Self-Emulsifying Drug Delivery System

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Abstract- *Oral drug administration is convenient and cost-effective, but low bioavailability is a major issue due to poor aqueous solubility. 40% of active substances are poorly water-soluble. To improve bioavailability, various technological strategies like solid dispersions, cyclodextrine complex formation, and micronization are used. Self-emulsifying drug delivery systems (SEDDS) have gained attention for enhancing oral bioavailability with reduced dose. SEDDS can form fine oil-in-water emulsions or micro-emulsions, potentially improving lipophilic drug absorption rates.*

I. INTRODUCTION

Nearly forty percent of novel drug candidates are poorly soluble in water, and oral administration of these medications is often linked to poor bioavailability, significant intra- and inter-individual variability, and insufficient dose proportionality in order to resolve these issues The use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles, and soild dispersions are just a few of the formulation techniques that are utilized.
In order to increase the oral bioavailability of lipophilic medications, lipid-based formulations have received a lot of attention lately. Self-emulsifying drug delivery systems (SEEDS) have received special attention.

Isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or, alternatively, one or more hydrophilic solvents and co-solvents / surfactants are known as SEEDs, or self emulsifying oil formulations.

These systems can form fine oil-in-water (o/w) emulsions or micro emulsions upon mild agitation followed by dilution in aqueous media, such as gastrointestinal fluids.
As a result, these systems may provide improved absorption rates and extents as well as more consistent plasma concentration profiles for lipophilic medications with dissolution limited oral absorption.

Examples of pharmaceutical products designed as self-emulsifying systems are displayed in Table 1.

Due to their potential to increase the bioavailability of substances classified as class II in the biopharmaceutical classification system, SEEDS formulations have also drawn attention (BCS)
Class II compounds have a high permeability and a low solubility in water.

In Table 2, we see the difference between SEED and SMEDDS

ADVANTAGE:-

- Preservation of delicate therapeutic compounds
- Enhanced uniformity in the absorption of drugs
- Medication delivery that is specifically aimed at a particular GIT absorption window
- Medication defense against the gut environment
- Management of the delivery profiles
- Decreased fluctuation, including the impact of food
- Elevated oral bioavailability that permits dosage reduction
- Excellent efficacy of drug loading
- Regarding dosage forms, each liquid and solid

LIMITATIONS:-

The absence of reliable predictive in vitro models for formulation evaluation is one of the challenges facing the development of self-emulsifying drug delivery systems and other lipid-based formulations.

Traditional methods of dissolving do not work because these formulations may require digestion before the drug is released.

An in vitro model that replicates the duodenum's digestive processes has been created to mimic this before assessing the strength of this in vitro model, more research and validation are required.

Different prototype lipid-based formulations must be created and tested in vivo in an appropriate animal model since subsequent development will be predicated on correlations between in vitro and in vivo data.

COMPOSITION:-

Self emulsifying process depends on

- The surfactant and oil's characteristics
- The degree of surfactant concentration
- The temperature at which emulsification takes place on its own

OIL:-

It has been possible to create self-dispersing formulations using both long and medium chain triglyceride oils with varying saturation levels.

Although unrefined edible oils offer the most natural foundation for lipid carriers, their limited capacity to dissolve substantial quantities of hydrophobic medications and their relatively challenging self-emulsification process

Due to their higher fluidity, better solubility, and self-emulsifying ability, medium chain triglycerides were preferred in earlier self-emulsifying formulations. However, it appears that these properties make them less appealing when compared to the new semi-synthetic medium chain derivatives, which are more accurately described as amphiphilic compounds with surfactant properties.

Organic solvents are acceptable to take orally. Ex: ethanol, propylene glycol, and polyethylene glycol can aid in the dissolution of in these circumstances, the hydrophilic oil in the formulation may be replaced by a more lipophilic surfactant.

SURFACTANTS:-

The most widely used excipients in self-dispersing systems are tween 80 and different liquid or solid ethoxylatedpolyglycolyzed glycerides, which are designed using non-ionic surfactants with a relatively high hydrophilic lipophilic balance.

While non-ionic surfactants are known to be less hazardous than ionic surface active agents, their effects on intestinal wall permeability may be somewhat reversible.

In self-emulsifying formulations, the typical surfactant concentration needed to create and preserve an emulsion state in the GI tract ranged from 30 to 60% W/W of the formulation.

The GI tract may become irritated by large amounts of surfactant. Therefore, in every situation, the surfactant vehicle's safety should be carefully considered.

In order to provide a good dispersing/self-emulsifying performance, the formulation must spread quickly in the aqueous environment and immediately form o/w droplets, which requires a high HLB and consequent hydrophilicity of the surfactant.

Due to their natural amphiphilic nature, the surface active agents are typically able to dissolve and even solubilize relatively large amounts of the hydrophobic drug.

The latter is crucial for maintaining the drug molecules' long-term solubility, which is essential for efficient absorption, and for avoiding precipitation within the GI lumen.

CO-SOLVENTS :-

Substantial concentrations of a medicine or hydrophilic surfactant in liquid base.

Co-solvents are added in the form of a aqueous solvent, such as glyceryl triacetate or triacetin, an acetylated derivative of glycerol.

Triacetin is a good choice because it can be used to dissolve a medication that is hydrophobic and is miscible in oil lipid phases.

CO-SURFACTANT:-

Co surfactant with an HLB value of 10–14 is typically used in SEDDS.

Alcohols with intermediate chain lengths, such as hexanol, pantanol, and octanol, are preferred as hydrophilic co-surfactants because they are known to lower the oil-water interface and promote the spontaneous formation of micro emulsions.

Table 3 provides a variety of surfactant co-solvent and oil examples.

FORMULATION:-

There is a wide range of liquid or waxy excipients that can be used in formulations for encapsulation in hard or soft gelatin or mixtures that disperse to produce fine colloidal emulsions. These excipients include oils, biological lipids, hydrophobic and hydrophilic surfactants, and water soluble co-solvents.

- The medication's solubility in various oil surfactants and co-solvents

- The phase diagram preparation and drug solubility are taken into consideration when choosing an oil surfactant and co-solvent.
- The process of creating SEDDS formulation by dissolving the medication in an oil surfactant and co-solvent combination.

Adding a medication to a SEDDS is essential because the medication modifies the ideal oil-surfactant ratio by partially interfering with the self-emulsification process. If using extended SEDDS, the gelling agent or polymer is added during formulation.

MECHANISM OF SELF-EMULSIFICATION:-

It's unclear exactly how self emulsification works at this point. Reiss, however, states that self-emulsification happens when the entropy change that promotes dispersion is larger than the energy needed to increase the dispersion's surface area.

Moreover, the energy needed to form a new surface between the two phases determines the free energy of a conventional emulsion formation, which is expressed by equation

$$\Delta G = \sum_{i} N_i \pi r_i^2 \sigma$$

Where N is the number of droplets of radius r, s is the interfacial energy, and G is the process's free energy (ignoring the mixing free energy).

The emulsion's two phases will eventually tend to separate from one another in order to decrease the interfacial area and, ultimately, the system's free energy.

As a result, conventional emulsifying agents stabilize the emulsions produced by aqueous dilution by forming a monolayer around the emulsion droplets, which lowers interfacial energy and acts as a barrier to coalescence.

In the case of self-emulsifying systems, either very little positive or negative free energy is needed to form the emulsion (thus the emulsification process occurs spontaneously).

By contracting local interfacial regions, destabilization occurs during emulsification, which requires very little energy input. The interfacial structure must not resist surface shearing in order for emulsification to take place. Previous research has proposed a correlation between the ease of emulsification and the ease of water penetration into the different LC or gel phases that form on the droplet surface.

Wakerly et al. state that when a binary mixture (oil and nonionic surfactant) is added to water, an interface between the oil and aqueous continuous phases forms. This is followed by water becoming soluble in the oil phase as a result of aqueous penetration through the interface.

This will keep happening up until the interface, where the solubilization limit is reached. Subsequent aqueous penetration will cause the dispersed LC phase to form.

Depending on the concentration of surfactant in the binary mixture, all material near the interface will eventually be LC as a result of the aqueous penetration. After the self-emulsification process is gently agitated, water rapidly penetrates the aqueous cores, causing interface disruption and droplet formation.

These self-emulsified systems' high stability to coalescence is thought to be caused by the LC interface around the oil droplets. Pouton et al. thoroughly investigated the role of the LC phase in the emulsion formation process. Later, Craig et al. investigated the self-emulsifying characteristics of a series of imwitor 742 (a mixture of moo- and diglycerides of capric and caprylic acids)/between 80 systems using a combination of particle size analysis and low frequency dielectric spectroscopy (LFDS).

The dielectric studies showed that, despite the relationship's obvious complexity, the emulsions'dormation may be connected to LC formation. The drug may change the properties of the emulsion by interacting with the LC phase, as indicated by the above technique. That being said, there is still no solid evidence linking spontaneous emulsification to the formation of LC.

CHARACTERIZATION:-

Visual assessment

This could offer crucial details regarding the mixture's micro- and self-emulsifying properties as well as the dispersion that results.

Thermodynaic stability studies:-

The performance of a lipid-based formulation is also highly dependent on its physical stability, which can be negatively impacted by drug precipitation in the excipient matrix. Furthermore, inadequate physical stability of the formulation may cause the excipient to phase separate, which would impact both the formulation's performance and appearance. Moreover, mismatches between the formulation and the shell of the gelatin capsules may cause brittleness, deformation, delayed disintegration, or insufficient drug release.

- Heating-cooling cycle: six cycles are conducted, ranging from 4°C to 45°C, with a minimum of 48 hours of storage at each temperature. Formulations that remain stable at these temperatures are then put through a centrifugation test.
- Centrifugation: Formulations that pass the test are centrifuged in cycles between 21ºC and + 25ºC degrees Celsius, and they are stored at each temperature for at least 48 hours while being spun at 3500 revolutions per minute for 30 minutes. Formulations that do not exhibit phase separation are then taken for the freeze that stress test.
- Freeze-thaw cycle: three freezes for the formulations that passed this test demonstrated good stability and no cracking or creaming of the phase separation.

DISPERSIBILITY TEST:-

Using a standard USP XXII dussolution apparatus II, the effectiveness of self-emulsification of oral nano- or micro-emulsion is evaluated. 500 ml of water at 37 + or _0.5ºC was mixed with one milliliter of each formulation. The following grading system is used to visually assess the in vitro performance of the formulation. A standard stainless steel dissolving paddle rotating at 50 rpm provided gentle agitation.

Grade-A: Quickly developing (in one minute) nanoemulsion possessing a transparent or blue appearance

Grade-B: Quickly forming bluish-white emulsion that is slightly less clear

Grade-C: Within two minutes, a fine, milky emulsion formed.

Grade-D: The emulsion is dull, grayish white, slightly oily, and takes longer than two minutes to emulsify.

Grade-E: Formulation with large oil globules visible on the surface and either poor or minimal emulsification

When distributed in the GIT, the formulations of Grades A and B will stay as nanoemulsions. While it is possible to recommend a Grade C formulation for SEDDS formulation.

TURBIDIMETRIC EVALUATION:-

Nepheloturbidimetric analysis is used to track the development of emulsification. A turbidimeter is used to measure the increase in turbidity when a fixed quantity of the self-emulsifying system is added to a fixed quantity of the suitable medium (0.1N hydrochloric acid) while stirring continuously (at 50 rpm) on a magnetic plate at room temperature. However, because the time needed for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

VISCOSITY DETERMINATION:-

Typically, the SEDDS system is given as hard or soft gelatin capsules so that it is simple to pour into capsules, and the system shouldn't be overly thick to cause issues. The micro emulsion's rheological characteristics are assessed Viscometer Brookfield This determination of viscosity validates if the system is w/o or o/w. A system is classified as either o/w or w/o depending on its viscosity; if it is unknown, it is classified as w/o.

Droplet size analysis and Particle size measurements:-

The emulsions' droplet sizes are ascertained through photon correlation spectroscopy, which employs a Zetasizer capable of measuring sizes ranging from 10 to 5000 nm to analyze variations in lightscattering resulting from the particles' Brownian motion.

Following external standardization with spherical polystyrene beads, light scattering is observed at 25°C at a 90° angle. The particle's nanometric size range remains unaltered even after being diluted with water 100 times, demonstrating the system's compatibility with excess water.

Zeta potential measurement:-

In conventional SEDDSs, the presence of free fatty acids results in a negative charge on an oil droplet, which is used to identify the droplets' charge.

Refractive index and Percentage Transmittance:-

The transparency of the formulation was demonstrated by the percent transmittance and refractive

index. Using a refractometer, the system's refractive index is determined by comparing a drop of solution on a slide to that of water (1.333).

With distilled water used as a blank, the UV spectrophotometer is used to measure the system's percent transmittance at a specific wavelength. A formulation is said to be transparent if its refractive index is close to that of water (1.333) and its percent transmittance is greater than 99 percent.

Electro conductivity study:-

Ionic or non-ionic surfactant, water, and oil make up the SEDD system. Thus, this test is meant to gauge the system's electroconductive properties. An electro conductometer is used to measure the system's electro conductivity.

In Vitro Diffusion study:-

Using a dialysis method, in vitro diffusion studies were carried out for each of the formulations created. Phosphate buffer, pH 6.8, was used as the dialyzing medium. A 7 cm length of pretreated cellulose dialysis tubing was tied off at one end with thread, and 1 ml of the self-emulsifying formulation and 0.5 ml of dialyzing medium were then added to it.

The other end of the tubing was threaded shut and left free to rotate in 200 milliliters of dialyzing medium. It was then continuously agitated at 100 revolutions per minute with a magnetic bead on a magnetic plate at 37 degrees Celsius. One milliliter aliquots were taken out at various intervals and further diluted. Every time, the dialyzing medium was replaced with fresh aliquot volume. Using a UV-visible spectrophotometer, these samples were quantitatively examined for drugs that were dialyzed across the membrane at the appropriate time.

Drug content:-

The drug is extracted from pre-weighed SEDDS by dissolving it in an appropriate solvent. Using an appropriate analytical technique, the drug content in the solvent extract was compared to the drug's standard solvent solution.

Biopharmaceutical Aspects:-

A thorough analysis has been conducted on the capacity of lipids and/or food to increase the bioavailability of poorly water-soluble medications.

Currently accepted theory holds that lipids may increase bioavailability through a variety of possible mechanisms, though these are not fully understood.

Alterations (reduction) in gastric transit:-

Increasing the amount of time available for dissolution and slowing delivery to the absorption site.

Increases in effective luminal drug solubility:-

The presence of lipids in the GI tract stimulates

An increase in the GI tract's ability to solubilize substances due to an increase in the secretion of phospholipids (PL) and cholesterol (CH) as well as bile salts (BS). These endogenous biliary lipids form intestinal mixed micelles known as BS/PL/CH. However, swelling of the micellar structures and an additional increase in solubilization capacity result from the intercalation of administered (exogenous) lipids into these BS structures, either directly (if sufficiently polar) or secondary to digestion.

Stimulation of intestinal lymphatic transport:-

Lipids may improve the degree of lymphatic transport and raise bioavailability of highly lipophilic drugs either directly or indirectly by reducing first-pass metabolism.

Changes in the biochemical barrier function of the GI tract:-

The p-glycoprotein efflux pump indicates that certain lipids and surfactants can inhibit intestinal efflux transporter activity. They can also lessen the degree of enterocyte-based metabolism.

Changes in the physical barrier function of the GI tract:-

It has been demonstrated that different mixtures of lipids, lipid digestion products, and surfactants have permeability-enhancing qualities. However, passive intestinal permeability is generally not considered to be a significant obstacle to the bioavailability of most poorly water-soluble, and particularly lipophilic, medications**.**

FACTORS AFFECTING SEDDS:

Polarity of the Lipophillic Phase:-

One of the primary factors controlling the drug release from the micro-emulsions is the polarity of the lipid

phase. The HLB, the fatty acid's chain length and degree of unsaturation, the hydrophilic portion's molecular weight, and the emulsifier's concentration all influence the droplet's polarity. Actually, the polarity indicates the drug's affinity for water or oil as well as the kind of force that is generated.

The drug will release into the aqueous phase more quickly due to the high polarity. Sang-Cheol Chi's observations, which show that the polarity of the oil phase used affects the rate of idebenone release from SEDDS, corroborate this. The formulation with the highest polarity oil phase yielded the highest release.

Nature and Dose of the Drug:-

Medications that are taken at very high dosages shouldn't be used with SEDDS unless they have very good solubility in at least one of the components, ideally the lipophillic phase. The most challenging medications for SEDDS delivery are those with restricted or decreased solubility in lipids and water.

The solubility of the drug in the oil phase has a significant impact on SEDDS's ability to maintain the drug in its solubilized form. As previously indicated, if a surfactant or co-surfactant is more heavily involved in the solubilization of the drug, there may be a chance of precipitation because the dilution of SEDDS will reduce the solvent capacity of the surfactant or co-surfactant.

Measurements of equilibrium solubility can be used to forecast possible occurrences of gut precipitation. Nonetheless, in the gut's solubilizing and colloidal stabilizing milieu, crystallization might proceed slowly. According to Pouton's research, it may take these formulations up to five days to reach equilibrium and up to 24 hours for the medication to stay in a super-saturated state. following the first emulsification event.

Hence, it may be claimed that these products have little chance of causing the medication to precipitate in the stomach prior to absorption, and that super-saturation may even improve absorption by raising the drug's thermodynamic activity. Practical techniques to forecast the destiny of medications following the dispersion of lipid systems in the gastro intestinal tract.

APPLICATIONS:-

Supersaturable SEDDS (S-SEDDS):-

The high surfactant level typically present in SEDDS formulations can lead to GI side-effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side-effects and achieve rapid absorption of poorly soluble drugs.

Once the formulation is released from an appropriate dosage form into an aqueous medium, the S-SEDDS approach aims to produce a prolonged supersaturated solution of the drug. The purpose of surpersaturation is to increase the thermodynamic activity of the drug beyond its solubility limit, which will increase the driving force for transit into and across the biological barrier.

Solid SEDDS:-

Typically, SEDDS are prepared as liquid dosage forms that can be taken orally in soft gelatine capsules; however, these capsules have certain drawbacks, particularly during the production process. Alternatively, liquid self-emulsifying ingredients can be mixed with a powder to make a solid dosage form (tablets, capsules).

Improvement in Solubility and Bioavailability:-

A drug's solubility is increased if it is formulated in SEDDS because, in the case of a Class-Λ drug (low solubility/high permeability), the dissolution step is avoided. The lipid matrix in SEDDS reacts easily with water to form an oil-in-water (o/w) emulsion of fine particles. The medication will be delivered to the gastrointestinal mucosa by the emulsion droplets in a dissolved state that is easily absorbed. Consequently, when medications are presented in SEDDS, an increase in AUC, or bioavailability and Cmax, is seen with many of them[7].

Protection against Biodegradation:-

Drugs with low solubility and GI tract degradation that result in low oral bioavailability may find particular benefit from the self-emulsifying drug delivery system's capacity to decrease degradation and enhance absorption. Numerous medications undergo physiological system degradation, which can be caused by the stomach's acidic pH, hydrolytic breakdown, enzymatic breakdown, etc. When these medications are administered as SEDDS, they can be effectively shielded from these deteriorating processes because the liquid crystalline phase in SEDDSmay function as a barrier between the medication and the deteriorating environment[7].

Table 1: Examples of pharmaceutical product formulated as Self-emulsifying systems

Drug name	Compound	Dosage form	Company
Neoral	Cyclosporine-A	Soft gelatin capsule	Norvatis
Norvir	Ritonavir	Soft gelatin capsule	Abbott laboratories
Fortovase	Saquinavir	Soft gelatin capsule	Hoffmann-la Roche inc.
Agenerase	Amrenavir	Soft gelatin capsule	Glaxo smith kline
Solufen	Ibuprofen	Hard gelatin capsule	Sanofi-Aventis
Lipirex	Fenofibrate	Hard gelatin capsule	Sanofi-Aventis

Table – 2:- Difference between SEEDS and SMEDDS

SEEDS	SMEDDS
Can be a simple binary formulation with the drug and lipidic excipients able to selfemulsify in contact with (GIF) Or A system comprising drug, surfactant, oil (also referred to as lipid phase).	Are composed of the drug compound, surfactant, cosurfactant, and oil (lipid phase)
Lipid droplets size in the dispersion ranges from 200nm-5µm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplets size in the dispersion is <200nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEEDS systems are not thermodynamically stable in conditions.	SEEDS systems are thermodynamically stable in water or physiologic conditions.

Table 3: Example of surfactants, co-surfactant and co-solvent Used in commercial formulations [7].

Excipient Name (commercial name)
Surfactants/co-surfactants
Polysorbate 20 (Tween 20)
Polysorbate 80 (Tween 80)
Sorbitanmonooleate (Span 80)
Polyoxy-40- hydrogenated castor oil (Cremophor RH40)
Polyoxyethylated glycerides (Labrafil M 2125 Cs)
Polyoxyethlated oleic glycerides (Labrafil M1944 Cs)
Co-solvents
Ethanol
Glycerin
Polypylene glycol
Polyethylene glycol
Lipid ingredients
Corn oil mono,di,,tri-glycerides
DL-alpha-Tocopherol
Fractionated triglyceride of palm seed oil (medium-chain triglyceride)
Medium chain mono-and di-glycerides
Corn oil
Olive oil
Oleic acid
Sesame oil
Soyabean oil
Peanut oil
Beeswax
Hydrogenated soyabean oil
Hydrogenated vegetable oils

II. CONCLUTION

The solubility/dissolution, absorption, and bioavailability of drugs that are poorly soluble in water were significantly enhanced by SEEDs. In terms of lowering production costs, streamlining industrial manufacturing, and enhancing patient compliance and stability, as an improvement or substitute for traditional liquid SEEDS is superior.

It is possible to prevent GI irritation and achieve controlled or sustained drug release. For the formulation of pharmaceutical compounds with low aqueous solubility, SEEDS offer a promising method. Using SEEDS can facilitate the oral delivery of hydrophobic drugs, as they have been demonstrated to significantly increase oral bioavailability.

Most of the time, the effectiveness of the SEEDS formulation depends on the particular case, so it is important to carefully consider the formulation's composition. The toxicity of the surfactant being used should be considered, since the SEEDS formulation typically uses a relatively high concentration of surfactants. Actually, the toxicity and self-emulsification potential of the surfactant under consideration for use need to be balanced. Two other significant factors that influence the efficiency of GI absorption are the size and charge of the oil droplet in the formed emulsion.

A viable method for formulating medication compounds with low aqueous solubility is the use of self-emulsifying drug delivery systems. SEDDSs have been demonstrated to significantly increase oral bioavailability and enable the oral delivery of hydrophobic medications. As this technology advances, SEDDSs will continue to open up new drug delivery applications and provide solutions for issues relating to the delivery of poorly soluble medications.

REFERENCES

[1] Gursoy R.N, Benita S. Self emulsifying drug delivery systems forimproved oral delivery of lipophilic drugs: Biomedicine andPharmacotherapy. 2004; 58:173-182.

[2] Abdalla A, Klein S, Mader K. A new Self emulsifying drugdelivery system for poorly soluble drugs: European Journal ofPharmaceutical Sciences. 2008; 35:357-464.

[3] Gershanik T, Benita S. Self-dispersing lipid formulations forimproving oral absorption of lipophilic drugs: EuropeanJournal of Pharmaceutics and Bio-pharmaceutics. 2000;50:179- 188.

[4] Tang B, Cheng G, Chun J. Development of solid self emulsifyingdrug delivery systems, preparation techniques and dosageforms: Drug Discovery Today. 2008;13:606-611.

[5] Craig D.Q.M, Barker S.A, Banning D, Booth S.W. An investigationinto the physicochemical properties of self-emulsifying systemsusing low frequency dielectric spectroscopy: International
Journal of Pharmaceutics. 1993; 96:147-155.

[6] Tang J.L, Sun J. Guihe Z. Self- Emulsifying Drug DeliverySystems: Strategy for Improving Oral Delivery of PoorlySoluble Drug, Current Drug Therapy. 2007;2:85-93.

[7] Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Handicap SRand Bhosale AV. “Self Emulsifying Drug Delivery System: AReview” Research J. Pharm. And Tech. 2008; 1(4): 313-323.

[8] Zhang P, Liu Y. Xu J. Preparation and Evaluation of SEEDS:International Journal of Pharmaceutics. 2008; 355:269-276.

[9] Patil P, Patil V, Paradkar A. Formulation of a self-emulsifyingsystem for oral delivery of simvastatin: In vitro and in vivoevaluation: Acta Pharm. 2007; 57:111-122.

[10] Gursoy R.N, Benita S. "Self-emulsifying drug delivery systemsfor improved oral delivery of lipophilic drugs," Biomedicineand Pharmacotherapy. 2004;58: 173-182.