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Evaluation of Micro-Emulsion for Poorly Water-Soluble Drugs

Kabra Harshada Manish, Asst. Prof. Shubham L. Hange, Dr. Surwase K.P
Kishori College of Pharmacy, Beed.

Abstract: *Solubilization of hydrophobic drugs with low aqueous solubility has been a major challenge in pharmaceutical development. The present research work aimed to formulate, develop, and optimize microemulsion and Self-Microemulsifying Drug Delivery Systems (SMEDDS) for the oral delivery of two poorly water-soluble, BCS Class II active pharmaceutical ingredients: Felodipine and Valsartan.*

An oil-in-water microemulsion system for Felodipine was successfully developed utilizing Capmul MCM as the oil phase, Tween 20 as the surfactant, and PEG 400 as the co-surfactant. The optimized formulation (F2) exhibited a low mean droplet size (15.12 nm), favorable zeta potential (-10.40 mV), and robust thermodynamic stability without phase separation. In vitro studies revealed an accelerated drug release profile (>85% within 1 hour), and in vivo absorption studies in rats demonstrated a 9.85-fold increase in the relative oral bioavailability compared to a plain drug suspension.

Simultaneously, a liquid SMEDDS formulation for Valsartan was optimized using Capmul MCM, Tween 80, and PEG 400. To address stability and handling limitations of liquid formulations, the optimized liquid SMEDDS was converted into a free-flowing Solid SMEDDS (S-SMEDDS) utilizing adsorption techniques onto a solid carrier combination of Aerosil 200 and Lactose anhydrous. The resulting Solid SMEDDS retained its self- microemulsifying properties, rapidly forming fine droplets (47.4 nm) upon aqueous dilution. The formulation displayed significant dissolution enhancement, achieving over 98% release within 45 minutes, significantly outperforming the marketed conventional tablet..

Keywords: Microemulsion, SMEDDS, Solid SMEDDS, Felodipine, Valsartan, Oral Bioavailability, Solubility Enhancement, Pseudo ternary Phase Diagram, Adsorption Technique

I. INTRODUCTION

1.1 Background of Poorly Water-Soluble Drugs:-

An increasing number of recently discovered drug substances exhibit poor water solubility and hence low absorption after oral administration. Technology Catalysts International reported in 2002 that approximately 35-40% of all new chemical compounds suffer from poor aqueous solubility[1,2]. Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potential pharmacodynamic activity. Furthermore, poorly water-soluble drugs currently on the market are administered at much higher individual doses than actually desired to achieve necessary plasma levels.

Methods to improve drug bioavailability may involve the alteration of various key factors that determine drug dissolution, as described by the Noyes-Whitney equation. The dissolution rate can be increased by increasing the surface area from where dissolution can take place, by decreasing the diffusional layer thickness, and by altering the solubility of the drug. Lipid formulations, and in particular Self-Micro-emulsifying Drug Delivery Systems (SMEDDS), can induce a considerable increase in dissolution rate as these strategies can simultaneously alter various of these factors.

An increasing number of recently discovered drug substances exhibit poor water solubility and hence low absorption after oral administration. Technology Catalysts International reported in 2002 that approximately 35-40% of all new chemical compounds suffer from poor aqueous solubility . The introduction of the Biopharmaceutical Classification System (BCS) has provided a basis to categorize drugs based on the two major parameters affecting absorption -

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solubility and permeability. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation.

Several strategies to improve the solubility and dissolution of poorly water soluble drugs have been developed and described in literature, which were at start primarily based on modifying the drug's physicochemical properties.

Particle size reduction and salt formation became frequently taken paths in a quest for dissolution improvement, but both methods revealed limitations[3,4]. As a result, altering drug solubility or dissolution through formulation approaches has become more and more

popular. Methods to improve drug bioavailability may involve the alteration of various key factors that determine drug dissolution, as described by the Noyes-Whitney equation .

$$\frac{dM}{dt} = \frac{D \cdot A \cdot (C_s - C_t)}{h}$$

In equation, dM/dt represents the dissolution rate, A the specific surface area of the drug particle, D the diffusion coefficient, h the diffusion layer thickness, Cs the saturation solubility and C1 the drug concentration at time t. That is, dissolution rate can be increased by increasing the surface area from where dissolution can take place, by decreasing the diffusional layer thickness and by altering the solubility of the drug.

Lipid formulations and in particular Self Micro Emulsifying Drug Delivery Systems (SMEDDS) can induce a considerable increase in dissolution rate as these strategies can simultaneously alter various of these factors. SMEDDS is a pre-mixture of drug, oil, surfactants and co-surfactants and is able to form microemulsion under gentle shaking or stirring spontaneously. Microemulsion is a very clear, isotropic, transparent and thermodynamically stable system with a very small particle size (below 100nm)[10] .The issue arose in particular when drug discovery moved from wet chemistry to combinatorial chemistry and high throughput screening in the mid 1990's. The properties of new chemical entities (NCE) shifted towards higher molecular weight and increasing lipophilicity, resulting in decreased aqueous solubility.

Due to poor aqueous solubility, many drug candidates become unsuccessful to reach the market in spite of exhibiting potential pharmacodynamic activity. Also, poorly water soluble drugs currently on the market are administered at much higher individual doses than actually desired to achieve necessary plasma levels.

The introduction of the Biopharmaceutical Classification System (BCS) has provided a basis to categorize drugs based on the two major parameters affecting absorption - solubility and permeability. Therefore, strategies to improve the aqueous solubility and the release rate of drugs are employed and are under constant investigation

1.3 Microemulsion and SMEDDS

Microemulsions are isotropic, thermodynamically stable, transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co-surfactant with a droplet size usually in the range of 10-100 nm. These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity.

Microemulsion as drug delivery tool show favorable properties like thermodynamic stability (long shelf-life), easy formation (zero interfacial tension and almost spontaneous formation), optical isotropy, ability to be sterilized by filtration, high surface area (high solubilization capacity) and very small droplet size. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion.

Microemulsions are isotropic, thermodynamically stable, transparent (or translucent) systems of oil, water, and surfactant, frequently in combination with a co-surfactant, with a droplet size usually in the range of 10-100 nm. Structurally, they are divided into oil-in-water (O/W), water-in-oil (W/O), and bicontinuous microemulsion .A flexible surfactant film enables the existence of several different structures like droplet-like shapes, aggregates, and bicontinuous structures, thereby broadening the range of microemulsion existence .

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SMEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and cosolvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsion upon mild agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide .

The basic difference between self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation (SEOF) and SMEDDS is SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 100 nm also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS .

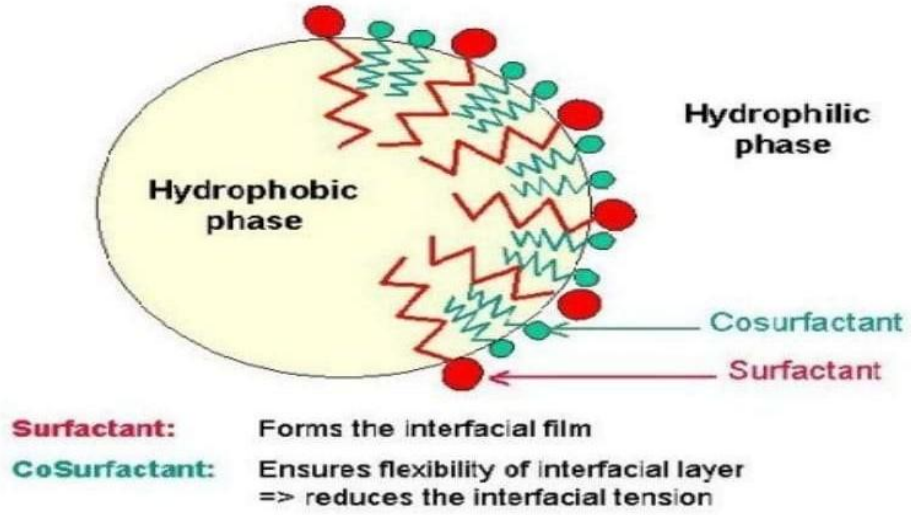

Fig: 1 . Structure of Microemulsion .

When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture.

A typical SMEDDS formulation contains oils, surfactants and if required an antioxidants. Often co-surfactants and co-solvents are added to improve the formulation characteristics .

Advantages of SMEDDS over Emulsion

 SMEDDS not only offer the same advantages of emulsions of facilitating the solubility of hydrophobic drugs, but also overcomes the drawback of the layering of emulsions after sitting for a long time. SMEDDS can be easily stored since it belongs to a thermodynamically stable system.

 Microemulsions formed by the SMEDDS exhibit good thermodynamics stability and optical transparency. The major difference between the above microemulsions and common emulsions lies in the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm (such droplets are called droplets of nano particles). Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form and it can easily penetrate

Adsorption to Solid Carriers:

Free-flowing powders may be obtained from liquid SE formulations by adsorption to solid carriers. The adsorption process is simple and involves the addition of the liquid formulation onto carriers by mixing in a blender. A significant benefit of the adsorption technique is good content uniformity, and SEDDS can be adsorbed at high levels (up to 70% w/w) onto suitable carriers. Solid carriers can be microporous inorganic substances, high surface-area colloidal

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inorganic adsorbent substances, cross-linked polymers, or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, and microcrystalline cellulose.

SMEDDS can exist in either liquid or solid states. SMEDDS are usually, limited to liquid dosage forms, because many excipients used in SMEDDS are not solids at room temperature. Given the advantages of solid dosage forms, solid self Microemulsifying drug delivery (S- SMEDDS) have been extensively exploited in recent years, as they frequently represent more effective alternatives to conventional liquid SMEDDS.

From the perspective of dosage forms, S-SMEDDS mean solid dosage forms with self- emulsification properties. S-SMEDDS focus on the incorporation of liquid/semisolid SE ingredients into powders/ nanoparticles by different solidification techniques (e.g. adsorptions to solid carriers, spray drying, melt extrusion, nanoparticle technology, and so on).

Such powders/nanoparticles, which refer to SE nanoparticles/dry emulsions/solid dispersions are usually further processed into other solid SE dosage forms, or, alternatively, filled into capsules (i.e. SE capsules). SE capsules also include those capsules into which liquid/semisolid SEDDS are directly filled without any solidifying excipient .

While liquid SMEDDS are highly effective, they are limited by the physical state of their components and potential interactions with gelatin capsule shells, such as moisture sensitivity and capsule softening. To address these issues, Solid-Self Microemulsifying Drug Delivery System (S-SMEDDS) have been explored. S-SMEDDS involve the incorporation of liquid/semisolid SMEDDS ingredients into solid powders or nanoparticles using techniques like adsorption onto solid carriers, spray drying, or melt extrusion.

Adsorption onto solid carriers (such as colloidal silicon dioxide or silicates) is a particularly simple and scalable technique that allows for the creation of free-flowing powders, which

1.6 Introduction to drugs used in study.

Cardiovascular disorders are the world's most prevalent diseases. With the general aging of the world's population and rapid socio-economic changes in the developing world, cardiovascular diseases are expected to increase further in the future. Hence, there is a great need for adequate pharmacotherapy to provide symptomatic prompt treatment and long-term protection.

Among the most beneficial medications currently available are those that interfere with the actions of angiotensin II and others are calcium channel blockers. Angiotensin II has a well- defined tropic effect on vascular and cardiac cells and the extracellular matrix. Over the last decade, several clinical trials have demonstrated the benefits of blocking angiotensin II.

In particular, the angiotensin-receptor blockers (ARBs), originally indicated for hypertension, have shown themselves to have cardiovascular benefits beyond lowering blood pressure.An increased understanding of the renin-angiotensin system and the development of angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists (such as valsartan) has formed a major part in these accomplishments.

Renin is released from the juxtaglomerular cells of the kidney and then cleaves its substrate, angiotensinogen, to form angiotensin-I. This is converted, by the angiotensin converting enzyme (ACE), to angiotensin-II.

In the cardiovascular system the products of this pathway are important in both blood pressure regulation and sodium and volume homeostasis; angiotensin-II has a number of important and complex physiological actions, notable among which is vasoconstriction which results in blood pressure elevation.

ACE inhibitors were first introduced for the treatment of hypertension but subsequent studies have shown that they are also able to reduce mortality and morbidity in congestive cardiac failure, decrease morbidity and mortality after myocardial infarction, prevent re-infarction, influence atherosclerosis and slow diabetic complications, including nephropathy.

Nevertheless, there are disadvantages and, in particular, ACE inhibitors degrade bradykinin, resulting in a prolongation if its normally short half-life; this and related effects seem to be

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II. LITERATURE REVIEW .

2.1 Review on Oral Microemulsions and SMEDDS .

The literature confirms that lipid-based delivery systems, specifically microemulsions and SMEDDS, significantly enhance the oral bioavailability of BCS Class II drugs.

Solubility and Dissolution Enhancement:

Research by Solanki et al. (2012) demonstrated that a Capmul MCM-based microemulsion formulation for Ampelopsin, using Cremophor EL and Transcutol P, achieved higher in vitro drug release compared to plain suspensions and commercial tablet formulations. Similarly, Patel et al. (2010) reported an 80.66-fold solubility enhancement of Clopidogrel using a Capmul microemulsion.

Bioavailability Improvement: Docetaxel microemulsions prepared by Yin et al. (2009) showed a dramatic increase in oral bioavailability in rats (34.42%) compared to the orally administered commercial product Taxotere (6.63%). Furthermore, Kang et al. (2004) developed SMEDDS for Simvastatin, which resulted in a 1.5-fold higher bioavailability compared to conventional tablets.

Intranasal and Topical Delivery: Beyond oral routes, studies have explored intranasal and topical delivery. Piao et al. (2010) developed Fexofenadine microemulsions for intranasal delivery, achieving an absolute bioavailability of 68% in rats. Kantarci et al. (2007) utilized Diclofenac sodium microemulsions for topical application, finding that formulations with propanol as a co-surfactant offered the highest flux value without causing skin irritation.

Considerable research has been conducted over the last decade exploring the potential of microemulsions to enhance the oral bioavailability of poorly water-soluble compounds.

Solanki SS et al. (2012) enhanced the dissolution rate and bioavailability of Ampelopsin, a common flavonoid, by developing a microemulsion.

2.2 Review on Self-Microemulsifying Drug Delivery Systems (SMEDDS) .

Mezghrani O et al. (2011) designed an optimized SMEDDS to enhance the bioavailability of astilbin. In-vitro drug release profiles using the reverse dialysis method showed 95% drug release after 4 hours. Bioavailability studies in beagle dogs demonstrated a significant enhancement, indicating the utility of SMEDDS as a drug carrier.

Cui J et al. (2009) formulated a SMEDDS to improve the solubility and oral absorption of curcumin. The optimal formulation comprised 57.5% surfactant, 30.0% co-surfactant, and 12.5% oil. The solubility of curcumin significantly increased to 21 mg/g, and oral absorption experiments in mice showed that SMEDDS significantly increased absorption compared with its suspension.

Ofokansi KC et al. (2009) investigated the use of Peanut oil and Tween 80 blends devoid of any co-surfactant for the delivery of the lipophilic drug griseofulvin. The SMEDDS showed enhanced and controlled dissolution, suggesting a strategy to overcome the irregular absorption behaviors associated with conventional griseofulvin tablets.

Lee et al. (2009) Daewoong pharmaceuticals CO., Ltd. disclosed in WO Patent WO/2009/022 the SMEDDS composition containing coenzyme Q 10 and method for preparing the same. They claimed improvement in solubility and bioavalability using polyglucerine fatty acid ester as surfactants and polyethylene-sorbitan fatty acid ester as cosurfactant.

Ofokansi KC et al. (2009) used Peanut oil and Tween 80 blends devoid of any cosurfactant and employed in the formulation of different batches of liquid SMEDDS and their suitability as vehicles for the delivery of a typical lipophilic drug griseofulvin was investigated. The release profile of griseofulvin from the optimized SMEDDS was evaluated in citrate/phosphate buffer solutions of pH 2.0, pH 6.5, and pH 7.4. The release of griseofulvin from the SMEDDS into aqueous media of pH 6.5 and pH 7.4 showed enhanced and controlled dissolution of the drug from the formulation. Incorporation of griseofulvin into this proposedformulation is suggested as a strategy to overcome the irregular dissolution and absorption behaviors often associated with conventional griseofulvin tablets.

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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 selfmicroemulsification 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.

Zang Yao et al. (2008) has prepared nobiletin SMEDDS and investigate its intestinal transport behavior using the single-pass intestinal perfusion (SPIP) method in rat. SPIP was performed in each isolated region of the small intestine over three concentrations of nobiletin and the effective permeability coefficients in rats were calculated. The intestinal permeability of nobiletin in SMEDDS, sub-microemulsions and micelles was compared. The Peff in jejunum at 15 µg/ml was significantly higher than that at 60 µg/mL ($p < 0.01$). The estimated human absorption of nobiletin for the SMEDDS dilutions was higher than that for sub- microemulsions ($p<0.01$) and similar to that of the micelles ($p>0.05$)

2.3 Review on Solid SMEDDS .

The evolution of SMEDDS towards solid dosage forms has been driven by the need for better storage stability.

Adsorption Techniques: Hu et al. (2012) utilized extrusion-spheronization to convert liquid SMEDDS of Sirolimus into solid pellets, which demonstrated faster redispersion and superior bioavailability compared to commercial tablets.

Carrier Effects: Oh et al. (2011) compared hydrophilic (dextran) and hydrophobic (colloidal silica) carriers for Flurbiprofen S-SMEDDS.

They found that while both carriers successfully stabilized the drug in an amorphous state, colloidal silica was more efficient at maintaining the droplet size (~100 nm) of the reconstituted microemulsion.

Hu X et al. (2012) prepared self-microemulsifying pellets to enhance the dissolution and oral absorption of the water-insoluble drug sirolimus via the extrusion-spheronization method. The optimal SMEDDS pellets showed a significantly quicker redispersion rate than the commercial Rapamune tablets, and pharmacokinetic studies in beagle dogs showed greater oral relative bioavailability.

Milovic M et al. (2012) investigated Solid SMEDDS as potential delivery systems for carbamazepine using different adsorbents like Neusilin and Sylysia. It was observed that with magnesium aluminometasilicate adsorbents, the release rate of the drug decreased with increasing specific surface area due to the entrapment of liquid SMEDDS inside the pores.

Kim DW et al. (2011) developed a novel flurbiprofen-loaded S-SMEDDS with improved oral bioavailability using gelatin as a solid carrier, the solid SMEDDS formulation was prepared by spray-drying the solutions containing liquid SMEDDS and gelatin. The liquid SMEDDS, composed of Labrafil M 1944 CS/Labrasol/Transcutol HP (12.5/80/7.5%) with 2% w/v flurbiprofen, gave a z-average diameter of about 100 nm. The flurbiprofen-loaded solid SMEDDS formulation gave a larger emulsion droplet size compared to liquid SMEDDS. It greatly improved the oral bioavailability of flurbiprofen in rats.

Huan D et al. (2011) studied the influences of silica on the absorption of S-SMEDDS. An in vitro lipolysis model was used to evaluate the influence of silica on selfmicroemulsifying drug delivery system digestion from intestinal tract. S-SMEDDS containing silica were prepared by extrusion/spheronization. The results showed that lipolysis rate and drug concentration in aqueous phase after intestinal lipolysis both increased by adding silica, which was benefit to drug absorption. And silica was not benefit to absorption for slowing drug release. Consistently, there was no significant influence of silica on intestinal absorption

Ito Y et al. (2010) formulated Oral gentamicin (GM) SMEDDS with PEG-8 caprylic/capric glycerides (Labrasol), and the mixture was solidified with several kinds of adsorbents. The used adsorbents were microporous calcium silicate (Florite RE), magnesium alminometa silicate (Neusilin US2), and silicon dioxide (Sylysia 320). The in vivo rat

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absorption study showed that Florite RE 10 mg preparation had the highest C(max) and AUC. These results suggested that an adsorbent system is useful as an oral solid delivery system of poorly absorbable drugs such as GM.

Legen I et al. (2008) in EP1961412 prepared free flowing and compressible powder comprising an admixture of drug containing SMEDDS and solid particle adsorbents.

2.4 Review on Drugs (Felodipine and Valsartan).

Felodipine:

Being a BCS Class II drug, its dissolution rate is the limiting factor for absorption.

Bazzo et al. (2012) improved its dissolution through incorporation into Eudragit E microparticles. Furthermore, Patil et al. (2009) developed an extended-release Felodipine self-nanoemulsifying system (SNES) using Miglyol 840 and Capmul MCM, achieving >90% drug release within 15 minutes.

Basalious EB et al. (2011) applied quality by design (QbD) for pharmaceutical development of felodipine solid mixture (FSM) containing hydrophilic carriers and/or polymeric surfactants, for easier development of controlled-release tablets of felodipine. Not only did the ternary mixture of Pluronic, HPMC with Inutec SP1 enhance the dissolution rate and inhibit crystallization of felodipine, but also they aided Carbopol 974 in controlling felodipine release from the tablet matrix. It could be concluded that a promising once-daily CR tablets of felodipine was successfully designed using QbD approach .

Karavas E et al. (2011) prepared solid dispersion systems of felodipine with polyvinyl pyrrolidone (PVP) in order to enhance solid state stability and release kinetics. The dispersion of FEL was found to be in nano-scale particle sizes and dependent on the FEL/PVP ratio.

The above dispersion shown a significant effect on the dissolution enhancement and the release kinetics of FEL, as it causes the pattern to change from linear to logarithmic. An impressive optimization of the dissolution profile is observed corresponding to a rapid release of FEL in the system containing 10% w/w of FEL, releasing 100% in approximately 20 min

Alonzo DE et al. (2011) prepared amorphous solid dispersions of Felodipine for bioavailability enhancement. The purpose of this research was twofold. First, the degree of supersaturation generated upon dissolution as a function of drug-polymer composition was investigated. Second, an investigation was conducted to correlate physical behavior upon dissolution with polymer loading.

Oral delivery is currently the gold standard in the pharmaceutical industry because it is considered to be the safest, most convenient, the highest patient compliant and the most economical way to deliver the medicine.

The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Selfmicroemulsifying drug delivery systems (SMEDDS) have attracted considerable attention from pharmaceutical scientists, who want to increase the oral bioavailability of such drugs with poor water solubility. Although many studies have been carried out, few drug products have actually been brought to market formulated as SMEDDS filled in capsules, which confirms the difficulty and challenge of the formulation, including the following:

Hygroscopic fills may cause rapid capsule softening and leaking.

• The interactions between lipid components and capsule shells are often observed.

• Drug migration into the capsule shell can affect its release mechanism.

To address these problems, solid-SMEDDS have been extensively explored in recent years because they are more physically stable, more effective and better patient compliant alternatives to the conventional liquid SEDDS. In this research work, adsorption on solid carrier technique was studied and employed as a tool to solidify the liquid self microemulsion.

Felodipine is a dihydropyridine calcium-channel blocker used alone or with an angiotensin- converting enzyme inhibitor to treat hypertension and chronic stable angina pectoris. The drug belongs to BCS class II (low solubility and high permeability). Felodipine is rapidly absorbed from the gastrointestinal tract and approximately 80% of an oral

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dose is absorbed. However, because of low solubility and extensive first pass metabolism, absolute bioavailability is only 15% and the metabolite is excreted primarily in the feces.

Microemulsion of Felodipine is expected to enhance the aqueous solubility and dissolution rate, minimize the variability in absorption and minimize the first pass hepatic metabolism. Enhancement of bioavailability of Felodipine can reduce the dose required to elicit the same pharmacological action and hence reduce the side effects associated with the drug.

Valsartan is a nonpeptide, orally active, and specific angiotensin II antagonist acting on the AT1 receptor subtype. It is categorized in angiotensin receptor blocker. Valsartan is poorly soluble and belongs to BCS class II. The drug is rapidly absorbed following oral administration, with a bioavailability of about 23%. Peak plasma concentrations of Valsartan occur 2 to 4 h after an oral dose and 94% to 97% of the drug is bound to plasma proteins. Rapid onset of action is desirable to provide fast relief in the treatment of heart failure. Therefore, it is necessary to enhance the aqueous solubility and dissolution rate of Valsartan to obtain faster onset of action, minimize the variability in absorption, minimize first pass hepatic metabolism and to improve its overall oral bioavailability.

From above discussions, the hypotheses of the work are as given below:

1. Lipid based formulation of Felodipine such as microemulsion is expected to be absorbed through the lymphatic route and hence the first pass hepatic metabolism can be decreased. Moreover, because the drug would be in solubilized form and in a fine state of sub-division, the absorption and bioavailability can be increased significantly.
2. Lipid delivery system in the form of SMEDDS could potentially increase the dissolution of Valsartan which in turn would enhance its absorption and bioavailability when administered orally .

3.2 Specific Objectives .

Following the research hypotheses, the specific objectives were set as follows:

- To formulate, develop, and optimize an oil-in-water microemulsion system for Felodipine using suitable oil, surfactant, and co-surfactant.
- To formulate, develop, and optimize an SMEDDS containing Valsartan using suitable oil, surfactant, and co-surfactant.
- To select formulation components, specifically oils, surfactants, and co-surfactants, based on rigorous drug solubility studies.
- To optimize the ratio of surfactant and co-surfactant required to formulate a stable microemulsion system using pseudo-ternary phase diagrams.
- To characterize the prepared microemulsion and SMEDDS systems regarding their physical and chemical properties.
- To perform and compare in-vitro intestinal permeability studies (ex-vivo drug release) for optimized microemulsion, SMEDDS, and plain drug suspensions.
- To develop and optimize a Solid-SMEDDS formulation of Valsartan by adsorbing the optimized liquid SMEDDS onto solid carriers and investigating the influence of hydrophilic and hydrophobic solid carriers on drug release.
- To compare the in-vitro drug release of optimized liquid SMEDDS and Solid SMEDDS with a marketed conventional tablet formulation of Valsartan.
- To perform a pharmacokinetic study using a suitable animal model to evaluate the oral bioavailability of Felodipine when delivered as a microemulsion versus a plain drug suspension.
- To conduct stability studies of the optimized microemulsion, SMEDDS, and Solid- SMEDDS systems to ensure long-term physical and chemical viability.

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IV. MATERIALS & METHODS

4.1 Research Methodology .

The research methodology was structured to ensure systematic development and evaluation. The work followed these key steps:

1. Identification and Characterization:Selected drugs (Felodipine and Valsartan) were characterized by melting point study, FTIR spectroscopy, and UV spectroscopy.
2. Analytical Method Establishment: Validation of UV spectrophotometric methods for Felodipine and Valsartan.
3. Oil Selection: Solubility studies of drugs in various oils, including Capmul MCM, Capryol 90, Captex 200P, Captex 355, and Isopropyl myristate.
4. Surfactant/Co-surfactant Selection: Screening of surfactants (Tween 20, Tween 80, Labrasol, Plurol Oleique, Cremophore EL) and co-surfactants (Transcutol P, PEG 400, Propylene Glycol, Labrafil) based on drug solubility.
5. Compatibility Study: Physical (phase separation, color change) and chemical (drug potency loss) compatibility testing of drugs with surfactants.
6. Optimization: Determination of microemulsion regions using pseudo-ternary phase diagrams via the water titration method, varying the ratios of oil and S_{mix}.
7. Formulation Development:

Felodipine Microemulsion: Developed using Capmul MCM (oil), Tween 20 (surfactant), and PEG 400 (co-surfactant) .
o Valsartan SMEDDS: Prepared using Capmul MCM (oil), Tween 80/Labrasol (surfactants), and Transcutol P/PEG 400 (co-surfactants) .

8. Characterization: Evaluation of appearance, clarity, thermodynamic stability, dispersibility, droplet size, zeta potential, polydispersivity index, dye solubility (for Felodipine), and conductivity (for Valsartan SMEDDS) .
9. Drug Release Studies: In-vitro dissolution testing and in-vitro intestinal permeability studies .
10. In-Vivo Study: Pharmacokinetic assessment in Male Wistar rats to compare the optimized Felodipine microemulsion with plain drug suspension.
11. Solid SMEDDS Development: Conversion of optimized liquid SMEDDS into solid dosage forms using adsorption on solid carriers (Aerosil 200, Lactose anhydrous, and Avicel PH 101).
12. Stability Testing: Assessment of robustness to dilution and accelerated stability testing (40 C / 75\% RH) for physical and chemical stability .

4.2 Methods of Preparation for Microemulsions .

The preparation of microemulsions and Self-Microemulsifying Drug Delivery Systems (SMEDDS) relies heavily on the spontaneous or low-energy formation of nanodroplets. In an industrial or laboratory setting, two primary methods are utilized. Water Titration Method (Spontaneous Emulsification) .

This is the most common method for preparing microemulsions at room temperature.

1. Preparation of Smix: The surfactant and co-surfactant are mixed in varying weight ratios (e.g., 1:1, 2:1, 3:1).
2. Drug Solubilization: The poorly soluble drug is accurately weighed and dissolved in the selected oil phase.
3. Blending: The drug-loaded oil is then mixed with the Smix to form a homogenous, isotropic pre-concentrate (this stage essentially represents a SMEDDS).
4. Titration: Water is added dropwise to this mixture under continuous, gentle magnetic stirring.
5. Observation: The transition from a clear liquid to a cloudy emulsion and back to a clear/translucent microemulsion is monitored to plot the pseudoternary phase.

Phase Inversion Temperature (PIT) Method This method is primarily used for microemulsions stabilized by non-ionic surfactants (like polyethoxylated surfactants), whose solubility depends highly on temperature.

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4.3 Routes of Administration.

While oral delivery is the primary focus for overcoming poor water solubility, the unique nanostructure of microemulsions allows them to be adapted for multiple routes of administration:

Oral Route:- As detailed previously, SMEDDS and liquid microemulsions protect drugs from gastric degradation, bypass dissolution rate-limiting steps, and promote lymphatic transport (avoiding hepatic first-pass metabolism). This is the most patient-compliant route for chronic therapies like valsartan and felodipine.

Topical and Transdermal Route:-The stratum corneum is a formidable barrier to drug penetration. Microemulsions act as excellent transdermal permeation enhancers. The lipophilic oil core partitions into the skin lipids, while the high concentration of surfactants disrupts the lipid bilayers of the skin. This makes microemulsions ideal for delivering antiviral drugs like acyclovir deep into the basal epidermis to treat herpetic lesions effectively.

Parenteral (Intravenous) Route:- O/W microemulsions can be formulated for IV injection to deliver highly hydrophobic drugs (like certain chemotherapeutics or anesthetics) without using toxic co-solvents like Cremophor EL. The droplets must be strictly < 100 nm to prevent pulmonary embolism and must be formulated with highly purified, biocompatible lipids and surfactants

4.4 Instruments (List of Equipments) .

The various analytical instruments and formulation equipments utilized throughout the research work, in order of their utilization, are detailed below. Proper calibration and standard operating procedures were followed for all instruments prior to use.

Table No 3. List of instruments required for the research work.

Sr. No.	Equipment / Instrument	Model & Make of the Equipment
1.	Digital weighing balance	Shimadzu electronic analytical balance
2.	FT IR Spectrometer	FTIR-Brucker alpha-E model
3.	UV-Visible Spectrophotometer	UV-1800 spectrophotometer, Shimadzu
4.	Magnetic Stirrer	MS500, Remi Equipments
5.	Droplet Size & Zeta Potential Analyzer	Malvern Zetasizer Nano ZS LU-227, Malvern Instruments
6.	Digital pH meter	Systronic, 361-micro pH meter
7.	Brookfield Viscometer	LVDVII+PRO, Brookfield, USA
8.	Bubble Tensiometer	BPA-800P
9.	Transmission Electron Microscope (TEM)	TEM-JEM-100SX, JEOL, Tokyo
10.	Dissolution Apparatus	Electrolab TDT-80L
11.	Organ Bath (Modified Diffusion Assembly)	SE 1 AW Orchid Scientifics India
12.	HPLC System	HPLC with UV-Visible Detector (SPD-10A, Shimadzu) and HPLC packed column

microemulsion, turbid emulsion, or gel). The appearance (transparency, opalescence, and isotropy) is recorded to demarcate the phase boundaries.

Phase Inversion Method

This method relies on changing the spontaneous curvature of the surfactant layer by manipulating environmental factors, such as temperature (Phase Inversion Temperature - PIT) or pH. For non-ionic surfactants, cooling the system causes a transition from an O/W microemulsion at low temperatures to a W/O microemulsion at higher temperatures. The system crosses a point of zero spontaneous curvature, promoting the formation of finely dispersed oil droplets.

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Method Developed by Boycott and Schulman

In this method, a coarse macro-emulsion is prepared first by adding the oil and surfactant mixture to a portion of the aqueous phase under temperature-controlled agitation. This mixture is subsequently titrated with a co-surfactant until the system turns clear (transparent), followed by dilution with water to achieve the desired concentration.

4.6 Development of Solid SMEDDS .

Solid SMEDDS (S-SMEDDS) are developed by converting liquid SMEDDS into free- flowing powders, which offer superior storage stability and processing versatility compared to their liquid counterparts.

Adsorption Technique

Procedure: The optimized liquid SMEDDS formulation (V1A) was converted into a dry powder by adsorbing the liquid onto solid carriers.

Solid Carriers: The carriers utilized in this study included:

o Colloidal Silicon Dioxide (Aerosil 200): Used as a hydrophobic adsorbent to provide structure.

o Lactose Anhydrous: Used as a hydrophilic adsorbent.

o Microcrystalline Cellulose (Avicel PH 101): Used as an insoluble carrier to provide mechanical strength.

V. RESULTS

5.1 Identification and Characterization Results .

The drug samples (Felodipine and Valsartan) were confirmed to be pure based on the following analytical results:

FTIR Spectroscopy

o Felodipine: Characteristic absorption bands observed at 3366 cm^{-1} (N-H stretching), 1688 cm^{-1} (C=O stretching), 1461 cm^{-1} (C=C ring stretching), and 564 cm^{-1} (C-Cl stretching) confirmed the structure.

o Valsartan: Characteristic peaks identified at 3100 cm^{-1} (N-H stretching), 1667 cm^{-1} (C=O stretching), 1512 cm^{-1} (N=N bond), and 1353 cm^{-1} (C=N bond) matched the reference spectrum from the Indian Pharmacopoeia 2010

.

UV Spectroscopy

o Felodipine: The lambda max in methanol was obtained at 360.50 nm.

o Valsartan: The lambda max in methanol was obtained at 250 nm, confirming compliance with IP 2010.

5.2 Excipient Selection and Drug-Surfactant Compatibility: The solubility studies were performed to determine the optimal carriers for the drugs.

Felodipine: The highest solubility was found in Capmul MCM (90 \pm 1.25 mg/ml) compared to other oils. PEG 400 and Tween 20 were selected as the co- surfactant and surfactant, respectively, due to their high solubilizing capacity (120 mg/ml each).

Valsartan: Capmul MCM provided the highest solubility (110 \pm 1.2 mg/ml). Compatibility studies revealed that combinations of Peceol/PEG 400 and Labrasol/PEG 400 for Valsartan resulted in precipitation, and were subsequently excluded. Tween 80/PEG 400 and Tween 80/Transcutol P combinations were determined to be stable.

5.4 Physical Evaluation and Thermodynamic Stability .

The formulations were evaluated to ensure they remained stable under various stress conditions.

Thermodynamic Stability Tests:

1. Heating-Cooling Cycle: Formulations were stored at 4 C and 45 C for six cycles, with 48 hours at each temperature.
2. Centrifugation: Samples were centrifuged at 3500 rpm for 30 minutes to check for phase separation.
3. Freeze-Thaw Cycle: Three cycles between -21 C and +25 C were performed.

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Results :

1. Felodipine Microemulsion: Formulations F1, F2, F3, and F5 passed all thermodynamic stress tests and the dispersibility test (Grade 'a'), while batches F7, F8, and F9 failed.
2. Valsartan SMEDDS: System V1 and V3 formulations passed the tests, whereas System V2 failed due to phase separation .
3. Dispersibility Test: Grade 'a' formulations (clear appearance) were prioritized for further study. Formulation F4 and batches F6–F9 were discarded due to failing the dispersibility criteria.

5.5 Droplet Size, Zeta Potential, and Viscosity :-

The physical properties of the optimized batches were evaluated to confirm the formation of a stable O/W system.

Droplet Size & PDI :

1. Felodipine: Batch F2 showed the smallest mean droplet size (15.12 pm 2.5 nm) and a PDI of 0.147, indicating a highly uniform system.
2. Valsartan: Batch V1A demonstrated the smallest droplet size (11.96 pm 1.3 nm) and a PDI of 0.233.

VI. DISCUSSION

6.1 Phase Behavior and Thermodynamic Stability .

The phase titration (water titration) method proved to be a highly effective approach for demarcating the microemulsification regions. The results indicated that the ratio of surfactant to co-surfactant (S/CoS) is the primary determinant of the microemulsion existence area. A ratio of 2:1 was found to be optimal for Felodipine, providing a wider single-phase region compared to 1:1 or 4:1 ratios.

The thermodynamic stability of these systems, confirmed by passing heating-cooling and freeze-thaw cycles, differentiates them from kinetic dispersions like coarse emulsions. Unlike coarse emulsions that are prone to creaming or phase separation over time, the microemulsions developed in this study achieved thermodynamic stability due to the ultra- low interfacial tension provided by the surfactant-co-surfactant film. This film acts as a mechanical barrier to coalescence, preventing the droplet growth that typically leads to instability.

6.2 Influence of Formulation Variables on Droplet Size .

The droplet size of the resultant microemulsion is the most critical parameter for ensuring physical stability and efficient drug loading.

Oil Concentration: The results demonstrated a direct correlation between oil concentration and droplet size; increasing the Capmul MCM content beyond 15 – 20% v/v resulted in increased viscosity and a shift toward larger, unstable droplet sizes.

Surfactant Concentration: Higher concentrations of S {mix} within the microemulsifying region were observed to increase the spontaneity of the emulsification process, as the surfactant molecules could more effectively partition at the interface, reducing the total free energy of the system.

6.3 Stabilization Mechanisms .

The physical stabilization of the developed microemulsions can be explained by the DLVO theory. According to this theory, the system remains stable due to the balance between

VII. CONCLUSION AND FUTURE SCOPE .

7.1 Conclusion .

The objective of the present research study was to formulate, develop, and optimize microemulsion systems for the oral delivery of poorly water-soluble active pharmaceutical ingredients.

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The research successfully demonstrated that lipid-based delivery systems, specifically microemulsions and Self-Microemulsifying Drug Delivery Systems (SMEDDS), are highly effective strategies for improving the bioavailability of poorly water-soluble drugs like Felodipine and Valsartan.

Key Formulation Findings: Capmul MCM was identified as an ideal oil phase for both drugs due to its high solubilizing capacity.

The optimized Felodipine microemulsion (F2) and Valsartan SMEDDS (V1A) exhibited excellent thermodynamic stability, with mean droplet sizes significantly below 100 nm, which is a prerequisite for enhanced intestinal absorption.

Performance Analysis: In-vitro dissolution and ex-vivo intestinal permeability studies consistently demonstrated that these lipid-based formulations provide faster drug release and superior permeability compared to conventional plain drug suspensions or marketed tablet formulations.

Solidification: The optimized liquid SMEDDS (V1A) was successfully converted into free-flowing Solid-SMEDDS (SS1) using adsorption onto solid carriers (Aerosil 200 and Lactose monohydrate).

Solid-state characterization (DSC and Microscopy) confirmed that the drug remained in an amorphous state or molecularly dispersed form within the solid matrix, which prevents crystallization and promotes rapid dissolution.

Stability: Accelerated stability testing conducted over 6 months confirmed that all optimized systems (F2, V1A, and SS1) were physically and chemically stable, retaining

7.2 Future Scope .

The current study has established the formulation and optimization of microemulsion and SMEDDS systems for Felodipine and Valsartan. Based on these promising results, the following directions are recommended for future research and development:

- Industrial Scale-up and Manufacturing Feasibility: While this research was conducted on a laboratory scale, future efforts should be directed toward the industrial-scale manufacturing of Solid-SMEDDS. Utilizing advanced industrial technologies—such as fluid-bed coating, high-shear granulation, or hot-melt extrusion—would be essential to assess the economic viability and technical feasibility of producing these formulations in large batches.
- In-depth Pharmacokinetic and Clinical Validation: While the current findings confirmed a 9.85-fold increase in the relative oral bioavailability of Felodipine in animal models (rat), future research should focus on multi-species pharmacokinetic evaluations (such as in beagle dogs) to better understand inter- species variations. Eventually, clinical trials in humans would be necessary to validate the therapeutic efficacy, safety, and PK/PD correlation of these optimized delivery systems .
- Controlled-Release Integration: The rapid drug release profile observed in Solid-SMEDDS (SS1) is ideal for immediate-release requirements. Future studies could explore the integration of rate-controlling polymers, such as Eudragit® or HPMC, within the solid matrix or as a functional coating layer. This would allow for the development of sustained-release Solid-SMEDDS, enabling a once-daily dosing regimen that would further enhance patient adherence to chronic anti-hypertensive therapy.
- Mechanistic Studies of Absorption: Further research utilizing fluorescent labeling and confocal microscopy could provide deeper insights into the specific intracellular trafficking pathways (e.g., transcellular vs. paracellular transport) taken by these microemulsion droplets within the enterocytes.
- Regulatory Compliance: As these systems utilize novel excipient combinations (e.g., Capmul MCM, Labrasol, Transcutol P), future work should focus on long-term

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