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Research Article

Study of Neusiln UFL2 and β-Cyclodexrtin as Solid Carriers in Solid Self-Microemulsifying Drug Delivery System of Atorvastatin Calcium Prepared by Spray Drying

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ABSTRACT

The main objectives of this work was, to study the effect of β-cyclodextrin and Neusilin UFL2 as a hydrophilic and a hydrophobic solid carrier respectively in solidification of self-microemulsifying drug delivery system prepared by spray drying technique. The liquid SMEDDS consisted of poorly water-soluble drug Atorvastatin calcium (10mg), and Capmul MCM (200mg) and Tween 20 (800mg) as oil and surfactant respectively. This formulation was spray dried by using the solid carrier in various formulations to carrier ratio. These spray dried formulation were characterized for flow properties, drug content, reconstitution and solid state properties. In-vitro dissolution test was carried out to observe the effect of solidification on release of drug and compare it with liquid SMEDDS and marketed formulation. The liquid SMEDDS to solid carrier ratio of 1:0.5 showed passable flow properties and high drug content. DSC, PXRD revealed that the drug in the solid SMEDDS was disperse in amorphous form while SEM results indicated that the particle formed were spherical with liquid formulation loading. In-vitro drug dissolution study indicated that after solidification the drug release was enhanced as compared to plain drug and marketed formulation. After three month stability study solid SMEDDS did not show any drug precipitation as well as phase separation. Thus it can be concluded that the solidification of liquid SMEDDS using these carrier retain the original performance with enhance stability.

Key-words: S-SMEDDS, Atorvastatin calcium, Neusilin UFL2, β-cyclodextrin, PXRD, DSC.

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INTRODUCTION

As a consequence of modern drug discovery techniques, there has been a steady increase in the number of new pharmacologically active lipophilic compounds that are poorly water-soluble. It is a great challenge for pharmaceutical scientists to convert those molecules into orally administered formulations with sufficient bioavailability. One of the most popular and commercially available formulation approaches for solving these problems is self-microemulsifying drug delivery systems (SMEDDS). SMEDDS is an isotropic mixture of oil, surfactant and /co-surfactant that can be used to solve the solubility problem and improve the drug absorption in gastrointestinal tract [1].

Traditional preparation of SMEDDS involves dissolution of drugs in oils and their blending with suitable solubilizing agents. However, SMEDDS formulations are normally prepared as liquids that produce some disadvantages such as high production costs, low stability and portability, low drug loading, irreversible drugs/excipients precipitation and few choices of dosage forms. More importantly, the large quantity (30–60%) of surfactants in the formulations can induce gastrointestinal (GI) irritation [2, 3].

To address these problems, Solid SMEDDS have been investigated, as an alternative approach. These systems require the solidification of liquid SMEDDS into powders/nanoparticles which can be converted to various solid dosage forms like tablets, capsule, and pellets and so on. Thus, S-SMEDDS will have combined advantages of SMEDDS such as enhanced solubility and bioavailability and with those of solid dosage forms, such as low production cost, convenience of process control, high stability and reproducibility, better patient compliance. Solid SMEDDS focus on the incorporation of liquid SMEDDS into powders/nano-particles by different solidification techniques such as freeze drying, spray drying, adsorptions to solid carriers, melt extrusion, nano-particles technology, and so on [2, 3].

Choice of solid carrier is very important that influence the performance of the solid SMEDDS. Ideal solid carrier should possess properties like; inert, high oil adsorption capacity, good flow property and compatible with the processing technology. Many solid carriers have being investigated for solidification of SMEDDS. Tao yi et.al used Dextran 40 as carrier for solidification of SMEDDS formulation consisting ethyl oleate, Labrasol, Cremophor RH 40 and nimodipine [4], Aerosil 200 was used as solid carrier by Dixti et.al for preparation of SNEDDS granules consisting , Ezetimibe, Capryol 90, Lauroglycol 90, Lauroglycol FCC, Ethyl laurate, Cremophor EL, Transcutol P. [5]. While Jun Hyeok kang et.al studied the effect of various solid carrier like Silicon dioxide, Magnesium stearate, PVA, Na-CMC and HP-β-CD on solidification of SNEDDS consisting of Labrafil M 1944 CS/Labrasol/Trasncutol HP (12.5/80/7.5 %) with 2 % w/v flurbiprofen [6]. It can be seen that the choice of solid carrier also depends on the liquid excipients that are used in formulation of liquid SMEDDS. Thus our aim is to observe the effect loading the same formulation developed on two carriers selected. In our previous study we have optimized a liquid SMEDDS formulation for Atorvastatin calcium which consist of Atorvastatin calcium (10 mg), Tween 20 (800 mg) and Capmul MCM (CAP) as oil (200 mg) [7]. The developed formulation proved to increases the dissolution of Atorvastatin calcium as compared to marketed formulation. Thus the aim of the present study was to convert this liquid SMEDDS formulation in to solid SMEDDS by spray drying using two different solid carriers and compare the effect of this carrier on solid SMEDDS.

MATERIALS AND METHODS

Materials

Atorvastatin calcium obtained as a gift sample from Wockhardt Pvt. Ltd. Aurangabad, India. Tween 20 and β-Cyclodextrin were purchased from S.D. fine chemicals Mumbai, India and Capmul MCM was obtained as gift sample from Abitec Corporation (USA). Neusilin UFL2 supplied by Fuji Chemical Japan through Gangwal Chemical Mumbai. All other excipients were used as received.

Methods

Preparation of liquid SMEDDS

Based on previous research by Bandivadekar et.al 2012 [7], the liquid SMEDDS consisting of Atorvastatin calcium (10 mg), Capmul MCM (200 mg) and Tween 20 (800 mg) was prepared as follow. Each component was weighed separately; Atorvastatin calcium was dispersed into the mixture of oil and surfactants into glass vials. Followed by gentle stirring and vortexing at 40°C until Atorvastatin calcium was completely dissolved. The formulation prepared was observed for isotropicity and drug precipitation. The mixture was stored at room temperature until used.

Preparation of solid SMEDDS

Two different carriers were used separately for formulation of solid SMEDDS Neusilin UFL2 and β-cyclodextrin. The formulation to carrier ratio of 1:2, 1:1, 1:0.5 and 1:0.25 were tried. Solid SMEDDS were prepared by spray drying using Labultima LU222 spray dryer. For preparation of feed, appropriate quantity of solid carrier was suspended or dissolved in beaker containing 200 ml of water. Then with constant stirring 5gm liquid atrovastatin loaded SMEDDS was added to that beaker and the solution was continuously stirred at room temperature for 15 min. to obtain good emulsion or suspension. Solid SMEDDS were obtained by spraying feed from the spray dryer using standard 0.7 mm nozzle. Spray drying parameter used for the process were Inlet temperature-120°C, Outlet temperature-70°C, Feed rate-5 ml/min and Aspiration rate-80%.

Characterization of solid SMEDDS

Angle of repose

Angle of repose has been defined as the maximum angle possible between the pile of powder and horizontal plane. The angle of repose for each solid SMEDDS formulation was determined by the funnel method. Angle of repose was calculated with the following formula

$$\theta = \tan^{-1} h/r$$

Where, θ -angle of repose, h -height of the pile and r -average radius of the powder cone.

Bulk density (BD)

Bulk density was determined by pouring gently 10 gm of solid SMEDDS through a glass funnel into 100 ml graduated cylinder. The bulk density was calculated as follows

$$\text{Bulk density } \frac{\text{gm}}{\text{ml}} = \text{Weight of sample/ Volume occupied by sample}$$

Tapped density (TD)

The 10 gm sample was poured gently through a glass funnel into a 100 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after tapping were recorded and tapped density was calculated as follows

$$\text{Tapped density } \frac{\text{gm}}{\text{ml}} = \text{Weight of sample/ Volume occupied by sample}$$

Carr's compressibility index (CI)

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials, because all of these can influence the observed compressibility index. The compressibility index of the powder blend was determined using Carr's compressibility index

$$CI = \left[\frac{TD - BD}{TD} \right] \times 100$$

Hausner's ratio

The Hausner's ratios are determined by measuring both the bulk volume and tapped volume of a powder. Formula used was as follows

$$\text{Hauser's ratio} = \frac{\text{Tapped bulk density}}{\text{Loose bulk density}}$$

Determination drug content

The drug content were determined by dissolving 1.0 gm of each solid SMEDDS separately in 50 ml methanol and stirred by vortex mixing. The solutions were filtered using 0.45 µm membrane filter and content were estimated by UV spectroscopy at 246 nm.

Evaluation of selected Solid SMEDDS

The formulations which show passable flow properties and high drug content are selected for further evaluation.

Reconstituted analysis of Solid SMEDDS

Self-emulsification Test

The efficiency of self-emulsification of solid SMEDDS was assessed using a standard USP XXII dissolution apparatus 2 (Labindia DS 8000). The 1.0 gm formulation was added to 500 mL of distilled water at 37 ± 0.5°C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations was visually assessed.

Cloud point measurement

About 1.0 gm of solid SMEDDS formulation was diluted with distilled water in the ratio of 1:100 and placed in a water bath with gradual increase in temperature and the point at which cloudiness occurred was noted as cloud point.

Globule size measurement

The 500 mg solid SMEDDS formulation was diluted with 250 ml distilled water. The droplet size so formed was determined by using a Particle Sizing Systems, Inc.Santa Barbara, Calif., USA able to measure sizes between 10 to 5000 nm.

Morphological analysis of solid SMEDDS

Scanning electron microscopy (SEM)

The outer macroscopic structure of the solid SMEDDS was investigated by SEM with a JEOL-JSM-6360A scanning electron microscope. The sample was fixed on a SEM-stub using double-sided adhesive tape and then coated with a thin layer of platinum.

Solid state analysis of Solid SMEDDS

Differential scanning calorimetry (DSC)

The physical state of Atorvastatin calcium in solid SMEDDS was characterized by the differential scanning calorimetry thermogram analysis (DSC 823 Mettler Toledo, Japan). The samples (about 3.00 mg) were placed in

standard aluminum pans, and dry nitrogen was used as effluent gas. All samples were scanned at a temperature from 30 °C to 500 °C with a heating rate of 10°C/min under a stream of nitrogen at a flow rate of 40 ml/min

X-ray powder diffraction (XRPD)

To verify the physical state of Atorvastatin calcium in solid SMEDDS, X-ray powder scattering measurements were carried out with a D-8 Advanced diffractometer (Germany). A voltage of 40 kV and a current of 40 mA for the generator were applied with Cu as the tube anode material. The solids were exposed to a Cu–K radiation, over a range of 2h angles from 10°–40°, at an angular speed of 2°(2h)/min,a sampling interval of 0.02.

***In Vitro* release study**

The *In-vitro* release profiles of solid SMEDDS were compared with plain drug(10mg) and marketed ATS tablet (ZIVAST-10mg).The quantitative *in-vitro* dissolution test was performed in 900 mL of phosphate buffer pH 6.8 maintained at 37 ± 0.5°C using USP XXIV type II dissolution apparatus (Labindia DS 8000). The paddles were rotated at 100 rpm. The solid SMEDDS equivalent to 10 mg of Atorvastatin Calcium and 10 mg of Atorvastatin Calcium plain were filled in '00' HPMC capsule. (Flofit TM, Associate capsule, Pune). 5 mL aliquots were collected periodically (5, 10, 15, 30, 45, 60min) and replaced with fresh dissolution medium. Aliquots, after filtration through 0.45mm membrane filters, were analyzed by UV-Vis spectrophotometer.

Stability Study

Thermodynamic Stability Study

a) Heating cooling cycle: Formulation was kept at 0°C & 45^0C for not less than 48hr for each temp. Cycle (3 cycles were studied)

b) Centrifugation study: The formulation which passes heating cooling cycle was subjected to centrifugation at 5000 rpm for 30 min.

Accelerated Stability Study

To assess the formulation stability was done according to ICH guidelines. The optimized solid SMEDDS were stored at 40° C/75% RH (Newtronics chamber) for 03 month and evaluated for cloud point, drug content and for self-emulsification time.

RESULTS AND DISCUSSION

Flow Properties

Atorvastatin calcium loaded solid SMEDDS were formulated by spray drying using Neusilin UFL2 and β-Cyclodextrin solid carriers separately at various ratios and evaluated for flow properties as shown in table 1. It can be seen at high formulation to carrier ratio produced oily product indicating the insufficiency of carrier loading capacity, but as the ratio decreased flow properties indicatives such as (Carr's Index, Hausner ratio and angle of repose) showed good values indicating optimum loading of the formulation.

The ratio 1:0.5 liquid formulation to carrier ratio showed passable flow properties for both Neusilin UFL2 solid SMEDDS and β-Cyclodextrin solid SMEDDS with optimum drug content was selected for further evaluation.

Evaluation of selected solid SMEDDS

Reconstitution properties and cloud point of Solid SMEDDS

Reconstitution properties judge the performance in-vivo. Self-emulsification time indicates the ability of the formulation to disperse readily in micron size globules. β-Cyclodextrin being water soluble helped in quick dispersion of the formulation into microemulsion while Neusilin UFL2 which is hydrophobic in nature took time

for dispersing the formulation and formed mixture of Neusilin UFL2 suspension and microemulsion of the formulation. Particle size was observed to be low for formulation consisting β-Cyclodextrin as solid carrier than the Neusilin UFL2, the globule produce were observed to be in micron size thus retaining the properties of liquid SMEDDS as shown in table 2.

TABLE 1: MICROMERITIC PROPERTIES AND DRUG CONTENT OF SOLID SMEDDS

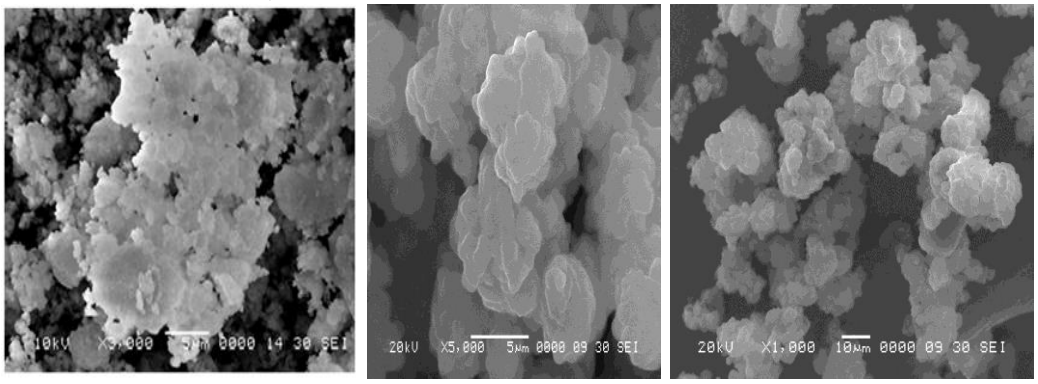
F:C Ratio	F+C (gm)	Neusilin S-SMEDDS							β-CD S-SMEDDS						
		Yield (gm)	Bulk Density (g/ml)	Tap Density (g/ml)	C.I. (%)	Hausner's Ratio	Angle of Repose	Drug Content /gm	Yield (gm)	Bulk Density (g/ml)	Tap Density (g/ml)	C.I. (%)	Hausner's Ratio	Angle of Repose	Drug Content /gm
1:2	**5+10**	12	0.1470	0.1851	20.55	1.25	33.42°	3.32 mg	12.5	0.147	0.166	13.28	1.13	35.37°	3.92 mg
1:1	**5+5**	8	0.1538	0.1818	15.38	1.18	38.65°	5.33 mg	7.5	0.185	0.208	12.47	1.12	41.34°	5.72 mg
1:0.5	**5+2.5**	6	0.1886	0.2173	13.20	1.15	40.49°	9.08 mg	4	0.222	0.250	11.12	1.12	43.53°	9.28 mg
1:0.25	**5+1.25**	2	Oily Product and Not Passable					-	1.6	Oily Product and Not Passable					-

TABLE 2: RECONSTITUTION PROPERTIES AND CLOUD POINT OF SOLID SMEDDS

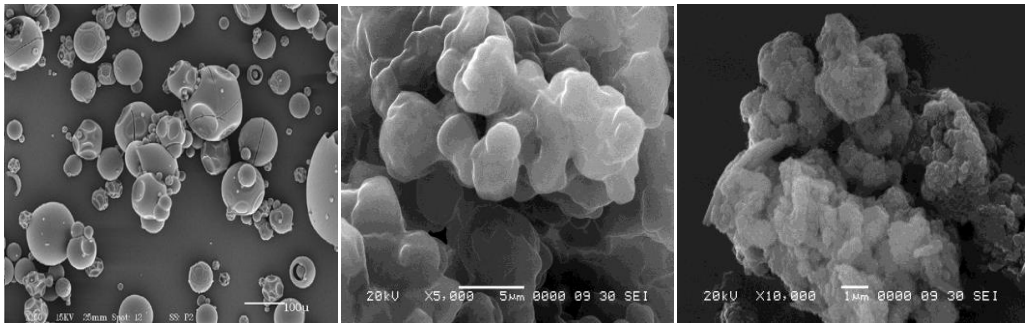
S-SMEDDS	Emulsification time	Globule size(nm)	Polydispersity index	Cloud Point(°c)
Neusiline UFL2	<2 min	2250.2 ± 0.43	3.3 ± 0.07	83±4
β-Cyclodextrin	<1.7min	409.3 ± 0.51	1.08 ± 0.03	85±2

Morphological analysis of Solid SMEDDS

The outer macroscopic structure of the solid SMEDDS was investigated by SEM. The scanning electron micrographs of solid carriers Neusilin UFL2, β-Cyclodextrin and solid SMEDDS are shown in Fig.1.The Neusilin UFL2 (Fig.1- a) appeared with a rough surface with porous particles. β-Cyclodextrin (Fig1-c) appeared as smooth-surfaced rectangular crystalline in shape. However, the solid SMEDDS (Fig. 1- b and d) appeared as smooth-surfaced particles, indicating that the liquid SMEDDS is absorbed or coated inside the pores of carriers. Furthermore, the solid SMEDDS had the particle size in µm.



a. Neusilin UFL2 b. Neusilin spray dried formulation



c. β-Cyclodextrin d. β-Cyclodextrin Spray dried formulation

Fig 1: Scanning electron micrographs

Solid State Characterization of S-SMEDDS

Differential scanning calorimetry

The DSC thermograms of Atorvastatin calcium showed a sharp endothermic peak at 159.20°C corresponding to its melting point and sharp peaks indicates that plain drug in crystalline state. No obvious peak of the drug were found in the solid SMEDDS of Atorvastatin calcium, indicating that the drug must be present in amorphous and molecularly dissolved state in solid SMEDDS (fig.2).

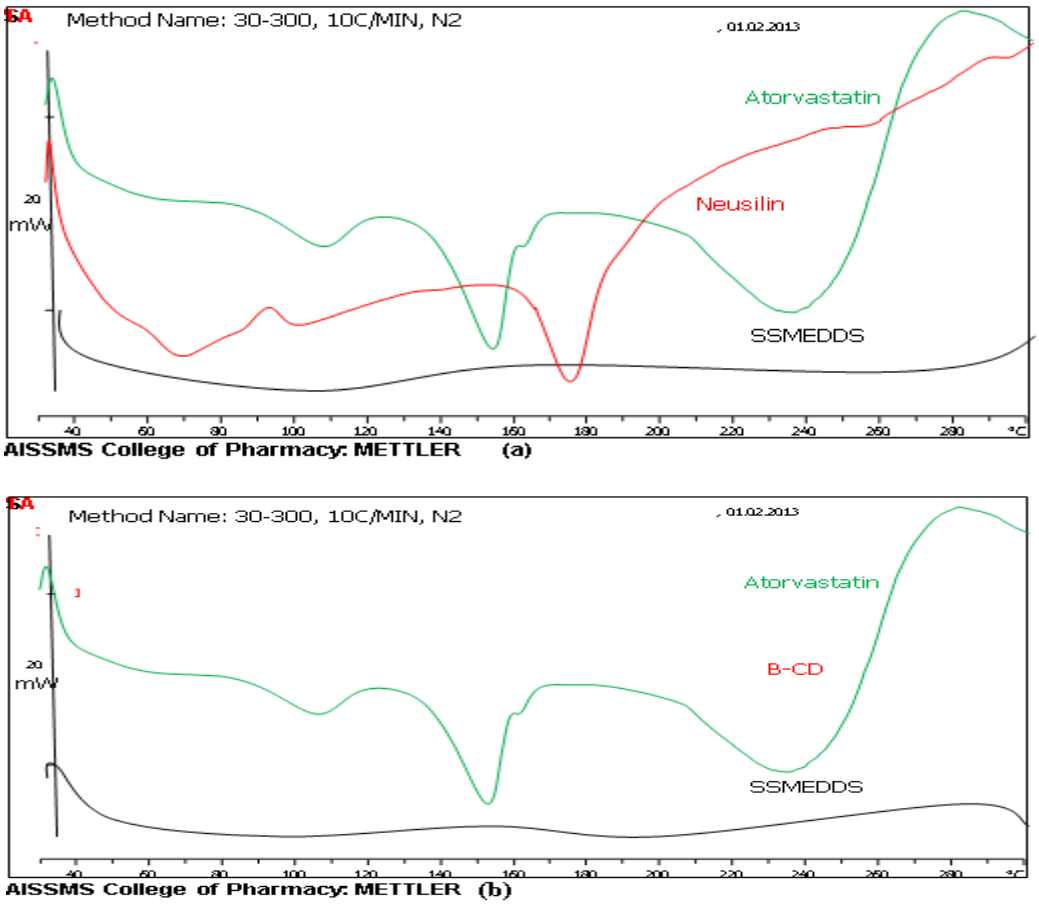
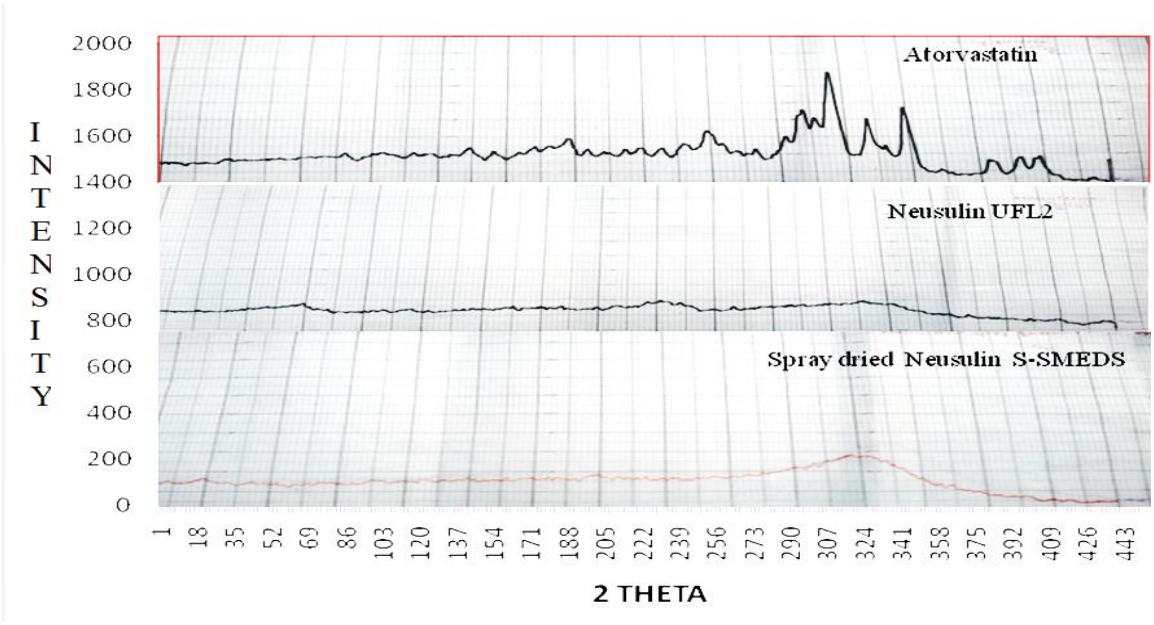


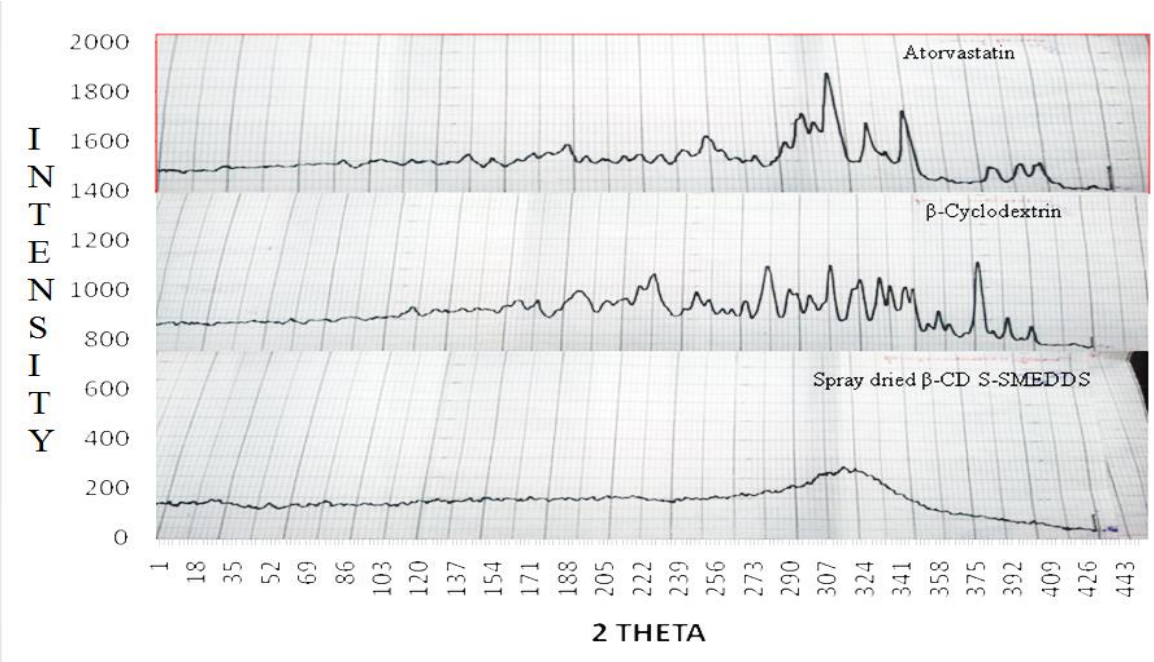
Fig 2: DSC Thermograms of (a) ATS, Neusilin UFL2 and Neusilin SSMEDDS. (b) ATS, β-Cyclodextrin and β-Cyclodextrin SSMEDDS.

X-Ray Powder Diffractometry

The powder X-ray diffractometry patterns are presented in (Fig.3.A and B). Atorvastatin calcium had sharp peaks at the diffraction angles, showing a typical crystalline pattern. Neusilin UFL2 showed no intrinsic peaks (Fig.3 A-2) and β -CD showed intrinsic peaks at various angles (Fig.3B-2). The S-SMEDDS formulations showed no peaks at diffraction angles, showing an amorphous pattern (Fig.3). Thus, the DSC and XRD results revels that Atorvastatin calcium was present in an amorphous state in the S-SMEDDS formulations prepared with carriers.



(A)



(B)

Fig 3: Powder X-ray diffraction patterns of A-(1) ATS (2) Neusulin UFL2 and (3) Neusilin SSMEDDS. B-(1) ATS (2) β-Cyclodextrin and (3) β-Cyclodextrin SSMEDDS.

Drug content determination

The drug content in solid SMEDDS formulations was found to be 9.08 ±0.07 mg in Neusulin UFL2 solid SMEDDS and 9.26±0.13 mg in β-Cyclodextrin solid SMEDDS indicating dose conformity.

***In vitro* drug release**

The *In vitro* drug release study is generally done as an quality control tool, during the production of dosage form to check either dosage form is releasing the drug according to predetermined specifications or not. Atorvastatin calcium a poorly water soluble drug, dissolution was enhanced by formulating it into SMEDDS as compared to marketed formulation. So it was a crucial task to improve the stability of the formulation by converting it into solid dosage form with retention of its original qualities.

As pre the *in-vitro* release shown in (fig.4) it was observed that the dissolution of Atorvastatin calcium in liquid SMEDDS, and Neusilin UFL2, β-Cyclodextrin solid SMEDDS was high as compared to plain drug suspension. Such observation can be because of the ability of SMEDDS formulation to enhance the dissolution of poorly soluble drugs. Comparing the release trend of Neusilin UFL2 and β-Cyclodextrin solid SMEDDS it was observed that the later showed enhance drug release against β-Cyclodextrin, such observation can be attributed to the interaction between the drug and the solid carrier mainly because of the hydrogen bonding. It can may because of more hydrogen bonding between β-Cyclodextrin and hydroxyl group of Atorvastatin calcium as compared to Neusilin UFL2 which must had hindered the release of the drug. Neusilin UFL2 showed better drug release than the marketed formulation proving better performance in-vivo.

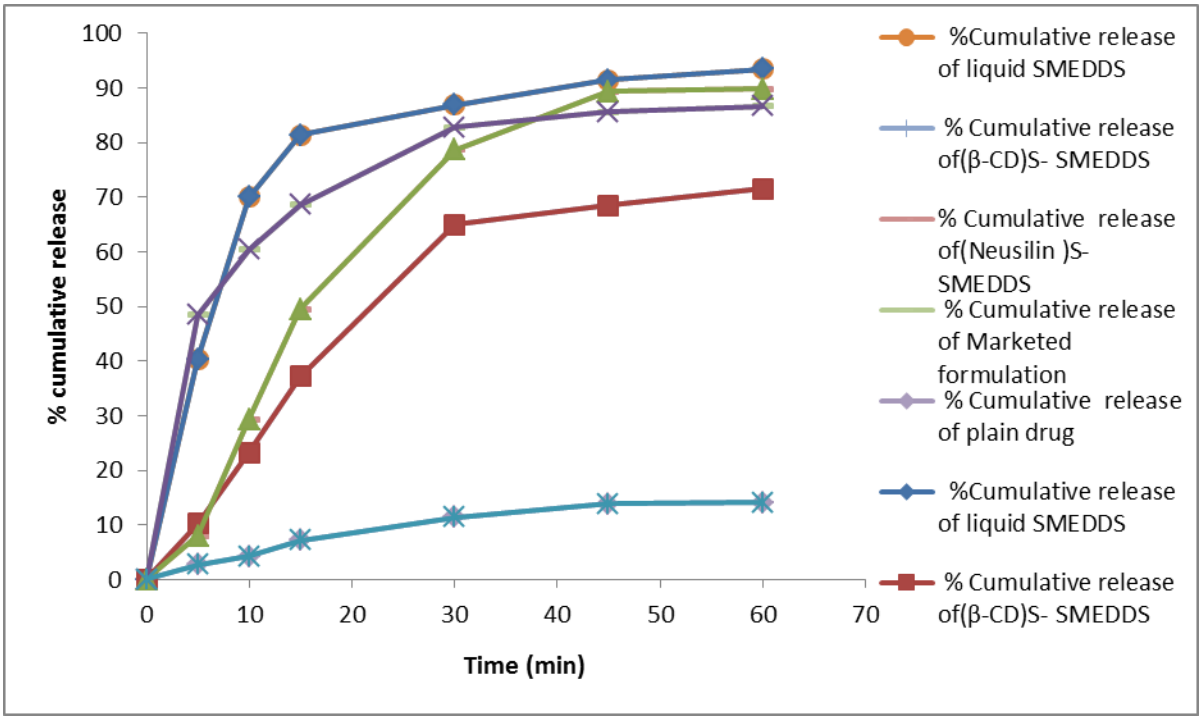


Fig 4: Dissolution profile of liquid SMEDDS, Neusilin SSMEDDS, β-Cyclodextrin SSMEDDS, Marketed formulation and plain ATS.

Stability Study

Thermodynamic Stability Study

The formulations were evaluated in terms of heating cooling cycle and centrifugation study, there was no phase separation in both solid SMEDDS. Table: 4.

Accelerated Stability Study

The Neusilin UFL2 and β-CD solid SMEDDS formulation were subjected to stability studies and evaluated in terms of drug content, cloud point and for self-emulsification time as shown in Table: 5.

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