanoparticles formulations showed good results in terms of drug content and encapsulation efficiency. This indicates that the method used for the formulation produced good yield and it was suitable and reproducible in nature. Formulation (F-8) showed the highest encapsulation efficiency. It was found that as the concentration of soya lecithin increased, the % of encapsulation efficiency was also increased. Permeation studies with dialysis membrane were carried out as per the method reported. The formulations showed good drug release from the lipid, the *in vitro* drug release profiles of all the formulations showed an initial burst effect, and followed by a slow drug release. The Enzalutamide release was faster for those solid lipid nanoparticles with higher drug content.

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