FORMULATION AND *IN-VITRO* EVALUATION OF LIQUID AND SOLID SELF MICROEMULSIFYING DRUG DELIVERY SYSTEM OF PITAVASTATIN CALCIUM

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND *IN VITRO* EVALUATION OF LIQUID AND SOLID SELF MICRO EMULSIFYING DRUG DELIVERYSYSTEM OF PITAVASTATIN CALCIUM"** is a bonafide work done by **Ms. K. MAHALAKSHMI (Reg.No:261611302), Department of Pharmaceutics, College of Pharmacy, Madurai Medical College** in partial fulfillment of The Tamil Nadu Dr.M.G.R Medical University rules and regulations for award of **MASTER OF PHARMACY IN PHARMACEUTICS** under my guidance and supervision during the academic year 2017–2018.

Name & Signature of the Guide

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CONTENTS

ABBREVIATIONS

%	Percentage
˚C	Degree Celsius
λmax	Maximum wavelength
µm	Micrometer
µg	Microgram
Abs.	Absorbance
AR	Analytical reagent
BCS	Biopharmaceutical classification system
Conc.	Concentration
CDR	Cumulative drug release
Cm	Centimeter
cps	Centipoises
DSC	Differential scanning colorimetri
e.g.	Example
etc	Excetra
FDA	Food and drug administration
FTIR	Fourrier transfer infrared
g	Gram
GIT	Gastro intestinal tract
IP	Indian pharmacopoeia

Kg	kilogram
L	Liter
mg	Milligram
min	Minute
ml	Milliliter
mm	Millimeter
nm	Nanometer
ppm	Parts per million
PXRD	Powdered X-ray diffraction
RH	Relative humidity
rpm	Rotation per minute
SD	Standard deviation
SEDDS	Self Emulsifying Drug Delivery System
SMEDDS	Self Micro Emulsifying Drug Delivery System
SEM	Scanning Electron Microscopy
UV	Ultra Violet spectrophotometry

CHAPTER I

INTRODUCTION

CHAPTER - I

INTRODUCTION

Most of the drugs are administered through the oral route; it has always been preferred route for the formulators over other routes. But this route is limited to such drug molecules which has poor aqueous solubility, which is one of the important parameters to achieve desired concentration of drug in systemic circulation for desired (anticipated) pharmacological response. A large number of potential drug candidates suffer from low aqueous solubility and low dissolution rate. This leads to low drug concentration at the absorption site and results in low oral bio availability. In BCS classification system these poor solubility drugs are classified as BCS class II drugs.

Biopharmaceutical Classification System (BCS):

Biopharmaceutics Classification System (BCS) was introduced in 1995 as a basis for predicting the likelihood of *In vitro-In vivo* correlations for immediate release dosage forms. BCS has been used as a regulatory Tool for the replacement of certain bioequivalence (BE) studies with accurate in vitro dissolution tests. This step certainly reduces timelines in the drug development process, both directly and indirectly, and reduces unnecessary drug exposure in healthy volunteers.

The BCS also takes account of the dissolution of the drug product and hence covers the three main factors which govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage forms.

- Dissolution rate
- Solubility
- Permeability

Solubility:

Solubility is defined as the maximum amount of solute that can be dissolved in a given amount of solvent. Quantitatively it is defined as "the concentration of the solute in a saturated solution at a certain temperature. Qualitatively the solubility may be defined as an interaction of two or more substances to form homogenous molecular dispersion. Solubility of a drug plays a prime role in controlling its dissolution from dosage form. Aqueous solubility of a drug is a major factor which determines its dissolution rate.

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability:

In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on mass balance determination or in comparison to an intravenous reference dose (absolute bioavailability study).

TABLE: BCS classification

	solubility	**permeability**
Class I	High solubility	High permeability
Class II	Low solubility	High permeability
Class III	High solubility	Low permeability
Class IV	Low solubility	Low permeability

Class I Drugs

Class I drugs exhibit a high absorption and a high dissolution. The rate limiting step is drug dissolution. Gastric emptying rate becomes the rate determining step if dissolution is very rapid. Generally 85% drug is released within 15 min dissolution study. According to FDA (1997) guideline, bioavailability and bioequivalence studies are unnecessary for such products. IVIVC would not be expected for these drugs. Examples include amitriptyline hydrochloride, chloroquine phosphate, chlorpheniramine maleate, chlorpromazine hydrochloride, cloxacillin sodium, phenytoin sodium, prednisolone, promethazine, propranolol hydrochloride, quinine sulfate, verapamil hydrochloride and warfarin sodium etc (Kasim et al. 2004).

Class II Drugs

Class II drugs have a high absorption but a low dissolution rate. *In-vivo* drug dissolution is then a rate limiting step for absorption except at a very high dose number. These drug exhibited variable bioavailability and need the enhancement in dissolution for increasing the bioavailability. *In vitro- In vivo* correlation (IVIVC) is usually expected for class II drugs.

Examples include phenytoin. danazol, ketoconazole, mefenamic acid, nifedinpine. felodipine, nicardipine, nisoldipine, atorvastatin calcium, simvastatin, rosuvastatin calcium etc (Kasim et al. 2004).

Class III Drugs

Permeability is rate limiting step for drug absorption of class III drugs. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage for factors. These drugs are problematic for controlled release development. These drugs showed the low bioavailability and need enhancement in permeability.

Examples include cimitidine, ranitidine, acyclovir, alendronate, captopril, enalaprilat neomycin B, atenolol etc (Kasim et al. 2004).

Class IV Drugs

Class IV drugs exhibit poor and variable bioavailability. Several factors such as dissolution rate, permeability and gastric emptying are the rate limiting steps for the drug absorption. These drugs are not suitable for controlled release formulation. Examples include acetazolamide, allopurinol, dapsone, doxycycline, nalidixic acid, sulfadiazine, sulfamethoxazole, trimethoprim etc (Kasim et al. 2004).

So oral route is not advisable for these poorly soluble drugs, which may be inefficient to achieve desired drug concentration on the site of action due to its poor solubility and dissolution.

METHODS TO OVER COME SOLUBILITY PROBLEMS:

Different formulation approaches like micronization, solid dispersion, and complexation with cyclodextrins have come up for the oral bioavailability of poorly water soluble drugs. Indeed, in some selected cases, these approaches have been successful but they offer many other disadvantages. The main problem with micronization is chemical / thermal stability. Many drugs may degrade and lose bioactivity when they are micronized by conventional method. For solid dispersion the amount of carriers used is often large, and thus if the dose of active ingredient is high, the tablets or capsules formed will be large in volume and difficult to swallow. Moreover, since the carriers used are usually expensive and freeze-drying or spray-drying method requires particular facilities and processes, leading to high production cost. Though, traditional solvent method can be adopted instead, it is difficult to deal with co- precipitates with high viscosity. Complexation with cyclodextrins techniques is not applicable for drug substances which are not soluble in both aqueous and organic solvents.

In many cases oral bioavailability of poor water soluble drugs may be enhanced when co- administered with meal rich in fat has led to increasing recent interest in the formulation of poorly water soluble drugs in lipids. Lipid suspension, solutions and emulsions have all been used to enhance the oral bioavailability but, more recently there have been much focus on the utility of self-microemulsifying drug delivery systems (SMEDDS).

SELF DISPERSING LIPID FORMULATION SYSTEM:

Various delivery systems for the lipophilic drugs are available such as microemulsion, lipid solution, lipid emulsion, dry emulsion, whose formulation involve large number of possible combination of excipient, so to understand these lipid based formulation a classification namely " Lipid formulation classification system have been introduced by Pouton in 2000 and recently updated (2006).

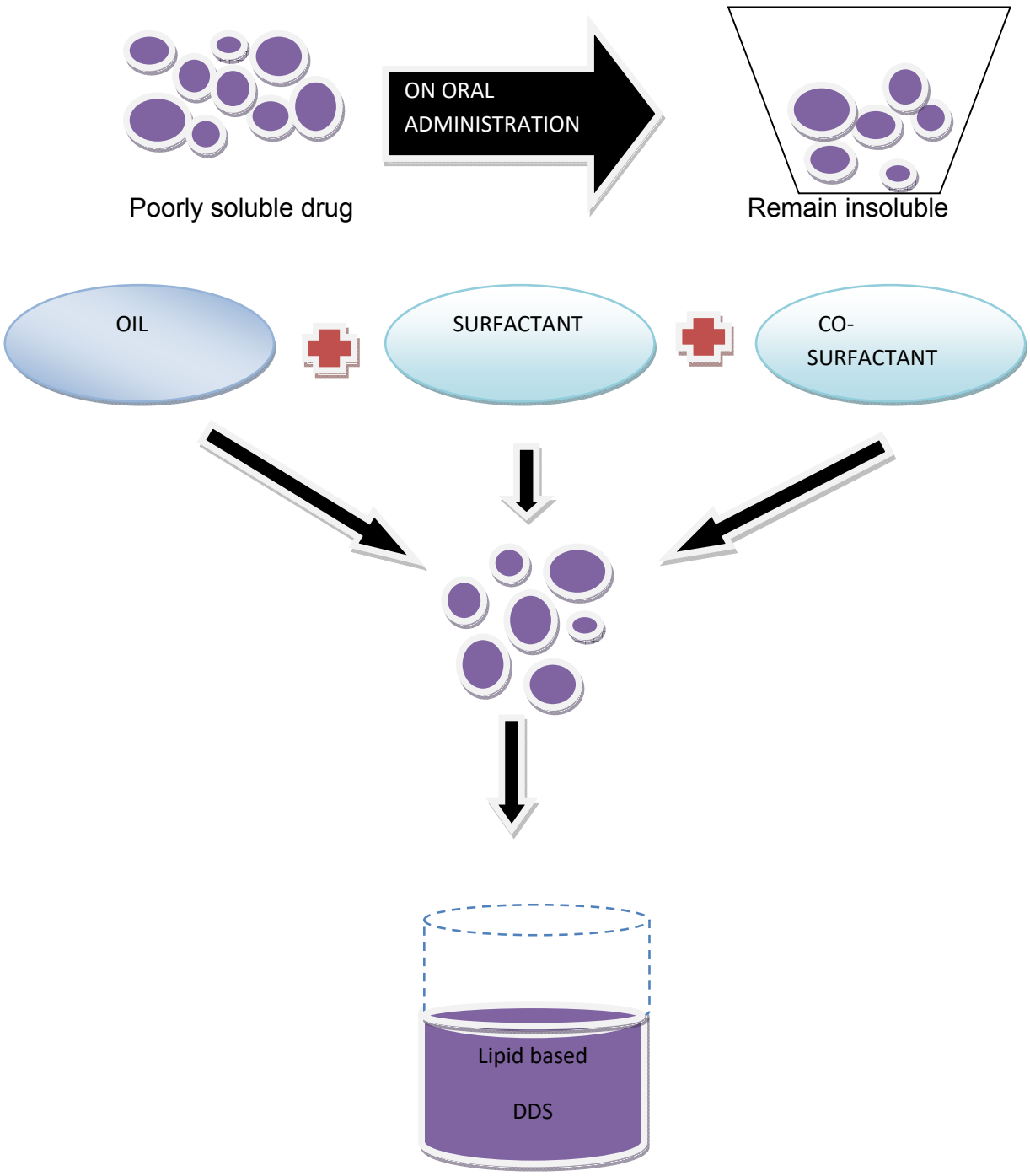


Figure: Diagramatic illustration of Lipid based formulation

Lipid formulation mainly comprises of

- Macro emulsion
- Micro emulsion
- Self micro emulsifying drug delivery system (SMEDDS).
- Solid –lipid nano particle(SLN),
- Liposomes and
- Lipolexes.

In recent years, much attention has been focused on lipid based formulation, with particular emphasis on SMEDDS.

Classification of lipid formulation system:

According to the composition and the effect of dilution and digestion on the ability to prevent precipitation of drug, lipid based formulations are broadly classified into four categories.

- Type I formulation
- Type II formulation
- Type III formulation, and
- Type IV formulation

Formulation type		Oil;tri,di &mono glycerides	Water-insoluble surfactants	Water-soluble surfactants	Hydrophilic cosolvents	Type of dispersion	Digestion requirement
Type I	oil	100	-	-	-	Limited or no dispersion	Requires digestion
Type II	SEDDS	40-80	20-60	-	-	Rapidly dispersing	Likely to be digested
Type III	III A SEDDS	40-80	-	20-40	0-40	Rapidly dispersing	Digestion may not be necessary
	III B SMEDDS	<20		20-50	20-50	Transparent dispersion	Digestion may not be necessary
Type IV	Oil free	-	0-20	30-80	0-50	Miscellar solution	Limited digestion

Type I systems consist of formulations which comprise drug in solution in triglycerides and/or mixed glycerides or in oil-in-water emulsion stabilized by low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. Generally, these systems exhibit poor initial aqueous dispersion and require digestion by pancreatic lipase/ co- lipase in the GIT to generate more amphiphilic lipid digestion products and promote drug transfer into the colloidal aqueous phase. Type I lipid formulations therefore represent a relatively simple formulation option for potent drugs or highly lipophilic compounds where drug solubility in oil is sufficient to allow incorporation of the required payload (dose).

Type II lipid formulations constitute SEDDS. Self-emulsification is generally obtained at surfactant contents above 25% (w/w). However at higher surfactant contents (greater than 50– 60% (w/w) depending on the materials) the progress of emulsification may be compromised by the formation of viscous liquid crystalline gels at the oil/water interface. Type II lipid- based formulations provide the advantage of overcoming the slow dissolution step typically observed with solid dosage forms and as described above generate large interfacial areas which in turn allows efficient partitioning of drug between the oil droplets and the aqueous phase from where absorption occurs.

Type III lipid-based formulations, commonly referred to as self-microemulsifying drug delivery systems (SMEDDS), are defined by the inclusion of hydrophilic surfactants (HLB>12) and co-solvents such as ethanol, propylene glycol and polyethylene glycol. Type III formulations can be further segregated (somewhat arbitrarily) into Type IIIA and Type IIIB formulations in order to identify more hydrophilic systems (Type IIIB) where the content of hydrophilic surfactants and co-solvents increases and the lipid content reduces. Type IIIB formulations typically achieve greater dispersion rates when compared with Type IIIA although the risk of drug precipitation on dispersion of the formulation is higher given the lower lipid content.

Type IV: In order to capture the recent trend towards formulations which contain predominantly hydrophilic surfactants and co-solvents, this category was recently added. Type IV formulations do not contain natural lipids and represent the most hydrophilic formulations. These formulations commonly offer increased drug payloads when compared to formulations containing simple glyceride lipids and also produce very fine dispersions when introduced in aqueous media. Little is known however, as to the solubilisation capacity of these systems *In vivo* and in particular whether they are equally capable of maintaining poorly water soluble drug in solution during passage along the GIT when compared with formulations comprising natural oils (Type II and Type III). An example of a Type IV formulation is the current capsule formulation of the HIV protease inhibitor amprenavir (Agenerase) which contains TPGS as a surfactant and PEG 400 and propylene glycol as co- solvents.

Self Micro Emulsifying Drug Delivery System (SMEDDS)

The self emulsifying drug delivery system (SEDDS), are well known for their potential as alternative approach for delivery of hydrophobic drugs, which are associated with poor water solubility and low oral bioavailability . SEDDSs are isotropic and thermodynamically stable solutions consisting of oil, surfactant, co-surfactant and drug mixtures that spontaneously form oil-in-water (o/w) emulsion when mixed with water under gentle stirring. The motility of stomach and intestine provides the agitation required for self- emulsification *in-vivo*. This spontaneous formation of an emulsion in the gastrointestinal tract presents the drug in a solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption . Apart from solubilization, the presence of lipid in the formulation further helps to improve bioavailability by enhancing the drug absorption. Selection of a suitable self-emulsifying formulation depends upon the assessment of the solubility of the drug in various components and the droplet size distribution of the resultant emulsion following self-emulsification. SEDDS are mostly prepared in liquid dosage form in soft and hard gelatin capsules. Solid SEDDS are new approach to make solid dosage form such as tablets, capsules etc.

Here it is essential to understand the differences between microemulsion and nano emulsions SMEDDS finally forms microelmulsion after oral administration. Micro emulsions are isotropic, thermodynamically stable systems composed of oil, water, surfactant and co-surfactants or co-solvents. The main driving force for microemulsion formation is the ultra low interfacial tension, which is usually achieved by the use of two or more emulsifiers (surfactant and co-surfactant). Out of the two emulsifiers used, one is essentially water soluble (surfactant) and the other one is oil soluble (co-surfactant).

Now a days SMEDDS has emerged as a vital strategy to formulate poor soluble compounds for bioavailability enhancement. However certain limitations are associated with SMEDDS formulations which include *in vivo* drug precipitation, formulation handling issues, limited lymphatic uptake, lack of predictive *in vitro* tests

and oxidation of unsaturated fatty acids. These limitations restrict their potential usage. Inclusion of polymers or precipitation inhibitors within lipid based formulations help to maintain drug super saturation after dispersion. This thereby, improves the bioavailability.

CHAPTER II

SELF MICRO EMULSIFYING DRUG DELIVERY- REVIEW

CHAPTER- II

SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM- REVIEW

Self Emulsifying Drug Delivery system (SMEDDS) is a new approach to improve the solubility of poorly soluble drugs. It can be ideally called as an isotropic mixture. Drugs which are lipophilic in nature can be formulated in this lipid based drug delivery system. SMEDDS improves solubility thereby increases dissolution rate and bioavailability of drugs. Drug, oil, surfactant, solvent and co-solvent are the components of SMEDDS. It forms small droplets due to agitation. The size of the droplet is 10- 100nm. Absorption of drug is improved by small droplets due to its ability to increase the interfacial surface area. In this system, the drug is dissolved in oil, solvent or surfactant .Co-solvents are used when required. Once it enters into the stomach it forms micro emulsion due to mild agitation. Agitation is caused by the digestive motility and intestine. SMEDDS is available as different dosage forms such as capsules, tablets, suppositories and topical preparations.

ADVANTAGES OF SMEDDS :

- Enhances oral bioavailability.
- Delivers peptides, protein.
- Available in both liquid and solid dosage form.
- Poorly water soluble drugs can be used.
- Improve patient compliance.
- The drug is protected by oil droplets.
- Drugs will not be affected by presence of food.
- Has reproducible drug absorption profile.
- Gives prolonged release due to use of appropriate Polymer.

Limitations Of SMEDDS :

- Lack of *in-vitro* models for evaluation.
- Dissolution test cannot be completely relied on, because this formulation depends on digestion.
- It causes GIT irritation due to the excess amount of Surfactant.
- Use of co-solvents can destroy the soft gelatin.

FACTORS AFFECTING SMEDDS

- **Dose of drug:** The drugs which have low solubility at high dose are not suitable for SMEDDS. The drugs required to administer at high dose should possess good solubility in the components used at least in oil phase.
- **Solubility of drug:** The drug should be highly soluble which influences its bioavailability. The incorporation of surfactants and co-surfactants at high concentration can cause risk of precipitation.
- **Polarity of lipid phase:** Release of drug is highly influenced by polarity of lipid phase. High polarity value increases the rate of release.
- **Droplet size and charge:** Smaller the droplet size and larger the surface area increases absorption and if the droplet is positively charged the drugs can penetrate into the physiological barrier in deep leads to improved bioavailability.

FORMULATION OF SMEDDS

The following should be considered in the formulation of SMEDDS.

- The solubility of the drug in different oil, surfactants and co-solvents
- The selection of oil, surfactant and co-surfactant based on the solubility of the drug
- Preparation of the phase diagram
- The preparation of SMEDDS formulation, by dissolving the drug in a mixture of oil, surfactant and co-surfactant.

COMPONENTS OF SMEDDS:

Self micro emulsification has been shown to be specific to

- The nature of the oil/surfactant pair.
- The surfactant concentration and oil/surfactant ratio.
- The temperature at which self emulsification occurs.

In support of these facts, it has also been demonstrated that only very specific pharmaceutical excipient combinations could lead to efficient self emulsifying systems.

Poorly water soluble drugs can be delivered orally by pre-dissolving the compounds in appropriate solvent and fill the formulation into capsules. The initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract can be overcome by this approach. The main problem is that the formulation may disperse in the GI tract which produces precipitation of drugs in the solution, It occurs mostly with hydrophilic solvents (e.g. polyethylene glycol). Occurrence of precipitation on dilution in the GIT can be avoided by dissolving the components in lipid vehicle. Water-soluble polymer can be used to aid solubility of the drug compound. For example, polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. Crystallisation of the polymer matrix due to thermodynamically stable state is one of the problems in this type of formulation that affects the physical stability of the product which can be studied by Differential scanning calorimetry or X-ray crystallography. SMEDDS are novel approach to enhance the solubility, bioavailability and protect the drug from gastric environment which gives better systemic absorption of drugs.

DRUG:

Lipophilicity and dose of the drug are the main criteria to be considered be considered before the development of SMEDDS formulation. Drugs which are administered at very high dose are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of

SMEDDS. Ideally drug should have low dose, log P≥ 2 and should not possess extensive first pass metabolism. High melting point drugs with log P values about 2 are poorly suited to SMEDDS. At the other end of the spectrum, lipophilic drugs with log P values greater than 5, are good candidates for SMEDDS.

OILS:

The oil represents one of the most important excipients in the self emulsifying formulations not only because it can solubilised marked amounts of the lipophilic drug or facilitate self emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self emulsifying formulations. Furthermore edible oils which could represent the logical and preferred lipid excipients choice for the development of SMEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification system with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SMEDDS formulation.

SURFACTANTS:

Several compounds exhibiting surfactant properties may be employed for the design of self emulsifying systems, but the choice is limited as very few surfactants are orally acceptable. The most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic –lipophilic balance (HLB). The most widely recommended ones being the non ionic surfactants

with a relatively high HLB value. the commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate (Tween 80). Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants. However these surfactants have a limited self emulsification capacity. Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SMEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. Surfactants are amphiphilic in nature and they can dissolve or solubilized relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS. (shukla Prachi et al. IRJP 2012,3(9)

CO-SURFACTANTS:

Co-surfactants ensures flexibility of the interfacial layer, i.e. it reduces the interfacial tension to a negative value. Co-surfactants form a flexible interfacial film in order to acquire different curvatures required to form micro emulsions over a wide range of compositions. Medium chain length alcohols (C3-C8) are commonly employed as co-surfactants. Organic solvents such as, ethanol, propylene glycol, and poly ethylene glycol are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. On the other hand alcohols have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SMEDDS leading to drug precipitation. Thus, alcohol free formulations have been designed, but their lipophilic drug dissolution ability may be limited.

MECHANISM OF SELF-EMULSIFICATION:

Self emulsification process occurs, when the entropy changes. The energy required to increase the surface area of the dispersion is smaller than

the dispersion. The free energy of conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation

$$\delta G = \Sigma N i \pi r i 2 \sigma$$

Where,

δG- is the free energy associated with the process (ignoring the free energy of mixing)

N- is the number of droplets of radius r

σ is the interfacial energy with time

The two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently, the free energy of the system. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets and hence, reduce the interfacial energy, as well as providing a barrier to coalescence.

In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously. Emulsification requires very little input energy, which involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing.

In earlier work it was suggested that the case of emulsification could be associated with the ease by which water penetrates into the various liquid crystal or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilisation of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilisation limit is reached close to the interface. Further aqueous penetration will result in the formation

of the dispersed liquid crystalline phase.

As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self emulsification process causes interface disruption and droplet formation. A combination of particle size analysis and low frequency dielectric spectroscopy was used to examine self-emulsifying properties of a series of Imwitor 742 (a mixture of mono and diglycerides of Caprylic acids/Tween 80) systems, which provided evidence that the formation of the emulsion may be associated with liquid crystal formation, although the relationship was clearly complex.

The presence of the drug may alter the emulsion characteristics, possibly by interacting with the liquid crystal phase. The droplet structure can pass from a reversed spherical droplet to a reversed rod-shaped droplet, hexagonal phase, lamellar phase, cubic phase or other structures until, after appropriate dilution, a spherical droplet will be formed again.

DOSAGE FORM DEVELOPMENT OF S-SMEDDS:

Various dosage forms of S-SMEDDS are

- Dry emulsions
- Self- emulsifying capsules
- Self –emulsifying sustained/controlled release tablets
- Self-emulsifying sustained/controlled pellets
- Self-emulsifying solid dispersions
- Self-emulsifying beads
- Self-emulsifying sustained release microspheres
- Self –emulsifying nanoparticles
- Self-emulsifying suppositories
- Self-emulsifying implant.

Self-emulsifying tablets:

Incorporation of lipid formulation into a solid dosage form combines the advantages of lipid-based drug delivery systems with those of solid dosage forms. Attama (2003) formulated a solid self-emulsifying formulation using goat fat and tween for the delivery of diclofenac. Fatty material was melted and mixed with surfactant and the drug incorporated into this mixture. This wet mass was poured into plastic molds and cooled to form a tablet. During the processing of this formulation it was observed that agitation during fabrication of tablets reduced the liquification time, resulting in faster emulsification. These results demonstrated that different formulation ratios possess varying dissolution profiles at constant speed/agitation, and the optimized formulation showed good release profiles with acceptable tablet properties.

Nazzal and Khan (2006), evaluated the effect of some parameters (colloidal silicates-X1, magnesium stearate mixing time X2, and compression force X3) on coenzyme Q10 (CoQ10) dissolution from tablets of eutectic based SMEFs. The optimized conditions (X1= 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face centred cubic design.

In order to significantly reduce the amount of solidifying excipients required for transformation of SEFs into solid dosage forms, gelled SEFs have been developed by Patil (2004). In this study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems. Colloidal silicon dio- xide served a dual purpose: (i) – reducing the amount of solidifying excipients required; and (ii) aiding in reducing drug release.

In a clinical study, it was found that SE tablets may be of use in reducing adverse effects (Schwarz, 2003). The incorporation of indomethacin (or other hydrophobic NSAIDs) in SE tablets was found to increase the penetration efficacy of the drug through the GI mucosal membranes, potentially reducing GI bleeding. The SEF in this study composed of glycerol monolaurate and Tyloxapol TM (a copolymer of alkyl phenol and formaldehyde). The tablets consistently maintained a higher active ingredient concentration in blood

plasma over the same time period compared with a non-emulsifying tablet.

Self-emulsifying powder formulation (SE powder formulation)

Arida *et al.* (2007) formulated an SE powder formulation in order to enhance the dissolution and absorption of the poorly water-soluble drug griseofulvin. Capmul GMO-50, poloxamer and myvacet were used as surfactants and co-surfactants. A significant enhancement in dissolution (without ultra-micronisation) and bioavailability of griseofulvin was observed.

Balakrishnan *et al.* (2009) developed a novel solid SEF of dexibuprofen using spray drying. Aerosil 200 was used as an inert solid carrier. Both i*n-vitro and in-vivo* studies were carried out. The optimization of the SEF composition was carried out by assessing solubility, prepa- ration of phase diagram, particle size analysis, drug release studies etc. The study showed that Labrafil M 1944 CS, Labrafil M 2125, Labrasol, Capryol 90 and Lauroglycol FCC could enhance the solubility of CoQ10 and provide the desired drug loading.

Self-emulsifying pellets (SE pellets)

Oral pellets are known to overcome the poor and variable GIT absorption of drugs and have shown the ability to reduce or eliminate the influence of food on bioavailability. Thus, it appears highly appealing to combine the advantages of pellets with those of SETs by formulating SE pellets. Kang *et al.* (2004) as part of their study to develop a self-emulsifying drug delivery system, have reported considerable differences in the solubility of simvastatin in a range of surfactants. The authors suggest that the properties of surfactants need to be considered when selecting them for the formulation of SE pellets.

Franceschinis *et al.* (2005) developed a new method for preparing self-emulsifying pellets by wet granulation consisting of a binder solution containing an oil (mono and diglycerides), polysorbate 80 and nimesulide as a model drug. The oil surfactant mixture was added to water to obtain binder solution. The prepared binder solutions were sprayed onto the granules (prepared from

microcrystalline cellulose and lactose) to give pellets. *In vivo* studies indicated significantly higher bioavailability with the prepared pellets in comparison to the corresponding emulsions.

Tuleu (2004) conducted a comparative bioavailability study of progesterone from SE pellet formulation, SE solution, capsule and an aqueous suspension in dogs. Complete drug release was seen within 30 min of capsule administration and within 5 min of administration of the self-emulsifying system. However, in the case of aqueous suspension the drug release was very low (~50% of the dose in 60 min). Plasma drug concentration was significantly higher when the drug was orally administered from self-emulsifying pellets and self-emulsifying solution when compared to aqueous suspension at the same dose.

Abdalla and Mader (2007) prepared three self- emulsifying pellet formulations by melting cithrol GMS (mono and diglycerides) and solutol HS 15. To this molten blend, the drug (diazepam) and dry microcrystalline cellulose (MCC) were added to obtain a suitable mass for extrusion. A dye was incorporated for assessment of self-emulsification and spin probe was added to assess the release kinetics and microenvironment of pellets. The results from the release study, with higher load of diazepam and lower volume of the dissolution media, indicated that the formulation was able to create and maintain a state of supersaturation for the poorly water-soluble diazepam. Nearly 90% of the drug was released within an hour while only 55% was released from the GMS/MCC pellets.

Wang *et al.* (2010) demonstrated that the extrusion/ spheronization technique is a large-scale production method for preparing solid SE pellets from the liquid SEF to improve oral absorption. SE pellets of a hydrophobic drug (nitrendipine) were prepared. Formulation stability and solubilisation capacity were noted. The system was optimized on the basis of equilibrium solubility, pseudo- ternary phase diagram and supersaturation studies. The liquid SEFs were solidified using adsorbents (porous silicon dioxide), MCC and lactose to form fine flowable powder. Crospovidone was added to the

formulation. The AUC of nitrendipine from the SE pellets was two-fold greater than the conventional tablets and was comparable with the liquid SEFs.

Controlled release self-emulsifying pellets

Serratoni and Newton (2007) observed that the release of methyl paraben (MP) and propyl parabens (PP) from pellet formulations could be controlled by incorporating them into self-emulsifying systems containing water soluble plasticiser and talc. Oil and surfactant were mixed and added to the damp mass of MCC and lactose mono- hydrate. Extrusion spheronization of the wet mass was carried out. The pellets obtained were initially coated with ethyl cellulose and subsequently with an aqueous solution of hydroxy propylmethyl cellulose in a fluid bed coater. Results obtained from the *in vitro* study revealed that the presence of self-emulsifying system enhanced drug release of MP and PP while the film coating considerably reduced the drug release from pellets.

Iosio *et al.* (2008) prepared two types of pellets containing vinpocetine (model insoluble drug) where Type I pellets contained a self-emulsifying system internally and an inert matrix externally, whereas Type II contained an inert matrix internally and a self-emulsifying system externally. Formulations were prepared in two steps. In the first step, the oil-surfactant mixture was added to water to form self-emulsifying systems whereas in the next stage this mixture was loaded onto MCC and lactose to form extrusion-spheronization mass for pellets. Results indicated that Type I pellets released 90% of vinpocetine within 30 min while the same quantity was released within 20 min from Type II pellets. The physical mixture of the excipients with drug was able to release around 25% of the drug in 60 min. Although both types of pellets demonstrated adequate morphological and technological characteristics, type II pellets showed better drug solubility and *in vivo* bioavailability. The above investigations suggest that a solid dosage form containing a self-emulsifying system is a promising approach for the formulation of drug compounds with poor aqueous solubility.

Self-emulsifying beads (SE beads)

Self-emulsifying beads can be formulated as a solid dosage form using smaller amounts of different excipients. Patil and Paradkar formulated an isotropic formulation of loratadine consisting of Captex 200, Cremophore EL and Capmul MCM. The SE mixture was loaded onto poly propylene beads (PPB) using the solvent evaporation method. Formulations were optimized for loading efficiency and *in vitro* drug release by evaluating their geometrical features such as bead size and pore architecture. Results indicated that the poly propylene beads are potential carriers for solidification of SE mixture, with sufficiently high SE mixture to PPB ratios for the solid form. The results indicated that self- emulsifying beads can be formulated as a solid dosage form with a minimal amount of solidifying agents.

Self-emulsifying sustained-release microspheres

You *et al*. (2006) prepared solid SE sustained-release microspheres of zedoary turmeric oil (oil phase) using the quasi-emulsion-solvent-diffusion method involving spherical crystallization. The release behaviour of zedoary turmeric oil from the formulation was found to be dependent upon the hydroxyl propyl methylcellulose acetate succinate to Aerosil 200 ratio. The plasma concentration time profiles after oral administration in rabbits showed a bioavailability of 135.6% compared with the conventional liquid SEFs.

Self-emulsifying implants (SE implants)

Research into SE implants has greatly increased the use and application of solid self-emulsifying formulation (S-SEF). Carmustine (BCNU) is a chemotherapeutic agent used to treat malignant brain tumours. However, its effectiveness is hindered by its short half life. In order to enhance its stability, the SEF of carmustine was formulated using tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glyceride). The self-emulsified BCNU was fabricated into wafers with a flat and smooth sur- face by compression moulding. The

release profile was compared with a wafer implant fabricated using poly (d, l-lactide-co-glycolide) acetic acid. It was found that SEF increased the *in vitro* half-life of BCNU to 130 min compared with 45 min with intact BCNU. The *in vitro* release of BCNU from self-emulsifying PLGA wafers was prolonged up to 7 days and was found to have higher *in vitro* anti-tumor activity (Chae *et al*., 2005).

Self-microemulsifying formulations

Self-micro emulsifying formulations (SMEFs) have attracted great attention recently. In an attempt to combine the advantages of SMEFs with those of solid dosage forms and overcome the shortcomings of liquid formulations, increasing attention has been focused on solid self-(micro) emulsifying formulations. The thermotropic stability of SMEFs and their high drug loading efficiency make them a promising system for low aqueous soluble drugs (Jannin *et al.,* 2007). SMEFs are usually placed in soft gelatin capsules, but can also be transformed into granules, pel- lets, powders for dry filled capsules or tablet preparations (Nazzal, Khan, 2006; Serratoni, Newton, 2007; Abdalla *et al.,* 2008; Tan *et al.,* 2009). The commercial success of the SMEF, Neoral® drew greater attention to the development of SMEFs. Many poorly water-soluble drugs such as acyclovir, atorvastatin, and fenofibrate have been reported to offer improved oral bioavailability by SMEFs (Wang *et al.,* 2006; Shen, Zhong, 2006; Patel, Vavia, 2007).

Postolache *et al.* (2002) compared the bioavailability of two cyclosporine capsule products with different pharmaceutical formulations. Results showed that the test cyclosporine non-SMEFs formulation was not bioequivalent to the cyclosporine SMEFs formulation due to a statistically significantly lower absorption rate. These authors demonstrated that the non-self microemulsifying capsules are not totally interchangeable with the self microemulsifying capsules unless validated clinical and laboratory conversion protocols for each kind of organ transplantation are enforced.

Catarzi *et al. (*2008) reported the comparative impact of Transcutol and Neusilin US2 on SMEFs. Results showed that the Neusilin- formulation resulted in hard tablets with a low tablet weight. However, Neusilin® tablets had similar disintegration times compare to Aeroperl (Evonik Degussa). The dissolution profile obtained from the tablets showed improved profile when compared to Glyburide alone. Zvonar *et al.* (2010) suggested that, SMEFs possessing a composition similar to microcapsules with Ca-pectinate shell and a drug loaded SMEFs as the core phase, would be a potential approach for enhancing low permeability and solubility of BCS class II drugs.

Self nanoemulsifying formulations (SNEFs)

The classical lipid nanoparticles that have been proposed for drug delivery are composed of solid lipids. A distinct advantage of SNEFs over polymeric nanoparticles is that the lipid matrix is made from physiologically tolerated lipid components, which decreases potential acute and chronic toxicity.

Nazzal *et al.* (2002) developed a SNEF based on the eutectic properties of ubiquinone (CoQ10) and also studied the progress of emulsion formation and drug release mechanisms by turbidimetry and droplet size analysis. Results obtained from study revealed that eutectic-based semisolid SEFs can overcome the drawbacks of the traditional emulsified systems such as low solubility and irreversible precipitation of the active drug in the vehicle with time.

Cyclosporine lipid nanoparticles (lipospheres) consisting of phospholipids, Span 80, Tween 80, Tricaprin, and Cremophor RH 40 were prepared (Bekerman *et al.,* 2004). The CsA dispersion systems prepared had a particle size ranging from 25 nm to 400 nm. Particles with a size of 25 nm showed maximum oral bioavailability.

In a study by Nepal *et al.*(2010), the surfactant–co-surfactant blend (Witepsol H35 and Solutol HS15) at a ratio of 1:4 led to sufficient reduction in

free energy of the system to resist thermodynamic instability of the nano-emulsion as well as providing a sufficient mechanical barrier to coalescence oil droplets.

Koynova *et al.* (2010) suggested the use of nano sized self-emulsifying lipid vesicles as carriers for the inclusion of lipophilic dietary supplements. These were proposed as good alternatives to liposomal preparations which pose problems in stability, sterilization, and non- reproducibility between batches.

Supersaturable self-emulsifying formulation

Supersaturation represents a potent technique for enhancing absorption by generating and maintaining a supersaturated state in the intestine. Such formulations contain both a reduced amount of surfactant(s) and a polymeric precipitation inhibitor (e.g., water-soluble cellulosic polymers, such as HPMC). These maintain a supersaturated state of the drug in the body. As the literature suggested, directly supersaturating a system with a drug during manufacture adds to the risk of recrystallization of the product. Various ways of inhibiting recrystallization have been identified. Thermodynamic "freezing" inside a polymer is one such option. Under storage conditions, the drug is mobilized by thermodynamic changes in the poly- meric structure. To avoid risk of direct supersaturation, several strategies can be employed, for example:

- Evaporation of a solvent from the system
- Activation of thermodynamically "frozen" drug- supersaturated islands by hydration.

However, attaining full knowledge of these processes, especially in a multi- component formulation, requires extensive research. Recently, Gao *et al.* (2008) investigated the mechanism responsible for the enhanced intestinal absorption of hydrophobic drugs from supersaturable SEFs containing HPMC. This effect could be attributed to enhanced permeation of drug to the enterocyte brush border region through the aqueous pathway by mimicking, or equilibrating with, the bile acid /bile acid mixed micelle pathway.

Techniques used to produce solid SMEDDS:

Various techniques have been employed to produce SMEDDS.

- **Spray drying:**

In this method, all the excipients are mixed together. The formulation is atomized into small droplets. The droplets are introduced into the drying chamber the temperature and airflow is maintained as per required. Further it can be prepared as capsules /tablets.

- **Adsorption onto solid carrier**

In this method the liquids are mixed with the excipients. The powdered mixture is filled into capsules or it can be formulated as tablets. The benefit of this technique is it ensures content uniformity.

- **Melt agglomeration:**

Powder agglomeration can be obtained by melt granulation. It is obtained by using binder which melts at low temperature.

- **Melt extrusion:**

It is a solvent free method. In this process, the raw material which has plastic properties converts into a product with uniform density and shape; it is obtained by forcing the raw material into a die. This process is carried out under controlled pressure, temperature and proper flow of product. The advantage of this method is high drug loading and content uniformity.

Limitations of SMEDDS:

Although SMEDDS formulations has several advantages, there are certain limitations associated with this system

1. Drug precipitation on dilution:

Diluted SMEDDS undergo precipitation of drug in gastro intestinal fluid. A common requirement for the lipid formulation is that they should be able to keep the drug in the solubilised form in the gastrointestinal tract. Precipitation of the drug from the system nullifies the advantage offered by the lipid based formulation system. The precipitation tendency of the drug on dilution is higher due to the dilution effect of the hydrophilic solvent. It thereby requires incorporation of polymers to minimize drug precipitation.

2. Encapsulation in soft gelatin capsules:

Most of the marketed SMEDDS formulations are available as soft gelatin capsule. However gelatin capsules are associated with few drawbacks. Manufacturing cost, transmissible spongiform encephalopathy (TSE) and consumer preference are the few issues associated with animal gelatin. Volatile co-solvents in self-micro emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs. These problem drive the market requirement to find substitute for soft gelatin capsules. The current alternative material of choice, to animal gelatin capsules are HPMC capsules. The HPMC capsule shell has been explored as an alternative approach for encapsulating supersaturable SMEDDS formulation.

3. Storage and handling:

Liquid SMEDDS exhibit problems in handling, storage and stability. Thus, formulating solid SMEDDS seems to be a logical solution to address these problems.

4. *Limited targeting to lymphatics:*

Targeting lymphatics confers two primary advantages over conventional absorption via the portal blood. First, transport through the intestinal lymph avoids pre-systemic hepatic metabolism and thereby enhances the concentration of orally administered drugs reaching the systemic circulation. Second, site-specific hepatic metabolism and thereby enhances the concentration of orally administered drugs reaching the systemic circulation. Second, site-specific drug delivery to lymphatic organs could be achieved. Normally high triglyceride solubility and high log P is required for lymphatic transport. However, the amount of drug transported into lymphatics is variable from drug to drug. Hence, lipophilicity and triglyceride solubility of drug in correlation with lymphatic transport needs to be completely understood and a more adequate predictive models is required

5. *Lack of good in vitro models:*

Another obstacle in the development of SMEDDS and other lipid-based formulations is the lack of good predicative *in vitro* models for the assessment of the formulations. Traditional dissolution methods do not work, as these formulations potentially are dependent on digestion of lipid in the gut, prior to release of the drug. Although to mimic this, an in vitro model simulating the digestive processes of the duodenum has been developed. This in vitro model needs further refinement and validation before its strength can be evaluated. Further development can be based on *in vitro- in vivo* correlations and therefore, different prototype lipid based formulations need to be developed and evaluated *in vivo* in a suitable animal model.

6. *Oxidation and polymorphism of the lipids used in formulation SMEDS:*

Lipid excipients containing unsaturated fatty acids and its derivatives are prone to lipid oxidation. This requires inclusion of lipid soluble antioxidant in capsule formation. Polymorphism associated with thermo-softening lipid

excipients requires specific process control in their application, in order to minimize polymorphic changes of the excipient matrix.

Handling and storage issues with liquid SMEDDS

SMEDDS are normally viscous liquids that are administered in hard or soft gelatin capsule. Lipid formulation may leach into and interact with the capsule shells. This may cause brittleness or softness of the capsule shell, leakage of the content and precipitation of the drug or excipients, especially at lower temperatures. To address these problems, several attempts have been made to transform liquid SMEDDS into solid SMEDDS dosage forms. These approaches combine the advantages of SMEDDS with those of solid dosage forms while overcoming the disadvantages of liquid SMEDDS. Formulating solid SMEDDS combine the advantages of SMEDDS with those of solid dosage forms, ie. Low production cost, convenience of process control, high stability, reproducibility, better patient compliance. Thus, the presentation of liquid SMEDDS in a solid dosage form provides more stable and robust dosage form with lower manufacturing costs.

CHAPTER III

LITERATURE REVIEW

CHAPTER - III

REVIEW OF LITERATURE

Tarkeshwar Prasad Shukla et al., (2017), were formulated Acetazolamide SMEDDS and evaluated. The optimized formula was selected to have the smallest mean particle size and the highest absolute Zeta potential, which should yield the formation of a stable emulsion. The *in vitro* dissolution indicated a significant improvement in Acetazolamide release characteristics. The preformulation study of drug was carried out initially in terms of physical appearance, melting point, solubility study, λ max determination (wavelength at maximum absorbance) solubility study, and results directed for the further course of formulation. The formulations were prepared with different ratios of oil, surfactant and co-surfactant. The SMEDDS were prepared and are evaluated in terms of droplet size, drug release etc. The system consist of Arachis Oil, Lutrol F-68, Triacetin & Propylene Glycol as oil phase, surfactant and co-surfactant respectively.NIP C1 & NIP C8 selected as optimized batches showed promising results. Zeta potential of NIP C8 indicates good stability. NIP C1 & NIP C8 showed Poly dispersity index below 0.3 which shows good uniformity in the droplet size distribution. Time of emulsification was under grade A (visual assessment criteria), thermodynamic stability testing & accelerated stability study was performed for optimized batches. In this study SMEDDS is a promising approach to improve the solubility, dissolution rate and bioavailability of Acetazolamide.

Yuxia Zhang et al., (2017), developed and evaluated colon-specific capsule with alginate beads containing a self-micro emulsifying drug delivery system (SMEDDS). The SMEDDS technique was used to improve the solubility of curcumin (Cur). After encapsulating the Curcumin -loaded SMEDDS, the alginate beads were placed inside an impermeable capsule body. A konjac glucomannan/lactose/hydroxypropyl methylcellulose (KG/Lac/ HPMC) plug tablet was then prepared and placed in the mouth of the capsule. The capsule demonstrated a pulsatile drug-release profile with a specific lag

time and subsequent sustained-release phase. The lag time was modified by changing the type of HPMC and the ratio of KG/Lac/HPMC. In addition, 0.5% b-mannase solution and 5% rat cecal solution were used to simulate the colon fluid, significantly decreasing the lag time of the capsule. The results show that the capsule has potential for use in colon-specific drug delivery and exhibits a sustained-release characteristic.

Pallavi Patharkar et al., (2016), were formulated and evaluated solid self emulsifying drug delivery system of Olmesartan Medoxomil by adsorption to solid carrier technique to improve the oral bioavailability of drug. The solubility of OLM was deterimiced in various vehicles kike oils, surfactants and co-surfactant. Pseudoternary phase diagrams were constructed to identify the efficient self emulsifying region. The system consists of Olmesartan, Acrysol k-150, Labrasol, Transcutol P as a drug, oil, surfactant and co-surfactant. The optimized liquid SMEDDS was transformed into a free flowing powder using Avicel or Aerosil 200 as the adsorbent. Prepared formulations were tested for microemulsifying properties and the resultant micro emulsions were evaluated for robustness to dilution, assessment of efficiency of self emulsification, emulsification time, turbidity measurement, viscosity, drug content and in-vitro dissolution. The physical state of the drug in solid self micro emulsifying powder was revealed by Differential Scanning Calorimetric and X-ray powder diffraction studies which indicated the presence of the drug was enhanced significantly from the SMEDDS formulations as compared to pure drug.

Karunakara reddy et al., (2016), formulated self micro emulsifying drug delivery system of atazanavir and evaluated for their properties and invitro release studies. Solubility of atazanavir was determined in various oils, surfactants, and co-surfactants. Pseudo ternary phase diagrams were constructed to determine the concentration range of oils, surfactant, and co-surfactant. The optimized formulation consists of castor oil as an oil phase, kolliphore RH as a surfactant and PEG 400 as a co-surfactant. The liquid SMEDDS formulations were prepared and evaluated for zeta potential, polydispersity index, % transmittance, drug content and invitro dissolution studies. Then the optimized liquid formulation (drug content -97.76%; drug

release-95.42%) was converted into free flowing powder using Neusilin US2. Then the solid SMEDDS were evaluated for drug content (97.89%). The solid SMEDDS showed better drug release than the pure drug of Atazanavir. So the SMEDDS approach may be useful for the enhancement of solubility of poorly water soluble compounds.

Xiaolin Bi et al., (2016), were developed a solid self-microemulsifying drug delivery system (S-SMEDDS to load the various active constituents of salvia (dried root of Salvia miltiorrhiza) which contains both lipophilic (e.g., tanshinone IIA, tanshinone I, cryptotanshinone and dihydrotanshinone I) and hydrophilic (e.g., danshensu and salvianolic acid B) constituents, into a single drug delivery system and improve their oral bioavailability. A prototype SMEDDS was designed using solubility studies and phase diagram construction, and characterized by self-emulsification performance, stability, morphology, droplet size, polydispersity index and zeta potential. Furthermore, the S-SMEDDS was prepared by dispersing liquid SMEDDS containing liposoluble extract into a solution containing aqueous extract and hydrophilic polymer, and then freeze-drying. *In vitro* release of tanshinone IIA, salvianolic acid B, cryptotanshinone and danshensu from the S-SMEDDS was examined; showing approximately 60%–80% of each active component was released from the S-SMEDDS *in vitro* within 20 min. In vivo bioavailability of these four constituents indicated that the S-SMEDDS showed superior in vivo oral absorption to a drug suspension after oral administration in rats. It can be concluded that the novel S-SMEDDS developed in this study increased the dissolution rate and improved the oral bioavailability of both lipophilic and hydrophilic constituents of salvia. Thus, the S-SMEDDS can be regarded as a promising new method by which to deliver salvia extract, and potentially other multicomponent drugs, by the oral route.

Nilesh mahadeo et al., (2016), were developed Liquid self micro emulsifying drug delivery system (L-SMEDDS) of Cefpodoxime proxetil (CFP) a poorly absorbable, high dose antibiotic having pH dependant solubility to overcome the problems associated with oral delivery. Solubility of CFP in various oils was determined to select the key components of SMEDDS.

Surfactants and co surfactants were screened and selected on the basis of their % transmittance. In this formulation Capmul MCM (650 mg of drug/1g of oil), Cremophore RH 40 (% T-90.12 %), Labrafil 2125 CS (% T-99.03%) were used as an oil, surfactant and co-surfactant respectively. Neusilin US2 was used as an adsorbing agent to convert optimized L-SMEDDS to Solid Self micro emulsifying drug delivery system (S-SMEDDS), which were then filled in hard gelatin capsule and evaluated further. The optimized L-SMEDDS shows Globule size 30-35 nm, Zeta potential -10 to -11 (negative ZETA POTENTIAL due to the presence of fatty acids in the structure of the excipients), Drug content 99.24±0.52 %. The S-SMEDDS shows acceptable flow properties, and Particle size of 33.40 nm, Polydispersibility index of 0.125, Zeta potential of -11.5 mv, Drug content of 98.32±0.14%. SEM studies showed that there is loss of crystalline structure of drug has been converted into amorphous state i.e completely solubilised in oil phase of L-SMEDDS and adsorbed on Neusilin US2 surface. FTIR studies confirmed that there is no drug- excipient interaction.

Bhalekar MR et al., (2016), formulated self micro emulsifying drug delivery system of Darunavir, an anti retroviral protease inhibitor to increase its solubility and bioavailability. The SMEDDS system compromising of Imwitor 988 as oil phase. Tween 20 and span 20 as binary surfactant system were optimized with respect to drug solubilization, particle size, zeta potential, dispersibility, optical clarity cloud point, in-vitro release and thermodynamic stability. SMEDDS system containing Imwitor 988 920%) and surfactant mix (Smix) (80%) showed maximum drug solubility with least particle size. The ex-vivo lymphatic uptake studies of Darunavir SMEDDS in presence of lymphatic uptake blocker showed 36. 69% drug permeation which increased to 64. 245 in absences of lymphatic blocker, indicating the drug transport by lymphatic path. C_{max} of Darunavir SMEDDS was higher than that of the marketed tablet. Pluronic f68 treated rats show lesser plasma concentration as compared to those administered with SMEDDS. The results suggest that SMEDDS is a promising drug delivery system to improve solubility and lymphatic transport of anti-HIV drug Darunavir.

Divya G. Shereker et al., (2016), were developed and evaluated Self-micro emulsifying drug delivery system (SMEDDS) of Ketoprofen, a widely prescribed analgesic drug which belongs to BCS class II and exhibit low and variable oral bioavailability due to its poor aqueous solubility. Solubility study, emulsification ability, ternary phase diagram and central composite design (CCD) were used as primary tools to select the components of the system and optimize the composition of liquid Ketoprofen SMEDDS. The globule size of optimized liquid SMEDDS was 105.08±5.16nm, zeta potential -4.23mV and polydispersity index 0.097, % Transmittance 98.45% and self emulsification time 28 sec. Optimized formulation F3 containing Oleic acid (10%), Tween 80 (30%) and Propylene glycol (60%) was adsorbed onto inert solid carrier Aerosil 200 in 1:1 ratio to form dry, free flowing powder. The liquid crystal phase viscosity increased significantly with increasing amount of aerosil 200 which in turn increase average globule size of solid SMEDDS (303.69±0.933nm) and slower the drug release. S-SMEDDS also characterized for DSC, XRD, SEM etc. The *in vitro* dissolution study indicates improved dissolution characteristics with higher percent drug release for solid SMEDDS (89.78%) compared to marketed preparation (81.26%) and pure drug (71.32%). In conclusion, S-SMEDDS for Ketoprofen holds promise to be developed as potential system for improved oral delivery.

Madhavi K et al., (2016), formulate solid self emulsifying drug delivery systems in order to improve the solubility of the highly lipophilic antihypertensive drug ramipril. The system was formulated by homogeneously mixing oils, surfactants and co-surfactants along with the drug component. Based on solubility studies Capmul PG8 NF, Gelucire 44/14 and Transcutol P were selected as oil, surfactant co-surfactant respectively in order to prepare liquid SMEDDS. Nine different liquid SMEDDS formulations were prepared and subjected to various evaluation tests in order to obtain optimized L-SMEDDS. Out of 9 different formulations S9 formulation was optimized as it formed thermodynamically stable emulsion without any drug precipitation and phase separation on storage and also showed least globule size (22.56 nm). The optimized formulation was loaded onto inert carrier (Sylysia FCP 350) to obtain S-SMEDDS, which shows acceptable flow properties. they were further

processed for solid state characterization such as XRD, DSC and SEM and the results confirmed the transformation of native crystalline nature of drug to an amorphous state. FTIR studies also confirmed no drug-excipient interaction. S-SMEDDS showed improved *invitro* dissolution behavior of Ramipril over that of pure drug.

Nilesh khutle et al., (2015), developed Self micro emulsifying drug delivery system of Pravastatin sodium (BCS Class III drug with high aqueous solubility and low permeability characteristics. The drug shows low absolute biovailability (approximately 17%) due to decreased permeability and high first pass extraction. So the study was designed to enhance the permeability characteristics of hydrophilic drugs and to protect them from hostile environment of gut. The solubility of Pravastatin sodium was determined to identify the oil phase of SMEDDS. Various surfactants and co-surfactants were screened for their ability to emulsify the selected oil. Pseudetenary phase diagrams were constructed to identify the efficient self-emulsifying region. The SMEDDS formulation was optimized by freeze thaw cycles, robustness to dilution and droplet size and zeta potential tests. The optimized L-SMEDDS formulation containing Pravastatin -10 mg, Capmul -100 mg, Cremophore RH 40 -66.66mg and Labrafil M 2125-33.33 mg was further evaluated by in-vitro and ex-vivo release studies. L-SMEDDS was further converted into T-SMEDDS by “Liquid loading technique”. T-SMEDDS of Pravastatin contained Neusilin, crosspovidone, magnesium stearate and L-SMEDDS loaded onto it. The results from both L-SMEDDS and T-SMEDDS suggest the potential use of SMEDDS to improve GI instability and intestinal permeability of BCS class III drug pravastatin

Kanav midha et al., (2015,) were formulate dispersible self microemulsifying (SMEDDS) tablet of atorvastatin for promoting its solubility and its oral bioavailability. The liquid SMEDDS were prepared by water titration method using oleic acid, Tween 80, and PEG 400 as oil, surfactant, and co-surfactant respectively. Then the L-SMEDDS were converted into solid SMEDDS by adsorption on solid carriers (Neusilin US2). The S-SMEDDS were blended with sodium starch glycolate (disintegrant) and tablet excipients

and compressed into tablets that were dispersible and self micro emulsifying in nature. All these formulations were assessed for various physicochemical parameters viz. weight variation, hardness, friability, disintegration test. *Invitro* studies of pure drug, SMEDDS, S-SMEDDS and dispersible SMEDDS tablets were carried out. Pure drug released only 29.84±0.16% up to 60 minutes and all the SMEDDS formulation released 100% of drug in comparatively lesser time. The optimized formulation containing 30% of oleic acid, 65% of tween 80 and 5% co-surfactant show the best results in *in vitro* studies. And FB1 (tablet) was considered to e the best since it release 100% drug in 35 mints and also has advantages over SMEDDS and S-SMEDDS in tms of stability and patient compliance.

Nilesh S. Kulkarni et al., (2015), developed rosuvastatin calcium-loaded self-nanoemulsifying powder for improved oral delivery of the drug. Solubility study was carried out in different oils, surfactants and co-surfactants. Based on the solubility study, liquid formulations were prepared using LAS/Capryol 90: Maisine 35-1 as oil phase and Tween 20 with Lutrol E400 as surfactant mixture (Smix). The liquid formulations were adsorbed onto Aerosil 200 in a ratio of 1: 0.25 % w/w to convert them into a solid form. The formulations were evaluated for globule size, zeta potential, and emulsion properties. Transmittance study, scanning electron microscopy, and in-vitro dissolution studies were carried out. Biochemical studies were carried out using a triton-induced hyperlipidemia model in Wistar rats. The developed formulations exhibited some desirable characteristics of self-emulsifying systems with nano-sized globules in the range 119.8 to 228.9 nm, rapid emulsification in approximately 60 s and transmittance of close to 100 %. In-vitro dissolution studies on the developed formulations indicate a 4-fold increase in drug release in 10 min, compared to the pure drug (ROC) while pharmacodynamic data showed significant improvement in oral bioavailability compared to the pure drug. the results concluded that the developed formulation containing the oils, LAS and combination of capryol 90 with Maisine 35-1, has the capability to improve the solubility and bioavailability of rosuvastatin calcium when formulated as a self-nanoemulsifying product.

Sujit Arun Desai et al., (2015), was formulated and liquid SMEDDS of Lovastatin and evaluated for its transparency, droplet size, zeta potential, viscosity, conductivity, percentage assay, and phase separation study. The micro emulsion produced by water titration method shows good particle size (95 nm). Refractive index and % transmittance showed good isotropic formulation. Solubilisation capacity of the system was also determined. An accelerated stability study of optimized system was carried out to check the stability of the formulation. The prepared micro emulsion was compared with the pure drug solution and commercially available Lovastatin tablet for in-vitro drug release. It revealed overall increase in release from micro emulsion (76.72%) compared to Lovastatin marketed tablet formulation (52.3%). Comparative oral absorption of Lovastatin from the micro emulsion and suspension of the commercially available Lovastatin was investigated through an in-vivo study in a rat model. FTIR studies revealed that there is no physical interaction between drug and excipients.

Anna Czajkowska-Kosnik et al., (2015), designed and characterized liquid and solid self-emulsifying drug delivery systems (SEDDS) for poorly soluble drug atorvastatin. To optimize the composition of liquid atorvastatin-SEDDS, solubility tests, pseudoternary phase diagrams, emulsification studies and other *in vitro* examinations (thermodynamic stability, droplet size and zeta potential analysis) were performed. Due to the disadvantages of liquid SEDDS (few choices for dosage forms, low stability and portability during the manufacturing process), attempts were also made to obtain solid SEDDS. Solid SEDDS were successfully obtained using the spray drying technique. Overall, the studies demonstrated the possibility of formulating liquid and solid SEEDS as promising carriers of atorvastatin. SEDDS, with their unique solubilization properties, provide the opportunity to deliver the lipophilic drugs to the gastrointestinal tract in a solubilized state, thus enhancing bioavailability of BCS class 2 drugs.

Vikas Bhandari et al., (2015), developed self emulsifying drug delivery system in liquid and then convert it into a pellet form that would result in improved solubility, dissolution and permeability of the poorly water

soluble drug carvedilol. Pellets were prepared using extrusion-spheronization technique incorporating liquid SEDDS (carvedilol, capmul MCM EP, cremophore EL, tween 20, propylene glycol), adsorbents (and crospovidone), microcrystalline cellulose and binder (povidone K-30). Ternary phase diagram was constructed to identify different oil-surfactant-cosurfactant mixtures according to the proportion of each point in it. The optimal CAR-SEDDS pellets showed a quicker redispersion with a droplet size of the reconstituted microemulsion being 160.47 nm, which was almost unchanged after solidification. SEM analysis confirmed good spherical appearance of solid pellets; DSC and XRD analysis confirmed that there was no crystalline carvedilol in the pellets. Pellets were then capable of transferring lipophilic compounds into the aqueous phase and significantly enhancing its release with respect to pure drug.

Vidyadhara. S et al., (2015), formulated and evaluated Rosuvastatin SMEEDS. The SMEDDS were prepared by simple admixing method using Capmul MCM and Capryol 90 as oils, Polaxomer 407 as surfactant and Transcutol HP and Soluphor P as co surfactants. The liquid SMEDDS were then converted into free flowing powder by adsorbing onto solid carrier magnesium aluminium silicate. Then the formulations were evaluated for particle size, phase separation, droplet size, drug content and for *in vitro* drug release. The FTIR and DSC analysis on optimized formulations revealed that there were no major interactions between drug and excipients. Among the prepared SMEEDS the formulations prepared with oil to co surfactant ratios of 1:3 shows highest rates of dissolution.

Krishna mohan chinnala et al., (2015), formulated Self micro emulsion of Furosemide which emulsify when exposed to the aqueous phase, and evaluated their properties and invitro release studies and determined whether they are able to improve oral bioavailability. Formulations from A to D, nonionic surfactant Tween 20 was used, and formulations E to H nonionic surfactant Cremophore RH 40 was used. From A-H Ethanol & oleic acid were used as co-surfactant and oil phase respectively. The minimal emulsification time was found with the formulations F(49sec), G (57sec), H (53sec) &D

(58sec). The highest emulsification time was found to be in the formulations A (1.23min). This may be due to the high viscosity of Tween 20. If the viscosity of the oil and co-surfactant used is also high or the content of Tween 20 is very high will lead to a low emulsification rate and the emulsification time will be greater.

Parul jaiswal et al., (2014), developed Self Micro Emulsifying drug delivery system of Telmisartan to overcome the problems of poor solubility and bioavailability. The formulation strategy included selection of oil phase based on saturated solubility studies and surfactant and co-surfactant screening on the basis of their emulsification ability. Ternary phase diagrams were constructed to identify the self-emulsifying region using a dilution method. The prepared formulations of SMEDDS were evaluated for their drug content, loading efficiency, morphology, globule size determination. Solid-SMEDDS were prepared by adsorption technique using microcrystalline cellulose (1% w/w) and were evaluated for micromeritic properties, scanning electron microscopy, differential scanning calorimetry, X-ray diffraction.The formulation containing om (20 mg), castor oil (30% w/w), tween 20 (55% w/w), propylene glycol (15% w/w) was concluded to be optimized. The optimized SMEDDS and solid-SMEDDS exhibited 100% *in vitro* drug release up to 120 min, which was significantly higher ($P < 0.05$, *t*-test) than that of the pure drug. Solid-SMEDDS may be considered as a better solid dosage form as solidified formulations are more ideal than liquid ones in terms of its stability. These results suggest the potential use of SMEDDS and solid-SMEDDS to improve the dissolution and hence oral bioavailability of poorly water-soluble drugs like telmisartan through oral route.

Ahmed A. Hussein et al., (2014), developed solid and liquid self-microemulsifying drug delivery system of poorly water soluble drug mebendazole using Aerosil 200 as solid carrier. Oleic acid, tween 80 and polypropylene glycol were selected as oil, surfactant and co-surfactant respectively and for preparation of stable SMEDDS, micro emulsion region was identified by using pseudo ternary phase diagram containing different proportion of surfactant: co- surfactant (1:1, 2:1 and 3:1), oil and water. In brief

S/ CoS mix means surfactant to co-surfactant and oil were mixed at ratio of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 manner. 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. Prepared optimised formula of microemulsion was evaluated for SEM, particle size analysis, polydispersity index, phase separation, viscosity determination, zeta potential, *in- vitro* dissolution study and *in- vivo* studies. The optimized microemulsion was converted into solid form by Spray Drying technique by using Aerosil 200 as solid carrier. Prepared SMEDDS was characterized for same parameters as that of microemulsion. Solid SMEDDS of mebendazole prepared using Aerosil 200 by spray drying technique showed good drug content uniformity. After reconstitution it formed microemulsion with micrometric range. *In-vitro* drug release and *in-vivo* plasma drug concentration of microemulsion and SMEDDS was much higher than that of marketed praparation. Hence lipid based drug delivery system may efficiently formulate microemulsion and which enhances dissolution rate and thus concomitantly bioavailability. In conclusion, self micro emulsifying drug delivery system has become promising tool to overcome bioavailability problems due to poor solubility.

Jawad akram et al., (2014), developed A self micro-emulsifying drug delivery system (SMEDDS) to enhance diffusion rate and oral bioavailability of Flurbiprofen. The solubility of Flurbiprofen was checked in different oils, surfactants, and co-surfactants and ternary phase diagrams were constructed to evaluate the micro-emulsion domain. The Flurbiprofen SMEDDS was prepared using Capmul MCM (oil), Tween 80 (surfactant), and polyethylene glycol 400 (co-surfactant). The particle size distribution, zeta potential, and polydispersity index were determined and found to be 12.3 nm, −0.746, and 0.138, respectively. Diffusion rate of Flurbiprofen was measured by In- Vitro dialysis bag method using phosphate buffer pH 6.8 as diffusion media. Developed high-performance liquid chromatography method was used to determine drug content in diffusion media. Oral bioavailability of Flurbiprofen SMEDDS was checked by using mice model. Results of diffusion rate and oral bioavailability of Flurbiprofen SMEDDS were compared with those of pure

drug solution and of marketed formulation. Diffusion of Flurbiprofen SMEDDS showed maximum drug release when compared to pure drug solution and marketed formulation. The area under curve and time showed significant improvement as the values obtained were 607ng h/mL and 1 h for SMEDDS in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase ($p<0.01$) in oral bioavailability of Flurbiprofen SMEDDS.

Yeole Monali et al., (2014) , developed a solid self-micro emulsifying drug delivery system (SMEDDS) of Racecadotril. Design of SMEDDS formulations helps to improve the oral absorption of highly lipophilic compounds. For formulation of stable SMEDDS, micro emulsion region was identified by constructing Pseudo ternary phase diagram for selected oil, surfactant, co-surfactant using water titration method. Stable SMEDDS was prepared in the ratio of 4:6 using combination of Capryol 90 and Captex 200 in the ratio of (1:1) as an oil, and Cremophore EL and Transcutol at the k_m value of 2:1. And the prepared liquid SMEDDS were evaluated for all parameters. Then the liquid SMEDDS were converted into solid SMEDDS using Aerosil 200 by adsorption technique. Prepared S-SMEDDS were evaluated for micromeretic properties, drug content, dispersibility test, self micro emulsification time, globule size, transparency test, *in vitro* drug release and *in vivo* study on male wistar albino rats. From the result it showed that drug released from S-SMEDDS formulations were found to be significantly higher as compared with that of pure drug and marketed formulation and from *in vivo* study it was found that S-SMEDDS showed lower frequency, stool volume and wet diarrheal drop as compared to L-SMEDDS, Plain drug and marketed formulation. Thus study concluded with S-SMEDDS provides useful solid dosage form to improve solubility and dissolution rate of Racecadotril and concomitantly bioavailability.

Maria Saifee et al., (2013), developed solid self micro emulsifying drug delivery system (S-SEDDS) with Aerosil 200 for enhancement of dissolution rate of model drug Glibenclamide (GBM). SEDDS was prepared using Capmul MCM C8TM, Cremophor RH 40TM, and Transcutol PTM as oil, surfactant and co-surfactant respectively. For formulation of stable SEDDS,

micro emulsion region was identified by constructing pseudo ternary phase diagram containing different proportion of surfactant: co-surfactant (1:1, 2:1 and 3:1), oil and water. Prepared SEDDS was evaluated for turbidity measurement, globule size and zeta potential, viscosity determination and % transmittance. S-SEDDS was prepared by adsorption technique using Aerosil 200 as solid carrier. Prepared S-SEDDS was evaluated for flow properties, drug content, and FTIR, SEM, DSC and in-vitro dissolution study. Results showed that prepared liquid SEDDS passed all evaluation tests. Globule size was found to be 142.8 nm with polydispersity index 0.396. S-SEDDS showed good flow property and drug content. From the experiment, it is clear that even after conversion of the liquid SEDDS into the solid one there was no significant alteration in the properties of solid SEDDS. *I*n-vitro dissolution studies showed that there was enhancement of dissolution rate of GBM as compared with that of plain drug and marketed formulation. From the results it is concluded that, Aerosil 200 can be used to develop S-SEDDS by adsorption technique to enhance dissolution rate of poorly water soluble model drug GBM.

Pranav V. Patel et al., (2013), developed and evaluated self micro emulsifying drug delivery system of Tacrolimus to enhance the poor solubility and bioavailability of tacrolimus. Solubility of the tacrolimus was estimated in various oils, surfactants, and co-surfactants. Various *in vitro* tests such as percentage transmittance, emulsification time, cloud point, precipitation, and thermodynamic stabilities were used to find out optimized formulations. Optimized liquid self micro-emulsifying (SMEDDS) were characterized by particle size analysis and converted in solid by using the Florite RE as an adsorbent, which is further characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM), X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FTIR), and particle size analysis. The optimized liquid SMEDDS formulation contained 10% Lauroglycol FCC as an oil, 60% Cremophor RH, and 30% PEG (polyethylene glycol) 400 as a surfactant and co-surfactant respectively. The optimized liquid and solid SMEDDS showed higher drug release than the marketed capsule and pure API (active pharmaceutical ingredient) powder. For optimized liquid SMEDDS

and solid SMEDDS, the globule sizes were found 113 nm and 209 nm respectively. The solid state characterization of solid-SMEDDS by SEM, DSC, FTIR, and XRD revealed the absence of crystalline tacrolimus in the solid-SMEDDS. Shelf-lives for liquid SMEDDS and solid SMEDDS were found to be 1.84 and 2.25 year respectively The results indicate that liquid SMEDDS and solid SMEDDS of tacrolimus, owing to nano-sized, have potential to enhance the absorption of the drug..

Hyma. P et al., (2013), developed self-microemulsifying drug delivery system (SMEDDS) of a poorly water soluble drug, pioglitazone. Phase solubility studies were conducted for the maximum solubility of pioglitazone. Highest was found in Tween 80 (surfactant) polyethylene glycol 400 (cosurfactant) and cottonseed oil. Ternary phase diagrams were constructed to evaluate microemulsion regions. FTIR analysis was done for investigating the drug–excipient interactions. The mean globule size of SMEDDS was observed to be below 200 nm for the optimized formulations and the zeta potential was negative. The dissolution of emulsion formulations was compared with commercial tablets; the results indicated that the rate of dissolution of developed formulations containing pioglitazone was 2 to 3 folds increased compared with that of commercial tablets. SEM studies were done for the shape and morphology of the globules. Thus, SMEDDS can be regarded as novel and commercially feasible alternative to the current pioglitazone formulations.

Smita S. Pimple et al., (2013), were developed Risperidone Self-micro emulsifying drug delivery system to enhance the solubility and dissolution of Risperidone, and evaluated for their potential. Primary tools used to select the components and to optimize the components of liquid SMEDDS were solubility study, emulsification ability ternary phase diagrams and central composite design (CCD). The liquid SMEDDS were formulated using Capryol m990 as oil, Cremophore EL and Transcutol Pas surfactant and co-surfactant. The liquid SMEDDS were evaluated for globule size, transmittance and self-emulsification time. Then the liquid SMEDDS converted into solid SMEDDS using Aerosil 200 by spray drying method. The SEM analysis, DSC, XRD

spectra reveal the presence of Risperidone in molecular state in solid SMEDDS. The *in vitro* dissolution study indicated improved dissolution characteristics with higher percent drug release for solid SMEDDS (92.30%) compared to marketed formulation(80.48%).

Bharat bhushan subudhi et al., (2013), developed self-micro emulsifying drug delivery system (SMEDDS) of Ibuprofen for investigating its intestinal transport behavior using the single-pass intestinal perfusion (SPIP) method in rat. Ibuprofen loaded SMEDDS (ISMEDDS) was developed and was characterized. The permeability behavior of Ibuprofen over three different concentrations (20, 30, and 40 µg/mL) was studied in each isolated region of rat intestine by SPIP method at a flow rate of 0.2 mL/min. The human intestinal permeability was predicted using the Lawrence compartment absorption and transit (CAT) model since effective permeability coefficients values for rat are highly correlated with those of human, and comparative intestinal permeability of Ibuprofen was carried out with plain drug suspension (PDS) and marketed formulation (MF). The developed ISMEDDS was stable, emulsified upon mild agitation with 44.4 nm ± 2.13 and 98.86% ± 1.21 as globule size and drug content, respectively. Higher in colon with no significant difference in jejunum, duodenum, and ileum was observed. The estimated human absorption of Ibuprofen for the SMEDDS was higher than that for PDS and MF. Developed ISMEDDS would possibly be advantageous in terms of minimized side effect, increased bioavailability, and hence the patient compliance.

Shailesh R. Prajapati et al., (2012), developed a self-microemulsifying drug delivery system (SMEDDS) of Olmesartan medoxomil (OLM) to enhance the oral absorption of OLM. The solubility of OLM in various oils, surfactants, and co-surfactants was determined. Pseudoternary phase diagrams were constructed using Acrysol EL 135, Tween 80, Transcutol P, and distilled water to identify the efficient self-microemulsification region. Prepared SMEDDS was further evaluated for its emulsification time, drug content, optical clarity, droplet size, zeta potential, *in vitro* dissolution, and *in vitro* and ex vivo drug diffusion study. The optimized formulation contained

OLM (20 mg), Tween 80 (33%v/v), Transcutol P (33%v/v), and Acrysol EL 135 (34%v/v) had shown the smallest particle size, maximum solubility, less emulsification time, good optical clarity, and *in vitro* release. The *in vitro*and ex vivo diffusion rate of the drug from the SMEDDS was significantly higher than that of the plain drug suspension. It was concluded that SMEDDS would be a promising drug delivery system for poorly water-soluble drugs by the oral route.

Arundhati Bhattacharyya et al., (2012), developed a self-emulsifying drug delivery system sss(SEDDS) of amphotericin B and evaluated the dissolution and permeability of amphotericin B from the formulation. The solubility of amphotericin B in various oils, surfactants and co-surfactants was determined. Various SMEDDS formulations were prepared with varying amounts of oil, surfactant and co-surfactant. Evaluation parameters for formulation optimization were drug content, self-emulsification, droplet size analysis, and precipitation studies. *In vitro* dissolution was studied in comparison to the pure drug. Permeability was studied using non-everted intestinal sac method. The optimized formulation consisted of glycerol mono-oleate (10%, w/w), tween 80 (36%, w/w), polyethylene glycol 400 (27%, w/w), and propylene glycol (27%, w/w) with a drug content of about 8 mg per ml. The self-emulsifying formulation showed 100% dissolution within 30 minutes whereas the pure drug exhibited a very poor rate of dissolution. *In vitro* intestinal permeability was studied by non-everted intestinal sac method using rat intestine. The self-emulsifying formulation showed 100% drug permeation within 30 minutes compared to negligible permeation from the drug suspension. The study was demonstrated that SMEDDS approach may be useful for enhancement of dissolution and intestinal permeation of amphotericin B belonging to class IV of Biopharmaceutic Classification System.

Shailesh T. Prajapati et al., (2012), were formulated and evaluated Self micro emulsifying drug delivery system (SMEDDS) of Olmesartan medoxomil (OLM) that has absolute bioavailability of only 26% due to the poor aqueous solubility (7.75 $\mu\mu$g/ml), to enhance the oral absorption of OLM. The solubility of OLM in various oils, surfactants, and cosurfactants was

determined. Pseudo ternary phase diagrams were constructed using Acrysol EL 135, Tween 80, Transcutol P, and distilled water to identify the effcient self-microemulsifcation region. Prepared SMEDDS was further evaluated for its emulsifcation time, drug content, optical clarity, droplet size, zeta potential, *in vitro* dissolution, and *in vitro* and ex vivo drug diffusion study. The optimized formulation S2 contained OLM (20 mg), Tween 80 (33%v/v), Transcutol P (33%v/v), and Acrysol EL 135 (34%v/v) had shown the smallest particle size, maximum solubility, less emulsifcation time, good optical clarity, and *in vitro* release. The *in vitro* and ex vivo diffusion rate of the drug from the SMEDDS was signifcantly higher than that of the plain drug suspension. It was concluded that SMEDDS would be a promising drug delivery system for poorly water-soluble drugs by the oral route.

Urvashi goyal et al., (2012), formulated Self-micro emulsifying drug delivery system (SMEDDS) of lovastatin to overcome the problems of poor solubility and bioavailability. The formulation strategy included selection of oil phase based on saturated solubility studies and surfactant and co-surfactant screening on the basis of their emulsification ability. Ternary phase diagrams were constructed to identify the self-emulsifying region. Capryol 90 (20 %) as oil, Cremophore RH40 (40 %) as surfactant and Transcutol P (40 %) as co-surfactant were concluded to be optimized components. The prepared SMEDDS was characterized through its droplet size, zeta potential, emulsification time, rheological determination and transmission electron microscopy. The optimized formulation exhibited 94 % *in vitro* drug release, which was significantly higher than that of the drug solution. In vivo studies using the Triton-induced hyperlipidemia model in Wistar rats revealed considerable reduction in lipid levels compared to pure lovastatin. The study confirmed the potential of lovastatin SMEDDS for oral administrations.

Suryakanta Swain et al., (2012), developed and evaluated novel solid self-nano emulsifying drug delivery systems (S-SNEDDS) of valsartan with improved oral bioavailability, and evaluated their *in vitro* and in vivo performance. Preliminary solubility studies were carried out and pseudoternary phase diagrams were constructed using blends of oils (Capmul

MCM), surfactant (Labrasol), and co-surfactant (Tween 20). The SNEDDS were systemically optimized by response surface methodology employing methodology employing 3^2 Box- Behnken design. The prepard SNEDDS were characterized for viscosity refractive index, globule size, zeta potential, and TEM. Optimized liquid SNEEDS were formulated into free flowing granules by adsorption on the porous carriers like Aerosil 200, Sylysia (350) and Neusilin US2, and compressed into tablets. *In vitro* dissolution studies of S-SNEDDS revealed that 3 to 3.5 fold increased in dissolution rate of the drug due to enhanced solubility. *In vivo* pharmacodynamic studies in wistar rats showed significant reduction in mean systolic BP by S-SNEDDS via oral suspension (p<0;05)owing to the drug absorption through lymphatic pathways. Solid-state characterization of S-SNEDDS using FT- IR and powder XRD studies confirmed lack of any significant interaction of drug with lipidic excipients and porous carriers. Further, the accelerated stability studies for 6 month revealed that S-SNEDDS are found to be stable without any change in physiochemical properties. Thus the present studies demonstrated the bio availability enhancement potential of porous carriers based S-SNEDDS for a BCS class II drug, valsartan.

Rohit ramesh shah et al., (2012), developed self-micro emulsifying drug delivery system (SMEDDS) to enhance the oral absorption of the poorly water-soluble drug, Efavirenz. The influence of the oil, surfactant and co-surfactant types on the drug solubility and their ratios on forming efficient and stable SMEDDS were investigated in detail. The SMEDDS were characterized by morphological observation, droplet size and zeta potential determination, freeze thawing and *in vitro* release study. The optimum formulation consisted of 45% Acconon MC-8 EP, 26.66% Cremophor EL and 13.33% Polyethylene glycol 400. *In vitro* release test showed a complete release of Efavirenz from SMEDDS in an approximately 4 h. The absorption of Efavirenz from SMEDDS showed increase in absorption compared with that of the marketed formulation. This study demonstrated the promising use of SMEDDS for the delivery of Efavirenz by the oral route.

Dhivyakumar bora et al., (2012), formulated self microemulsifying drug delivery system (SMEDDS) of Atorvastatin (BCS class II),which is very

slightly soluble in water. The solubility of atorvastatin in individual microemulsion components viz. oil and surfactants was determined. The surfactants were screened for emulsification ability. Based on the solubility determinations and emulsification properties sunflower oil and surfactants cremophor RH 40 and capmul MCM C8 were selected for further study. The solubility of atorvastatin in different ratios of selected oil and surfactants was determined. The composition of oil:surfactants with maximum solubility for atorvastatin was used for SMEDDS formulation. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsions. The microemulsions were evaluated for emulsion droplet size, self emulsification and phase separation, *In vitro* dissolution and stability. The SMEDDS formulation showed complete release in 30 min. as compared with the plain drug, which showed a limited dissolution rate. Thus the study demonstrated that SMEDDS is a promising drug delivery system to enhance the bioavailability of poorly water soluble drugs.

Solanki S et al., (2012), enhanced the dissolution rate and bioavailability of Ampelopsin, one of the most common flavonoids by developing microemulsion. Capmul MCM-based ME formulation with Cremophor EL as surfactant and Transcutol as cosurfactant was developed for oral delivery of ampelopsin. The optimised microemulsion formulation containing ampelopsin, Capmul MCM (5.5%), Cremophor EL (25%), Transcutol P (8.5%), and distilled water showed higher *in vitro* drug release, as compared to plain drug suspension and the suspension of commercially available tablet. These results demonstrate the potential use of ME for improving the bioavailability of poor water soluble compounds, such as ampelopsin[1].

Gundogdu E et al., (2012), formulated imatinib (IM) loaded to oral water-in-oil (w/o) microemulsions as an alternative formulation for cancer therapy and evaluated the cytotoxic effect of microemulsions Caco-2 and MCF-7. Moreover, permeability studies were also performed with Caco-2 cells. According to cytotoxicity studies, all formulations did not exert a cytotoxic effect on Caco-2 cells. The permeability studies of IM across Caco-2

cells showed that permeability value from apical to basolateral was higher than permeability value of other formulations. In conclusion, the microemulsion formulations as a drug carrier, especially M3IM formulation, may be used as an effective alternative breast cancer therapy for oral delivery of Imatinib.

Ramesh jakki et al., (2012), prepared a self-micro emulsifying drug delivery system (SMEDDS) for enhan- cement of oral bioavailability of domperidone, a poorly water soluble drug. The solubility of the drug was determined in various vehicles. A pseudo ternary phase diagram was constructed to identify the self-micro emulsification region. The *in vitro* self-micro emulsification properties and droplet size analysis of SMEDDS were studied following their addition to water under mild agitation. Further, the resultant formulations were investigated for clarity, phase separation, globule size, effect of pH and dilutions (1:100, 1:500, 1:1000) and freeze-thaw stability. The optimized formulation of SMEDDS used for *in vitro* dissolution and bioavailability assessment, contained oil (Labrafac CC, 25 %, *m/m*), surfactant (Tween 80, 55 %, *m/m*), and co-surfactant (Transcutol, 20 %, *m/m*). The preliminary oral bio- availability of domperidone from SMEDDS was 1.92-fold higher compared to that of domperidone suspension in rats. The results suggested a significant increase ($p < 0.05$) in oral bioavailability of domperidone from SMEDDSS than that of the conventional formulation.

Du H et al., (2012), reform the dosage forms of andrographolide to improve its aqueous solubility and oral bioavailability. A formulation of O/W microemulsion consisting of an oil phase of isopropyl myristate, a surfactant phase of Tween 80, a co-surfactant of alcohol, and water was found to be ideal, with mean droplet size of 15.9 nm, a high capacity of solubilisation for andrographolide. Such an andrographolide-loaded microemulsion was stable by monitoring the time, temperature and gravity-dependent change, and had a much better anti-inflammatory effect and a higher biological availability than andrographolide tablets.

Park JH et al., (2011), investigated the effects of silymarin, on oral bioavailability of paclitaxel in rats, and to compare pharmacokinetic parameters of paclitaxel between a commercial formulation of paclitaxel and a paclitaxel microemulsion. Oral bioavailability of paclitaxel in a Taxol® formulation was enhanced in the combination with silymarin. In particular, the mean maximum plasma concentration and the mean area under the plasma concentration-time curve of paclitaxel in the formulation were significantly increased 3- fold and 5-fold compared with control, respectively, following oral co-administration with 10mg/kg of silymarin ($p<0.01$). When the paclitaxel microemulsion was co-administered with silymarin orally, it caused a maximum increase in the absolute bioavailability of paclitaxel.

Hetal thaker et al., (2011), formulated and evaluated Raloxifene self micro emulsifying drug delivery system. Raloxifene is a second generation selective estrogen receptor modulator used to prevent osteoporosis in postmenopausal women. The bioavailability of drug is only 2% because of extensive hepatic first pass metabolism. The SMEDDS were prepared by employing dimple admixing method using Capmul MCM C8, Tween 20 and akrysol K140 and PEG 200. The concentration range of surfactant and co-surfactant was choose by constructing Pseudo ternary phase diagram. The prepared formulations were characterized for drug loading, size, transparency, zeta potential and *in vitro* intestinal permeability. The results indicated that high drug loading, optimum size and desired zeta potential was achieved. The TEM studies indicated the absence of aggregation. The *in vitro* permeability results showed that the permeation of the drug from the self micro emulsion was significantly higher than that obtained from the drug dispersion and marketed formulation.

Sajal Kumar Jha et al., (2011), developed an oral microemulsion formulation for enhancing the bioavailability of famotidine is a BCS class III drugs which are known to have high solubility but low permeability. An Olive oil based microemulsion formulation with Tween 80 as surfactant and PEG 400 as cosurfactant was developed for oral delivery of famotidine. A single isotropic region, which was considered to be a bicontinuous microemulsion, was found in the pseudoternary phase diagrams developed at various

Tween80: PEG 400: oil ratios. The microemulsion system was also investigated in terms of other characteristics, such as viscosity, pH, conductivity, clarity, particle size, *in vitro* drug release, *in vitro* intestinal permeability study compared to the plain drug solution (64.18%). The developed microemulsion system improved the permeability (93.43%) by increasing the lipophillicity due to the oil phase and also by destabilizing the membrane stability due the surfactants and may be used as an enhanced delivery of BCS class III drugs.

M. Nagaraju Patro et al., (2010), developed a stable self micro emulsifying drug delivery system (SMEDDS) of valproic acid (VPA) and evaluated its *in vitro* potential. The solubility of VPA was determined in various vehicles. Pseudo ternary phase diagrams were used to evaluate the micro emulsification existence area and the release rate of VPA was investigated using a dissolution method. SMEDDS were characterized for clarity, precipitation and particle size distribution. Formulation development and screening was done based on results of solubility from phase diagram. The optimized formulation used for *in vitro* dissolution was composed of castor oil (38.4 %), Cremaphor RH 40 (42.4 %), PEG 400 (14.4 %). The SMEDDS formulation showed complete release in 15 min. as compared with the plain drug and conventional marketed formulation which showed a limited dissolution rate. VPA loaded SMEDDS were subjected to various conditions of storage as per ICH guidelines for 3 months. VPA SMEDDS successfully withstood the stability testing. It has been found that dissolution profile of valproic acid from SMEDDS was much improved than valproic acid.

Maulik J.Patel et al., (2010), developed Self-micro emulsifying drug delivery system (SMEDDS) of Lovastatin to increase the solubility and oral bioavailability of Lovastatin. To formulate the SMEDDS, solubility study was performed in different excipients and the excipients are selected based on the solubility of lovastatin. Microemulsion region was decided by preparing ternary phase diagram. Drug excipients interaction was demonstrated by performing DSC and FTIR studies. After preliminary study, SMEDDS were formulated using sunflower oil, Acrsol K 140, Capmul MCM C8, and PEG 400 as oil, surfactant, co-surfactant and co-solvent respectively. The SMEDDS were

prepared by simple admixing method. The prepared SMEDDS were evaluated for macroscopic evaluation visal assessments, self emulsification, transmittance test, droplet size, zeta potential and stability study, *in vitro* dissolution. The droplet size was found to be 18 t0 24 nm. Drug release was found to be up to 92% in one hour. Release data was compare with marketed product. It showed that the release from the SMEDDS was better than that of the marketed formulation. It was concluded that the SMEDDS is a promising drug delivery for enhancing oral bioavailability of poorly soluble drugs.

Jill B. Shukla et al., (2010), formulated Self micro emulsifying drug delivery system (SMEDDS) of Candesartan cilexetil and evaluated it's *in vitro* and *in vivo* potential. The solubility of Candesartun cilexetil was determined in various vehicles. Pseudo ternary phase diagrams were used to evaluate the micro emulsification existence area, and the release rate of Candesartann cilexetil was investigated by using *in vitro* dissolution studies. Formulation development and screening was done by the results obtained from the phase diagrams. The optimized formulation was composed of Transcutol P as an oil, Capryol 90 as surfactant and plurol oleique as co-surfactant. And this was evaluated for various parameters the SMEDDS formulation showed complete release in 60 minutes. Thus the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of Candesartan cilexetil to improve its bioavailability.

Cui J et al., (2009), prepared a self-microemulsifying drug delivery system to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened via solubility studies of curcumin and compatibility tests. The optimal formulation of SMEDDS was comprised of 57.5% surfactant, 30.0% co- surfactant and 12.5% oil (ethyl oleate). The solubility of curcumin (21 mg/g) significantly increased in SMEDDS. The average particle size of SMEDDS-containing curcumin was about 21 nm when diluted in water. No significant variations in particle size and curcumin content in SMEDDS were observed over a period of 3 months at 4 degrees C. The results of oral absorption experiment in mice showed that SMEDDS could significantly increase the oral absorption of curcumin compared with its suspension.

Mandawgadea SD et al., (2008) has investigated SMEDDS of β-Artemether (BAM) using a novel, indigenous natural lipophile (N-LCT) as an oily phase. SMEDDS based on N-LCT and commercially available modified oil (capryol90) was formulated. Comparative *in vivo* anti-malarial performance of the developed SMEDDS was evaluated against the (Larither) in Swiss male mice infected with lethal ANKA strain of Plasmodium berghei. Both the BAM–SMEDDS showed excellent self- microemulsification efficiency and released >98% of the drug in just 15 min whereas Larither showed only 46% drug release at the end of 1h. The anti-malarial studies revealed that BAM–SMEDDS resulted in significant improvement in the anti-malarial activity ($P < 0.05$) as compared to that of (Larither) and BAM solubilized in the oily phases and surfactant.

Ying chen et al (2008), formulated and evaluated self-microemulsifying drug delivery system (SMEDDS of vinpocetine (VIP), a poor water-soluble drug) to increase the solubility, dissolution rate and oral bioavailability. The formulations of VIP-SMEDDS were optimized by solubility assay, compatibility tests, and pseudo-ternary phase diagrams analysis. The optimal ratio in the formulation of SMEDDS was found to be Labrafac : oleic acid : Cremophor EL : Transcutol P=40 : 10 : 40 : 10 (w/w). The average particle diameter of VIP was less than 50 nm. *In vitro* dissolution study indicated that the dialysis method in reverse was better than the ultra filtration method and the dialysis method in simulating the drug *in vivo* environment. Comparing with VIP crude drug power and commercial tablets, (−) VIP-SMEDDS caused a 3.4- and 2.9-fold increase in the percent of accumulated dissolution at 3 h. Further study on the absorption property of VIP-SMEDDS employing *in situ* intestine of rats demonstrated that VIP in SMEDDS could be well-absorbed in general intestinal tract without specific absorption sites. In addition, the developed SMEDDS formulations significantly improved the oral bioavailability of VIP in rats. Relative bioavailability of (−) VIP-SMEDDS and (+) VIP-SMEDDS increased by 1.85- and 1.91-fold, respectively, in relative of VIP crude powder suspension. The mechanisms of enhanced bioavailability of VIP might contribute to the improved release, enhanced lymphatic transport, and increased intestinal permeability of the drug.

Ashok R. Patel et al., (2007), developed SMEDDS (self-microemulsifying drug delivery system) of fenofibrate and evaluated its *in vitro* and in vivo potential. The solubility of fenofibrate was determined in various vehicles. Pseudoternary phase diagrams were used to evaluate the microemulsification existence area, and the release rate of fenofibrate was investi- gated using an *in vitro* dissolution test. SMEDDS formulations were tested for microemulsifying properties, and the resultant microemulsions were evaluated for clarity, precipitation, and particle size distribution. Formulation development and screening was done based on results obtained from phase diagrams and characteristics of resultant microemulsions. The optimized formulation was composed of Labrafac CM10 (31.5%), Tween 80 (47.3%), and polyethylene glycol 400 (12.7%). The SMEDDS formulation showed complete release in 15 min-utes as compared with the plain drug, which showed a limited dissolution rate. Comparative pharmacodynamic evaluation was investigated in terms of lipid-lowering efficacy, using a Triton-induced hypercholesterolemia model in rats. The SMEDDS formulation significantly reduced serum lipid levels in phases I and II of the Triton test, as compared with plain fenofibrate. The optimized formulation was then subjected to stability studies and was found to be stable over 12 months. Thus, the study confirmed that the SMEDDS formulation can be used as a possible alternative to traditional oral formulations of fenofibrate to improve its bioavailability

Ghosh PK et al., (2006), developed microemulsion system of Acyclovir for improvement of oral bioavailability. A labrafac-based microemulsion formulation with labrasol as surfactant and plurol oleique as co-surfactant was developed for oral delivery of Acyclovir. With the increase of labrasol concentration, the microemulsion region area and the amount of water and labrafac solubilized into the microemulsion system increased; however, the increase of plurol oleique percentage produced opposite effects. Acyclovir, a poorly soluble drug, displayed high solubility in a microemulsion formulation using labrafac (10%), labrasol (32%), plurol oleique (8%), and water (50%). The *in vitro* intraduodenal diffusion and *in vivo* study revealed an increase of bioavailability (12.78 times) after oral administration of the microemulsion formulation as compared with the commercially available tablets.

CHAPTER IV

AIM OF THE WORK

CHAPTER - IV

AIM OF THE WORK

Most of the New Chemical Entities (NCE) that are being discovered are lipophillic in nature and have poor aqueous solubility, thereby posing problems in their formulation into delivery systems. Because of their low aqueous solubility and low permeability, dissolution and/or release rate from the delivery system forms the rate-limiting step in their absorption and systemic availability. More than 60% of potential drug products suffer from poor water solubility. For the therapeutic delivery of such drugs, having poor aqueous solubility, number of technologies had been developed like solid dispersions, cyclodextrins, micronization, nano particles, permeation enhancer, etc.

Although some approaches are available for enhancing the dissolution of poorly soluble drugs, but has certain drawbacks like low drug loading and large dose.

Pitavastatin as a synthetic lipid lowering agent is an inhibitor of 3-hydroxy-3-methyl-glutaryl-co-enzyme A (HMGCoA) reductase which catalyzes the conversion of HMGCoA to mevalonate an early rate -limiting step in choloesterol biosynthesis;this then results in a compensatory incresase in the expression of LDL receptors on hepatocyte membranies and a stimulation of LDL catabolisam. In addition to the ability of HMGCoA reductase inhibitors to decrease levels of high sensitivity C reactive protein (hsCRP),they also possess pleiotropic properties including endothelilal function, reducd inflammation at the site of the coronary plaque, inhibiton of platelet aggregation ,and anticoagulant effects. The absolute oral bioavailability of Pitavastatin following oral administration is 58%-60%. It is soluble in ethyl alcohol and very slightly soluble in water. (Harish Chander *et al*., 2011)

The Self-microemulsifying drug delivery system is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophillic drugs and to improve the oral bioavailability of poorly

absorbed drugs and also drugs are protected from hostile environment in gut. SMEDDS are isotropic mixture of oil, surfactant, drug and sometime containing co-surfactant and administered orally which on mild agitation with GI fluids forms O/W microemulsion.

The present study is carried out to develop L-SMEDDS and S-SMEDDS of Pitavastatin in order to enhance the solubility and bioavailability by providing a lipidic environment to the drug which ensure its better solubility. The components to prepare the L-SMEDDS are choosed based on the solubility studies and % transmittance value. The concentration of components is optimized by constructing Pseudo ternary phase diagrams. The liquid SMEDDS of pitavastatin are prepared by simple admixing method, and then converted into S-SMEDDS on an inert carrier by adsorption technique. The best formulation is selected based on the drug content, *invitro* dissolution studies, particle size and solubility studies. The *in vitro* dissolution profile of S-SMEDDS of Pitavastatn is compared with the pure drug and conventional tablet.

CHAPTER V

PLAN OF WORK

CHAPTER-V

PLAN OF WORK

1. STANDARD CURVES FOR PITAVASTATIN

- Preparation of calibration medium
- Estimation of absorption maximum (λ_{max}).
- Preparation of standard curve.

2. PREFORMULATION (COMPATABILITY) STUDIES

- Fourier Transform infra-red spectroscopic study.
- Differential scanning calorimetric studies. (DSC)

3. FORMULATION OF PITAVASTATIN LIQUID SMEDDS

The liquid SMEDDS are prepared by simple admixing method. The preparation process involves following steps.

- Determining solubility of Pitavastatin in various oil, surfactant, and co-surfactant.
- Screening of surfactant and co-surfactant.
- Construction of Pseudo ternary phase diagram.
- Formulation of liquid SMEDDS.

4. CHARACTERIZATION OF PITAVASTATIN LIQUID SMEDDS

- Visual assessment
- Dispersibilty test
- Determination of Self emulsification time.
- Thermodynamic stability studies.
- Cloud point measurement.
- Robustness to Dilution.
- Refractive index and Percentage Transmittance.
- Determination of viscosity.
- Determination of Drug content.

5. **Conversion of liquid SMEDDS into Solid SMEDDS:**

The liquid SMEDDS are converted into solid SMEDDS by adsorption technique. In this method the Liquid SMEDDS are mixed with MCC at 1:1 w/w ratio to produce S-SMEDDS.

6. **Characterization of S-SMEDDS:**
    - Determination of micromerertic properties
    - Determination of Drug content.
    - Determination of *In vitro* drug release study.
    - Comparison of release profile with pure drug and conventional tablet.

7. **Selection on Best formulation**:

The best formulation is selected depending on the results obtained from physiochemical characterization, drug content and *in vitro* drug release studies.

8. **Evaluation of Best formulation:**

The best formulation will be evaluated for,

- Fourier transform infra-red spectroscopic (FT-IR).
- Scanning Electron Microscopy (SEM).
- X-ray Powder Diffraction (XRPD).
- Differential Scanning Colorimetry.

CHAPTER VI

MATERIALS AND EQUIPMENTS

CHAPTER -VI

MATERIALS AND EQUIPMENTS

MATERIALS USED

TABLE 1:

MATERIALS NAME	SUPPLIERS
Pitavastatin Calcium	Gift sample from Shasun pharmaceuticals, Cudalore.
Capryol 90	High Purity Laboratory Chemicals (P) Ltd, Mumbai.
Oleic acid	High Purity Laboratory Chemicals (P) Ltd, Mumbai.
Sunflower oil	Universal Scientific Appliances, Madurai.
Sesame oil	Universal Scientific Appliances, Madurai.
Castor oil	Universal Scientific Appliances, Madurai.
Tween 20	R.K. Diagnostics, Madurai.
Tween 80	R.K. Diagnostics, Madurai.
Cremophor RH 40	Madras pharma, Chennai.
Span 80	Universal Scientific Appliances, Madurai.
Micro crystalline cellulose	Madras pharma, Chennai.
Polyethylene glycol 400	Gift sample from Pharmafabrikon, Madurai
Propylene glycol	Gift sample from Pharmafabrikon, Madurai

EQUIPMENTS

TABLE-2

EQUIPMENTS NAME	MANUFACTURER'S
Electronic weighing balance	A & D Company, Japan.
UV-Visible spectrophotometer	Shimadzu Corporation, Japan.
Infrared spectroscopy	Spectrum RX-1, Perkin Elmer, German.
Differential Scanning Calorimeter	DSC Q 200, USA.
Scanning electron microscope	Hitachi X650, Tokyo, Japan.
Particle size analyzer	Nano ZS 90, Malvern Instruments Ltd.,UK
Freeze dryer	Lyodel-Delvac Pumps Pvt. Ltd, USA.
Mechanical shaker	Secor, India.
Dissolution apparatus	Labindia – Disso 2000, India.
Ultra Sonicator	Vibronic's Ultrasonic processor, India.
X-ray diffractometer	Digaku XRD-462, Japan.

CHAPTER VII

DRUG PROFILE

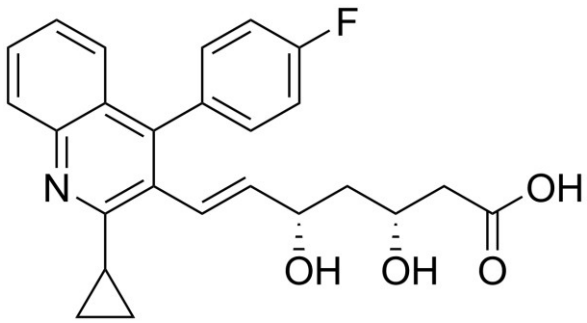
CHAPTER VII

DRUG PROFILE

DRUG NAME : PITAVASTATIN

SYNONYM : PITAVASTATIA, PITAVASTATINE,

STRUCTURAL FORMULA :



CHEMICAL FORMULA : $C_{25}H_{24}FNO_4$

IUPAC NAME : (3R,5S,6E)-7-[2-2-[(2S)-cyclopropyl-4-(4 fluorophenyl)quinoline-3-yl]-3,-5-di hydroxyhept-6-enoic acid.-

DESCRIPTION

Nature : An off white to yellowish powder Pitavastatin is freely soluble in ethanol and very slightly soluble in water

Molecular weight : 421.461 g/mol

pKa : 5.36

Melting point : >138 °C

Bolilng point : 692.0±55.0ºC at760mmHg

Index of Refraction : 1.680

HISTORY OF PITAVASTATIN

Pitavastatin (previously known itavastatin, itabavastatin, nisvastatin) was discovered in JAPAN by NISSAN CHEMICAL INDUSTRIES and developed further by KOWA pharmaceuticals, TOKYO. Pitavastatin was approved for use in the united states by the FDA on 08/03/2009 under the trade name Livalo. Pitavastatin has been also approved by the Medicines and Helathcare products Regulatory Agency (MHRA) in UK on August 2010. (Reid,J; Reckless, J.P.D et al 2006)

PHARMACOLOGY

It is a calcium slat of Pitavastatin, a novel statin that induces plaque regression and elevates HDL cholesterol level.

MECHANISM OF ACTION

Pitavastatin competitively inhibits HMG-CoA reductase, which is a rate-determining enzyme involved with biosynthesis of cholesterol, in a manner of competition with the substrate so that it inhibits cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to liver is accelerated and then the plasma TC decreases. Further, the sustained inhibition of cholesterol synthesis in the liver decreases level of very low density lipoproteins.

PHARMACOKINETICS

a) Absorption

Pitavastatin is rapidly absorbed from the upper gastrointestinal tract and peak concentrations are achieved in one hour after oral administration.

C_{max} is decreased by 43%, if the drug is taken with a fatty meal. Unchanged drug undergoes enterohepatic circulation and is well absorbed from the jejunum and ileum. The absolute bioavailability of Pitavastatin is 51%.

b) Distribution

Pitavastatin is more than 99% protein bound in human plasma, mainly to albumin and alpha 1-acid glycoprotein, and the mean volume of distribution is approximately 148 L. Pitavastatin is actively transported into hepatocytes, the site of action and metabolism, by multiple hepatic transporters including OATP1B1 and OATP1B3. Plasma AUC is variable with an approximately 4-fold range between the highest and lowest values. Studies with SLCO1B1 (the gene which encodes OATP1B1) suggests that polymorphism of this gene could account for much of the variability in AUC. Pitavastatin is not a substrate for p-glycoprotein.

C) Volume of distribution

Mean volume of distribution at steady-state of Pitavastatin is approximately 148 liters.

d) Protein binding:

>99%,primariliy to albumin and alpha 1-acid glycoprotein.

e) Metabolism

Mainly by liver through glucuronidation. The principal metabolite is the inactive lactone which is formed via an ester-type Pitavastatin glucuronide conjugate by UDP glucuronosyltransferase (UGT1A3 and 2B7). In vitro studies, using 13 human cytochrome P450 (CYP) isoforms, indicate that the metabolism of Pitavastatin by CYP is minimal; CYP2C9 (and to a lesser extent CYP2C8) is responsible for the metabolism of Pitavastatin to minor metabolite.

f) Excretion

Unchanged Pitavastatin is rapidly cleared from the liver in the bile, but undergoes enterohepatic recirculation, contributing to its duration of action. The plasma elimination half-life ranges from 5.7 hours (single dose) to 8.9 hours (steady state) and clearance is 23.6 liter/hour.

g) Route of elimination

79% feces

15% urine

DOSAGE FORMS : film coated tablet of varying concentration are available.

Tablet oral 1 mg

Tablet oral 1.045 mg

Tablet oral 2 mg

Tablet oral 2.09 mg

Tablet oral 4 mg

Tablet oral 4.18 mg

ADVERSE REACTIONS

Rhabdomyolysis with myoglobinuria and acute renal failure and myopathy(including myosistis).

CONTRAINDICATIONS

Hypersenstivity to Pitavastatin or any component of the formulation; active liver disease;pregnancy, lactation,co-admistered with cyclosporine.

DRUG INTERACTIONS

a) Atorvastatin

The serum concentration of Pitavastatin can be increased when it is combined with atorvastatin

b) Benzocaine

The serum concentration of Pitavastatin can be increased when it is combined with benzocaine.

c) Caffeine

The serum concentration of Pitavastatin can be increased when it is combined with caffeine.

d)cyclosporine

The serum concentratin of Pitavastatin can be decreased when it is combined with cyclosporine.

e) Lopinavir/Ritonavir

The metabolisam of Pitavastatin can be decreased when combine with lopinavir.

f) Erythromycin

Erythromycin significantly increased Pitavastatin exposure. In patients taking erythromycin, a dose of Pitavastatin 1mg once daily should not be exceeded.

g) Rifampin

Rifampin significantly increased pitavstatin exposure.In patients taking rifampin, a dose of Pitavastatin once daily should not be exceeded.

h) Fibrates

It is known that the risk of myopathy during treatment with HMG-CoA reductase inhibitors may be increased with concurrent administration of fibtrates, pitavstatin should be administrated with caution when used concomitantly with gemfibrozil or other fibrates.

i) Lovastatin

The serum concentration of pitavstatin can be increased when it is combine with Lovastatin.

j) Niacin

The risk of skeletal muscle effects may be enhanced when Pitavastatin is used in combination with niacin;a reduction in Pitavastatin dosage should be considered in this setting.

k) Warfarin

Pitavastatin had no significant pharmacokinetic interaction with R-ans S- warfarin. Pitavstatin had no significant effcet on prothrombin time(PT) and international normalized ratio when administered to patients receiving chronic warfarin. However, patients receiving warfarin should have their PT and INR monitored when Pitavastatin is added to their theraphy.

FOOD INTERACTION

Do not take with red yeast rice. It may increase the risk of myopathy of Pitavastatin via pharmacokinetic synergism. Red yeast rice contain monocolin k. (similar to lovastatin)

OVER DOSE

There is no known specific treatment in the event of over dose of Pitavastatin.in the event of over dose, the patient should be treated symptomatically and supportive measures instituted as required. Hemolysis is unlikely to be of benefit due to high protein binding ratio of Pitavastatin.

BRAND NAME

Livazo(coated tablets) Livalo (flim coatessd tablets)

CHAPTER VIII

EXCIPIENTS PROFILE

CHAPTER –VIII

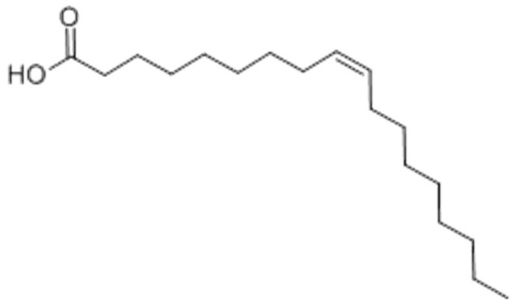
EXCIPIENTS PROFILE

1. OLEIC ACID

SYNONYM:

1. 9 Octadecenoic Acid
2. 9-Octadecenoic Acid
3. cis 9 Octadecenoic Acid
4. cis-9-Octadecenoic Acid
5. Oleate
6. Oleic Acid

STRUCTURE:



EMPIRICAL FORMULA : $C_{18}H_{34}O_2$

MOLECULAR WEIGHT : 282.47g/mol

DESCRIPTION:

- **Colour :** colourless to pale yellowish
- **Odour :** Odourless
- **Taste :** Peculiar lard-like taste
- **Solubility :** Insoluble in water; soluble in ethanol, ether, acetone, chloroform, dimethyl formamide and dimethyl sulfoxide
- **Meltilng point :** 13 to 14oC
- **Viscosity :** 25.6 cp at 30oC

- **Density :** 0.89g/mL at 25oC
- **Refractive index :** 1.377

FUNCTIONAL CATEGORY:

- Emulsifying agent;
- Skin penetrant

SAFETY:

Oleic acid is used in oral and topical pharmaceutical formulations.

2. CAPRYOL 90

SYNONYM:

Propylene glycol monocaprylate 90%

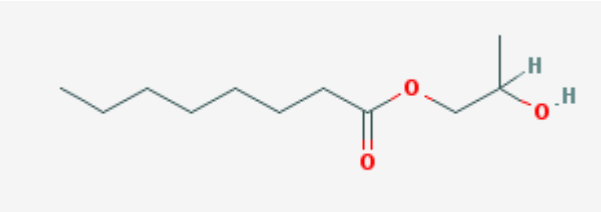
MOLECULAR FORMULA:

$C_{11}H_{22}O_3$

MOLECULAR WEIGHT:

202.29

STRUCTURE :



DESCRIPTION:

- **Colour :** Colourless oily liquid
- **Taste :** Bitter taste.
- **Odour :** Faint
- **Solubility :** miscible with ethanol and organic solvents.

In soluble in water.

- **HLB value** **:** 6
- **Saponification value** **:** 270-290mg KOH/g

FUNCTIONAL CATEGORY:

- Bioavailability enhancer
- Solubiliser
- Penetration enhancer
- Surfactant in Microemulsion.

3. SESAME OIL

SYNONYM:

Sextra;

Sesame oil,

Gingilli oil.

DESCRIPTION:

- **Colour** **:** a pale yellow liquid
- **Taste** **:** Pleasant taste
- **Odour** **:** Pleasant grain like odour.
- **Solubility** **:** Soluble in chloroform
- **Melting point** **:** -50^{o}C
- **Density** **:** 0.919
- **Refractive index** **:** 1.47-1.746

FUNCTIONAL CATEGORY:

- Used as an ayurvedic medicine as a massaging agent
- In food preparation.

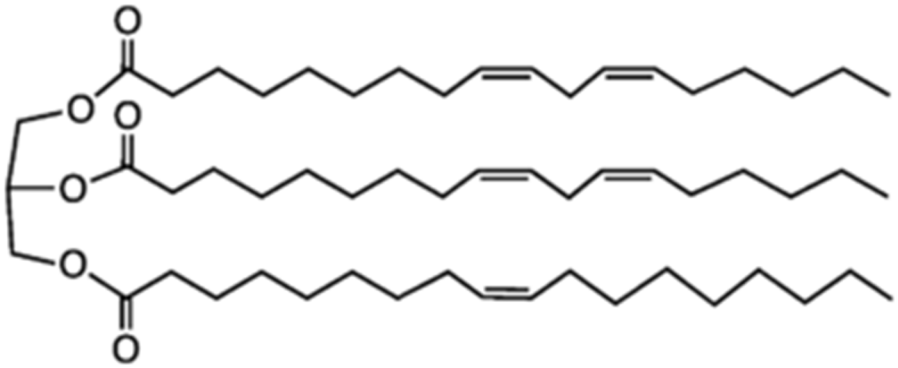
4. SUNFLOWER OIL

SYNONYM :

Sunflower oil

Sunflower seed oil

STRUCTURE:



DESCRIPTION:

- **Colour** : Yellow color viscous liquid
- **Taste** : Pleasant taste.
- **Odour** : Pleasant odour
- **Solubility** : Insoluble in water. Miscible with organic solvents.
- **Flash point** : >1100 C
- **Viscosity** : 0.04914 kg/m
- **Density** : 918.8 kg/m
- **Refractive index** : 1.4735

FUNCTIONAL CATEGORY:

- In food preparation
- Dietary supplement
- Fuel to run engines

5. CASTOR OIL

SYNONYM:

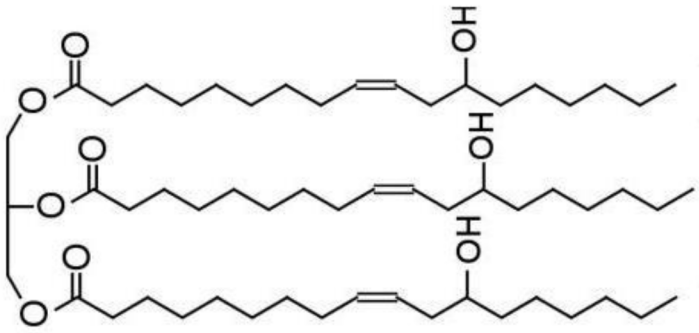
Ricinus oil,

cotton seed oil.

MOLECULAR FORMULA : C57H104O9

MOLECULAR WEIGHT : 933.45g/mol

STRUCTURE:



DESCRIPTION:

- **Colour** : Colourless to pale yellowish viscous liquid
- **Taste** : Nauseating taste
- **Odour** : Nauseating odour
- **Solubility** : Insoluble in water. Miscible with ethanol
- **Boiling point** : 313^{o}C
- **Viscosity** : 1000 mPa at 20^{o}C
- **Saponification value :** 128.6
- **Density** : 961kg/m3

FUNCTIONAL CATEGORY:

- Emolient,
- oleaginous vehicle,
- solvent.

6. TWEEN 80

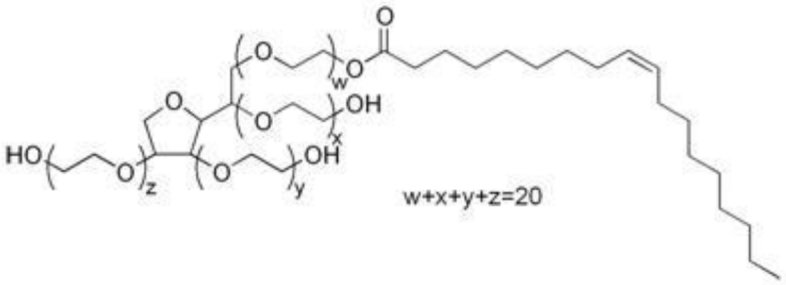
SYNONYM :

Polysorbate 80

MOLECULAR FORMULA: C64H124O26

MOLECULAR WEIGHT: 1310

STRUCTURE:



DESCRIPTION:

- **Colour :** Colourless to pale yellow colour
- **Taste :** Bitter taste.
- **Odour :** Characteristic odour
- **Solubility :** very soluble in water, soluble in ethanol, methanol, toluene
- **Viscosity :** 425mPa at 25oC
- **HLB value :** 15
- **Density :** 1.06-1.09g/ml

FUNCTIONAL CATEGORY:

- Dispesing agent;
- emulsifying agent;
- nonionic surfactant;
- solubilising agent;
- suspending agent;
- wetting agent.

7. CREMOPHOR RH 40

Chemical name : Polyoxyl 40 hydrogenated

- **Colour** : White to yellowish thin paste.
- **Taste** : Very faint odour
- **Odour** : Very faint taste
- **Solubility** : Soluble in water, ethanol, 2-propanol, n-propanol, ethyl acetate chloroform, carbon tetra chloride, and toluene.
- **HLB value** : 14-16
- **Saponification value :** 50-60

METHOD OF MANUFACTURING: Reacting hydrogenated castor oil with ethylene oxide.

FUNCTIONAL CATEGORY:

Solubilizers,

In perfume compositions.

8. POLYETHYLENE GLYCOL 400

SYNONYM:

Carbowax;

Carbowax Sentry;

Lipoxol;

Lutrol E;

macrogola;

PEG;

Pluriol E and

polyoxyethylene glycol.

MOLECULAR FORMULA: HOCH2 (CH2OCH2)8.7CH2OH

MOLECULAR WEIGHT: 380-420 g/mol

DESCRIPTION:

- **Colour** **:** Colorless liquid
- **Taste** **:** Bitter
- **Odour** **:** Charaticcteric
- **Solubility** **:** Soluble in water, Acetone, Alcohols, Benzene, Glycerin.
- **Viscosity** **:** 105-130 mPas
- **HLB value** **:** 16
- **Density** **:** 1.120

INCOMPATIBILITIES:

The chemical reactivity of polyethylene glycols is mainly confined to the two terminal hydroxyl groups, which can be either esterified or etherified. However, all grades can exhibit some oxidizing activity owing to the presence of peroxide impurities and secondary products formed by autoxidation. Liquid and solid polyethylene glycol grades may be incompatible with some coloring agents.

STABILITY AND STORAGE:

Polyethylene glycols are chemically stable in air and in solution, although grades with a molecular weight less than 2000 are hygroscopic. Polyethylene glycols do not support microbial growth, and they do not become rancid. Polyethylene glycols and aqueous polyethylene glycol solutions can be sterilized by autoclaving, filtration, or gamma irradiation.

9.PROPYLENE GLYCOL

SYNONYM:

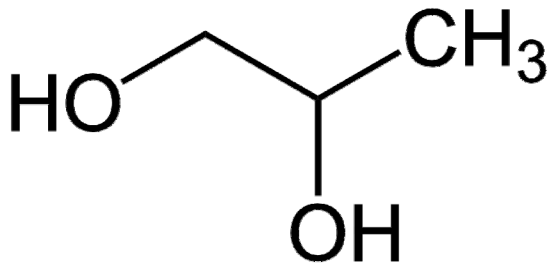
Ethanediol,

Ethylene glycol

MOLECULAR FORMULA: $C_3H_8O_2$

MOLECULAR WEIGHT: 76.10 g/mol

STRUCTURE:



DESCRIPTION:

- **Colour** : Viscous colourless liquid
- **Taste** : Sweet Taste.
- **Odour** : Faint odour
- **Solubility** : Miscible with Acetone, Chloroform, Water, ethanol and diethyl ether.
- **Melting point:** -59^{o}C
- **Viscosity** : 0.042 Pas
- **HLB value** : 3.4
- **Density** : 1.036g/cm^3
- **Refractive index:** 1.4399

FUNCTIONAL CATEGORY:

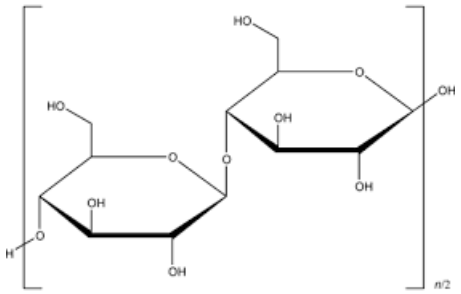
Stabilizer,

Solvent,

Humectant

10. MICROCRYSTALLINE CELLULOSE

STRUCTURE



SYNONYM:

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristallinum; Celphere; Ceolus KG; crystalline cellulose; E460; Emcocel Ethispheres; Fibrocel; MCC Sanaq; Pharmacel; Tabulose; Vivapur.

Empirical Formula: (C6H10O5)n

Molecular weight: 36000g/mol

FUNCTIONAL CATEGORY:

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrates.

DESCRIPTION:

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles.

SOLUBILITY:

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

PH:

pH 5.0-7.5

MELTING POINT:

Chars at 260–2708C.

INCOMPATIBILITIES:

Microcrystalline cellulose is incompatible with strong oxidizing agents.

STABILITY & STORAGE CONDITION:

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

HANDLING PRECAUTION:

Microcrystalline cellulose may be irritant to the eyes. Gloves, eye protection, and a dust mask are recommended

APPLICATIONS:

1. Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression Processes.
2. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful in tableting.
3. Microcrystalline cellulose is also used in cosmetics and food products;

CHAPTER IX

EXPERIMENTAL PROTOCOL

CHAPTER IX

EXPERIMENTAL PROTOCAL

Preformulation study:

Preformulation study is the process of optimizing the delivery of drug through determination of physicochemical properties of the new compound that could affect drug performance and development of an efficacious, stable and safe dosage forms, first preformulation studies were performed. Various preformulation studies which were carried out are discussed in following sections.

IDENTIFICATION:

1. Determination of melting point:

Melting point of Pitavastatin was determined by using open capillary tube method in digital melting ploint apparatus.

Method:

In this method the capillary tube was sealed with gentle heating from one end. Then the small quantity of Pitavastatin was filled into the sealed capillary. Capillary existed tied to the tube containing the oil phase in such a way that the sealed part of the capillary containing Pitavastatin was dipped into the oil. Gently the oil bath was heated. As soon as the powder starts melting, the heating was stopped and the temperature was note down.

2. Solubility of Pitavastatin:

Solubility of Pitavastatin was determined in various medias like ethanol, methanol, Dichloromethane, Dimethylsulfoxide, 6.8 phosphate buffer etc.

3. Drug-Excipients Compatibility studies :

A proper design and formulation of dosage form require consideration of physical, chemical and biological characteristics of both drug and excipients

used in formulation of the product. Compatibility must be established between active drug and other excipients to produce a stable, efficacious, attractive and safe product. Hence before producing the actual formulation compatibility of drug with different excipients was tested using the FTIR and DSC techniques.

Fourier Transmittance Infra-Red (FTIR):

In order to check the integrity (compatibility) of the drug in the formulations FTIR spectra of formulations along with the pure drug and other excipients were obtained and compared using shimadzu FTIR spectrophotometer. In the present study potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in spectrophotometer and spectrum was recorded.

Differential scanning Calorimetry (DSC):

Differential scanning calorimeter or DSC is a thermo analytical technique in which difference in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. Both the sample and reference mentioned at nearly sample temperature throughout the experiment.

Method:

Accurately weighed Pitavastatin was analyzed by using an automatic thermal analyzer system (DSC60 Shimadzu Corporation, Japan0. Sealed and perforated aluminium pans were used in this experiment for all the samples. Temperature calibrations were performed using indium as standard. An empty pan sealed in the same way as for the sample was used as a reference. The entire samples were run at a scanning rate of 10^{o}C/min from 50^{o}-300^{o}C.

4. STANDARD CURVES FOR PITAVASTATIN

Phosphate buffer pH 6.8 (Indian pharmacopoeia 2017)

A known volume (50 ml) of 0.2 M potassium dihydrogen phosphate is placed in a 200 ml volumetric flask. 22.4 ml of 0.2M sodium hydroxide is added and makeup to the volume with distilled water.

0.2M potassium di hydrogen phosphate:

A known quantity (27.218g) of potassium di hydrogen phosphate is dissolved and diluted to 1000 ml with water.

0.2 M sodium hydroxide:

A known quantity (8 g) of sodium hydroxide is dissolved and makeup to 1000 ml with water.

Determination of λ_{max} :

Standard stock solution containing Pitavastatin was prepared by dissolving 100 mg of Pitavastatin in 10 ml of Dimethyl sulphoxide in 100 ml volumetric flask to dissolve the drug. Then the volume was made up to 100 ml using phosphate buffer of pH 6.8 to obtain a concentration of 100µg/ml. the stock solution is further diluted using a phosphate buffer pH (6.8) to prepare 10 µg/ml concentration. The resultant solution was scanned in the range of 200-400 nm in UV spectrophotometer (UV -1700 shimadzu Corporation, Japan) to get absorption maximum (λ_{max}) using phosphate buffer as blank. The wave length of maximum absorbance considered for further studies.

Preparation of standard curves:

From the above prepared stock solution, solutions containing 2 to 10 µg/ml concentrations were prepared using the phosphate buffer pH 6.8 solution. The absorbance of these solutions are measured at λ_{max} by UV-spectophotometer (UV-1700Sshimadzu corporation Japan). A standard curve is plotted using concentration on x-axis and the absorbance obtained on Y-axis.

5. FORMULATION OF PITAVASTATIN SELF MICRO EMULSION:

The SMEDDS of Pitavastatin were prepared by simple admixing method. The preparation process involves following steps.

I. Determination of solubility of Pitavastatin in various vehicles.(oil, surfactant, and co-surfactant.
II. Selection of oil, surfactant and co-surfactant based on the solubility and % transmittance.
III. Construction of pseudo ternary phase diagram.
IV. Formulation of SMEDDS by dissolving the drug in a mixture of oil, surfactant and co-surfactant.

Determination of solubility of Pitavastatin:

Solubility of Pitavastatin in various oils (Capryol 90, oleic acid, castor oil, sesame oil, castor oil), surfactants (tween 20, tween 60, tween 80, cremophor RH, span 80), co-surfactant (Propylene glycol, poly ethylene glycol 400) was determined by dissolving an excess amount of Pitavastatin in 2 ml of each of selected oils, surfactant and co-surfactant in stoppered vials. The mixtures were continuously stirred using vortex mixer for 10 min and kept at 37^{o} C±0.5^{o} C in water bath shaker for 78 hours to attain equilibrium. The equilibrated samples were centrifuged (3000 rpm for 15 mins) and supernatant was filtered through 0.45 µm membrane filter and diluted with suitable solvent. Drug content was quantified by using ultraviolet - visible (UV_VIS) spectrophotometer.

Screening of surfactant:

In order to find appropriate surfactant with good solubilising capacity, an emulsifying ability of different surfactants (tween 20, tween 60, tween 80, cremophore RH, and span 80) with the screened oil was investigated. 300 mg of oil phase and 300 mg of surfactant were weighed and vortexed for two minutes followed by warming at 40- 45 C for 30 seconds. So we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through 0.45µm membrane filter in a

volumetric flask. Number of flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected.

Screening of co-surfactant:

In order to find appropriate co- surfactant with good solubilising capacity, after screening of an oil emulsifying ability of different co- surfactants (Propylene glycol, poly ethylene glycol 400) with the screened oil was investigated. 300 mg of oil phase and 300 mg of surfactant were weighed and vortexed for two minutes followed by warming at 40- 45 C for 30 seconds. So we can obtain an isotropic mixture. 50 mg of isotropic mixture was taken and diluted with double distilled water previously filtered through 0.45µm membrane filter in a volumetric flask. Number of flask inversions was observed visually to form a clear emulsion. The resulting emulsions allowed standing for 2 hours after that transmittance were observed at 638 nm. The co- surfactant which forms a clear emulsion with lesser number of inversions and with more transmittance was selected.

Construction of pseudo ternary phase diagram:

Phase diagrams are constructed to obtain the proportion of components that can result in maximum microemulsion existence area. These diagrams were constructed with oil, surfactant/co-surfactant and water using water titration method at room temperature. The procedure consisted of preparing solutions of different ratio of surfactant to co-surfactant by weight such as 1:1, 2:1, 3:1, etc, these solutions then vortexed for 5 mins and placed at 50^{o} C for one hour, so that an isotropic mixture was obtained. Each of these solutions were used for preparing a mixture containing oil and S_{mix} (mixture of surfactant and co-surfactant) in the following ratios by weight, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 and after preparation vortexed for 5 mins followed by placing in oven at 50^{o} C for one hour. All the mixtures were then placed at room temperature for 24 hour. Water from 5 % to 95 % of the mixtures was

observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion, whereas clear isotropic solution would indicate the formation of micro emulsion. Percentage of oil, $S_{mix,}$ water at which clear mixture was formed was selected and the values were used to construct ternary phase diagram.

FORMULATION OF LIQUID SMEDDS:

From the ternary phase diagram ratio of surfactant to co-surfactant was optimized. Then by varying ratio of oil to S_{mix}, different formulations were prepared. Formulations were prepared by preparing optimized ratio of S_{mix} first, for this surfactant and co-surfactant were accurately weighed and then vortexed for 5-10 mints. After that S_{mix} was placed in oven at 50^0 C for one hour. Oil with different ratio was added to $S_{mix.}$ Then these formulations were vortexed for 5-10 mints and placed in oven at 50^o C for one hour so that an isotropic mixture was formed. Drug was loaded to these isotropic mixtures at the end and vortexed by vortex shaker until clear solution was obtained.

CHARACTERIZATION OF LIQUID SMEDDS:

Visual assessment

Pitavastatin liquid SMEDDS was diluted with purified water (100 ml) and gently stirred with magnetic stirrer. Temperature should be 37^0 C.

Dispersibility test

The dispersibility test of SMEDDS was carried out to acssess to compatibility to disperse into emulsion and the size of resulting globules to categorize them as SMEDDS. It was carried by using a standard USP paddle typw dissolution test apparatus, formulation was added to 500 ml of water at 37 0.5 C and the paddle was rotated at 50 rpm. On titration with water the SMEDDS formulation forms a mixture which was of different type. Depending upon which the in vitro performance of formulation can be assessed.

S. no	Dispersibility and appearance	Grade	Time to self emulsify (minutes)
1	Rapidly forming (within 1 min) Nano or microemulsion having a clear or bluish appearance.	A	Within 1
2	Rapidly forming, slightly clear emulsion having a bluish white appearance	B	Within 1
3	Fine milky emulsion that formed within 2 minutes.	C	Within 2
4	Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 mints).	D	Within 3
5	Exhibit poor or minimal with large oil droplets presents on the surface.	E	Within 3

Determination of self-emulsification time:

The emulsification time of SMEDDS was determined according to Chinese pharmacopoeia (2005 version), dissolution apparatus. One ml of each formulation was added drop wise to 500 ml distilled water at 37±0.5^{o} C. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time assessed visually.

Thermodynamic stability studies:

The physical stability of a lipid formulation is very important for its performance as its can be adversely affected by precipitation of drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic

efficiency. Also the incompatibilities between formulation and shell of capsule may cause brittleness, softness, and deleted disintegration or incomplete release of drug. The following cycles was carried out for these studies.

Heating cooling cycle

The optimized SMEDDS formulations were diluted with 100 times distilled water. Six cycles between cooling temperature (4^{o}C) and heating temperature (45^{o} C) with exposure at each temperature for not less than 48 hours were carried. That formulation, which was stable, then was subjected to centrifugation test.

Centrifugation

In order to estimate metastable systems, the optimized SMEDDS formulations were diluted with 100 times distilled water. Which pass heating-cooling cycles are centrifuged at 3500 rpm for 30 mints. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

Freeze thaw cycle

This test was performed for accelerated stability testing of Nano emulsion formulation. In this study three freez thaw cycle of formulations were exposed between temperatures 21^{o} C-25^{o} C for each temperature cycles not more than 48 hours. For the better estimation of accelerated stability studies six such cycles should be run for each batch of formulation. The formulations which showed the maximum stability were selected for further study.

Cloud point measurement:

Dilute the formulation 1 ml with 1000 ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy or turbid. It gives the information about the stability of the micro emulsion at body temperature.

Robustness to dilution:

Robustness to dilution was studied by diluting SMEDDS to 50, 100, 1000 times with water, phosphate buffer pH 6.8, phosphate buffer pH 7.4. The diluted SMEDDS were stored for 12 hour and observed for any signs of phase separation or drug precipitation.

Refractive index and percent transmittance:

Refractive index and percent transmittance proved the transparency of formulation. The refractive index measured using Abbes refractometer. The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. Stability of micro emulsion formulation with respect to dilution is checked by diluting one ml of formulation with 100 ml of distilled water and measuring transmittance using U.V. Spectrophotometer. Transmittance of samples is measured at 638 nm and for each sample three replicate assays are performed.

Viscosity determination:

The rheological properties of the micro emulsion are evaluated by Ostwald visco meter. These viscosity determinations confirm whether the system is w\o or o\w. If system has low viscosity, then it is o/w type of the system and if high viscosities then it are w\o type of the system.

Absolute drug content in L-SMEDDS:

Liquid SMEDDS containing Pitavastatin, equivalent to 4 mg was diluted in suitable quantity of methanol. The sample was mixed thoroughly to dissolve the drug in methanol by stirring. The solvent extract is filtered through 0.45 µm membrane filter. Drug content was determined by measuring the absorbance in UV spectro photometer against the standard solvent solution of drug.

Conversion of liquid SMEDDS into solid S-SMEDDS:

Solid SMEDDS were prepared by mixing liquid SMEDDS containing Pitavastatin with microcrystalline cellulose (MCC) in 1:1 proportion. Liquid

SMEDDS was added drop wise over MCC and homogenized using glass rod to ensure uniform distribution of formulation in a china dish.

Physiochemical characterization of SMEDDS:

Micromeritic properties:

Prepared solid- SMEDDS was evaluated for micromeritic properties such as angle of repose, bulk density and tapped density, compressibility index and Hausner's ratio.

a) Angle of Repose

Angle of Repose is defined as the maximum angle possible between the surface of the pile of powder and horizontal plane. Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion. A static heap will slide when the angle of inclination is large enough to overcome frictional forces and stop when gravitational forces balance the forces. The sides of heap will make an angle with horizontal which is called angle of repose. (Satyabrata Bhanja et al., 2013)

Angle of Repose (ø) = $\tan^{-1}$ (h / r)

Where, h = height of the heap,

r = radius of the heap

TABLE 2:

Angle of Repose	Type of Flow
<20	Excellent
20 – 30	Good
30 – 35	Moderate
35 – 40	Poor
>40	Very Poor

b) Bulk Density:

Bulk density denotes the total density of the material. It includes the true volume of interparticle spaces and intraparticle pores. The packing of particles is mainly responsible for bulk. Bulk density is the ratio between a given mass of powder and its bulk volume. Apparent bulk density is determined by pouring the weighed granules into a graduated cylinder via funnel and measuring the volume. Density is calculated by using the formula, (SatyabrataBhanjaal.,2013)

$$\text{Bulk density} = \frac{\text{weight of the powder}}{\text{Bulk volume of the powder}} = \frac{W}{V_o}$$

c) Tapped Density:

A known quantity of sample is transferred to a graduated cylinder and placed on tapped density apparatus and operated for a fixed number of taps (100).It is the ratio of weight of sample to tapped volume.(Satyabrata Bhanja et al., 2013)

$$\text{Tapped density} = \frac{\text{Weight of the powder (W)}}{\text{Tapped volume of powder } V_f}$$

d) Compressibility (or) Carr's index:

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug is studied by using the following formula.

$$\text{Carr's index (\%)} = \frac{\text{Tapped density - bulk density}}{\text{Tapped density}} \times 100$$

TABLE 3:

Compressibility Index (%)	Type of Flow
5-15%	Excellent
15-25%	Good
>25%	Extremely poor

e) Hausner's ratio:

Hausner's ratio is defined as the ratio of tapped density to bulk density of the powders. The Hausner's ratio is a number that is correlated to the flowability of a powder (or) granular material. It is calculated by using the formula,

$$\text{Hausner 's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Where,

$_o$= Bulk density g/ml.

$_t$ = Tapped density g/ml.

The values less than 1.25 indicate good flow (=20% Carr), whereas greater than 1.25 indicates poor flow (=33% Carr) Between 1.25 and 1.5, added glidant normally improves flow. (SatyabrataBhanja et al,2013)

Drug content:

The S-SMEDDS containing Pitavastatin, equivalent to 4 mg was diluted in suitable quantity of methanol and sonicated for 10-15 mints. Then it was filtered through 0.45µm membrane filter. Drug content was analyzed by measuring absorbance using UV spectrophotometer.

***Invitro* drug release from S-SMEDDS:**

The *in vitro* drug release of prepared S-SMEDDS was assessed in triplicate using United States Pharmacopoeia (USP) Dissolution Type II apparatus (Paddle type) at 37±0.5^{o} C. S-SMEDDS containing 4 mg equivalent of drug was placed in 900 ml of dissolution medium (phosphate buffer pH 6.8with methanol in 9:1 ratio). The revolution speed of the paddle was maintained at 100 rpm. At predetermined time intervals, 5 ml of dissolution medium was collected, filtered and the same volume of fresh dissolution medium was replenished to maintain the sink conditions. The samples were analyzed for the drug concentration using UV-VIS spectrophotometer at 245 nm

f) Release Kinetics:

The results of *in vitro* release profiles obtained for all the formulations were fitted into five models of data treatment as follows:

1. Cumulative percent drug released versus time (zero-order kinetic model).
2. Log cumulative percent drug remaining versus time. (First-order kinetic model).
3. Cumulative percent drug released versus square root of time (Higuchi's model).
4. Log cumulative percent drug released versus log time (Korsmeyer-Peppasequation).
5. Cumulative percent drug released versus cube root of time (Hixson and Crowell'scubic root law of dissolution)

Zero Order Kinetics A zero-order releases would be predicted by the following equation.

$$\mathbf{A_t = A_0 - K_0 t} \quad \text{.....(6)}$$

Where:

A_t = Drug release at time't'

A_0 = Initial drug concentration

K_0 = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_0.

1) **First Order Kinetics:** A first-order release would be predicted by the following equation

$$\textbf{Log C = Log } C_0 \textbf{ – 303.2Kt} \quad \text{..... (7)}$$

Where:

C = Amount of drug remained at time 't'

C_0= Initial amount of drug.

K = First-order rate constant (hr).

When the data are plotted as a log of percent cumulative drug release remaining versus time yields a straight line, indicating that the release follows First-order kinetics.

The constant 'K' can be obtained by multiplying 2.303 with slope values.

2.Higuchi's Model

Drug released from the matrix devices by diffusion has been described by following Higuchi's classical diffusion equation.

$$Q = \left(\frac{D\varepsilon}{\tau}(2A - \varepsilon C_s)C_s t\right)^{1/2} \quad \text{..... (8)}$$

Where,

Q = Amount of drug released at time't'

D = Diffusion coefficient of the drug in the matrix

A = Total amount of drug in unit volume of matrix

C_S = The solubility of the drug in the diffusion medium

ε = Porosity of the matrix τ = Tortuosity t = Time (hrs) at which 'Q' amount of drug is released.

Equation-8 may be simplified if one assumes that D, C_S and A are constant. Then equation-8 becomes:

$$Q = Kt^{1/2} \quad \text{..... (9)}$$

When the data is plotted according to equation-4 i.e., cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

3) Korsmeyer and Peppas Model

The release rates from controlled release polymeric matrices can be described by the equation (10) proposed by korsmeyer et al.

$$n\ Q = K_1 t \quad \text{..... (10)}$$

Q is the percentage of drug released at time't', K is a kinetic constant incorporating structural and geometric characteristics of the tablets and 'n' is the diffusional exponent indicative of the release mechanism.

4) Hixson and Crowell's cubic root law of dissolution

The Noyes-Whitney's equation assumes that surface area of the dissolving solid remains constant during dissolution, which is practically not possible for dissolving particles. Hence, dissolution methods that involve use of constant surface area discs are employed to determine the rate of dissolution.

To account for the particle size decrease and change in surface area accompanying dissolution, Hixson and Crowell's cubic root law of dissolution is used:

$$W_0^{1/3} - W^{1/3} = Kt$$

EVALUATION OF BEST FORMULATION:

a) Infrared (IR) spectroscopic studies:

Infrared (IR) spectrum analysisare carried out for the selected formulation of Liquid SMEDDS and S-SMEDDS to find out the interactions between the drug and excipients by using IR spectrophotometer (Spectrum RX-1 Perkin Elmer, German). The pellets are prepared on KBr-press under hydraulic pressure of 150kg / cm^2; the spectra is scanned over the wave number range of 4000 to 400 cm^{-1} at the ambient temperature (Sinco.C *et al*., 2011).

b) Morphological studies of S-SMEDDS by using Scanning Electron Microscopy (SEM):

Morphological evaluation of the selected Pitavastatin nanocrystal formulation is carried out in scanning electron microscope (SEM) (Hitachi X650, Tokyo, Japan). All samples are examined on a brass stub using carbon double-sided tape. Powder samples are glued and mounted on metal sample plates. The samples are gold coated (thickness ≈15–20 nm) with a sputter coater (Fison Instruments, UK) using an electrical potential of 2.0 kV at 25 mA for 10 min. An excitation voltage of 20 kV was used in the experiments (Yuan Gao *et al*., 2011).

c) X-ray Powder Diffraction (XRPD) analysis:

The crystalline state of the samples, including the drug and freeze-dried powders are studied in X-ray diffractometer (XRD-462, Digaku, Japan). XRPD is carried out in symmetrical reflection mode using Copper line as the source of radiation and the wavelength is set at 1.5405A°. Standard runs using a 40 kV and 30 mA in this process. Samples are performed with a scanning rate of 0.1000°/min and the scanning range of the 2 from the initial angle 4° to the final angle 90° (Dianrui Zhang *et al*., 2011).

d) Determination of Particle size and Zeta potential:

The mean particle size (z-average), and zeta potential of Pitavastatin SMEDDS formulations are determined by dynamic light scattering technique using a zeta size analyzer (Nano ZS 90, Malvern Instruments Ltd., UK). The freeze dried powders are redispersed with water to obtain a proper scattering intensity before measurement (Dianrui Zhang *et al*., 2014).

e) Differential Scanning Calorimetry:

Physical state of Pitavastatin in S-SMEDDS was characterized using differential scanning calorimeter, thermo grams of Pitavastatin, and S-SMEDDS were measured in Perkin elmer pyris(Shelton, CT) equipped with an intracooler 2P cooler accessory.Samples of 4mg are placed in standard aluminium pans and sealed with a lid.

Heating scans by 10^0C/min, is applied with a nitrogen purge of 20ml/min, over a temperature range of 35^0C to 380^0C. An empty aluminium pan is used as reference**. (Solanki. D.*et al., 2013).***

CHAPTER X

RESULTS AND DISCUSSION
TABLES & FIGURES

CHAPTER X

RESULTS AND DISCUSSION

1. STANDARD CURVES FOR PITAVASTATIN

a) Preparation of dissolution medium

The calibration medium was (phosphate buffer and pH 6.8) was prepared by as per the I.P procedure (I.P 2014)

b) Estimation of absorption maximum (λmax)

The λ_{max} of Pitavastatin was estimated by scanning the 10µg/ml concentration of the drug solution in buffer solution of phosphate buffer pH (6.8). It showed the λ max of 245nm (Narendra Chary., *et al*., 2012) in phosphate buffer solution of pH (6.8). The result was shown in **table 1 and figure 1**. The linear correlation coefficient was found to be 0.9993 for pH (6.8). Pitavastatin obeys the Beer's law within the concentration range of 2 to 10 µg/ml.

2. Infrared (IR) spectroscopic studies

Infrared (IR) spectroscopic studies were carried out to confirm the compatibility between drug and excipients used for the preparation of SMEDDS. The IR studies were performed for pure drug, stabilizers and physical mixture of drug with stabilizers. The spectra studied at 4000cm^{-1} to 400 cm^{-1} were shown in **(Table 15)** and **(Figure 2(a)-2(f)**. The principal peaks for pure drug were observed at wave numbers 3066 cm^{-1}, 2958 cm^{-1}, 3003 cm^{-1}, 1720 cm^{-1}, 1490 cm^{-1} and 1219.01 cm^{-1}, 678.94 cm^{-1}. THE results clearly indicated that there was **no interaction** between the drug and excipients and the drug was present in its unchanged form.

3. FORMULATION OF PITAVASTATIN SELF MICRO EMULSION:

The SMEDDS of Pitavastatin were prepared by simple admixing method. The preparation process involves following steps.

i. Determination of solubility of pitavastatin in various vehicles.(oil, surfactant, and co-surfactant.
ii. Selection of oil, surfactant and co-surfactant based on the solubility and % transmittance.
iii. Construction of pseudo ternary phase diagram.
iv. Formulation of SMEDDS by dissolving the drug in a mixture of oil, surfactant and co-surfactant.

Determination of solubility :

The components in the formulation of SMEDDS were selected to have maximum solubility of Pitavastatin along with good miscibility with each other to produce an isotropic and stable system. Solubility of pitavastatin in various vehicles was screened and the results are presented in **Table 2 and figure 4.** Pitavastain had significantly higher solubility in oleic acid (97.89±0.081%) and capryol 90 (93.69±0.38%) other than castor oil, Sesame oil, sunflower oil. Among surfactant and co-surfactants, Tween 80 (90.22±0.37%), Cremophor RH (88.73±0.24%), Propylene glycol (93.07±1.26%) showed highest solubility. Therefore, **oleic acid** and **Capryol 90** were selected as oil phase based on solubility studies.

Screening of components:

Surfactants and co-surfactants are selected based on the % Transmittance. Out of various surfactants and co-surfactant screened Tween 80 revealed (93.52±0.22%), and with oleic acid. And Cremophor RH RH 40 revealed 97.65±0.28%. Tween 80 and Cremophor RH RH 40 showed the highest value amongst all. Hence both are selected for the development of the formulation.

Similarly, in case with co-surfactants Propylene glycol resulted in higher % Transmittance value (95.29±0.10% and 97.82±0.27%) for both the oils oleic

acid and Capryol 90 respectively. Hence Tween 80 and Cremophor RH RH 40 were selected as surfactants to form a stable emulsion. And Propylene glycol was selected as a co-surfactant. And the results were shown in **Table (3) and figure 5 (a) & 5 (b).**

Construction of Pseudo ternary phase diagram:

The microemulsion region was determined by plotting data in pseudo ternary phase diagram. The selected oil, surfactants and co-surfactants were used to formulate micro emulsion. Nine different combination of oil and S_{mix} were selected to construct phase diagram for two types of formulation (oleic acid and Capryol 90). The ratio of S_{mix} was selected as 1:1, 2:1, 3:1. The diagrams are depicted in **figure (6) and (7).** From the figures for the oleic acid formulation it showed that S_{mix} ratio of 3:1 **(figure 6 c)** has more emulsification area as compared to S_{mix} ratio of 1:1 and 2:1. And for the Capryol 90 formulation S_{mix} ration of 2:1 **(figure 7 b)** have more emulsification area as compared to 1:1 and 3:1. Hence for the formulation of SMEDDS the ratio of surfactant mixture was kept as 3:1 for oleic acid formulation and 2:1 for the Capryol 90 formulation.

FORMULATION OF LIQUID SMEDDS:

Based on the pseudoternary phase diagrams, the formulation with the best self-emulsifying properties, containing oleic acid (10-50%) with S_{mix} of Tween 80 and Propylene glycol (50-90%), and Capryol 90 (10-50%) with S of Cremophor RH RH 40 and Propylene glycol (50-90%) were formulated with varying ratios of oil, surfactatnt and co-surfactant as shown in **Table 4 (a), 4 (b).**

CHARACTERIZATION OF LIQUID SMEDDS:

Dispersibility test and Visual assessment

Pitavastatin liquid SMEDDS was diluted with purified water (100 ml) and gently stirred with magnetic stirrer. Temperature should be 37^0 C. The results represented in **Table 5(a) & 5(b).**

Visual assessment of liquid SMEDDS formulation

Thermodynamic stability studies:

SMEDDS are thermodynamically stable systems and are formed at a particular concentration of oil, surfactant and water, with no phase separation, creaming or cracking. It is the thermostability which differentiates nano or microemulsion from emulsions that have kinetic stability and will eventually phase separate. Thus, the formulations were subjected to different thermodynamic stability by using heating cooling cycle, centrifugation and freeze thaw cycle stress tests. Those formulations, which survived thermodynamic stability tests, were taken for further studies. It was observed that formulation OF3 ,OF5, OF6, CF3 and CF6 did not pass the thermodynamic stress tests and thus were dropped for further study .The results are as shown in **Table 6 (a), 6(b).**

Cloud point measurement:

Dilute the formulation 1 ml with 1000 ml of water in beaker and placed on a water bath with gradually increasing the temperature until the diluted formulation turned to cloudy or turbid. It gives the information about the stability of the micro emulsion at body temperature. The results are represented in **table 7.** The cloud point of all the SMEDDS except OF3, OF5, OF6, CF3, CF5 and CF6 was found to be higher than 85^{o}C, which indicates that micro emulsion will be stable at physiological temperature without risk of phase separation.

Formulations OF3, OF5, OF6, CF3, CF5 and CF6 shows phase separation due to precipitation of drug. So these cannot be considered as the good formulations due to phase separation at higher temperature

Robustness to dilution:

After diluting SMEDDS to 50, 100 and 1000 times with water, buffer pH 7.4 and pH 6.8 and storing for 12 h, it was observed that there was no sign of phase separation or drug precipitation in formulations except OF3, OF5, OF6, CF3, CF5 and CF, which turned hazy after standing for long hours. Hence, formulations OF3, OF5, OF6, CF3, CF5 and CF6 were rejected as they were also showing phase separation and became hazy on dilution. The results were shown in **Table 8 (a) and 8 (b).**

Refractive index and percent transmittance:

Refractive Index and percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing drop of solution on slide and then compare it with water (RI=1.333). If refractive index is similar to refractive index of water and percentage transmittance above 90%, then formulations have a transparent nature. The results of Refractive index and percentage Transmittance are shown in **Table 9.** Formulation OF6 , OF7 ,OF9, CF1, CF2, CF3, CF4, CF8, and CF9 have transmittance value greater than 90%, suggesting their clarity. And the refractive index of formulation OF2, OF8, and CF4, CF8, CF9 has the values nearest to RI of water.

Viscosity determination: OF3, OF5, OF6, CF3, CF5 and CF6 were rejected due to instability. Remaining formulations were subjected to viscosity determination.

From the viscosity determination it was observed that as the concentration of co-surfactant increased viscosity of the formulation also increased. So formulation F1-F4 was highly viscous due to higher co-surfactant concentration.

The concentration of surfactant also increases the viscosity of the formulation. It was expected that F5-F9 would show the highest viscosity due to high concentration of oil. Out of 18 formulations, **CF8 and OF8 (oil-45% and Smixture-55%)** shown optimum viscosity due to optimum concentration of oil, surfactant and co-surfactant. The results were shown in **table 10.**

Absolute drug content in L-SMEDDS:

Drug content was determined by measuring the absorbance in UV spectro photometer. The results are in the range of 92.79 %-97.43%. The results are represented in Table 11 and figure 8 (a) and 8 (b). From the results, formulation OF8 (97.8±0.08%) and CF8 (97.33±0.52%) show the highest drug content amongst all the other formulations.

Conversion of liquid SMEDDS into solid S-SMEDDS:

Solid SMEDDS were prepared by mixing liquid SMEDDS containing pitavastatin with microcrystalline cellulose (MCC) in 1:1 proportion. Liquid SMEDDS was added drop wise over MCC and homogenized using glass rod to ensure uniform distribution of formulation in a china dish.

Characterization of S-SMEDDS:

a) Micromeretic properties:

Angle of Repose

Angle of repose for the best formulation (OF8 and CF8) was 26°54’ and 28o38’ respectively. The results suggested that the powder blend of formulation shows good flow properties. The result of angle of repose of best formulation was shown in **table 12 a & b.**

Bulk density (gm /ml)

The bulk density for the best formulations (CF8 & OF8) were 0.3436±0.006g/ml and 0.3423±0.006g/ml.The results indicated that the powder blends of formulation have good flow properties. The results were summarized in **table12 a & b.**

Tapped density (gm/ml)

Tapped density for the best formulation (CF8 & OF8) 0.4043±0.001g/ml and 0.404±0.001g/ml respectively. The results indicating the presence of smaller particles occupying the voids between the bigger particles. The results were summarized in **table 12 a & b.**

Carr's index

The Carr's index of the best formulation CF8 & OF8 was found to be 15.01±0.001% and 15.27±0.001%, which indicated that the powder blend was good. The results were summarized in **table 12 a & b.**

Hausner's ratio:

The Hausner ratio of the best formulation (CF8 & OF8) was found to be 1.17±0.002 and 1.18±0.002. Since a very low Hausner ratio (<1.25) was obtained the formulations showed better property. The results were summarized in **table 12 a & b.**

Drug content:

The drug content of all the S-SMEDDS formulations (OF1-OF9) and (C1-CF9) were in the range of 96.54 % to 98.02 %. The results are represented in **Table 13, & figure 9 (a) & 9 (b)** and it suggests that uniform distribution of drug in the formulation. Formulation OF8 (98±0.09%) and CF8 (98.02±0.07%) show the highest drug content amongst all other formulations.

***In vitro* drug release from S-SMEDDS:**

The dissolution study was carried out in phosphate buffer of pH 6.8 for two hours. The in vitro dissolution studies of all the formulations were compared with pure drug and conventional tablet. The results of in vitro drug release studies from Pitavastatin SMEDDS formulation were represented in **Table 14(a) and 14(b).**

The results suggest that the % release of all the formulations is greater than that of the pure drug (59.25%±0.20) and conventional tablet (64.72%±0.21).

Formulation CF8 and OF8 shown the highest percentage drug release of 82.14±0.15% and 80.52±0.12% at the end of two hours respectively than the other formulations.

SELECTION OF BEST FORMULATION:

From the above characterization, the two formulations OF9 and CF8 were selected as the best formulation showing,

For OF8

% Transmittance	94.28±0.22
Refractive index	1.333±0.0004
Drug content	98.13±0.09%
In vitro drug release	80.52±0.12% for two hours

For CF8

% Transmittance	95.08±0.16
Refractive index	1.333±0.0004
Drug content	98.02±0.07
In vitro drug release	82.14±0.15

COMPARISON OF IN VITRO DRUG RELEASE OF BEST FORMULATION WITH PURE DRUG AND MARKETED CONVENTIONAL TABLET:

The comparison of in vitro drug release profile of best formulation is compared with that of the pure drug and conventional tablet. It represented in **figure 12.**

Pure drug	(59.25%±0.20)
Conventional tablet	(64.72%±0.21)
OF8	(80.52% ±0.12)
CF8	(82.14%±0.15)

KINETICS ANALYSIS

The *in vitro* dissolution study results were fitted into 0 order first order Higuchi Koresmeyer peppas and Hixson Crowel model to find out the *in vitro* kinetic release studies. The result indicated the the values follow first order reaction.

According to values of koresmeyer peppas equation which is greater than one indicates it follows supercase II transport which means it follows more than one mechanism.

EVALUATION OF BEST FORMULATION:

a) Infrared (IR) spectroscopic studies:

Infrared (IR) spectroscopic studies were carried out for pure drug, excipients and selected SMEDDS formulations (CF8 and OF8). The spectra studied at 4000cm-1 to 400 cm-1 were shown in **(Table 15) and (Figure 18(a)to 18(e))**. It was found from the spectra that there was no major shifting as well as any loss of functional peaks in the spectra of drug, excipients and selected formulations (CF8 & OF8). This clearly indicated that there was no interaction between the drug and the polymer and the drug was present in its unchanged form.

b) Morphological studies of S-SMEDDS by using Scanning Electron Microscopy (SEM):

The surface morphology of the pure drug and solid SMEDDS were examined by the SEM and the images are represented in figure 19 (a) and 19(b). The typical crystalline structure of Pitavastatin as shown in figure 19 (a) was absent in S-SMEDDS of Pitavastatin, which indicates the transformation of the drug from crystalline state tto amorphous state i.e the drug is completely solubilised in oil phase of L-SMEDDS.

c) X-ray Powder Diffraction (XRPD) analysis:

The PXRD patterns of pure drug (Pitavastatin) and formulations (OF8 & CF8) were presented in (Figure 20(a) and 20(b).The XRPD patterns of pure

drug showed numerous sharp peaks (at 2θ 15.00°, 16.80°, 20.90°, 23.00°, 25.40° and 34.31°) which are the characteristic of a crystalline compound. And these peaks are absent in the PXRD pattern of SMEDDS indicating the transformation crystalline nature to Amorphous nature.

d) Determination of Particle size and Zeta potential:

The results of Particle size, zeta potential and Polydispersibility index of the best formulations CF8 and OF8 was shown in **figure 21 (a) -21 (d).** The particle size of the S-SMEDDS was found to be 139.5 nm and 621.3 nm with polydispersibility index of 0.291 and 0.377 for OF8 and CF8 respectively. Since the value of polydispersibility index is less than 1 indicates uniform distribution of droplets throughout the formulation. And the zeta potential values of the best formulation were found to be -23.9 and -20.9 for CF8 and OF8 respectively. The negative zeta potential indicates the stable formulation.

e) Differential Scanning Calorimetry:

Physical state of Pitavastatin in S-SMEDDS was characterized using differential scanning calorimeter. The DSC thermogram of S-SMEDDS formulation were shown in figure 22. The DSC thermogram of Pitavastatin showed a characteristic, sharp endothermic peak at corresponding to its melting point (less than 138^{o}C) and it indicates the crystalline nature of the drug. The DSC analysis of prepared SMEDDS formulation revealed negligible change in the melting point of Pitavastatin in the presence excipients, indicating no modification or interaction between the drug and excipients.

TABLE 1: CALIBRATION OF PITAVASTATIN CALCIUM USING PHOSPHATE BUFFER OF pH 6.8

S. No	Concentration (µg/ml)	Absorbance ±SD
1	1	0.109±0.004
2	2	0.201±0.009
3	3	0.282±0.014
4	4	0.371±0.019
5	5	0.465±0.008
6	6	0.557±0.003
7	7	0.637±0.013
8	8	0.739±0.013
9	9	0.827±0.013
10	10	0.92±0.013

REGRESSION VALUE: 0.99935±0.0002

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TABLE 2: SOLUBILITY OF PITAVASTATIN CALCIUM IN VARIOUS VEHICLES

S.NO	VEHICLE	SOLUBILITY (%)
1	Oleic acid	97.89±0.06
2	Capryol 90	93.69±0.31
3	Castor oil	20.44±0.41
4	Sesame oil	15.61±0.15
5	Sunflower oil	14.42±0.33
6	Tween 20	77.02±0.33
7	Twen 60	51.14±0.13
8	Tween 80	90.22±0.30
9	Cremophor RH 40	88.73±0.19
10	Span 80	30.64±0.15
11	Propylene glycol	93.07±1.03
12	Poly ethylene glycol 400	87.61±0.4

TABLE 3: % TRANSMITTANCE VALUES OF SURFACTANTS AND CO SURFACTANTS

S.NO	COMPONENTS	% TRANSMITTANCE VALUE	
		WITH OLEIC ACID	WITH CAPRYOL 90
1	Tween 20	35.15±0.14	93.72±0.14
2	Tween 60	40.62±0.25	84.77±0.14
3	Tween 80	93.52±0.22	87.70±0.28
4	Cremophor RH40	48.44±0.19	97.65±0.28
5	Span 80	40.37±0.09	53.78±0.37
6	PEG 400	93.30±0.17	94.36±0.20
7	Propylene glycol	95.29±0.10	97.82±0.27

TABLE 4 (a): FORMULATION OF SMEDDS USING OLEIC ACID, TWEEN 80, AND PROPYLENE GLYCOL AT THE S_{MIX} RATIO OF 3:1

FORMULATION CODE	DRUG	OLEIC AC-ID (%)	$S_{MIXTURE}$(TWEEN 80:PROPYLENE GLYCOL)(3:1) (%)
OF1	4 mg	10	90
OF2	4 mg	15	85
OF3	4 mg	20	80
OF4	4 mg	25	75
OF5	4 mg	30	70
OF6	4 mg	35	65
OF7	4 mg	40	60
OF8	4 mg	45	55
OF9	4 mg	50	50

TABLE 4 (b): FORMULATION OF SMEDDS USING CAPRYOL 90, CREMOPHORE RH AND PROPYLENE GLYCOL AT THE S_{MIX} RATIO OF 2:1.

FORMULATION CODE	DRUG	CAPRYOL 90 (%)	$S_{MIXTURE}$(CREMOPHORE RH:PROPYLENE GLYCOL)(2:1) (%)
CF1	4 mg	10	90
CF2	4 mg	15	85
CF3	4 mg	20	80
CF4	4 mg	25	75
CF5	4 mg	30	70
CF6	4 mg	35	65
CF7	4 mg	40	60
CF8	4 mg	45	55
CF9	4 mg	50	50

TABLE 5 (a): DISPERSIBILITY TEST AND VISUAL ASSESSMENT OF SMEDDS FORMULATION

CODE NO.	DISPERSIBILITY AND APPEAR-ANCE	SE TIME	GRADE
OF1	Clear and Transparent	Within 1 mint	A
OF2	Dull	Within1 mint	C
OF3	Transparent	Within 2 mints	B
OF4	clear	Within 1 mint	B
OF5	Dull	Within1 mint	A
OF6	Transparent	Within 1 mint	B
OF7	Clear	Within 3 mints	D
OF8	clear	Within 1 mints	D
OF9	clear	Within 1 mint	A

TABLE 5 (b): DISPERSIBILITY TEST AND VISUAL ASSESSMENT OF SMEDDS FORMULATION

CODE NO.	DISPERSIBILITY AND APPEAR-ANCE	SE TIME	GRADE
CF1	Clear and transparent	within 1 mint	A
CF2	Clear	within 1 mint	A
CF3	Transparent	within 1 mint	B
CF4	Clear	within 2 mints	A
CF5	Transparent	within 1 mint	A
CF6	Transparent	within 2 mints	B
CF7	Dull	within 3 mints	D
CF8	Clear	within 1 mint	A
CF9	Turbid	within 1 mint	E

TABLE 6 (a): THERMODYNAMIC STABILITY ASSESSMENT OF OLEIC ACID SMEDDS.

Formulation	Heating cooling cycle	Centrifugation	freeze thaw cycle
OF1	√	√	√
OF2	√	√	√
OF3	×	×	×
OF4	√	√	√
OF5	×	×	×
OF6	×	×	×
OF7	√	×	×
OF8	√	√	√
OF9	√	√	√

√ - Passed ×-Failed

TABLE 6 (b): THERMODYNAMIC STABILITY ASSESSMENT OF CAPRYOL 90 SMEDDS.

Formulation	Heating cooling cycle	Centrifugation	Freeze thaw cycle
CF1	√	√	√
CF2	√	√	√
CF3	×	×	×
CF4	√	√	√
CF5	√	√	√
CF6	√	√	√
CF7	√	√	√
CF8	√	√	√
CF9	√	√	√

√ - Passed ×-Failed

TABLE 7: MEASUREMENT OF CLOUD POINT

S.NO	FORMULATION	CLOUDPOINT (^{0}C)	FORMULATION	CLOUD POINT (^{O} C)
1	OF1	86.5	CF1	85.6
2	OF2	86	CF2	85
3	OF3	UNSTABLE	CF3	UNSTABLE
4	OF4	85	CF4	85
5	OF5	UNSTABLE	CF5	UNSTABLE
6	OF6	UNSTABLE	CF6	UNSTABLE
7	OF7	85	CF7	85
8	OF8	88	CF8	87
9	OF9	87	CF9	86

TABLE 8 (a): RESULTS OF ROBUSTNESS TO DILUTION

S.NO	MEDIUM	PHASE SEPARATION								
		OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
1	Distilled water	No	No	No	No	No	No	No	No	No
2	Phosphate buffer pH 6.8pH	No	No	No	No	No	yes	No	No	No
3	Phosphate buffer pH7.4	No	No	Yes	No	Yes	Yes	No	No	No

TABLE 8 (b): RESULTS OF ROBUSTNESS TO DILUTION

S.NO	MEDIUM	PHASE SEPARATION								
		CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
1	Distilled water	No	No	No	No	No	No	No	No	No
2	Phosphate buffer pH 6.8pH	No	No	Yes	No	No	yes	No	No	No
3	Phosphate buffer pH7.4	No	No	Yes	No	Yes	No	No	No	No

TABLE 9: REFRACTIVE INDEX AND % TRANSMITTANCE VALUES

S.NO	FORMULATION	REFRACTIVE INDEX	%TRANSMITTANCE	FORMULATION	REFRACTIVE INDEX	%TRANSMITTANCE
1	OF1	1.341±0.0004	74.90±0.22	CF1	1.330±0.0004	93.38±0.17
2	OF2	1.338±0.0004	68.79±0.19	CF2	1.336±0.0004	90.58±0.23
3	OF3	UNSTABLE	UNSTABLE	CF3	UNSTABLE	UNSTABLE
4	OF4	1.340±0.0004	85.10±0.2	CF4	1.334±0.0004	91.04±0.20
5	OF5	UNSTABLE	UNSTABLE	CF5	UNSTABLE	UNSTABLE
6	OF6	UNSTABLE	UNSTABLE	CF6	UNSTABLE	UNSTABLE
7	OF7	1.340±0.0004	93.44±0.23	CF7	1.324±0.0004	80.10±0.21
8	OF8	1.333±0.0004	89.21±0.15	CF8	1.333±0.0004	97.47±0.18
9	OF9	1.338±0.0004	94.28±0.22	CF9	1.334±0.0004	95.08±0.16

TABLE 10: VISCOSITY MEASUREMENT OF SMEDDS

S.NO	FORMUALTION	VISCOSITY (cps)	FORMULATION	VISCOSITY (cps)
1	**OF1**	0.24540.002	**CF1**	0.8351±0.003
2	**OF2**	0.2476±0.0006	**CF2**	0.8342±0.004
3	**OF4**	0.2438±0.003	**CF4**	0.8251±0.005
4	**OF7**	0.2435±0.003	**CF7**	0.8234±0.004
5	**OF8**	0.2456±0.001	**CF8**	0.8178±0.005
6	**OF9**	0.2928±0.002	**CF9**	0.8034±0.04

TABLE 11: DRUG CONTENT FOR L-SMEDDS

S.NO	FORMULATION	DRUG CONTENT (%)	FORMULATION	DRUG CONTENT (%)
1	**OF1**	96.53±0.04	**CF1**	96.41±0.10
2	**OF2**	95.45±0.12	**CF2**	95.30±0.16
3	**OF3**	97.23±0.05	**CF3**	92.79±0.16
4	**OF4**	97.24±0.10	**CF4**	95.67±0.12
5	**OF5**	97.07±0.17	**CF5**	96.83±0.13
6	**OF6**	97.26±0.22	**CF6**	97.22±0.14
7	**OF7**	96.37±0.14	**CF7**	97.29 ±0.22
8	**OF8**	97.8±0.08	**CF8**	97.33±0.52
9	**OF9**	97.43±0.09	**CF9**	97.17±0.50

TABLE 13: DRUG CONTENT OF S-SMEDDS FORMULATION

S.NO	FORMULATION	DRUG CONTENT (%)	FORMULATION	DRUG CONTENT (%)
1	OF1	97.28±0.05	CF1	97.54±0.11
2	OF2	96.86±0.08	CF2	97.50±0.15
3	OF3	96.79±0.07	CF3	96.62±0.18
4	OF4	97.48±0.13	CF4	97.82±0.12
5	OF5	97.38±0.04	CF5	97.30±0.02
6	OF6	97.59±0.06	CF6	97.52±0.15
7	OF7	96.54±0.21	CF7	97.72±0.03
8	OF8	98±0.09	CF8	98.02±0.07
9	OF9	92.13±0.09	CF9	97.73±0.08

TABLE 12 (a): CHARACTERIZATION OF MICROMERITIC PROPERTIES OF S- SMEDDS

S.NO	PARAMETER	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
1	Angle of Repose	28°12'± 1 °23'	28°13± 0° 43'	28°21'± 0° 21'	28°21'± 0 °21'	28°14'± 0° 12'	28°26'± 0 °32'	28°34'± 0° 46'	28°38' ±1°39'	28°31' ± 0 °51'
2	Bulk density g/ml	0.3422 ± 0.006	0.3416 ± 0.006	0.3423 ± 0.006	0.3381 ± 0.006	0.3445 ± 0.006	0.3423 ± 0.006	0.3427 ± 0.006	0.3436 ± 0.006	0.3425 ± 0.006
3	Tapped density	0.4023 ± 0.001	0.4034 ± 0.001	0.4041 ± 0.001	0.4045 ± 0.001	0.4021 ± 0.01	0.4035 ± 0.006	0.4042 ± 0.006	0.4043 ± 0.001	0.4038 ± 0.006
4	Carr's index %	15.17 ± 0.001	15.18 ± 0.001	15.02 ± 0.001	15.02 ±0.001	15.18 ±0.001	15.12 ±0.001	15.17 ±0.001	15.01 ±0.001	15.18 ±0.001
5	Hausner's ratio	1.18 ±0.02	1.17 ±0.02	1.19 ±0.02	1.18 ±0.02	1.17 ±0.02	1.17 ±0.02	1.18 ±0.02	1.17 ±0.002	1.19 ±0.02

TABLE 12 (B): CHARACTERIZATION OF MICROMERITIC PROPERTIES.

S.NO	PARAME-TER	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
1	Angle of Repose	28°12± 1 °23’	28°13± 0 °43’	28°21± 0 °21’	28°21± 0 °21’	28°14± 0 °12’	28°26± 0 °32’	28°34± 0 °46’	26°54’± 1°39’	28°31± 0 °51’
2	Bulk density g/ml	0.3422 ± 0.006	0.3416 ±0.006	0.3423 ±0.006	0.3381 ±0.006	0.3445 ±0.006	0.3423 ±0.006	0.3427 ±0.006	0.3423 ±0.006	0.3425 0.006
3	Tapped density	0.4023 ±0.001	0.4034 ±0.001	0.4041 ±0.001	0.4045 ±0.001	0.4021 ±0.01	0.4035 ±0.006	0.4042 ±0.006	0.4040 ±0.001	0.4038 ±0.006
4	Carr’s index %	15.17 ±0.001	15.18 ±0.001	15.02 ±0.001	15.02 ±0.001	15.18 ±0.001	15.12 ±0.001	15.17 ±0.001	15.27 ±0.001	15.18 ±0.001
5	Hausner’s ratio	1.18 ±0.02	1.17 ±0.02	1.19 ±0.02	1.18 ±0.02	1.17 ±0.02	1.17 ±0.02	1.18 ±0.02	1.18 ±0.02	1.19 ±0.02

TIME IN MINUTES	% CUMULATIVE DRUG RELEASE								
	OF1	OF2	OF3	OF4	OF5	OF6	OF7	OF8	OF9
0	0	0	0	0	0	0	0	0	0
5	67.22 ±0.45	66.57 ±0.17	63.56 ±0.18	63.56 ±0.18	68.75± 0.48	65.07 ±0.36	69.59 ±0.39	69.49 ±0.16	69.19 ±0.511
10	71.57 ±0.67	70.21 ±0.53	66.48 ±0.15	66.41 ±0.31	69.73 ±0.23	66.27 ±0.36	70.59 ±0.13	70.41 ±0.17	70.67 ±0.34
20	72.07 ±0.15	71.55 ±0.09	70.74 ±0.25	69.6 8±0.18	70.3 7±0.08	68.02 ±0.27	71.67 ±0.28	71.19 ±0.18	72.96 ±0.20
30	73.53 ±0.10	72.52 ±0.13	71.2 7±0.13	70.88 ±0.41	71.06 ±0.21	69.86 ±0.31	72.65 ±0.31	72.22 ±0.13	73.55 ±0.13
45	74.27 ±0.16	73.31 ±0.23	71.88 ±0.24	71.59 ±0.32	71.98 ±0.34	71.05 ±0.21	74.54 ±0.23	73.20 ±0.12	75.53 ±0.13
60	74.72 ±0.07	74.6 3±0.17	73.09 ±0.28	71.86 ±0.31	73.1 1±0.29	72.71 ±0.37	76.63 ±0.30	74.38 ±0.14	77.01 ±0.40
80	75.15 ±0.20	75.67 ±0.21	74.30 ±0.35	72.71 ±0.28	73.97 ±0.26	74.62 ±0.16	77.52 ±0.23	75.63 ±0.17	79.21 ±0.47
100	75.66 ±0.30	76.07 ±0.46	75.44 ±0.20	73.46 ±0.20	74.89± 0.37	75.50 ±0.19	79.06 ±0.46	76.86 ±0.47	80.10 ±0.18
120	76.72 ±0.27	77.16 ±0.24	76.39 ±0.25	74.53 ±0.15	76.23 ±0.11	76.59 ±0.14	80.03 ±0.33	77.66 ±0.64	80.52 ±0.12

TABLE 14 (a): CUMULATIVE PERCENTAGE DRUG RELEASE FOR OLEIC ACID SMEDDS FORMULATION FOR 2 HOURS.

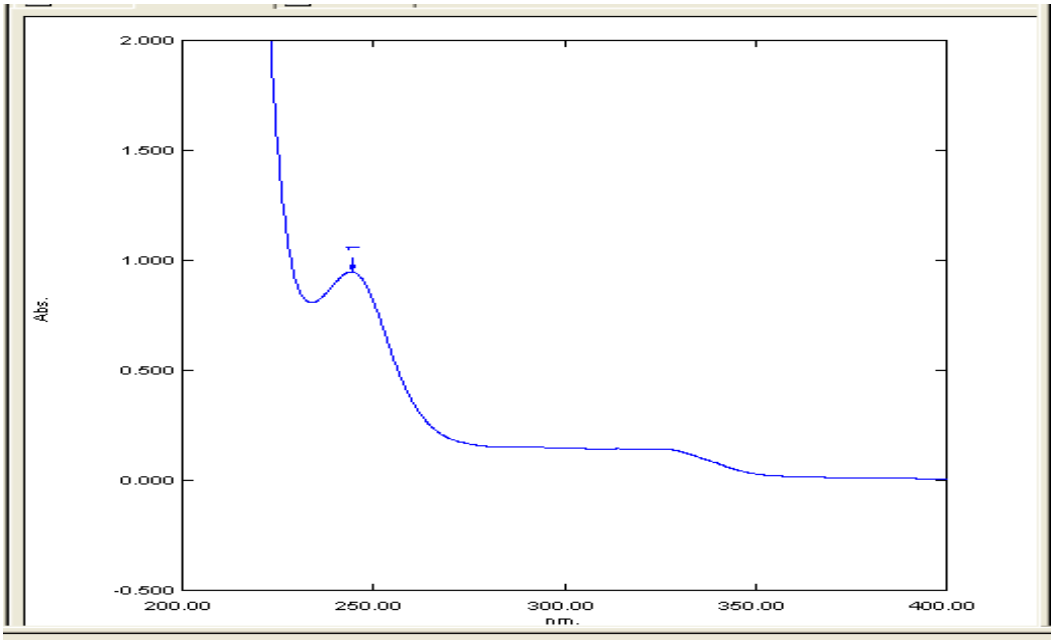
TIME IN MINTS	% CUMULATIVE DRUG RELEASE								
	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CF8	CF9
0	0	0	0	0	0	0	0	0	0
5	68.98 ±0.31	63.75 ±0.32	67.05 ±0.09	66.46 ±0.10	70.59 ±0.24	67.05 ±0.33	71.22 ±0.14	71.85 ±0.34	72.43 ±0.17
10	70.31 ±0.17	65.62 ±0.23	68.18 ±0.32	67.81 ±0.26	71.58 ±0.35	68.12 ±0.25	72.42 ±0.22	73.36 ±0.06	73.74 ±0.20
20	70.98 ±0.12	67.25 ±0.43	70.04 ±0.44	69.67 ±0.17	72.70 ±0.24	69.13 ±0.10	73.70 ±0.35	74.65 ±0.18	75.26 ±0.24
30	71.63 ±0.08	68.59 ±0.13	70.66 ±0.41	70.42 ±0.12	74.36 ±0.65	70.80 ±0.27	75.69 ±0.29	76.25 ±0.59	77.06 ±0.32
45	73 ±0.16	69.76 ±0.31	73.47 ±0.26	71.28 ±0.20	75.74 ±0.35	72.57 ±0.13	76.69 ±0.20	77.27 ±0.50	78.62 ±0.21
60	73.62 ±0.13	71.01 ±0.23	75.05 ±0.21	72.26 ±0.47	76.85 ±0.31	74.54 ±0.29	77.61 ±0.34	79.11 ±0.51	79.78 ±0.45
80	75.02 ±0.13	71.89 ±0.21	76.67 ±0.20	73.56 ±0.46	78.21 ±0.13	75.57 ±0.37	78.71±0 .35	80.14 ±0.18	80.59 ±0.22
100	75.72 ±0.16	72.85 ±0.27	78.46 ±0.35	74.53 ±0.34	79.40 ±0.22	76.72 ±0.16	80.64 ±0.21	80.93 ±0.17	81.58 ±0.31
120	76.46 ±0.10	74.79 ±0.32	79.59 ±0.16	77.02 ±0.24	80.45 ±0.18	78.51 ±0.38	81.77 ±0.21	82.14 ±0.15	81.98 ±0.25

TABLE 14 (b): CUMULATIVE PERCENTAGE DRUG RELEASE FOR CAPRYOL SMEDDS FORMULATION FOR 2 HOURS.

FORMULATION CODE	ZERO ORDER KINETICES		FIRST ORDER KINETICES		HIGUCHI MODEL		KORSMEYER PEPPAS MODEL		HIXSON CROWEL MODEL	
	R^2	$K_0(h^{-1})$	R^2	$K_0(h^{-1})$	R^2	$K_H(h^{-1/2})$	R^2	n	R^2	$K_{HC}(h^{-1/3})$
OF1	0.977	2.382	0.955	-0.038	0.979	18.01	0.973	1.459	0.936	-0.126
OF2	0.969	2.325	0.960	-0.037	0.981	17.25	0.959	1.524	0.949	-0.118
OF3	0.969	4.490	0.953	-0.036	0.983	17.18	0.964	1.451	0.944	-0.122
OF4	0.945	4.113	0.967	-0.031	0.963	15.48	0.936	1.497	0.906	-0.122
OF5	0.993	3.855	0.941	-0.029	0.992	15.77	0.949	1.452	0.927	-0.107
OF6	0.963	5.524	0.887	-0.054	0.972	21.31	0.956	1.470	0.921	-0.156
OF7	0.967	5.613	0.967	-0.054	0.977	21.73	0.959	1.483	0.924	-0.173
OF8	0.979	5.618	0.961	-0.054	0.966	22.01	0.948	1.453	0.938	-0.079
OF9	0.976	5.566	0.966	-0.050	0.974	21.73	0.954	1.518	0.932	-0.165
CF1	0.963	5.381	0.919	-0.049	0.980	20.77	0.953	1.573	0.914	-0.146
CF2	0.935	5.138	0.954	-0.047	0.978	19.61	0.947	1.541	0.894	-0.107
CF3	0.971	5.249	0.941	-0.045	0.980	20.44	0.959	1.464	0.939	-0.104
CF4	0.960	4.995	0.943	-0.043	0.986	19.38	0.976	1.475	0.976	-0.101
CF5	0.964	5.219	0.930	-0.044	0.984	20.37	0.960	1.471	0.937	-0.089
CF6	0.965	4.632	0.965	-0.043	0.982	17.76	0.966	1.484	0.971	-0.087
CF7	0.960	5.820	0.942	-0.038	0.949	22.60	0.942	1.462	0.941	-0.142
CF8	0.942	6.306	0.953	-0.060	0.989	25.04	0.981	1.520	0.982	-0.144
CF9	0.900	6.178	0.935	-0.061	0.983	24.54	0.976	1.537	0.980	-0.137

Table 15: *IN VITRO* KINETIC RELEASE STUDIES OF PITAVASTATIN SOLID SMEDDS

FIGURE 1: DETERMINATION OF λ_{max} FOR PITAVASTATIN CALCIUM



S.NO	WAVELENGTH	ABSORBANCE	DESCRIPTION
1	245nm	0.987	10µg/ml

FIGURE 1 (a): CALIBRATION CURVE FOR PITAVASTATIN CALCIUM USING PHOSPHATE BUFFER pH 6.8.

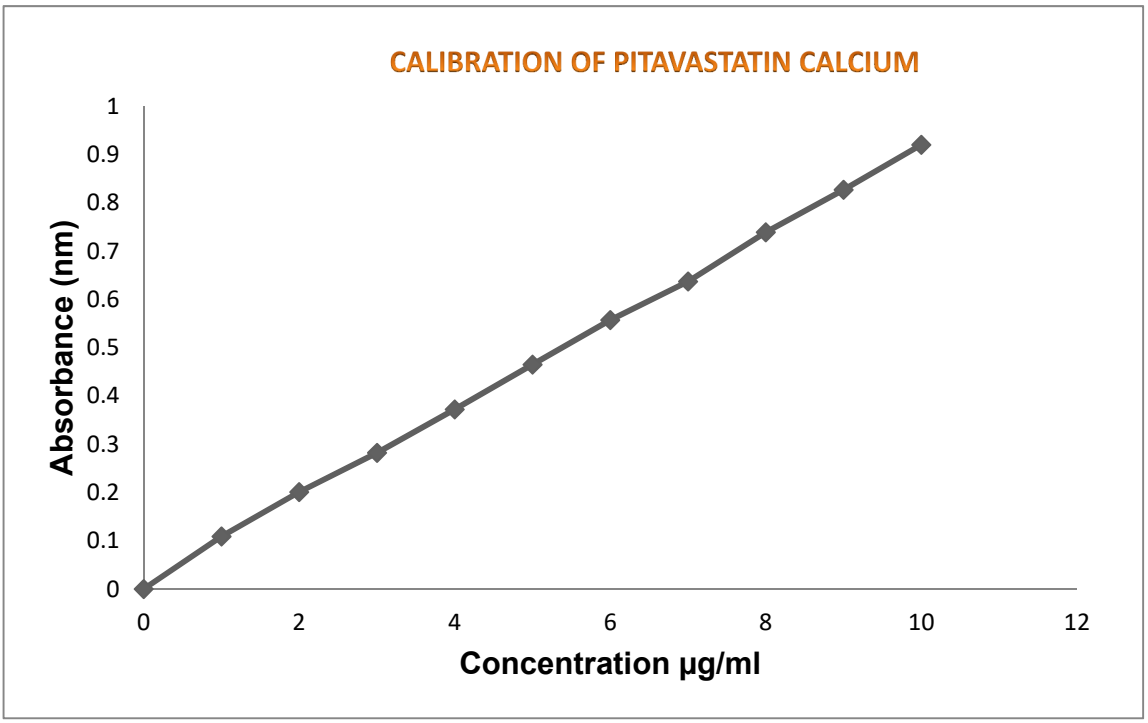


FIGURE 2 (a): IR SPECTRA OF PURE PITAVASTATIN CALCIUM

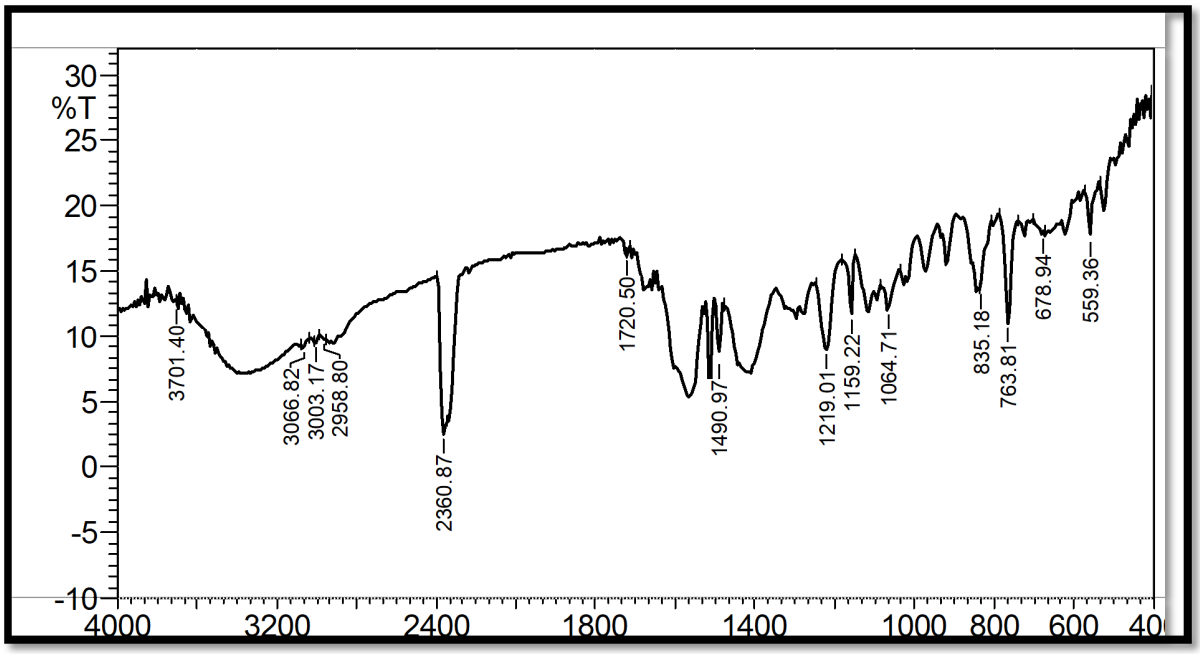


FIGURE 2 (b): IR SPECTRA OF OLEIC ACID

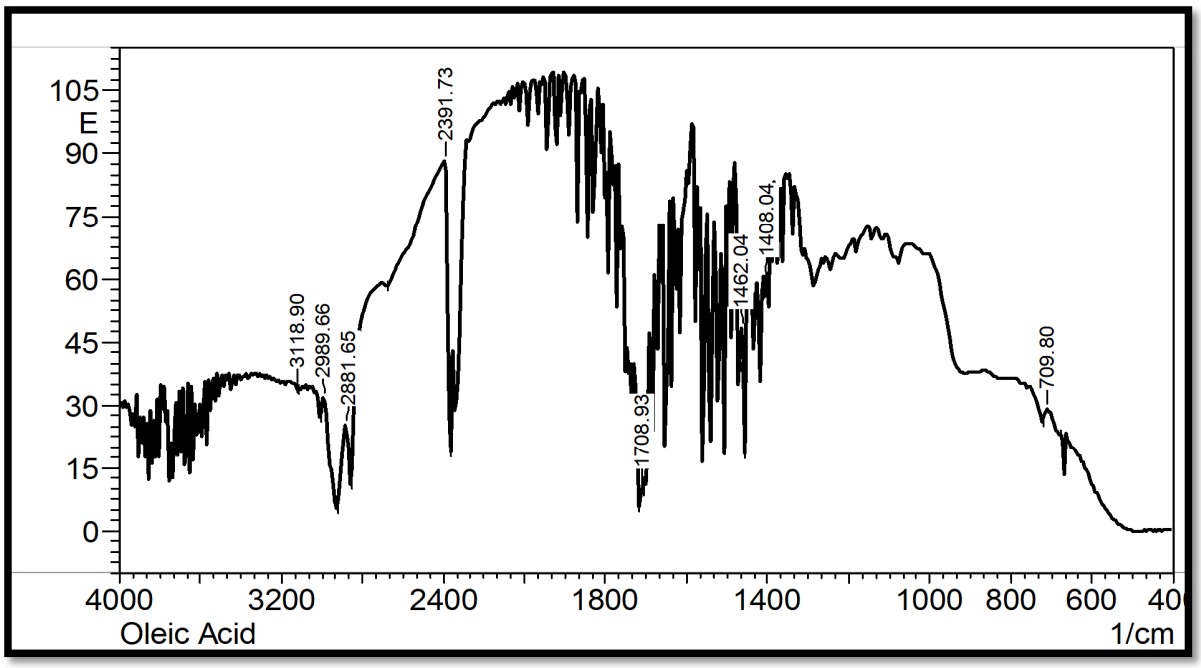


FIGURE 2 (c): IR SPECTRA OF CAPRYOL 90

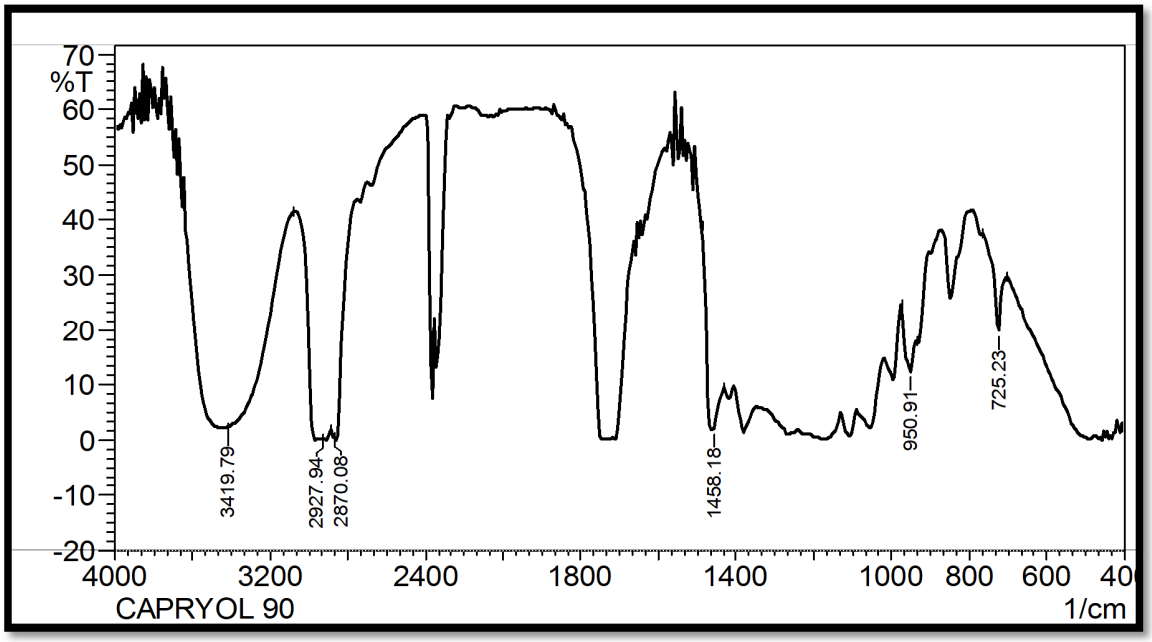


FIGURE 2 (d): IR SPECTRA OF TWEEN 80

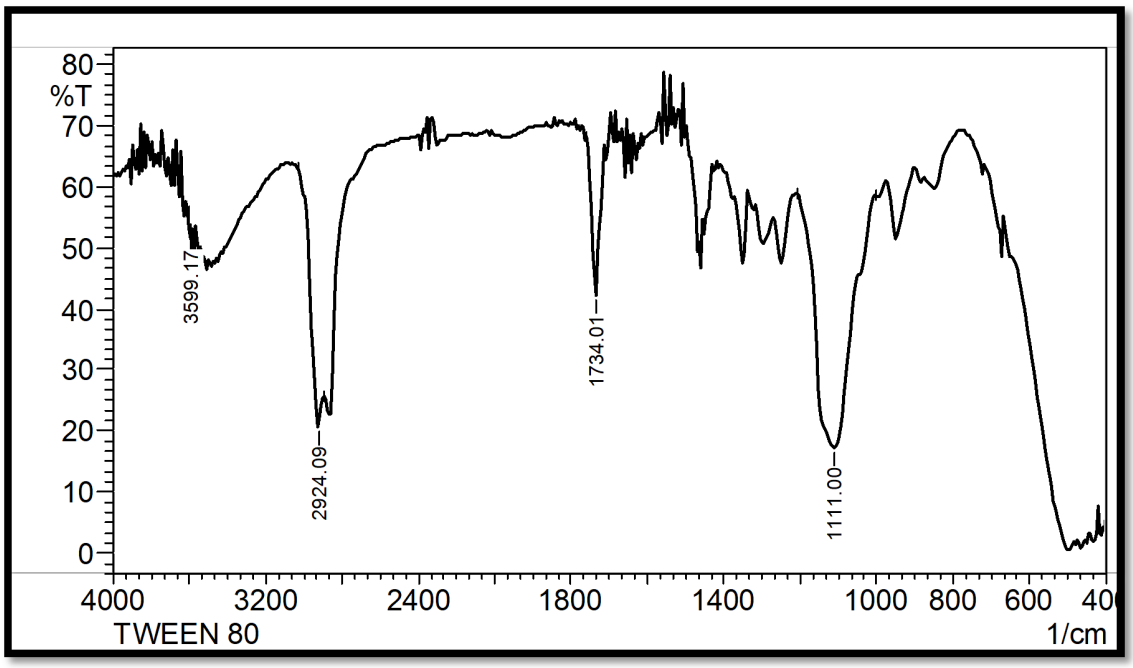


FIGURE 2 (e): IR SPECTRA OF PROPYLENE GLYCOL

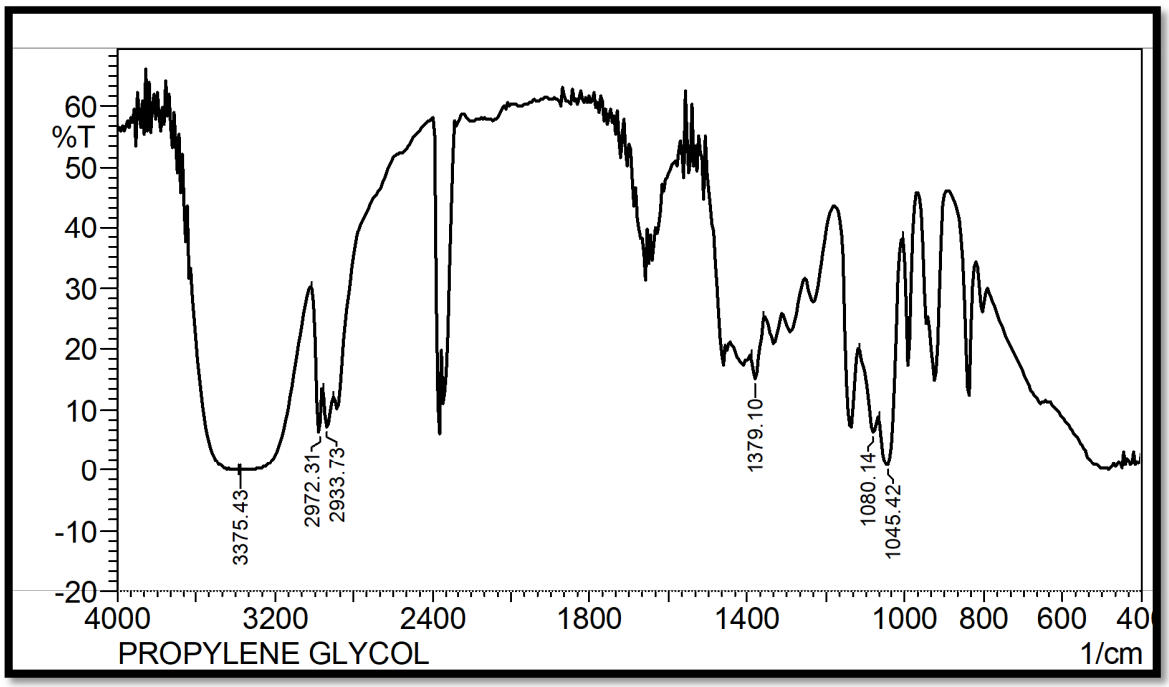


FIGURE 2 (f): IR SPECTRA OF MICRO CRYSTALLINE CELLULOSE

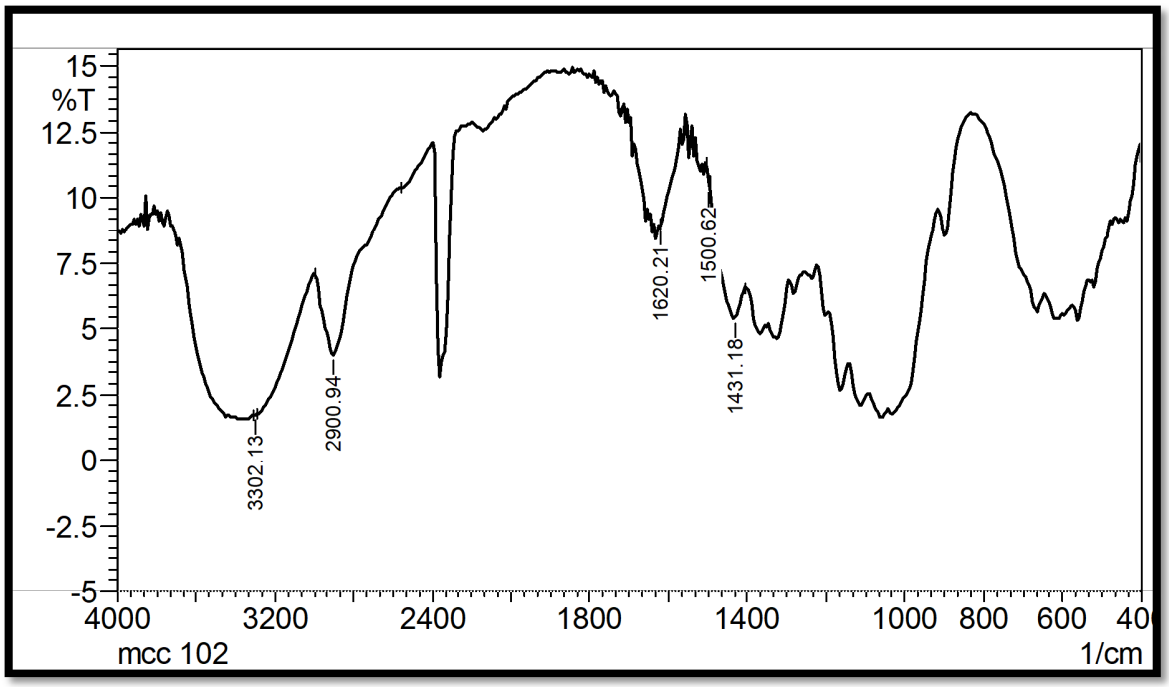


TABLE 16: IR INTERPRETATION OF COMPONENTS OF SMEDDS.

S.NO	MATERIAL	PEAK OBSERVATION
1	Pitavastatin	3066.82 cm^{-1}, 3003.17 cm^{-1}, 2958.80 cm^{-1}, 1720.50 cm^{-1}, 1490.97 cm^{-1},1219.01 cm^{-1},678.94 cm^{-1}
2	Oleic acid	3318.90 cm^{-1}, 2989.66 cm^{-1}, 2881 cm^{-1},1708.93 cm^{-1}, 1462.4 cm^{-1}, 1408 cm^{-1}, 709.8 cm^{-1}
3	Capryol 90	3421 cm^{-1}, 2928 cm^{-1},2871 cm^{-1}
4	Tween 80	3599.17 cm^{-1} , 2924.09 cm^{-1} , 1734.01 cm^{-1} , 1111 cm^{-1}
5	Propylene glycol	3375.43 cm^{-1} , 2972 cm^{-1}, 2933.73 cm^{-1},1379.^{10} cm^{-1} , 1080.14 cm^{-1} , 1045.42 cm^{-1}
6.	MCC 102	3302.13 cm^{-1}, 2900.94 cm^{-1}, 1620.21 cm^{-1}, 1500.62 cm^{-1} , 1431.18 cm^{-1}

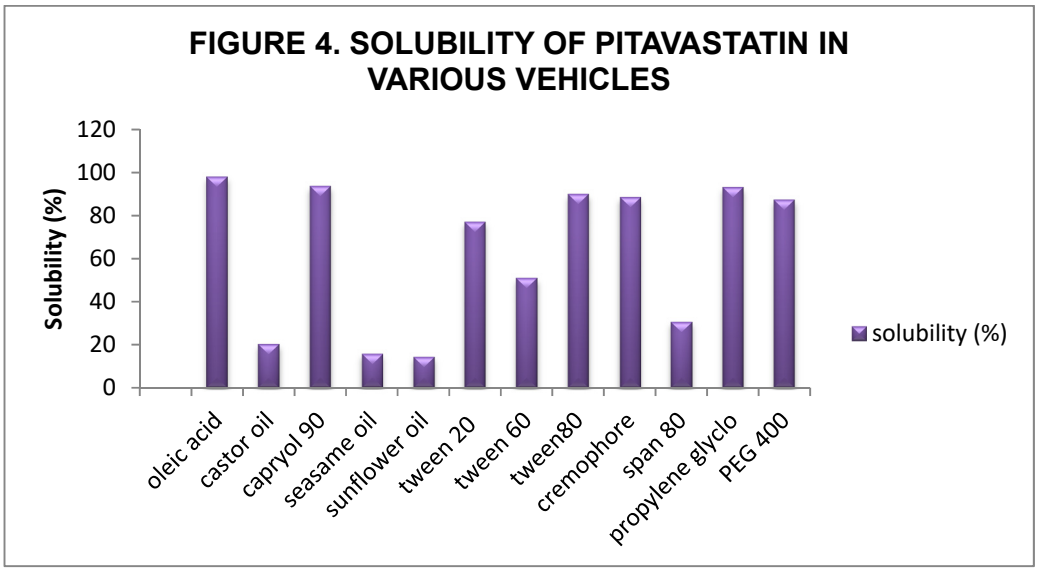


FIGURE 4. SOLUBILITY OF PITAVASTATIN IN VARIOUS VEHICLES
Solubility (%)
120
100
80
60
40
20
0
oleic acid
castor oil
capryol 90
seasame oil
sunflower oil
tween 20
tween 60
tween80
cremophore
span 80
propylene glyclo
PEG 400
solubility (%)

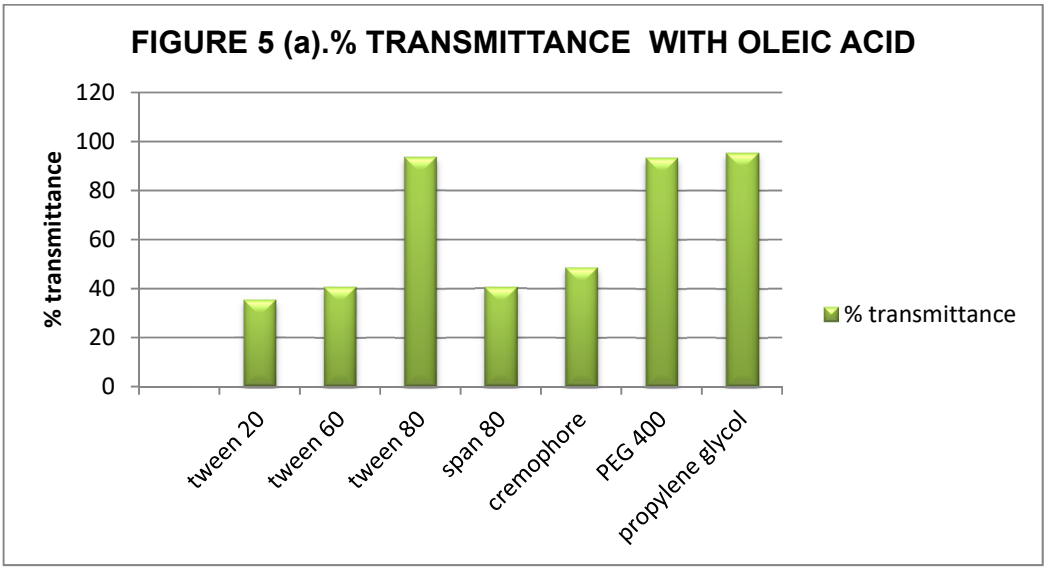


FIGURE 5 (a).% TRANSMITTANCE WITH OLEIC ACID
% transmittance
120
100
80
60
40
20
0
tween 20
tween 60
tween 80
span 80
cremophore
PEG 400
propylene glycol
% transmittance

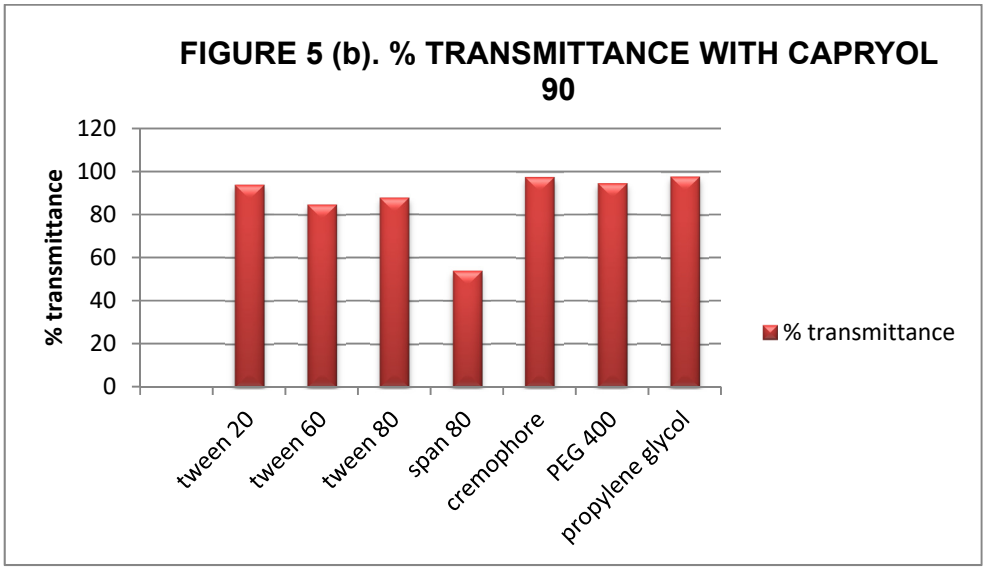


FIGURE 6 : PHASE DIAGRAM FOR OLEIC ACID & TWEEN 80: PROPYLENE GLYCOL

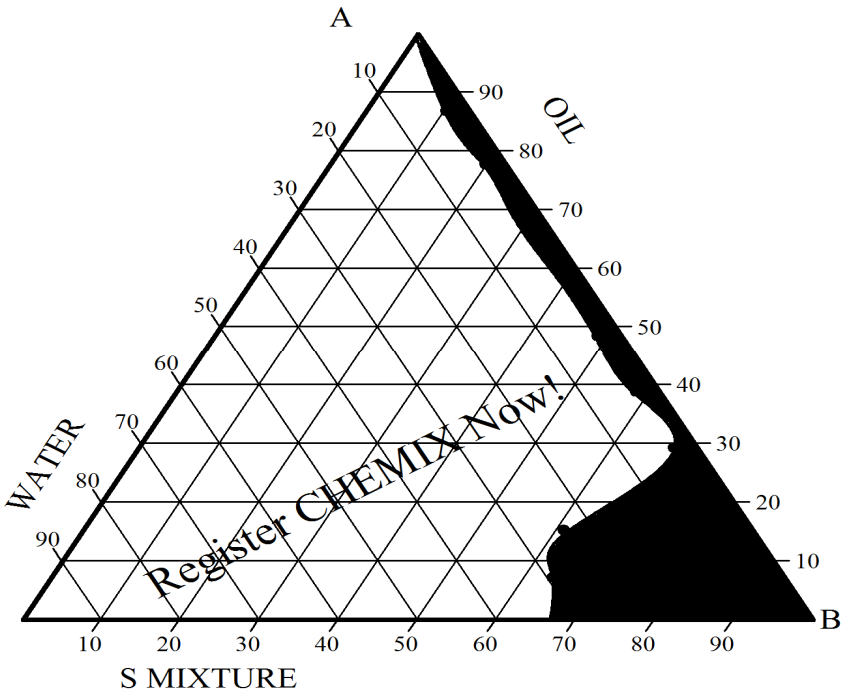


FIGURE 6 (a): $S_{MIXTURE}$ RATIO OF 1:1

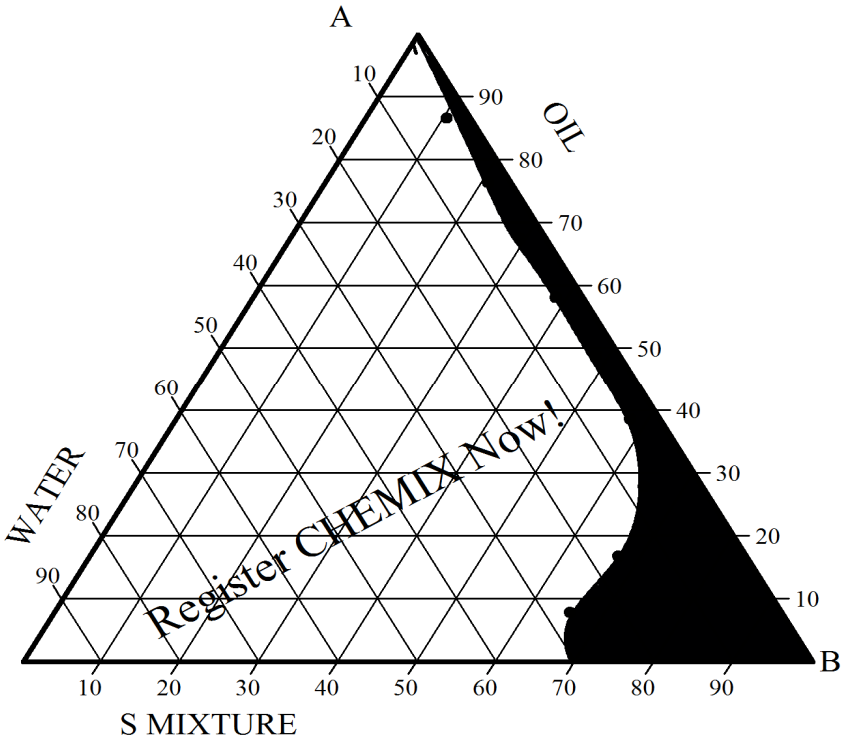


FIGURE 6 (b): $S_{MIXTURE}$ RATIO OF 2:1

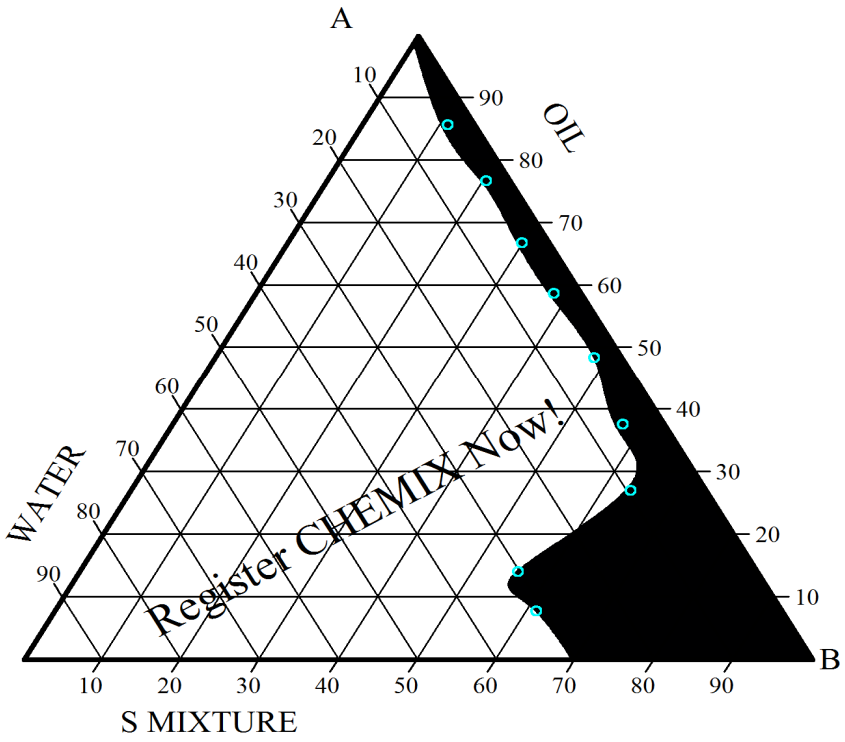


FIGURE 6 (c): S MIXTURE RATIO OF 3:1

FIGURE 7: PHASE DIAGRAM FOR CAPRYOL 90 AND CREMO-PHORE:PROPYLENE GCOL

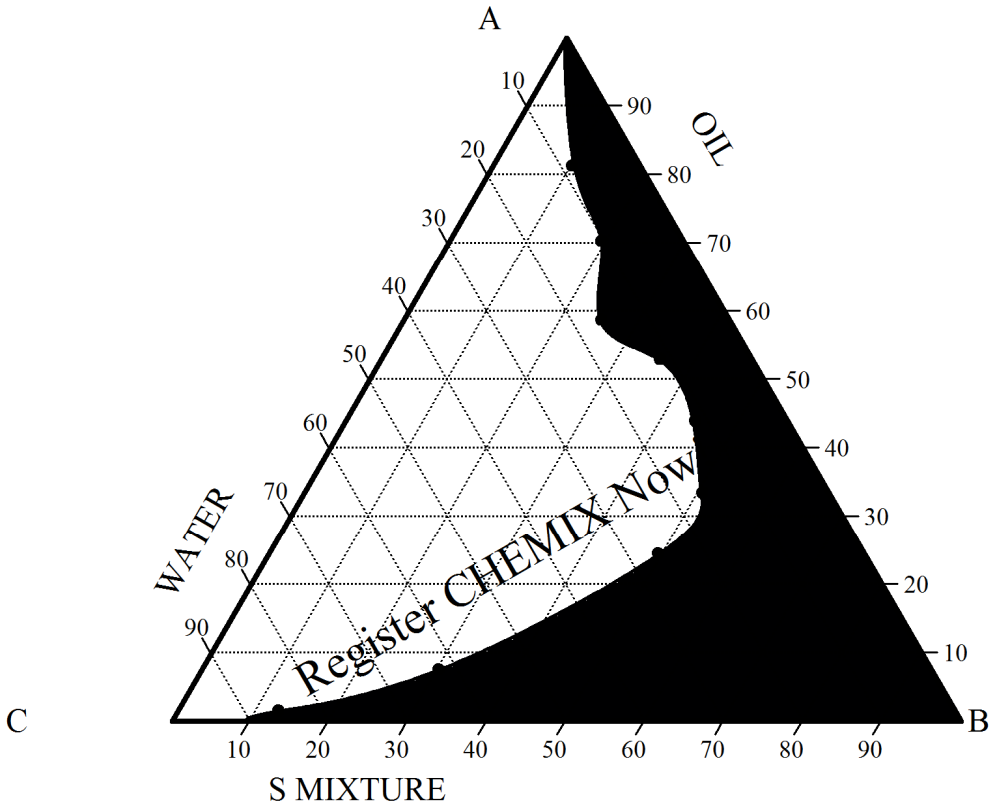


FIGURE 7 (a): $S_{MIXTURE}$ RATIO OF 1:1

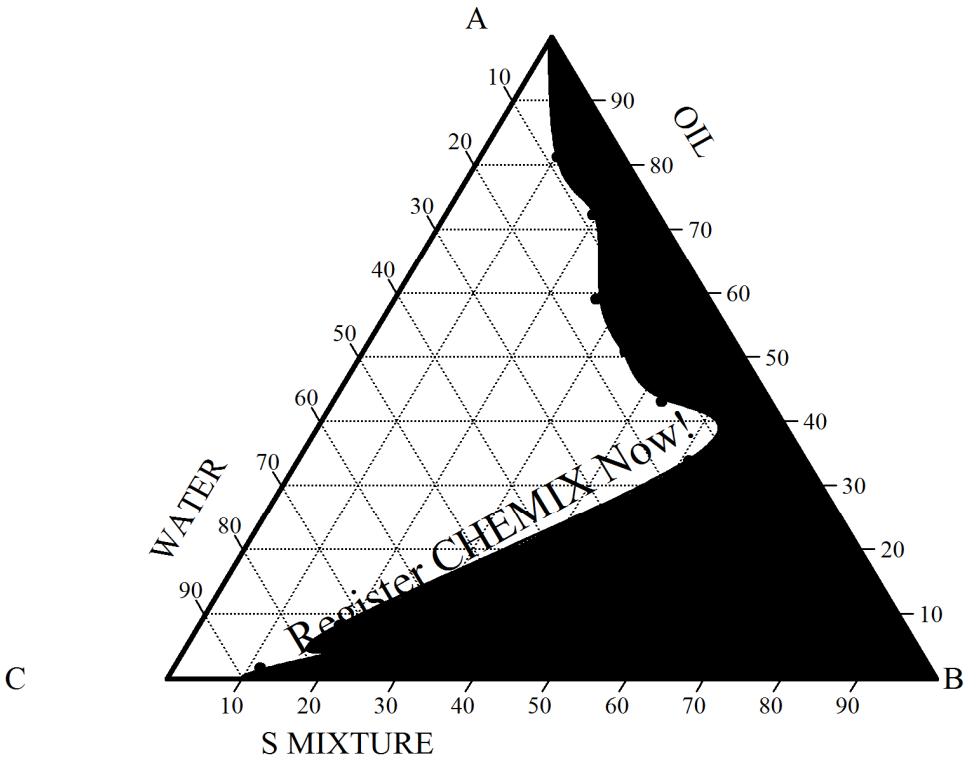


FIGURE 7 (b): $S_{MIXTURE}$ RATIO OF 2:1

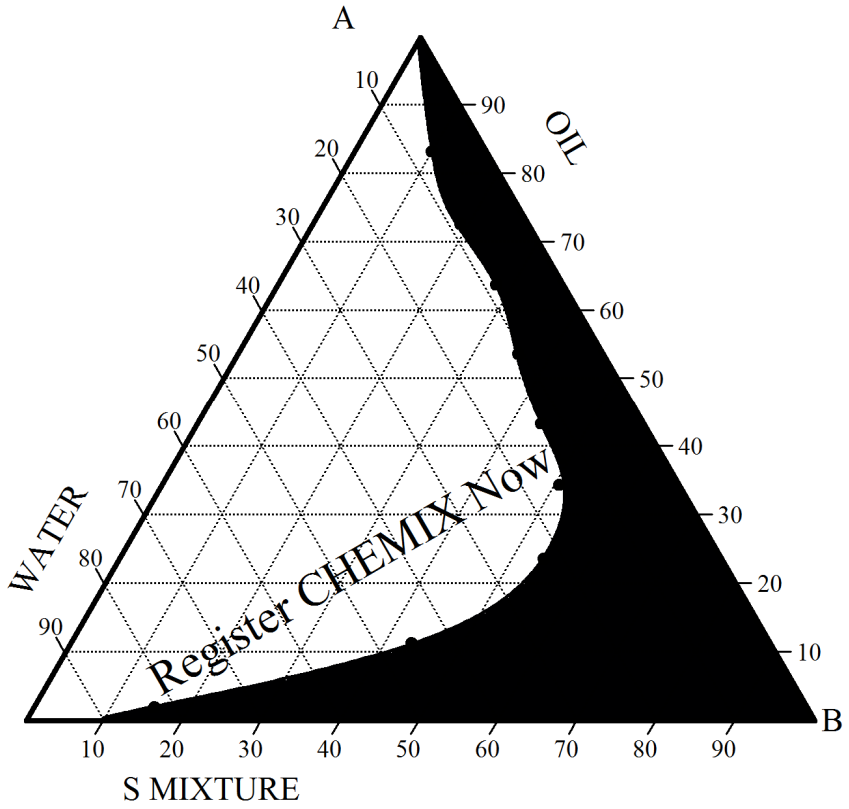
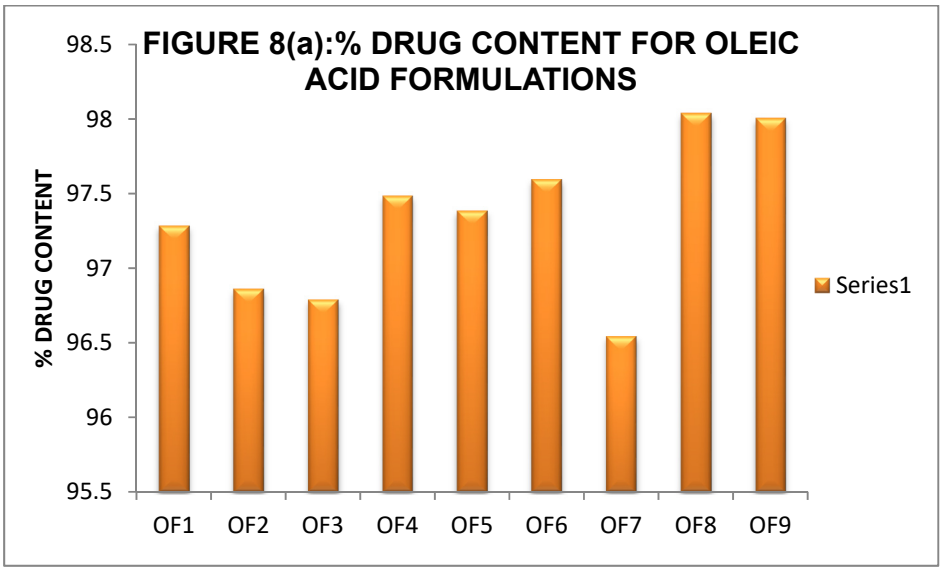


FIGURE 7 (C): $S_{MIXTURE}$ RATIO OF 3:1



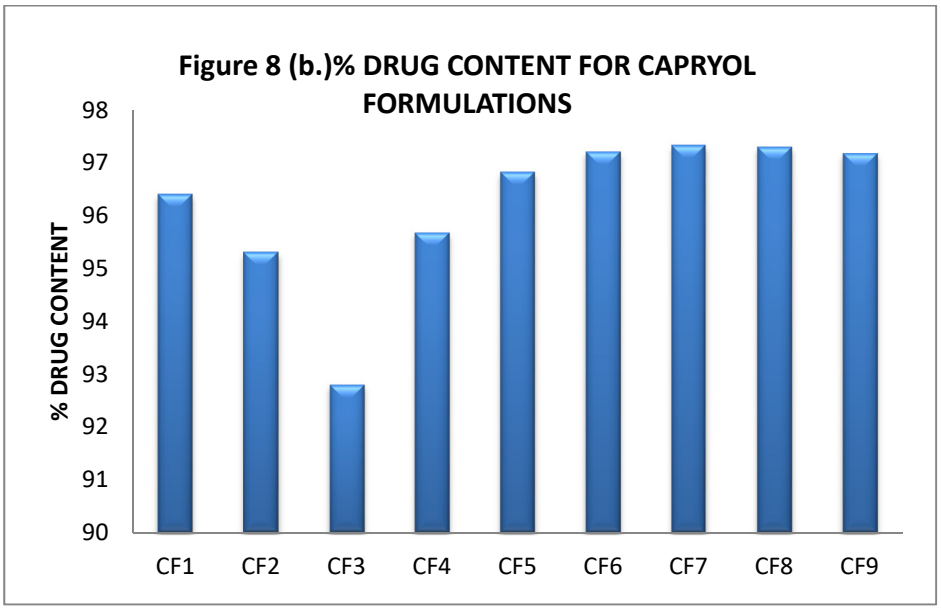


Figure 8 (b.)% DRUG CONTENT FOR CAPRYOL FORMULATIONS
% DRUG CONTENT
98
97
96
95
94
93
92
91
90
CF1
CF2
CF3
CF4
CF5
CF6
CF7
CF8
CF9

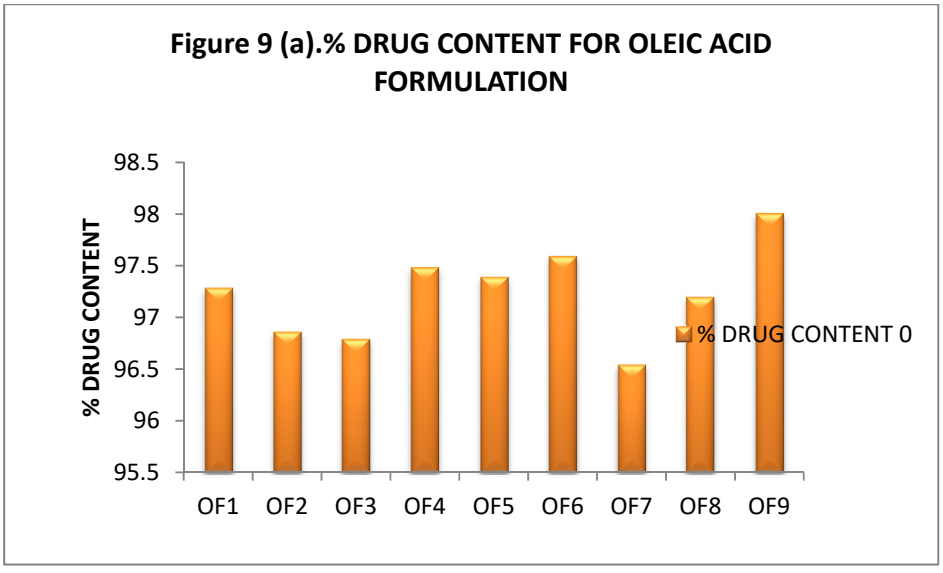


Figure 9 (a).% DRUG CONTENT FOR OLEIC ACID FORMULATION
% DRUG CONTENT
98.5
98
97.5
97
96.5
96
95.5
OF1
OF2
OF3
OF4
OF5
OF6
OF7
OF8
OF9
% DRUG CONTENT 0

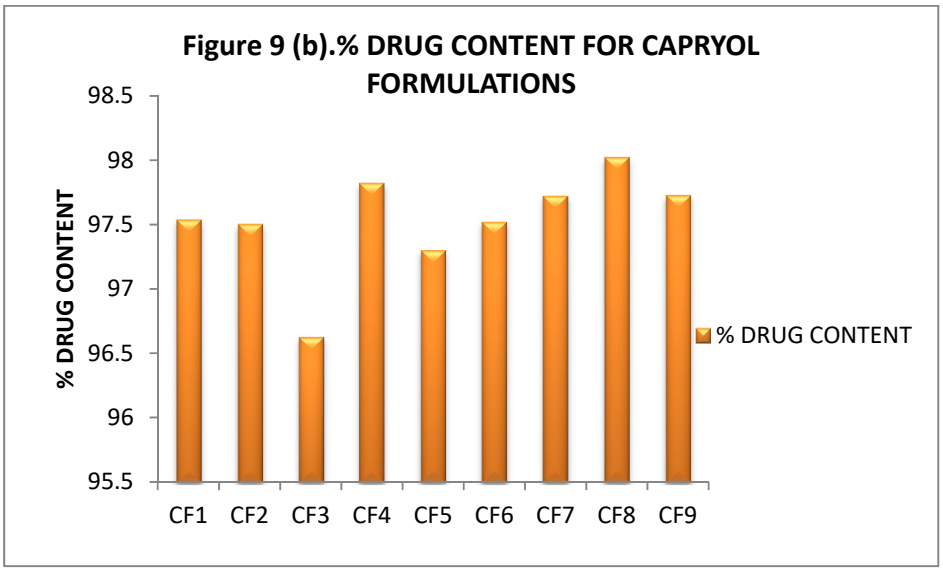
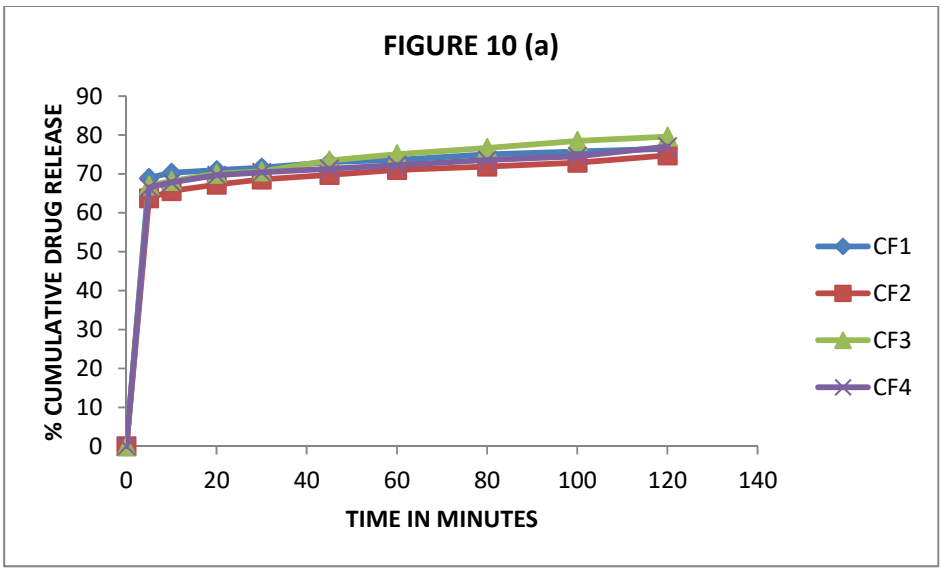


FIGURE 10 : COMPARISION OF *IN VITRO* RELEASE OF S-SMEDDS OF PITAVASTATIN-CAPRYOL FORMULATION



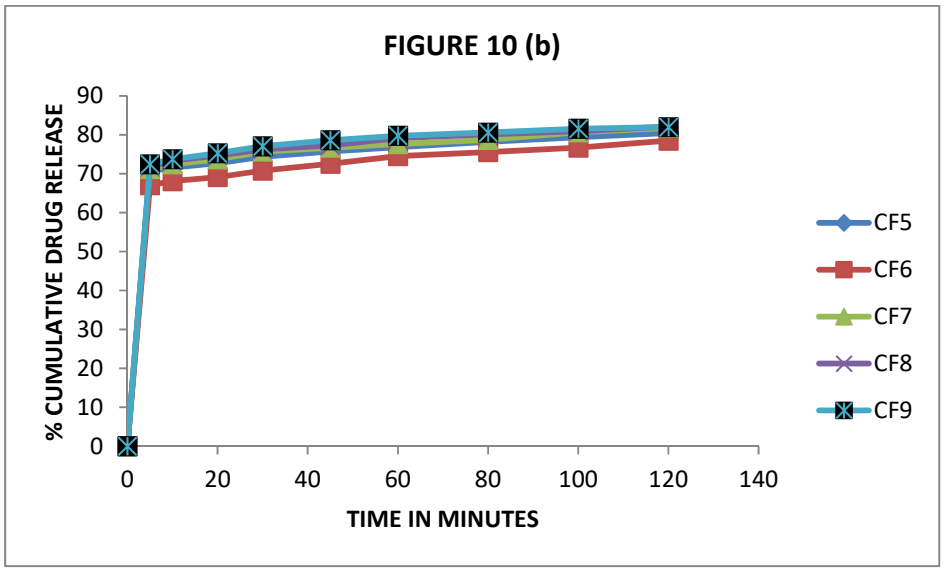
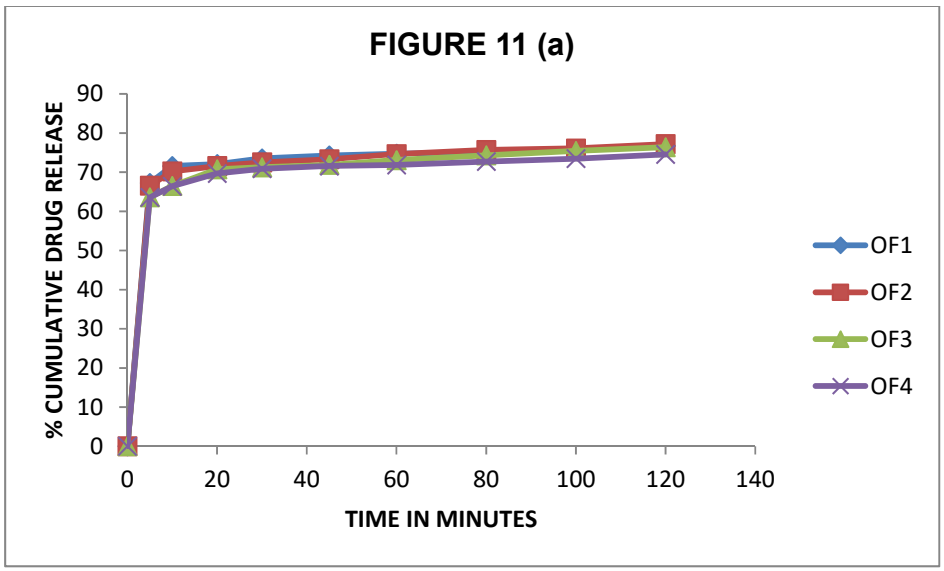


FIGURE 11: COMPARISION OF *IN VITRO* RELEASE OF S-SMEDDS OF PITAVASTATIN-OLEIC ACID FORMULATION



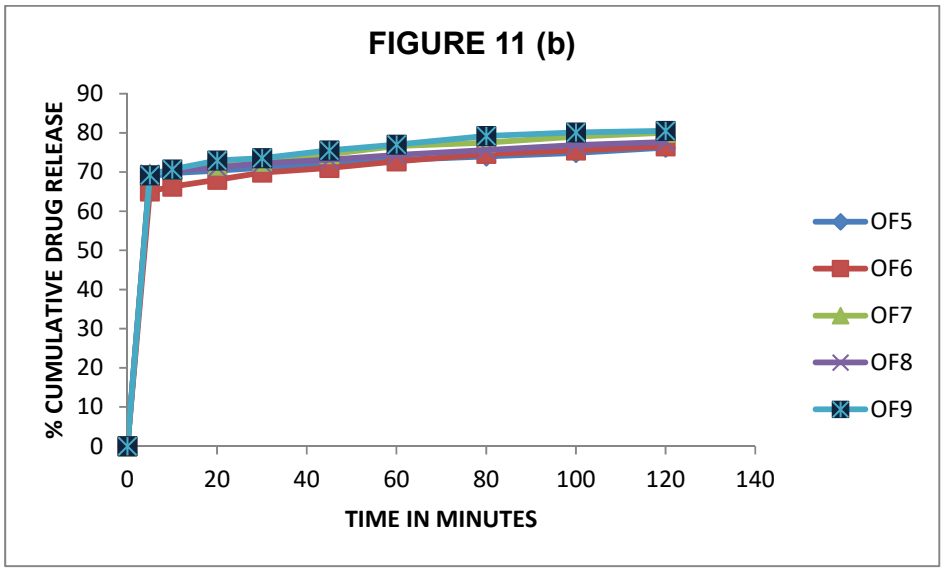


FIGURE 12 : COMPARISION OF *IN VITRO* DRUG RELEASE OF PURE DRUG, CONVENTIONAL TABLET AND SMEDDS FORMULATION

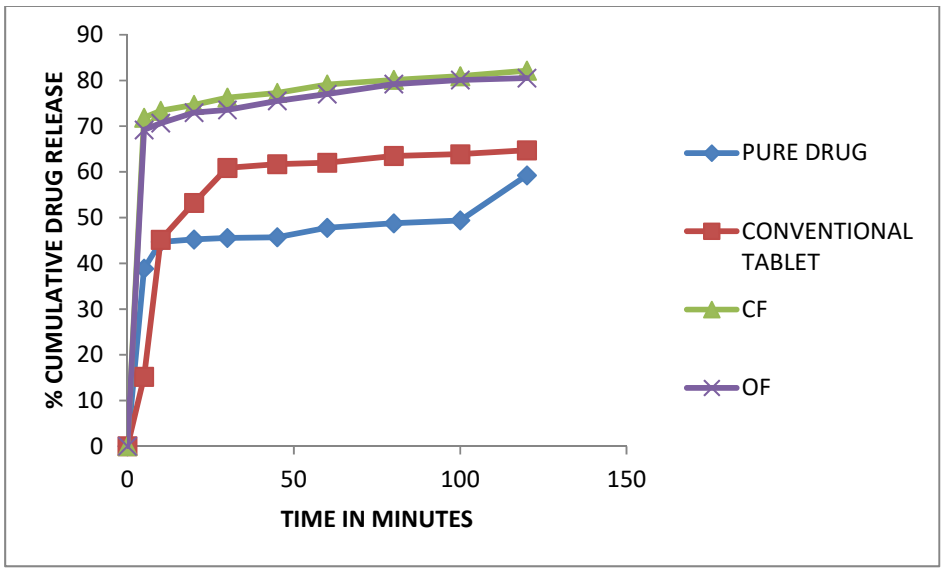
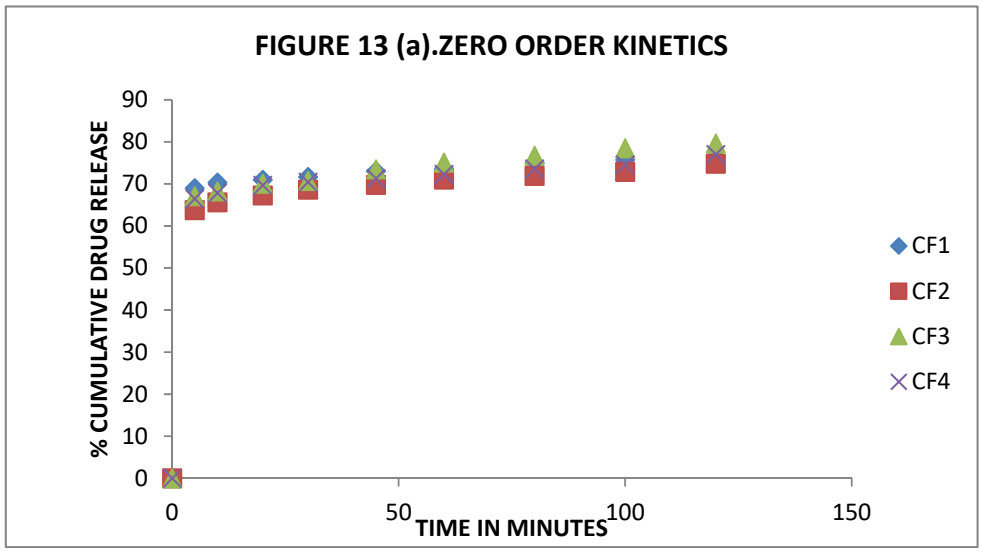
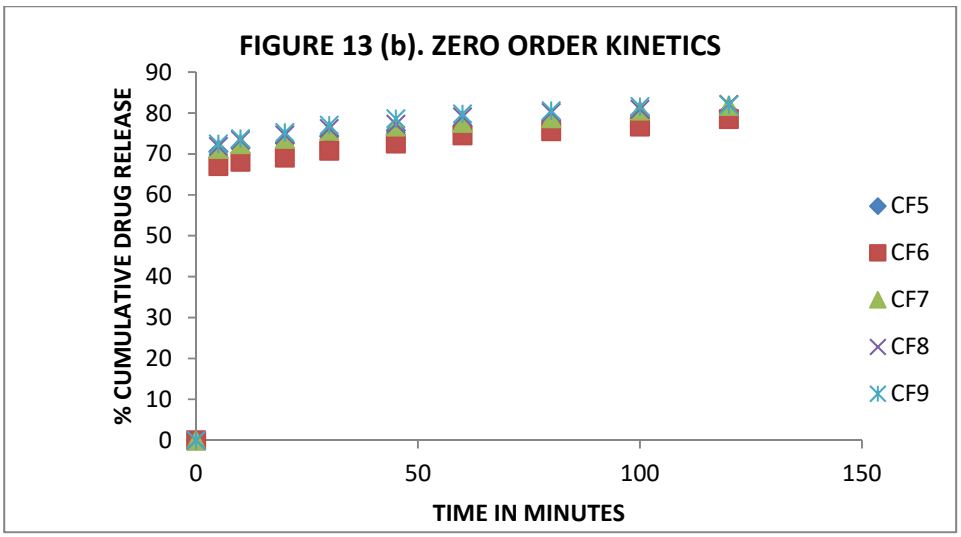


FIGURE 13.COMPARISION OF *IN VITRO* ZERO ORDER KINETICS OF PITAVASTATIN SMEDDS





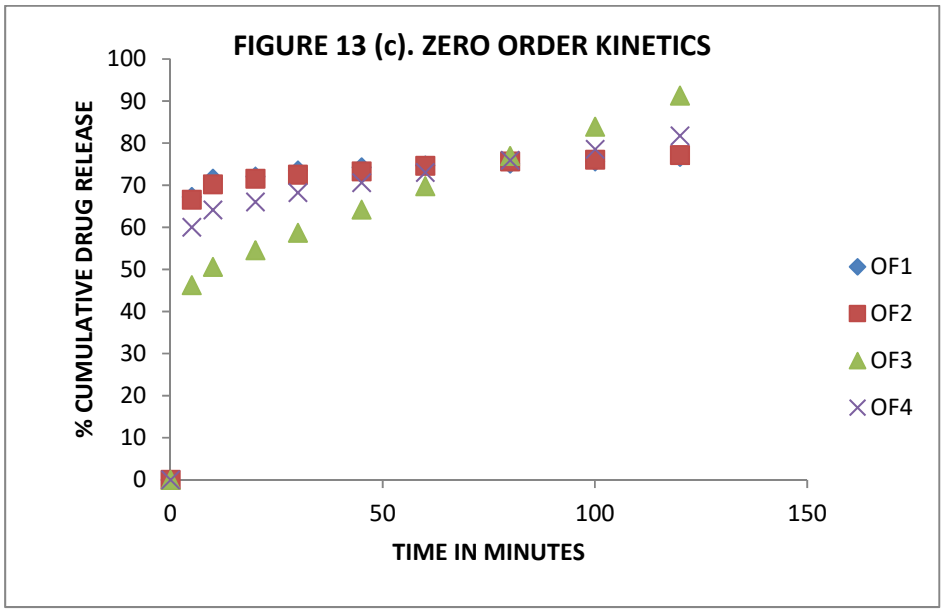


FIGURE 13 (c). ZERO ORDER KINETICS
% CUMULATIVE DRUG RELEASE
100
90
80
70
60
50
40
30
20
10
0
0
50
100
150
TIME IN MINUTES
OF1
OF2
OF3
OF4

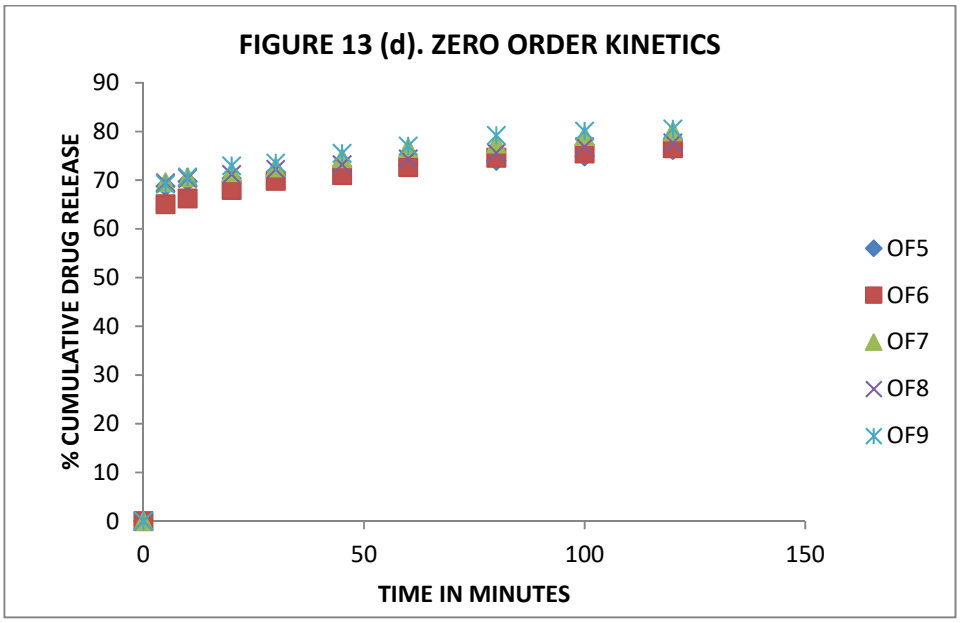
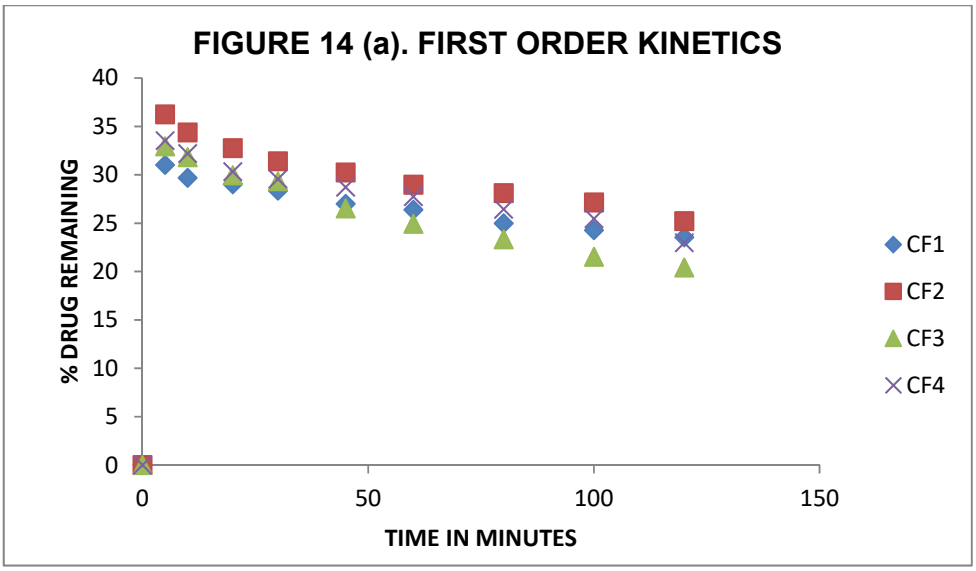
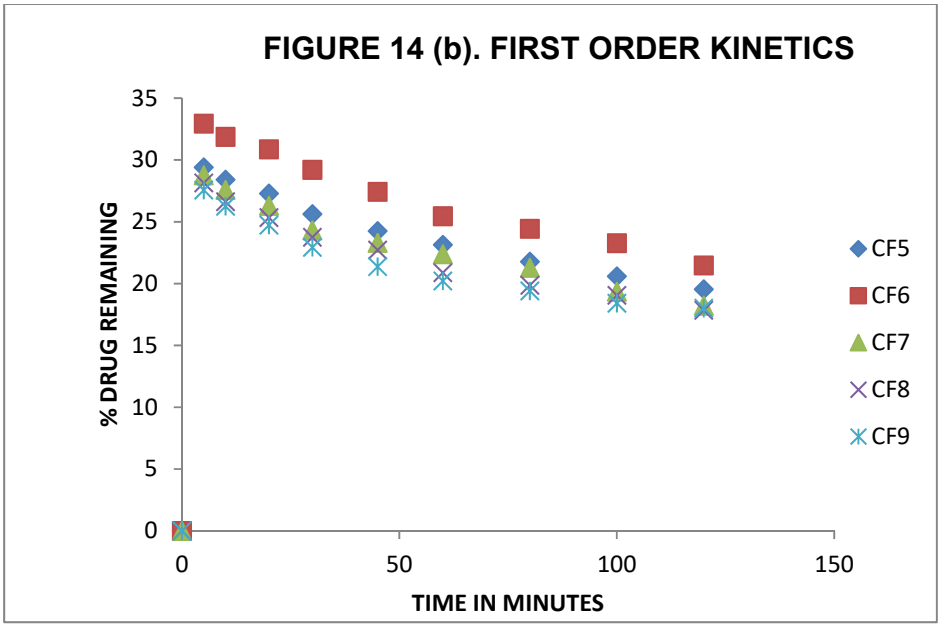


FIGURE 13 (d). ZERO ORDER KINETICS
% CUMULATIVE DRUG RELEASE
90
80
70
60
50
40
30
20
10
0
0
50
100
150
TIME IN MINUTES
OF5
OF6
OF7
OF8
OF9

FIGURE 14.COMPARISION OF *IN VITRO* FIRST ORDER KINETICS OF PITAVASTATIN SMEDDS





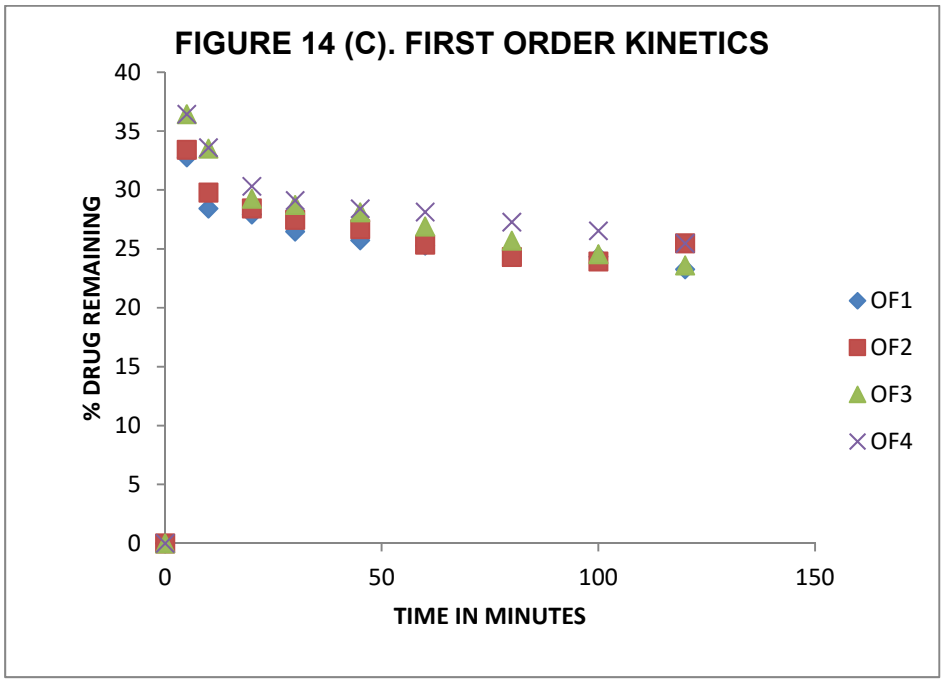


FIGURE 14 (C). FIRST ORDER KINETICS
% DRUG REMAINING
40
35
30
25
20
15
10
5
0
0
50
100
150
TIME IN MINUTES
OF1
OF2
OF3
OF4

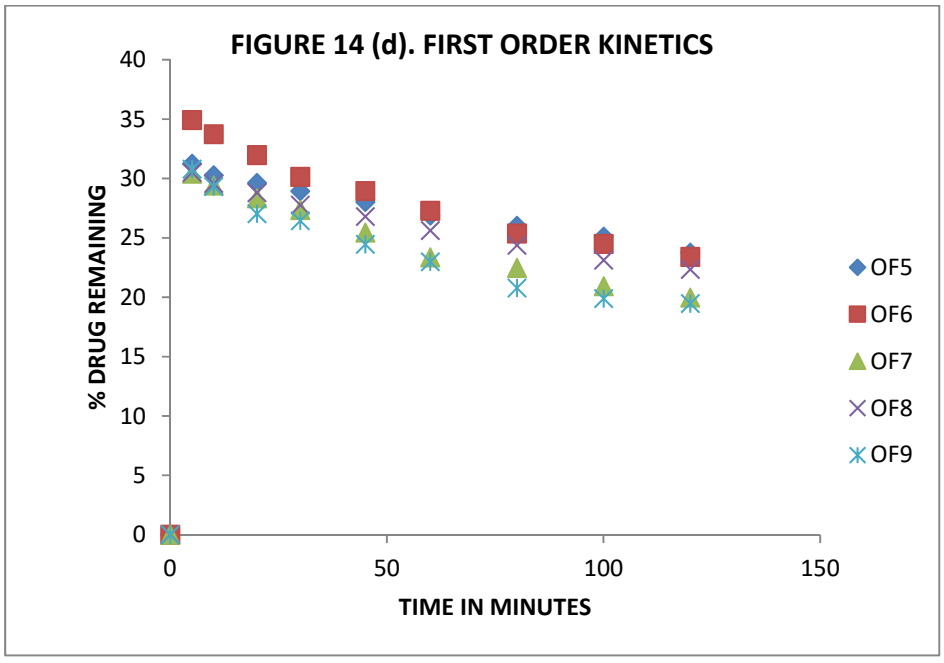
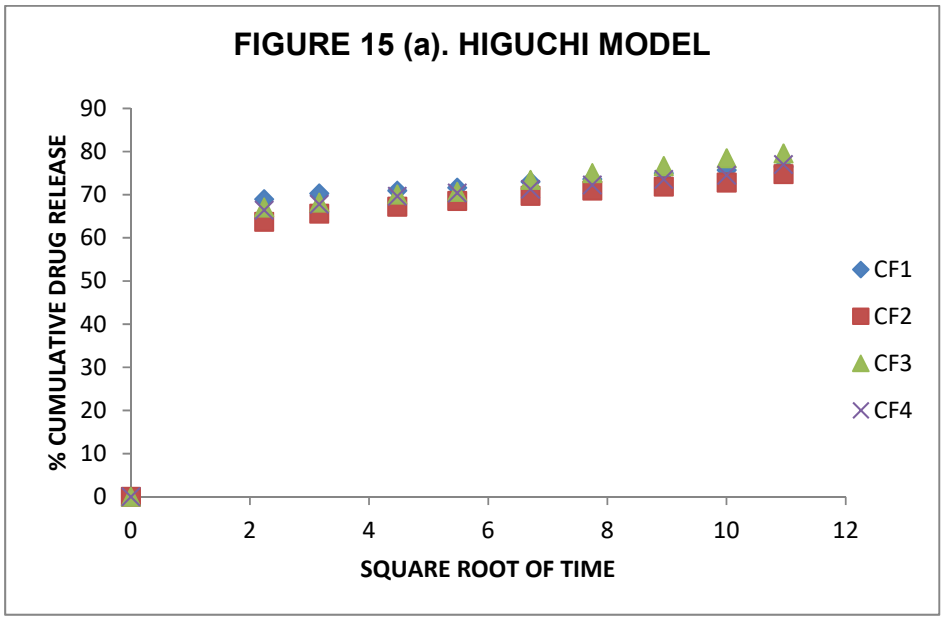
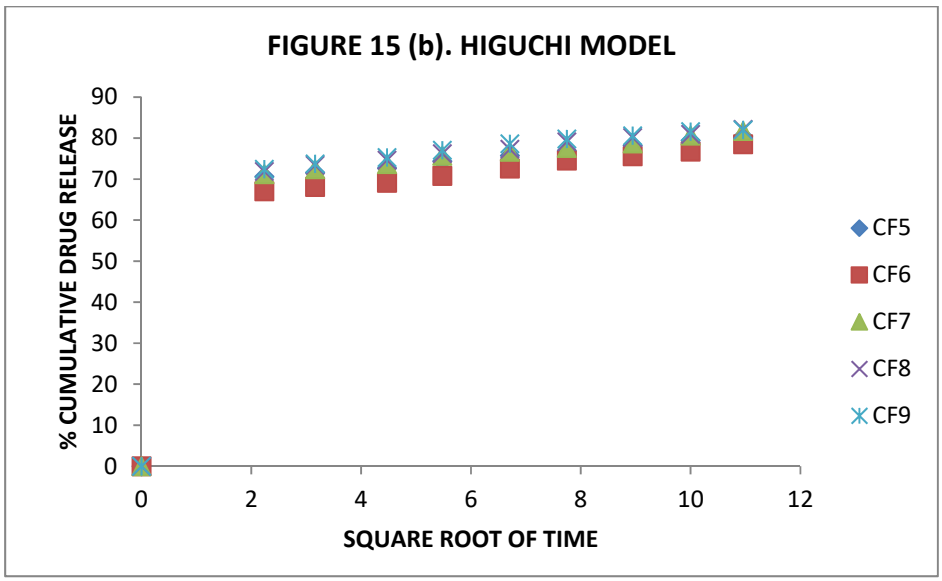


FIGURE 14 (d). FIRST ORDER KINETICS
% DRUG REMAINING
40
35
30
25
20
15
10
5
0
0
50
100
150
TIME IN MINUTES
OF5
OF6
OF7
OF8
OF9

FIGURE 15.COMPARISION OF *IN VITRO* HIGUCHI MODEL RELEASE KINETICS OF

PITAVASTATIN SMEDDS





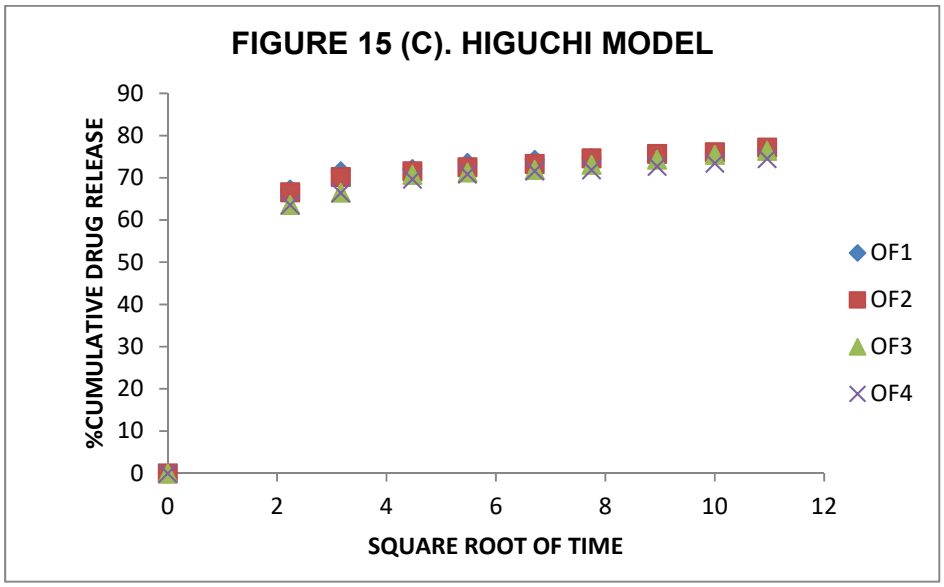


FIGURE 15 (C). HIGUCHI MODEL
%CUMULATIVE DRUG RELEASE
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
SQUARE ROOT OF TIME
OF1
OF2
OF3
OF4

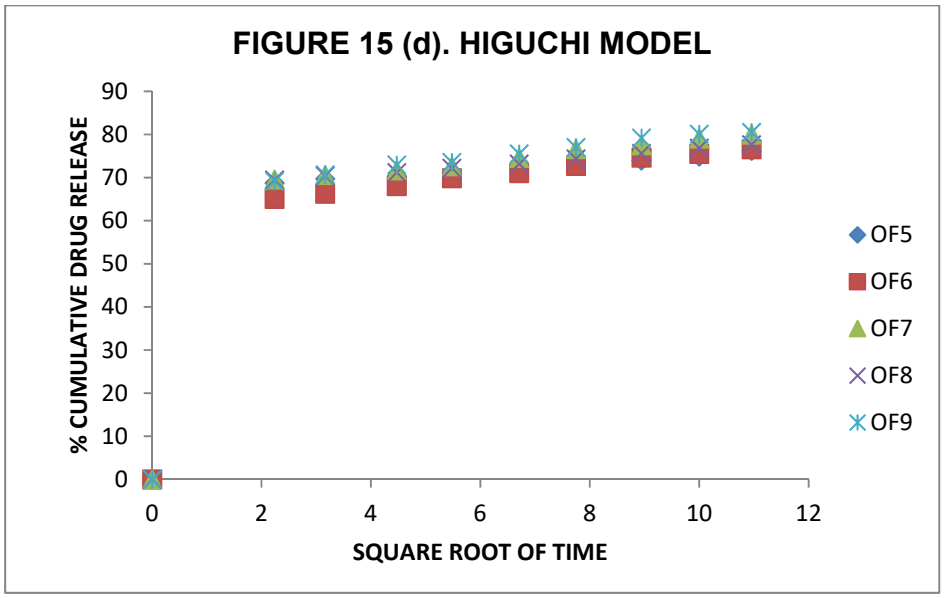
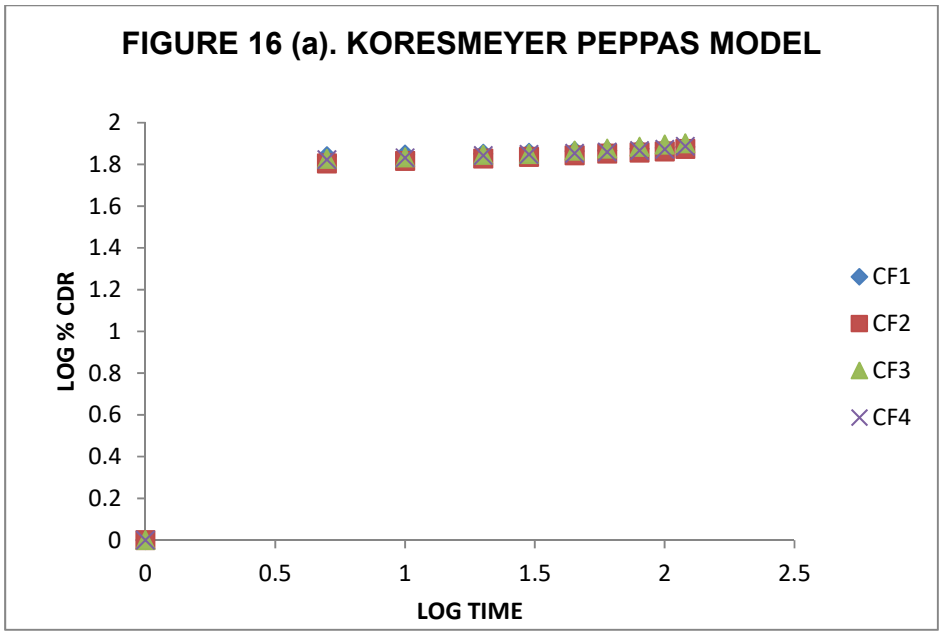
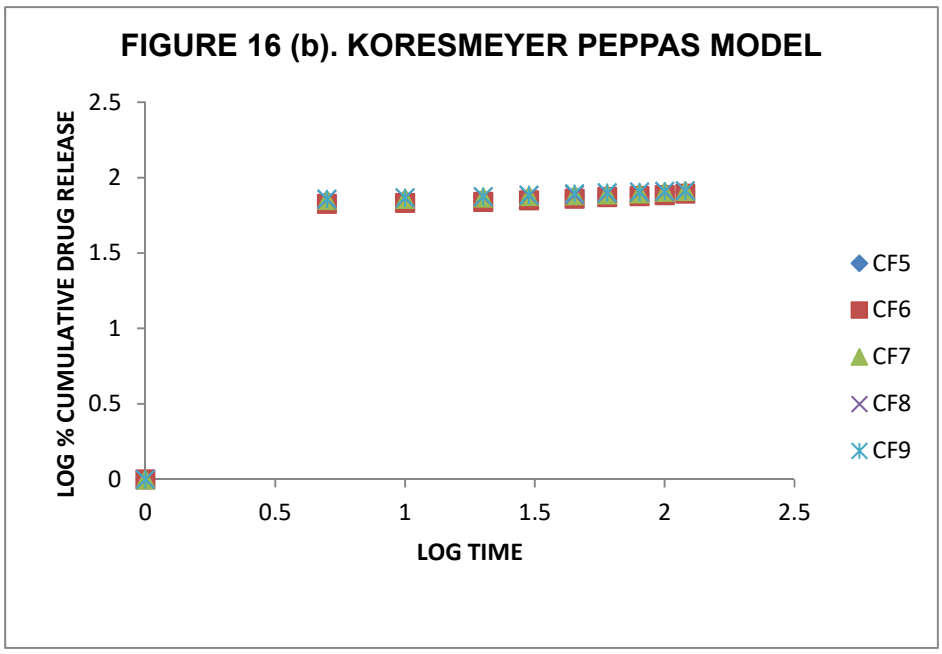


FIGURE 15 (d). HIGUCHI MODEL
% CUMULATIVE DRUG RELEASE
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
SQUARE ROOT OF TIME
OF5
OF6
OF7
OF8
OF9

FIGURE 16: COMPARISION OF *IN VITRO* KORSEMEYER PEPPAS MODEL RELEASE KINETICS OF PITAVASTATIN SMEDDS.





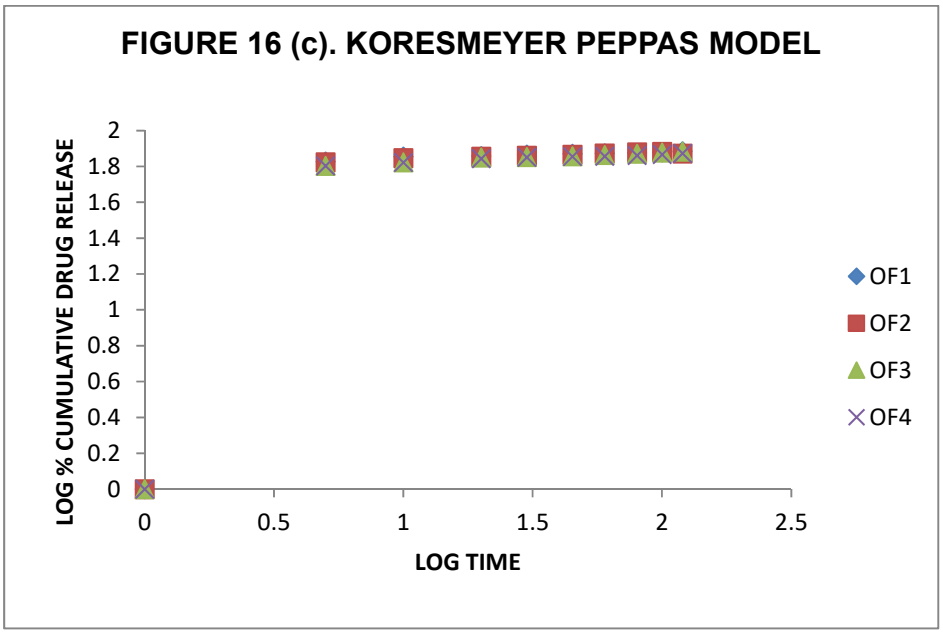


FIGURE 16 (c). KORESMEYER PEPPAS MODEL
LOG % CUMULATIVE DRUG RELEASE
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0
0.5
1
1.5
2
2.5
LOG TIME
OF1
OF2
OF3
OF4

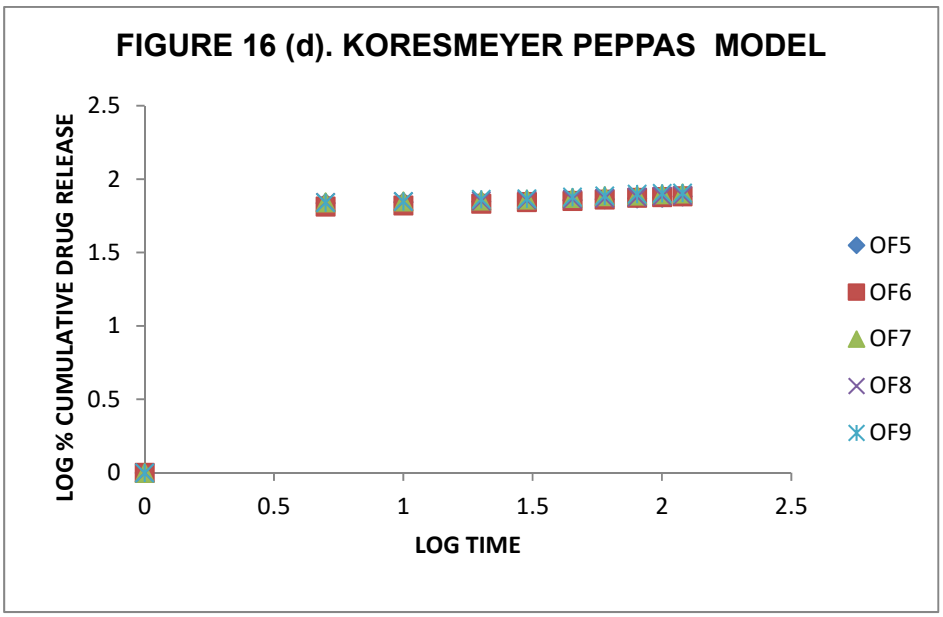
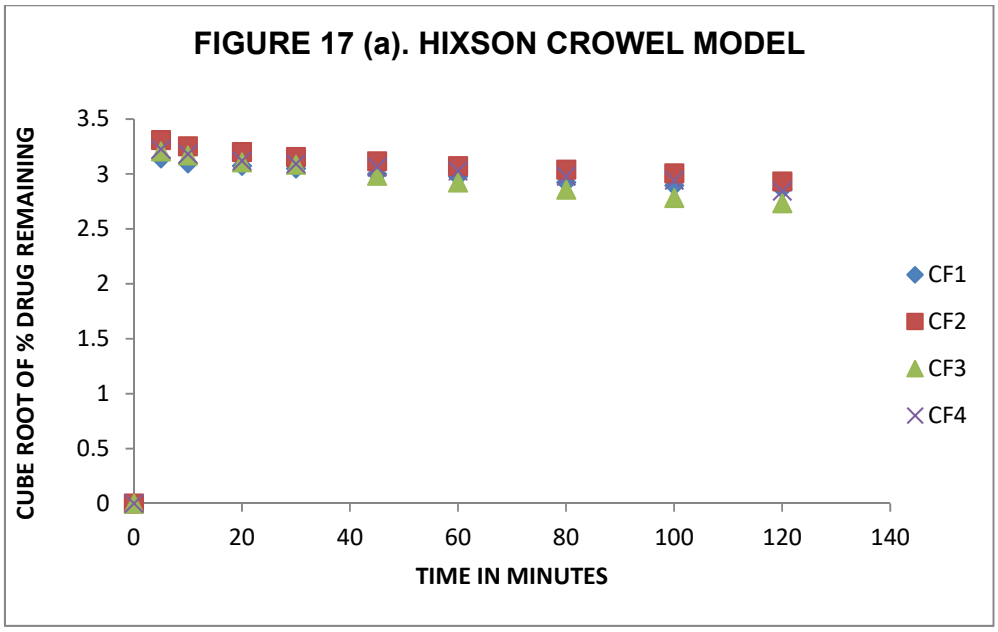
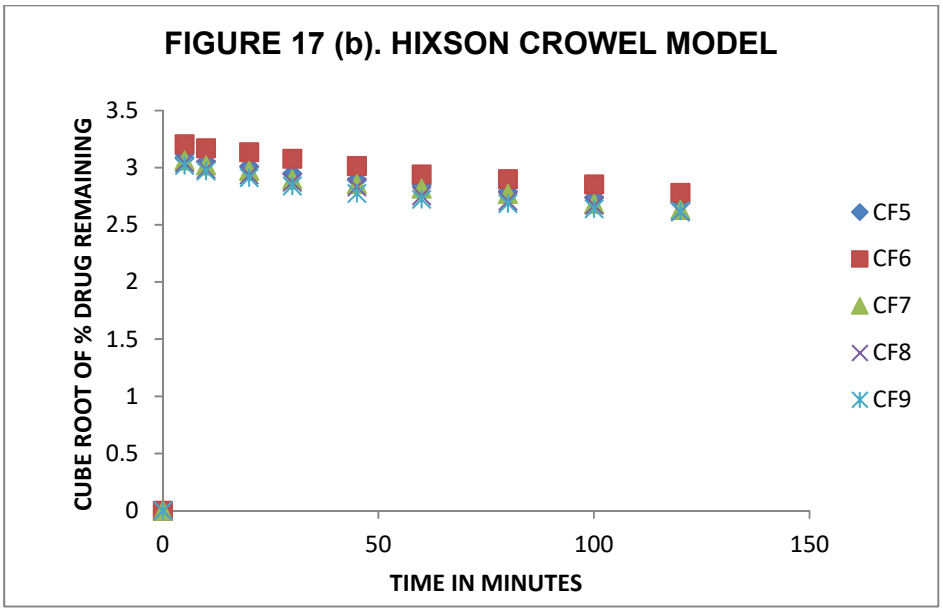


FIGURE 16 (d). KORESMEYER PEPPAS MODEL
LOG % CUMULATIVE DRUG RELEASE
2.5
2
1.5
1
0.5
0
0
0.5
1
1.5
2
2.5
LOG TIME
OF5
OF6
OF7
OF8
OF9

FIGURE 17. COMPARISION OF *IN VITRO* HIXON CROWEL MODEL RELEASE KINETICS OF PITAVASTATIN SMEDDS





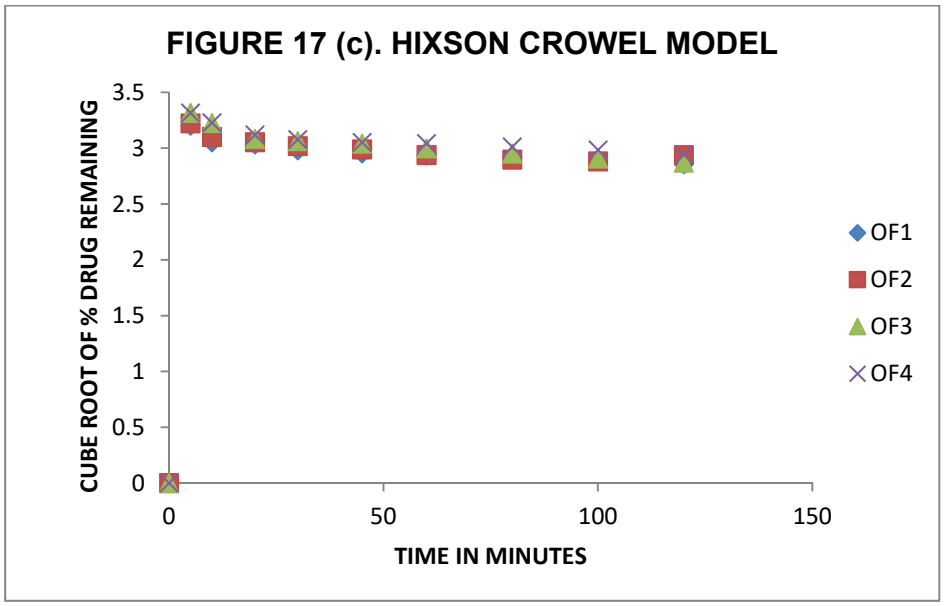


FIGURE 17 (c). HIXSON CROWEL MODEL
CUBE ROOT OF % DRUG REMAINING
3.5
3
2.5
2
1.5
1
0.5
0
0
50
100
150
TIME IN MINUTES
OF1
OF2
OF3
OF4

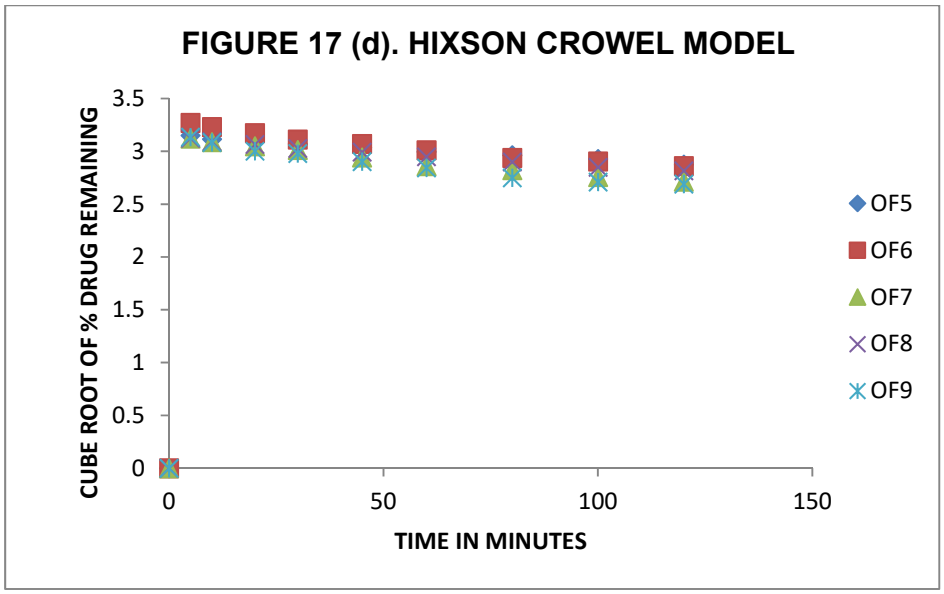


FIGURE 17 (d). HIXSON CROWEL MODEL
CUBE ROOT OF % DRUG REMAINING
3.5
3
2.5
2
1.5
1
0.5
0
0
50
100
150
TIME IN MINUTES
OF5
OF6
OF7
OF8
OF9

FIGURE 18: FTIR SPECTRA

FIGURE 18 (a): FTIR SPECTRA OF PURE PITAVASTATIN CALCIUM

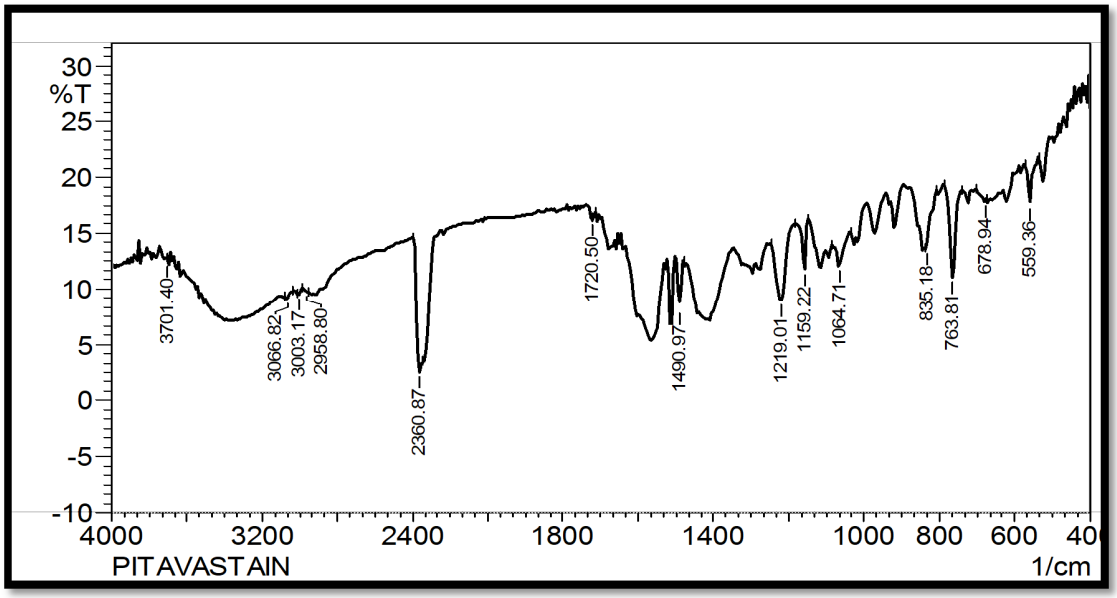


FIGURE 18 (b): FTIR SPECTRA OF LIQUID SMEDDS OF PITAVASTATIN USING OLEIC ACID, TWEEN 80 AND PROPYLENE GLYCOL

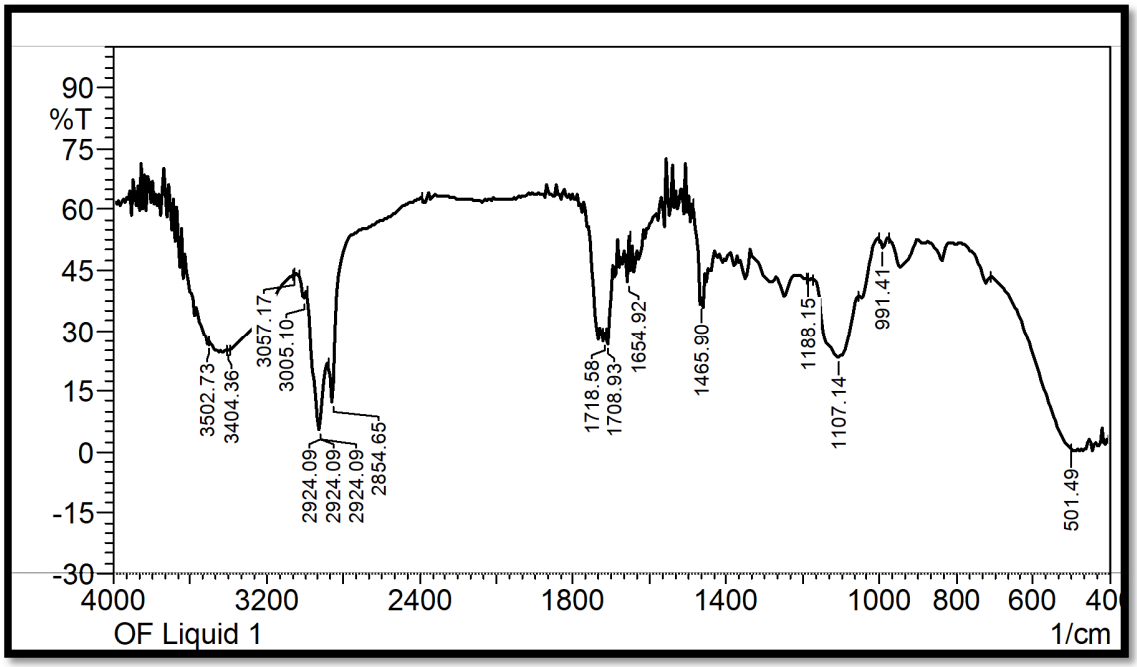


FIGURE 18 (c): FTIR SPECTRA OF LIQUID SMEDDS OF PITAVASTATIN USING CAPRYOL 90, CREMOPHORE RH 40 AND PG

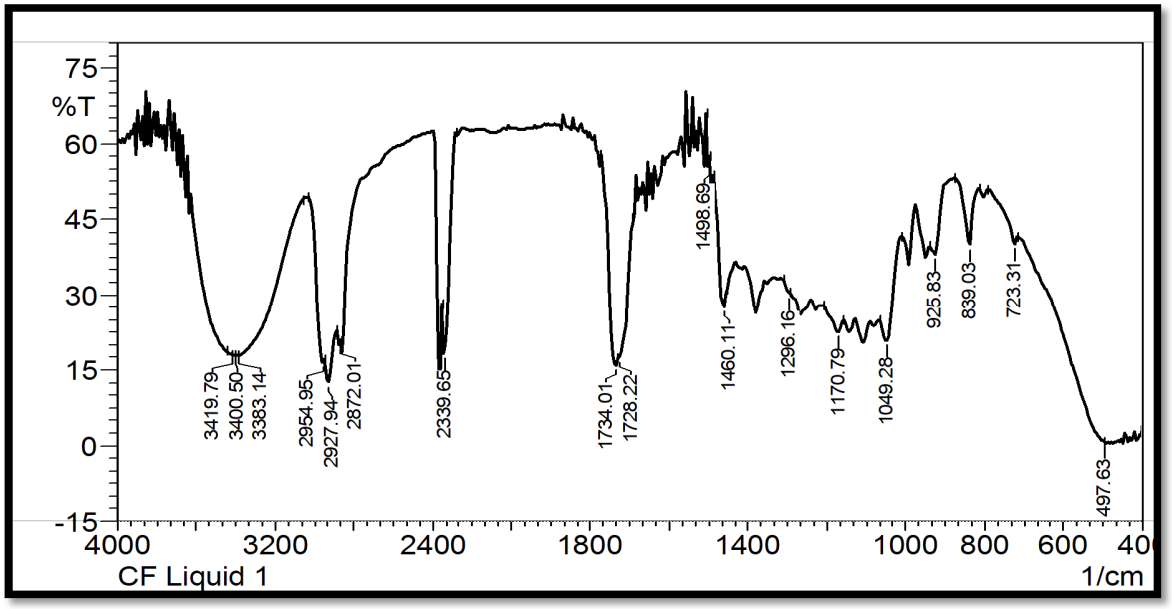


FIGURE 18 (d): FTIR SPECTRA OF SOLID SMEDDS OF PITAVASTATIN USING OLEIC ACID, TWEEN 80 AND PG

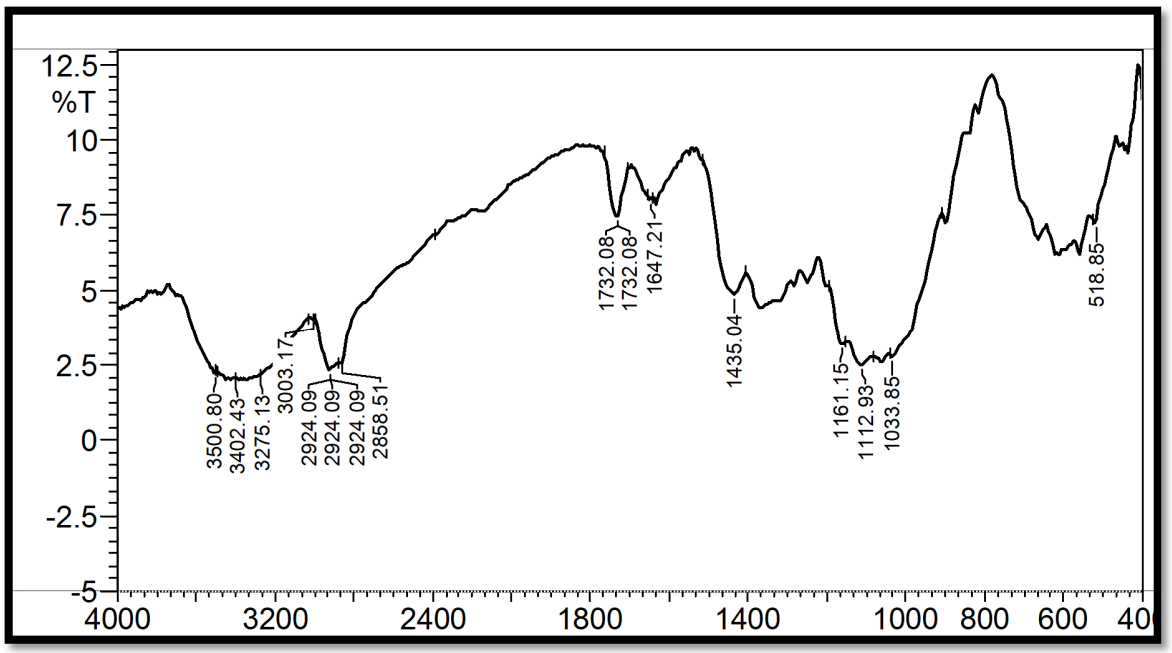


FIGURE 18 (e): FTIR SPECTRA OF SOLID SMEDDS OF PITAVASTATIN USING CAPRYOL 90, CREMOPHORE RH 40 AND PG

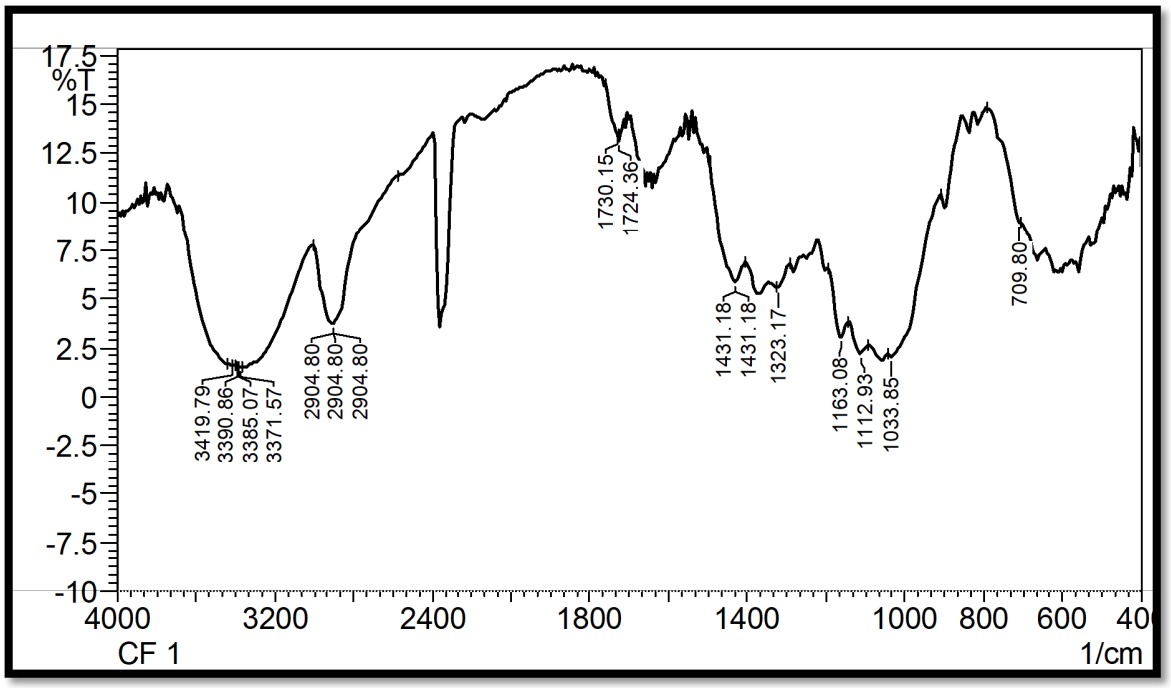


FIGURE 19 (a): SEM IMAGE OF PURE PITAVASTATIN CALCIUM

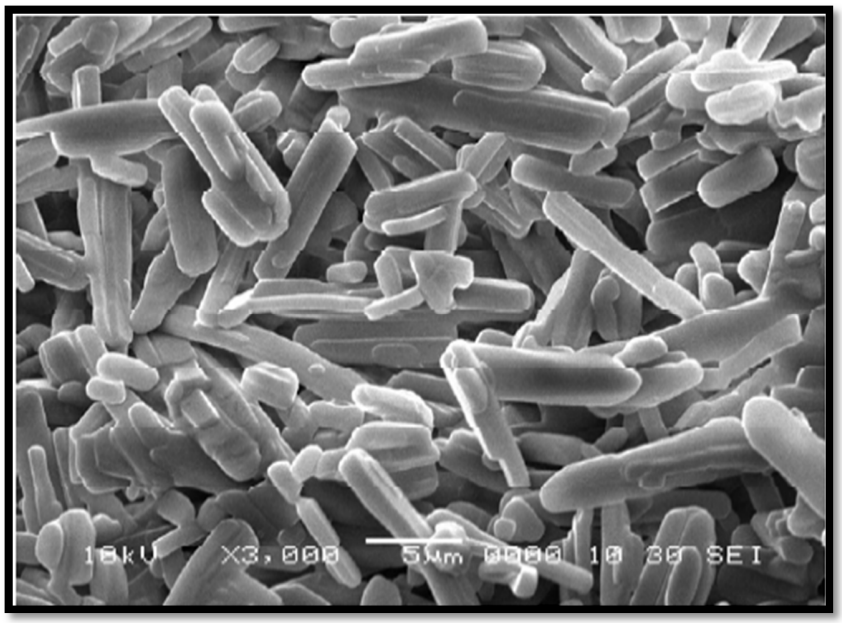


FIGURE 19 (b): SEM IMAGE OF PREPARED SOLID SMEDDS OF PITAVAS-TATIN

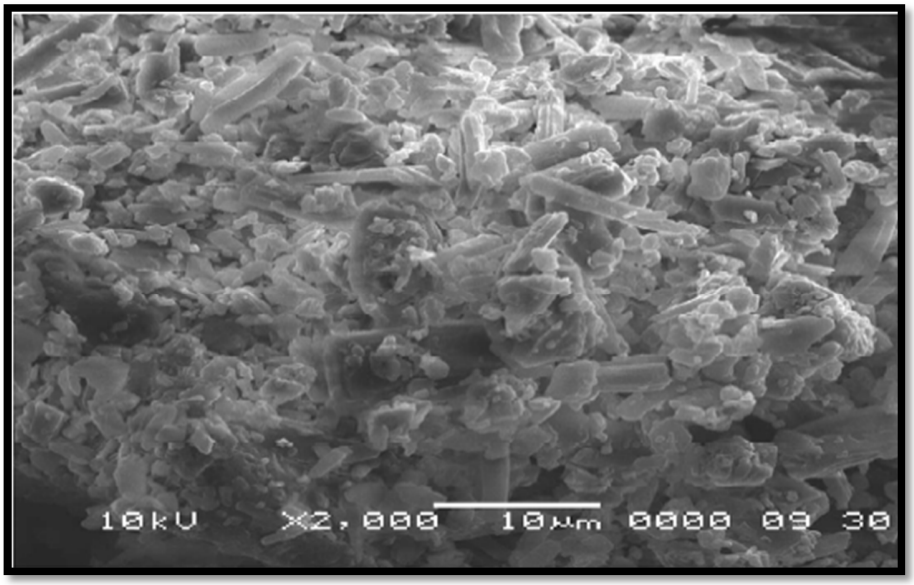


FIGURE 20 (a): PXRD PATTERN SMEDDS FORMULATION

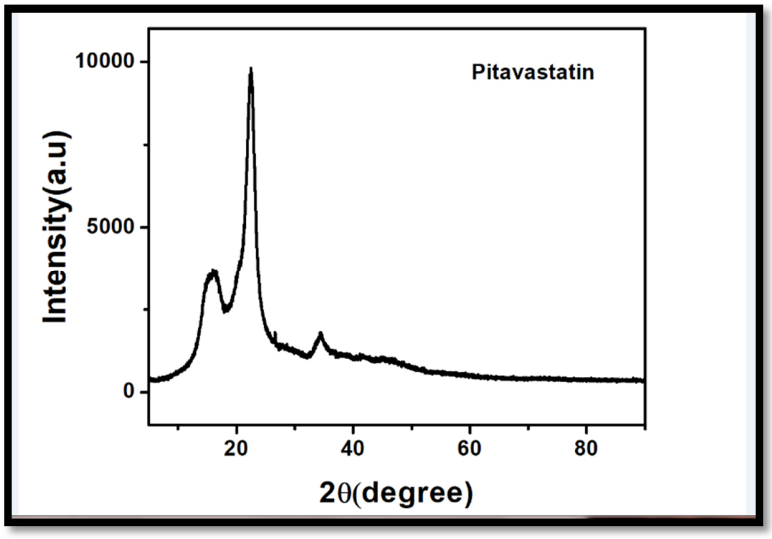


FIGURE 20 (b): PXRD PATTERN OF PURE DRUG

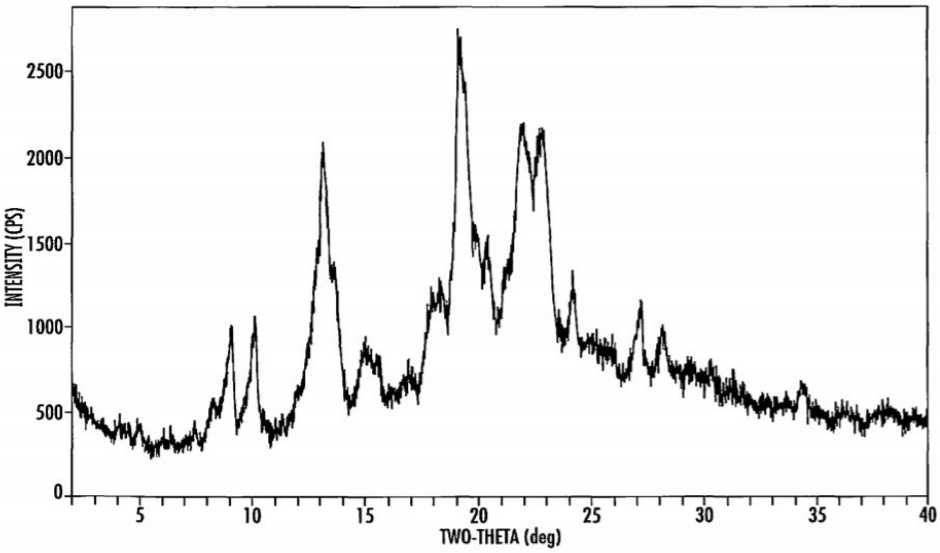


FIGURE 21: ZETA POTENTIAL ANALYSIS

FIGURE 21 (a): ZETA POTENTIAL CURVE FOR CF8

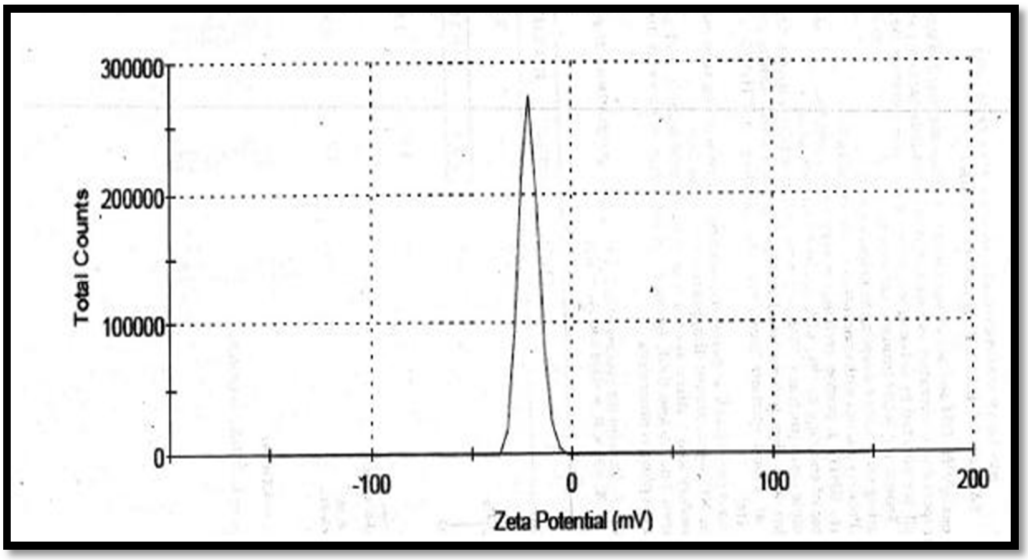
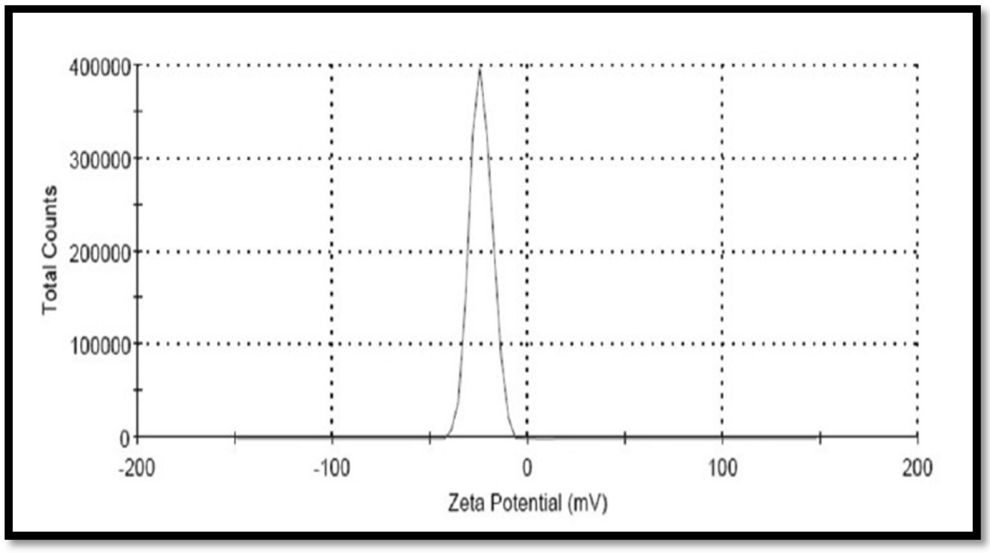


FIGURE 21 (b): ZETA POTENTIAL CURVE FOR OF9 FORMULATION



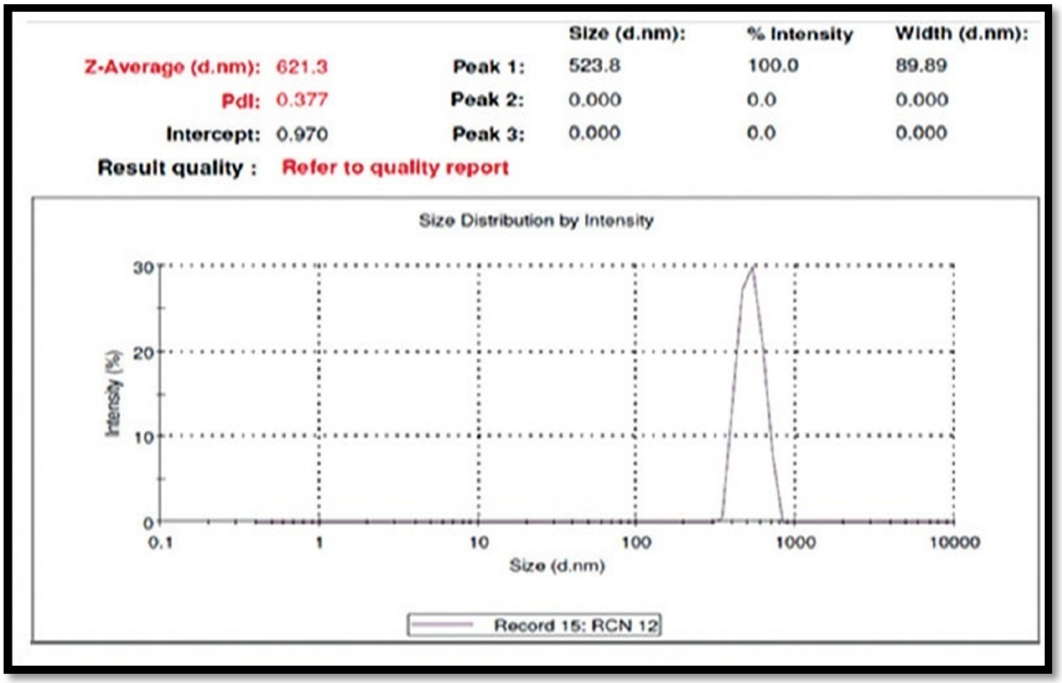
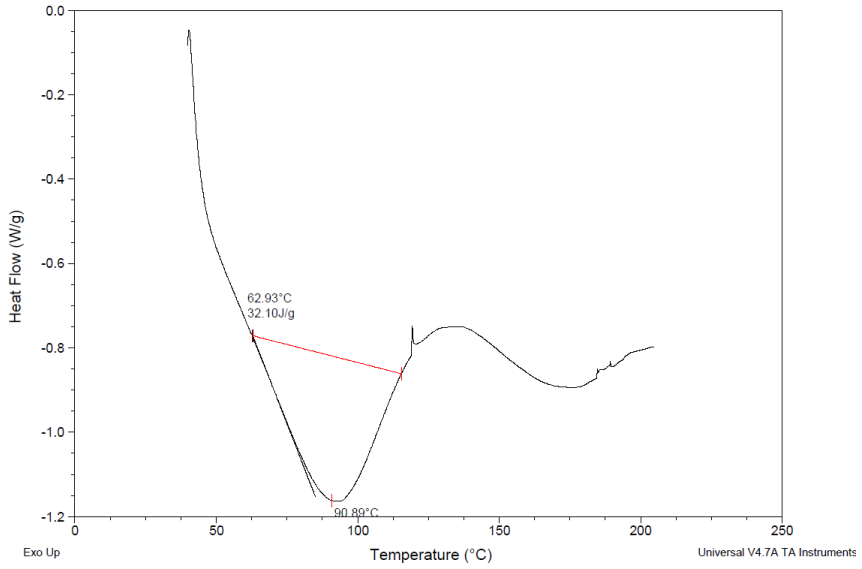


FIGURE 21 (C) : PARTICLE SIZE DISTRIBUTION FOR CF8

FIGURE 22 : DSC THERMOGRAM OF BEST FORMULATION



CHAPTER XI

SUMMARY AND CONCLUSION

CHAPTER – XI

SUMMARY AND CONCLUSION

- In the present study, an attempt has been made to develop Self Micro Emulsifying Drug Delivery system of Pitavastatin in order to enhance the solubility and dissolution rate by incorporating the drug in a lipid vehicle.
- The results of compatability studies by **Infrared spectroscopy** and **differential scanning calorimetry (DSC)**, showed **no interaction** between the drug and excipients.
- Various oils, surfactants and co-surfactants are optimized based on their solulbilising capacity and % transmittance values.
- The solubility of Pitavastatin was found to higher in **oleic acid (97.89%±0.06)** and **Capryol 90 (93.69%±0.31**)
- Pseudo ternary phase diagrams were constructed to get the maximum self emulsification region of SMEDDS, and the optimum concentration of oil was found to be 10-50% and $S_{mixture}$ was found to be 50-90% for both oils.
- Two different type of Pitavastatin liquid SMEDDS were successfully prepared at different ratios of oil, surfactant and co-surfactant by simple admixing method, namely CF1-CF9 and OF1-OF9.
- The prepared SMEDDS were evaluated for their physiochemical parameters. (Dispersibility test, visual assessment, self emulsification time, % transmittance and Refractive index).
- The RI of formulation ranges from **1.333 to 1.348**.
- The % transmittance value for all the formulation ranges from 68 -97%. And the formulation which shown % transmittance value of above 90% provides clear emulsion. **CF8** and **OF8** shows maximum % transmittance (**97.47±0.18%** and **94.28±0.22%)**

- The drug content of liquid SMEDDS ranges from 92- 98 %. Formulation **CF8** and **OF8** shown maximum drug content. (**98.02±0.07%** and **98.23±0.17%** respectively)

- Then the liquid SMEDDS were converted into S-SMEDDS by adsorption technique by mixing it with Micro crystalline Cellulose at 1:1 w/w ratio.

- *In vitro* release study of all the formulations were shown an increased drug release. Dissolution rate of all the formulations were improved when compared to pure drug.

- The dissolution study was carried out in pH 6. 8 buffer for 2 hours. The formulations shown higher rate of drug release than that of the pure drug and marketed formulation, and all formulations showed 60-82% of drug release within two hours. **Formulation OF8 and CF8 shows 80.52±0.12% and 82.14±0.15% respectively, which is higher rate than the pure drug (59.25±0.20%) and conventional tablet (64.72±0.21%)**

- Particle size analyzer used to explore the particle size of Pitavastatin SMEDDS showed a suitable particle size of **139.5 nm** and **0.621nm** for **OF8** and **CF8** respectively.

- The polydispersibility index of selected SMEDDS formulations (**CF8 & OF8**) were **0.377 and 0.291,** which indicated a broad size distribution of particles.

- Zeta potential value of Pitavastatin SMEDDS showed a negative surface charge (- **23.9mv and -20.9mv**).

- SEM studies confirmed the morphology of the solid SMEDDS.

- The crystalline state of the formulation was altered according to the XRPD analysis. It confirms the solubilisation of drug.

CONCLUSION

Pitavastain is a poorly water soluble drug, and its bioavailability is only about 60% due it is poor solubility. When administering this poorly soluble compound with hydrophilic carriers will enhance the solubility of the drug.

Hence, it was concluded that Self Micro Emulsifying drug delivery system is a good approach to enhance the solubility and dissolution property of Pitavastatin. The composition of optimized formulation [CF8 consist of Capryol 90 as oil(45%), Cremophore RH(41.2%) as surfactant and Propylene glycol(13.75%) as co-surfactant and OF8 consist of Oleic acid (45%), Tween 80 (41.2%) and Propylene glycol (13.75%)] containing 4mg of Pitavastatin calcium showing drug release for solid SMEDDS formulation (82.14% & 80.52%), Particle size (139.5 nm & 621.3nm), Zeta potential (-23.29 & -20.9), viscosity (0. 8824 cP). In-vitro drug release of the C8 and OF8 was highly significant compared to pure drug and marketed conventional tablet. Here the liquid SMEDDS are successfully converted into solid SMEDDS using MCC by adsorption technique.

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