Research Article

Design and Evaluation of Self-Emulsifying Drug Delivery Systems of Atazanavir Bi Sulfate

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ABSTRACT

The main purpose of this study was to formulate lipid based self-micro emulsifying drug delivery system (SMEDDS) that result in improved solubility, dissolution of the poorly water soluble drug Atazanavir, which a lipophilic drug and widely used in the treatment of HIV. Solubility of Atazanavir was determined in various vehicles such as oils, surfactants and co-surfactants. Ternary phase diagram were constructed to identify the most efficient self-emulsification region. The optimized formula for Atazanavir SMEDDS consisting of triacitine (25%w/w), Span20 (50%w/w) and transcutol HP (25%w/w). The liquid SMEDDS were converted to solid SMEDDS by using Aerosil 200 as adsorbent. The Atazanavir SMEDDS in liquid and solid formulation rapidly formed fine oil-water micro emulsions, with mean particle size of 65.8 nm and zeta potential is found to be -9.2 MV. The *in-vitro* drug release rate and extent of release of Atazanavir from S-SMEDDS found to be 84.84% at 1 hour by using pH 6.8 buffer. The formulation was filled in "00" size hard gelatin capsules were found to be stable up to 6 months under intermediate and accelerated conditions. These studies demonstrated that the novel SMEDDS formulations in liquid and solid forms are promising strategies for the formulation of poorly soluble lipophilic drugs with less solubility and oral bioavailability.

Keywords: SMEDDS, Atazanavir Bi Sulfate, solubility, dissolution.

INTRODUCTION

Approximately one third of the drugs emerging from drug discovery programs are poorly water soluble, presenting the pharmaceutical scientist with several problems when developing formulations for such active pharmaceutical ingredients (API). Most of the conventional oral dosage forms are poorly water soluble drugs. In usual solid oral drugs are mean to pass through the gastrointestinal tract which means the drug has to dissolve in the GI fluids before it can be absorbed. Thus, their rate and extent of absorption is largely dependent on the rate of dissolution.[1]

Solubility is the phenomenon of dissolution of solute in solvent to give a homogenous system. It is one of the important parameter to achieve desired concentration of drug in systemic circulation (for desired pharmacological response).

The level of potency is related to permeability or solubility of the dosage form. Selection of solubility improving method depends on drug property, site of absorption and required dosage form characteristics.

Mechanism of Self-Emulsification

The mechanism, by virtue of which self-emulsification tends to occur has not yet been thoroughly elucidated.

Nevertheless, it has been suggested that self-emulsification takes place when the entropy change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases.

The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus, minimize the free energy of the system(s).

The conventional emulsifying agents stabilize emulsions resulting from aqueous dilution by forming a monolayer around the emulsion droplets, reducing the interfacial energy and forming a barrier to coalescence.

On the other hand, emulsification occurs spontaneously with SEDDS, as the free energy required to form the emulsion is low, whether positive or negative. For emulsification to take place, it is vital for the interfacial structure to offer negligible or no resistance against surface shearing. The ease of emulsification has been suggested to be related to the ease of water penetration into various liquid crystals or gel phases formed on the surface of the droplet. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture (oil/non-ionic surfactant) to water. This is followed by solubilization within the oil phase, as a result of aqueous penetration through the interface. Invariably, this tends to occur until the solubilization limit is attained close to the interphase. Further, aqueous penetration will lead to the formation of the dispersed liquid crystal phase.

Ultimately, everything that is in close proximity with the interface will be liquid crystal, the actual amount of which depends upon the emulsifier concentration in the binary mixture. Hence, following gentle agitation of the self-

emulsifying system, water rapidly penetrates into the aqueous cores leading to interface disruption and droplet formation.

Human Immunodeficiency Virus (HIV)

Human Immunodeficiency Virus usually attacks the immune system. Lentiviruses are in turn part of a larger group of viruses known as retroviruses. Retroviruses are the exception because their genes are composed of Ribonucleic Acid (RNA). The name 'lentivirus' literally means 'slow virus' because they take such a long time to produce any adverse effects in the body. There are two types of HIV: HIV-1 and HIV-2. HIV-2 is less easily transmitted, and the period between initial infection and illness is longer in the case of HIV-2. Worldwide, the predominant virus is HIV-1, and generally when people refer to HIV without specifying the type of virus they will be referring to HIV-1. The relatively uncommon HIV-2 type is concentrated in West Africa and is rarely found elsewhere.[1]

Acquired Immune Deficiency Syndrome (AIDS)

AIDS is a disease of the human immune system caused by the HIV[2]. The illness interferes with the immune system, making people with AIDS much more likely to get infections, including opportunistic infections and tumors that do not affect people with working immune systems. This susceptibility gets worse as the disease continues. HIV is transmitted in many ways, such as: sexual intercourse, contaminated blood transfusions, hypodermic needles, during pregnancy (between mother and baby) and from breastfeeding. It can be transmitted by any contact of a mucous membrane or the bloodstream with a bodily fluid that has the virus in it, such as the blood, semen, vaginal fluid, preseminal fluid, or breast milk from an infected person.[3]

AIDS is a clinical consequence of infection with HIV. HIV primarily infects vital organs of the human immune system such as CD4+ T cells (a subset of T cells), macrophages and dendritic cells. It directly and indirectly destroys CD4+ T cells.

Once the number of CD4+ T cells per microliter of blood drops below 200, cellular immunity is lost. Acute HIV infection usually progresses over time to clinical latent HIV infection and then to early symptomatic HIV infection and later to AIDS, which is identified either on the basis of the amount of CD4+ T cells remaining in the blood, and/or the presence of infections.[4]

The virus and disease are often referred to together as HIV/AIDS. The disease is a major health problem in many parts of the world, and is considered a pandemic, a disease outbreak that is not only present over a large area but is actively spreading.[5] In 2009, the World Health Organization (WHO) estimated that there are 33.4 million people worldwide living with HIV/AIDS, with 2.7 million new HIV infections per year and 2.0 million annual deaths due to AIDS.[6] In 2007, UNAIDS estimated: 33.2 million people worldwide were HIV positive; AIDS killed 2.1 million people in the course of that year, including 330,000 children, and 76% of those deaths occurred in sub-Saharan Africa.[7] According to UNAIDS 2009 report, worldwide some 60 million people have been infected since the start of the pandemic, with some 25 million deaths, and 14 million orphaned children in southern Africa alone.[7] However, with the adherence to HAART the efficacy rate of the available treatment has increased up to 85% against the AIDS as well as secondary diseases such as Kaposi's sarcoma.[8,9]

Antiretroviral (ARV) Drug Treatment

Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV. The aim of antiretroviral treatment is to keep the amount of HIV in the body at a low level.

This stops any weakening of the immune system and allows it to recover from any damage that HIV might have caused already. The treatment consists of drugs that have to be taken every day for the rest of a person's life. If only one drug was taken, HIV would quickly become resistant to it and the drug would stop working.

There are different classes of ARV drugs that act on different stages of the HIV life-cycle. HIV can easily develop resistance to individual ARV therapies, but it is harder for HIV to become drug-resistant when multiple ARV drugs with varied mechanisms of action are combined into a single HIV treatment.

Taking two or more ARV at the same time vastly reduces the rate at which resistance would develop, making treatment more effective in the long term.

Table 1: Classification of ARV drugs

Antiretroviral Drug Class	Mechanism of Action	Generic Name of Drugs
Fusion or Entry Inhibitors	Prevent HIV from binding to or entering human immune cells	Enfuvirtide, Maraviroc
Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs)	NRTIs inhibit reverse transcription by being incorporated into the newly synthesized viral DNA strand as faulty nucleotides	Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abcavir, Emtricitabine, Tenofovir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	NNRTIs inhibit reverse transcriptase by binding to an allosteric site of the enzyme	Efavarinz, Nevirapine, Loviride, Delavirdine, Etravirine, Rilpivirine, Lersivirine

Protease Inhibitors (PIs)	PIs target viral assembly by inhibiting the activity of protease, an enzyme used by HIV to cleave nascent proteins for the final assembly of new virions.	Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Tipranavir, Lopinavir, Darunavir, Atazanavir, Nelfinavir
Integrase Inhibitors	Inhibit the enzyme integrase, which is responsible for integration of viral DNA into the DNA of the infected cell.	Raltegravir

Table 2: Classification of the SMEDDS formulation in accordance to comparative grades

Grade	Dispersibility and Appearance
A	Rapid forming emulsion, which is clear and transparent in appearance
B	Rapid forming, slight less clear emulsion, which has a bluish white appearance
C	Bright white emulsion or grayish white emulsion with a slight oily appearance that is slow to emulsify
D	Exhibit poor or minimal emulsification with large oils droplets present on the surface

Table 3: Oil, surfactants and co-surfactants grouped in different combinations

Group	Oil	Surfactant	Co-surfactant
1	Triacetin	Span 20	Transcutol HP
2	Triacetin	Span 20	PEG 400
3	Triacetin	Acconon MC8-2	Transcutol HP
4	Triacetin	Acconon MC8-2	PEG 400
5	Triacetin	Span 20	Transcutol HP
6	Triacetin	Span 20	PEG 400
7	Triacetin	Acconon MC8-2	Transcutol HP
8	Triacetin	Acconon MC8-2	PEG 400

Table 4: Release profile of standard ATV, MF, L- and S-SMEDDS in dissolution media (1% SLS in water).

	% Cumulative Drug Release ± SD (n=3)			
Time (min)	Standard ATV	MF	L-SMEDDS	S-SMEDDS
5	4.72 ± 2.52	19.54 ± 0.75	92.46 ± 1.20	82.27 ± 1.06
10	10.59 ± 3.00	32.93 ± 1.51	94.25 ± 0.83	87.51 ± 2.88
15	19.58 ± 5.00	48.58 ± 1.60	95.78 ± 0.58	92.64 ± 2.48
30	33.36 ± 4.03	70.28 ± 1.08	97.81 ± 0.92	96.33 ± 0.72
45	41.47 ± 5.54	81.92 ± 1.47	98.55 ± 0.54	98.42 ± 0.34
60	49.05 ± 5.13	94.97 ± 0.44	99.77 ± 0.42	98.78 ± 0.44

Table 5: Comparison of Dissolution Parameters*

	Standard ATV`	MF	L-SMEDDS	S-SMEDDS
DE_5%	2.36 ± 1.26	9.776 ± 0.37	46.20 ± 0.60	41.13 ± 0.53
DE_{60}%	29.36 ± 4.26	62.40 ± 0.41	93.06 ± 0.58	90.60 ± 0.96
DE_5%	4.73 ± 2.26	19.54 ± 0.75	92.46 ± 1.21	82.25 ± 1.05
DE_{60}%	49.05 ± 5.26	94.99 ± 0.54	99.78 ± 0.41	98.79 ± 0.45
DE_{50}%	>60	16.2 ± 0.97	2.72± 0.004	3.05 ± 0.08
MDT (min)	24.17 ± 1.63	20.58 ± 0.08	4.02 ± 0.29	4.98 ± 0.44
AUC	1762 ± 5	3473 ± 8	5585 ± 75	5435 ± 58.36

*Mean ± S.D. (n=3), DE: dissolution efficiency, DP: Dissolution percentage, t50%: time required for release 50% of drug, t50%: time required for release 50% of drug, MDT: mean dissolution time, AUC: Area under curve. Standard ATV demonstrated the lowest permeability

Current Limitations of ARV Drug Therapy

ARV drug therapy has contributed significantly to improved patient/disease management, its current use is associated with several disadvantages and inconveniences to the HIV/AIDS patient.[10] Many ARV drugs undergo extensive first pass metabolism and gastrointestinal degradation leading to low and erratic bioavailability. The half-life for several ARV drugs is short, which then requires frequent administration of doses leading to decreased patient compliance.[11] A major limitation is that HIV is localised in certain inaccessible compartments of the body such as the CNS, the lymphatic system and within the macrophages. These sites cannot be accessed by the majority of drugs in the therapeutic concentrations required and the drugs also cannot be maintained for the necessary duration at the site of HIV localization.[12] These sub-therapeutic drug concentrations and short residence time at the required sites of action contribute significantly to both the failure of eliminating HIV from these reservoirs, and the development of multidrug-resistance against the ARV drugs.[13] The severe side effects associated with ARV therapy can therefore be attributed to the subsequent large doses essential for achieving a therapeutic effect, due to the inadequate drug concentrations at the site of action, and/or the poor bioavailability of several ARV drugs. These drugs also suffer from physico-chemical problems such as poor solubility that may lead to formulation difficulties.[14,15] Strategies currently being investigated to overcome these limitations include the identification of new and chemical modification of existing chemical entities, the examination of various dosing regimens, as well as the design and development of novel drug delivery systems (NDDS) that can improve the efficacy of both existing and new ARV drugs. More specifically, in the past decade there has been an explosion of interest in the development of NDDS for the incorporation of ARV drugs as a way of circumventing the problems described above and optimizing the treatment of HIV/AIDS patients. NDDS present an opportunity for formulation scientists to overcome the many challenges associated with ARV drug therapy. The nanometer size and high surface area to volume ratio which affect the pharmacokinetics and bio distribution of the associated drug molecule are main features of NDDS.

Atazanavir

Atazanavir is classified as a BCS II drug (high permeability/low solubility). The free base of Atazanavir does not have sufficient bioavailability. Therefore, quite a number of different acid addition of salts for example: Hydrochloride, Methanesulphonate (mesylate), Sulphates and bisulphate salts have been tested for the purpose of developing an orally administrable drug form. Owing to its good solubility in comparison with the other salts. Atazanavir bisulphate is used for producing the currently available oral drug forms.

Mechanism of Action

Atazanavir is an azapeptide HIV-1 protease inhibitor (PI). The compound selectively inhibits the virus-specific processing of viral Gag-Pol proteins in HIV-1 infected cells, thus preventing formation of mature virions and infection of other cells.

MATERIALS AND METHODS

Atazanavir was gifted by Hetero drugs LTD.,(Andhra Pradesh, India). Capsules (Reyataz 300, BMS.) were purchased from local pharmacy. Excipients used for formulation development are shown in Table 3 and were used as received.

Chemicals and reagents used for the preparation of buffers, analytical solutions, and other general experimental purposes. Purified HPLC grade water was obtained by filtering double distilled water through nylon filter paper 0.45 µm pore size and 47 mm diameter.

Solubility Study

To find out appropriate oils and surfactants as compositions of SMEDDS, the solubility of drug in various oils and surfactants was determined. An excess amount of drug was added to 1 ml of oil or surfactant. The resultant mixtures were shaken at 37°C for 72 h, followed by centrifugation at 8000 rpm for 10 min. The supernatant was diluted with methanol; the drug concentration was quantified by HPLC.

Pseudoternary Phase Diagram

The first step towards the formulation development was to determine the feasibility of the micro emulsion formation. The boundaries of the microemulsion domains were determined by plotting pseudoternary phase diagrams for the components short listed from solubility studies. The pseudoternary phase diagram of oil, surfactant co-surfactant mixture and doubled distilled water was plotted using water titration method.[16] Pseudo ternary phase diagrams were constructed in order to obtain the concentration range of components for the existing region of microemulsions. The weight ratio of surfactant to co-surfactant was varied as 1:1, 2:1 and 3:1. For each pseudoternary phase diagram at a specific surfactant/co-surfactant weight ratio, the mixtures of oil, surfactant and co-surfactant were prepared with the weight ratio of oil to the mixture of surfactant and co-surfactant at 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9, respectively. To the resultant mixtures, water was added drop wise till the first sign of turbidity in order to identify the end point and after equilibrium; if the system became clear then the water addition was continued. The concentrations of the components were recorded in order to complete the pseudoternary phase diagrams, and then the contents of oil, surfactant, co-surfactant and water an appropriate weight ratios were selected based on these results. In order to prepare SMEDDS, selection of microemulsion region from phase diagram was based

on the fact that solution remains clear even on infinite dilution.

Self-emulsification and Dispersilbility Test

Ternary mixtures with varying compositions of oil, surfactant and co-surfactant were prepared. For any mixture, the total percent of oil, surfactant and co-surfactant concentrations was always kept at 100%. Ternary phase diagrams of oil, surfactant and co-surfactant were plotted, each of them representing an apex of the triangle. The mixture was introduced into 250 ml of water in a glass beaker at 37°C and the contents were mixed gently with a magnetic stir bar. After being equilibrated, the efficiency of self-emulsification, dispersibility, and appearance was observed visually according to the grading systems shown in Table 2.[17,18] Grade A region was SMEDDS region that formed clear microemulsions after infinite dilution. Phase diagrams were constructed identifying the good self-emulsifying region. All studies were repeated thrice, with similar observations being made between repeats.

Optimization of ATV loaded L-SMEDDS by Factorial Design

In SMEDDS, the amount of oil, surfactant and co-surfactant depends on each other. If the percentage of one component is increased, then percentage of one or more of the other components must be decreased. The total concentration of the three components summed to 100%. Based on this information, mixture experimental design was generated by Design-Expert®8.0 software for three component system to conduct the study. SMEDDS components were selected based on the results of phase diagram and self-emulsification test. A total of twenty fine experiments were designed by the software with 6 vertices, 6 centres of edges, 6 axial check blends, 6 interior check blends and 1 overall centroid points. Dependent variables were mean droplet size (MDS) (B1) and % T (B2). After generating the polynomial equations relating the dependent and independent variables, the process was optimized for the responses B1 and B2 values. Optimization was performed to obtain the levels of independent variables, which minimize B1 while maximizing B2.

Preparation of L-SMEDDS

After careful evaluation, Triacetin as oil, span 20 as surfactant and transcutol HP as co-surfactant were selected as a SME mixture for drug delivery. L-SMEDDS formulation was prepared by dissolving 300 mg of ATV in the optimized SME mixture consisting of Triacetin (25%w/w), Span 20 (50%w/w) and transcutol HP (25%w/w). Briefly, oil and surfactant and co-surfactant were accurately weighed into glass vials according to their ratios. Then, the components were mixed by gentle stirring and vortex mixing at 37°C until ATV was completely dissolved. The mixture was observed for any signs of turbidity or phase separation for a period of 48 hours.

Preparation of S-SMEDDS

For the preparation of S-SMEDDS, L-SMEDDS was mixed with various solid carriers namely dibasic calcium phosphate, anhydrous lactose, microcrystalline cellulose, calcium carbonate, magnesium carbonate, Aerosil 200, aluminium and magnesium silicate, in various ratios (2:1, 1:1, 1:2 and 1:4).

Briefly the, L-SMEDDS was added drop wise over the solid adsorbent contained in a broad bottom beaker. After each addition, the mixture was homogenized using glass rod to ensure uniform distribution of the droplet.[19] The adsorbent that was required in a small amount to give a free flowing S-SMEDDS was chosen for the further studies.

Evaluation Studies

Characterization of ATV loaded SMEDDS formulations (L-SMEDDS)

Droplet size measurement

The droplet size and PolyDispersity Index (PDI) of L-SMEDDS and S-SMEDDS, 100 times diluted with double distilled water, were determined using a Malvern Zeta Sizer Nano ZS 90 (Malvern Instruments, Malvern, UK). The PDI indicates the width of a particle distribution (e.g. 0.0 for a narrow, 0.5 for a very broad distribution).

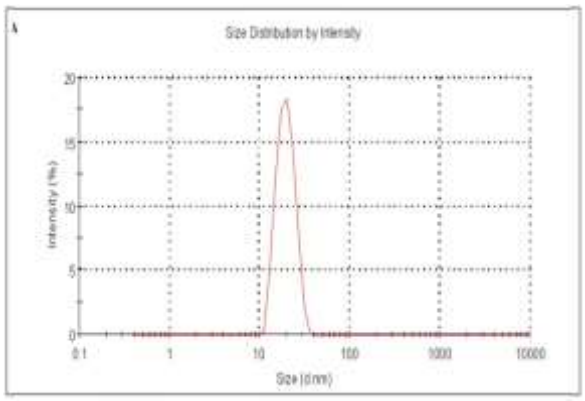

Figure 1: Droplet Size Distribution Curve

Zeta Potential Measurement

The ZP is a measure of the electric charge at the surface of the particles indicating the physical stability of colloidal systems.[20] ZP was measured using a Zeta Sizer Nano ZS 90 (Malvern Instruments, Malvern, UK). Each sample was suitably diluted with double distilled filtered water and placed in a disposable zeta cell. The ZP values were assessed by determining the particle electrophoretic mobility. The electrophoretic mobility was converted to the ZP via the Helmholtz–Smoluchowski equation.

% T Measurement

A total of 1 ml of SMEDDS formulation was diluted 100 times with double distilled water. The % T of diluted SMEDDS was measured at 255 nm using UV spectrophotometer (UV 1700, Shimadzu, Japan) keeping double distilled water as a blank.

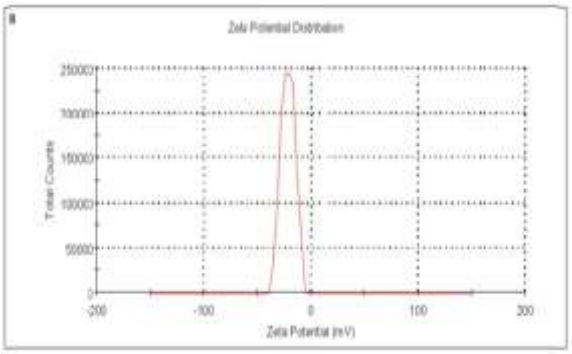

Figure 2: ZP curve of optimized ATV L-SMEDDS after dilution with double distilled water

Conductance

Type of microemulsion (o/w or w/o) can be determined by measure of conductance. It was measured by conductivity meter. The electro conductivity of the resultant system was measured by an electro conductometer (CM 180 conductivity meter, Elico, Mumbai, India). For the conductivity measurements, the tested microemulsions were prepared with a 0.01N aqueous solution of sodium chloride instead of distilled water.

Cloud Point Measurement

ATV SMEDDS was diluted with water in the ratio of 1:100, and the sample was placed in a water bath with the temperature increasing gradually, spectrophotometric analysis was carried out to measure % T of the sample.[20]

pH

pH of SMEDDS diluted with double distilled water were measured using pH meter

Characterization of ATV loaded SMEDDS Formulations (S-SMEDDS)

DSC Analysis

The physical state of ATV in S-SMEDDS was characterized by DSC (Shimadz, Japan). Thermograms of standard ATV powder, Aerosil 200, their physical mixture (PM) and S-SMEDDS were recorded in order to characterize the physical state of ATV. A heating rate of 10°C/min was employed in the range of 25-300°C with nitrogen atmosphere supplied at 40 ml/min. Each sample was taken (4-8 mg) in an aluminium pan, crimped and sealed. An empty aluminum pan was used as reference.

XRD Analysis

XRD diffracto grams of standard ATV powder, Aerosil 200, their PM and S-SMEDDS were obtained using Bruker AXS D8 Advance X-ray diffracto meter. Scans were performed between $5° < 2\theta < 80°$.

Morphology of L-SMEDDS and S-SMEDDS

The microstructure of micro-emulsions from L-SMEDDS and from S-SMEDDS was investigated by TEM (Tecnai 20 Philips).

For TEM analysis, L-SMEDDS and S- SMEDDS was diluted with double distilled water and a drop of it was placed on a carbon-coated copper grid (300 mesh, 3mm) and air dried. Morphological evaluation of S-SMEDDS was conducted through SEM (JSM 6380 LV, JEOL, Japan). For SEM analysis, the S-SMEDDS, Aerosil 200 and standard ATV were fixed on a brass stub using carbon double sided tape. The samples were then subjected to conductive coating with Au-Pd (80% - 20%). The SEM was operated at an acceleration voltage of 20 kV.

Dissolution Study

In vitro dissolution studies of L-SMEDDS, S-SMEDDS and MF containing 50 mg of ATV and 50 mg of standard ATV were performed in 1% SLS in water according to the United States Pharmacopeia (USP) using dissolution apparatus II (paddle method).[21] The dissolution medium used in this work was reported in the "Dissolution Methods for Drug Products" guide of Food and Drug Administration.

The experiments were performed on 900 ml media (1% SLS in water) at 37 ± 0.5 °C at a rotation speed of 50 rpm. At preselected time intervals, 5 ml samples were withdrawn and replaced with 5 ml of pre-thermo stated fresh dissolution medium. Samples were filtered through 0.1 µm syringe filter, the resulting filtrate was diluted with mobile phase and 20 µl was injected into the HPLC for analysis.

Dissolution tests were performed in triplicate. Graph of percent cumulative drug release vs. time was plotted.

Dissolution profiles were evaluated on the basis of dissolution efficiency (DE) and percentage of drug dissolved (DP) at 5 min and 60 min, time needed to dissolve 50% of drug (t50%), area under the curve (AUC) and mean dissolution time (MDT).

An add-in program (DD solver) for comparison of drug dissolution profiles was used to calculate different dissolution parameters.[22]

Assay

Optimized SMEDDS were analyzed to determine the content of ATV in SMEDDS. Systems were diluted as per method and amount of drug was determined by validated HPLC method.

PAMPA Study

The effective permeability (Pe) values for the standard ATV, MF L- and S-SMEDDS are reported in below Table 6. The L-and S-SMEDDS represents significant improvement in permeability than the MF in PAMPA model Standard ATV demonstrated the lowest permeability whereas L- and S-SMEDDS showed high **Pe** value. There was no significant difference observed between L- and S-SMEDDS. Thus, this is an indication that passive permeation of the drug has improved considerably on formulating into SMEDDS.

Morphology of SEDDS

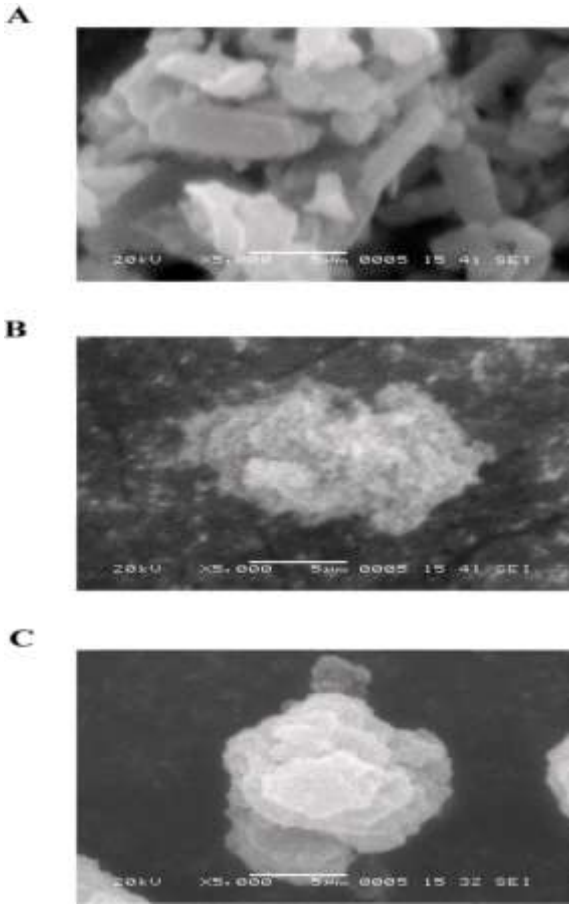

Figure 3: SEM images of (A) standard ATV (B) Aerosil 200 and (C) S-SMEDDS.

Table 6: Effective Permeability Values by PAMPA Study

	Effective permeability (Pe) ± S.D. (10^{-6} cm/s)
Standard ATV	15.92 ± 1.03
Marketed Formulation	16.74 ± 0.81
L-SMEDDS	21.36 ± 0.90
S-SMEDDS	19.98 ± 1.23

SUMMARY AND CONCLUSION

The purpose of this study was to develop an oral administrable SMEDDS of the poorly water soluble drug, ATV. Solubility evaluation, pseudoternary phase diagram and self-emulsification test were carried out to select excipients of SMEDDS. Composition of ATV loaded SMEDDS was optimized using factorial design. Optimal SMEDDS contains Triacetin as oil phase, span 20 as a surfactant and transcutol HP as co-surfactant, in the ratio of 25:50:25 %w/w, formulates SMEDDS with lower droplet size (31.4 nm), PDI (0.125), and ZP (-19.8 mV) values. The L-SMEDDS converted into S-SMEDDS using Aerosil 200 as a solid carrier. Both DSC measurements and X-ray diffraction analysis suggested that ATV in the S-SMEDDS may be in the molecular dispersion state. Following self-emulsification in water the droplet size distribution of the S-SMEDDS was nearly same to the L-SMEDDS, and the in vitro dissolution performance was similar for L- and S-SMEDDS both significantly higher than the Marketed Formulation.

The L- and S-SMEDDS were physically and chemically stable over 6 months. The *in vitro* transport study in PAMPA model demonstrated that L- and S-SMEDDS was successful in enhancing the permeation of ATV. The results of in situ absorption of ATV in rat intestine suggested that SMEDDS played an important role in absorption enhancing effect. Pharmacokinetic evaluation clearly showed that the ATV loaded L- and S-SMEDDS exhibited improved pharmacokinetic properties compared to the Marketed Formulation.

The oral bioavailability of ATV from S-SMEDDS was 2.16-fold higher than the Marketed Formulation and no significant difference compared with the L-SMEDDS. Our results illustrated the potential use of S-SMEDDS to dispense poorly water soluble drug by oral route.

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