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SELF-MICRO EMULSIFYING DRUG DELIVERY SYSTEM (SMDDS): A NOVEL APPROACH FOR ENHANCEMENT OF BIOAVAILABILITY

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ABSTRACT

The oral delivery of lipophillic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-micro emulsifying drug delivery systems (SMEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SMEDDS are isotropic mixtures of oils, surfactants, solvents and co-solvents and drugs with a unique ability to form fine oil in water microemulsiom upon mild agitation following dilution with aqueous phase. The efficiency of oral absorption of the drug compound from the SMEDDS depends on many formulations related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size all of which in essence determine the self-micro emulsifying ability. Approximately 40%of new chemical entities exhibit poor aqueous solubility and present a major challenge to modern drug delivery system, because of their low bioavailability.

KEYWORDS: Self micro emulsifying drug delivery system (SMDDS), Oral bioavailability, Lipophillic compounds, Poorly water soluble drugs.

INTRODUCTION

Self-micro emulsifying drug delivery system(SMEDDS) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) microemulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids.[1] SMEDDS spread readily in the GI tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification. SEDDS typically produce emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SMEDDS are physically stable formulations that are easy to manufacture. Thus, for lipophilic drug compounds that exhibit dissolution rate-limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood-time. SMEDDS formulation is in theory, comparatively simple. The key step is to find a suitable oil surfactant mixture that can dissolve the drug within the required therapeutic concentration. The SMEDDS mixture can be filled in either soft or hard gela-

tine capsules. 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.[2]

ADVANTAGES OF SMEDDS:

Improvement in oral bioavailability:

Dissolution rate dependant absorption is a major factor that limits the bioavailability of numerous poorly water-soluble drugs. The ability of SMEDDS to present the drug to GIT in solubilised and micro emulsified form (globule size between 1-100 nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. E.g. In case of halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation.[3]

Ease of manufacture and scale-up:

Ease of manufacture and scale up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles, etc., dealing with improvement of bio-availability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large-scale manufacturing. This explains the interest of industry in the SMEDDS.

Reduction in inter-subject and intra-subject variability and food effects:

There are several drugs, which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a boon for such drugs. Several research papers specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer reproducibility of plasma profile is available. [4]

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:

One unique property that makes SMEDDS superior as compared to the other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of prodrug by cholinesterase can be protected if polysorbate 20 is emulsifier in micro emulsion formulation.[5] These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides.[6]

No influence of lipid digestion process:

Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influenced by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessarily digested before the drug is absorbed as they present the drug in micro-emulsified form, which can easily penetrate the mucin, and water unstirred layer**.**

Increased drug loading capacity:

SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<log P>4) are typically low in natural lipids and much greater in amphilic surfactants, co surfactants and co-solvents.

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 thermodynamics 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 nanoparticles). 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 the gastrointestinal tract and be absorbed. The bioavailability of the drug is therefore improved.
- SMEDDS offer numerous delivery options like filled hard gelatin capsules or soft gelatin capsules or can be formulated in to tablets whereas emulsions can only be given as an oral solution.
- Emulsion cannot be autoclaved as they have phase inversion temperature, while SMEDDS can be autoclaved.

DISADVANTAGES OF SMEDDS

- One of the obstacles for the development of SMEDDS and other lipid-based formulations is the lack of good predicative *in vitro* models for assessment of the formulations.
- Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- This *in vitro* model needs further development and validation before its strength can be evaluated.
- Further development will be based on *in vitro* - *in vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which irritate GIT.

- Moreover, volatile co solvents in the conventional self-microemulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- The precipitation tendency of the drug on dilution may be higher due to the dilution effect of the hydrophilic solvent.
- Formulations containing several components become more challenging to validate.

EXCIPIENTS USED IN SEDDS:

Pharmaceutical acceptability of excipients and the toxicity issues of the components used makes the selection of excipients really critical. There is a great restriction as which excipeints to be used. Early studies revealed that the self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration and oil/surfactant ratio, the concentration and nature of co-surfactant and surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. These important discoveries were further supported by the fact that only very specific combinations of pharmaceutical excipients led to efficient selfmicroemulsifying systems.

SMEDDS formulation containing following components

- Oil phase
- Primary surfactant
- Secondary surfactant (co-surfactant)

Oil phase

The oil represents one of the most important excipients in the SMEDDS formulation not only because it can solubilize the required dose 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 (LCT and MCT) 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 excipient 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 systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties.[7] They offer formulative and physiologicaladvantages and their degradation products resemble the natural end products of intestinal digestion. Novel semisynthetic 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.[8] This is in accordance with findings of Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the li-

pid/water interfaces than LCT associated with a more rapid hydrolysis of MCT. In general, when using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

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 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.[6] 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.[8] 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 solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SMEDDS.[9] There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size, this could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface.[10] On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations.[11] This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including: improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability and decreased/inhibited p-glycoprotein drug efflux. However, the large quantity of surfactant may cause moderate reversible changes in intestinal wall permeability or may irritate the GI tract. Formulation effect and surfactant concentration on gastrointestinal mucosa should ideally be investigated in each case.[12]

Co-solvents:

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of cosurfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to

a very small even transient negative value. At this value the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough

to make interfacial tension positive again. This process known as 'spontaneous emulsification' forms the microemulsion. However, the use of co-surfactant in self emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SMEDDS, but also to solubilisation of the drug in the SMEDDS. Organic solvents, suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), etc) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as cosurfactant in the self emulsifying drug delivery systems, although alcohol- free self-emulsifying microemulsions have also been described in the literature. Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatin or hard sealed gelatin capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophillic drug dissolution ability of the alcohol free formulation may be limited. Hence, proper choice has to be made during selection of components.

Mechanism of self-emulsification

In emulsification process the free energy (ΔG) associated is given by the equation:

$\Delta G = \Sigma N i \pi r i$ ---------- (1)

In which 'N' is Number of droplets with radius 'r' and 'σ' is interfacial energy.

The mechanism by which self-emulsification occurs is not yet well understood. Nevertheless, it has been suggested that self-emulsification takes place when the entropy

change favoring dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of a conventional emulsion formulation is a direct function of the energy required to create a new surface between the oil and water phases. The two phases of the emulsion tend to separate with time to reduce the interfacial area and thus the free energy of the system. The conventional emulsifying agent stabilizes emulsion resulting from aqueous dilution by forming amonolayer around the emulsion droplets, reducing the interfacial energy and forming a barrier to coalescence. On the other hand, emulsification occurs spontaneously with SEDDS because the free energy required to form the emulsion is either low and positive or negative. It is necessary for the interfacial structure to show no resistance against surface shearing in order for emulsification to take place. The ease of emulsification was suggested to be related to the ease of water penetration into the various LC or gel phases formed on the surface of the droplets. The interface between the oil and aqueous continuous phases is formed upon addition of a binary mixture. This is followed by the solubilization of water within the oil phases as

a result of aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interphase. Further aqueous penetration will loaded to the formation of the dispersed LC phase. In the end, everything that is in close proximity with the interface will be LC, the actual amount of which depends on the surfactant concentration in the binary mixture. Thus, following gentle agitation of the self-emulsifying system, water will rapidly penetrate into the aqueous cores and lead to interface disruptions and droplet formation. As a consequence of the LC interface formation surrounding the oil droplets, SEDDS become very stable coalescence. Detailed studies have been carried out to determine the involvement of LC phase in the emulsion formation process. Also, particle size analysis and low frequency dielectric spectroscopy (LFDS) were utilized to examine the self-emulsifying properties of a series of lmwitor 742 (a mixture of mono- and diglycerides of capric acids)/ Tween 80 system. The results suggested that there might be a complex relationship between LC formation and emulsion formation. Moreover, the presence of the drug compound may alter the emulsion characteristics, probably by interacting with the LC phase. Nevertheless, the correlation between the LC formation and spontaneous emulsification has still not been established.[2]

Table: Bioavailability Enhancement of Some Drugs Using SMDDS Technology

Sr.No.	Drug (SMDDS System)	Category	Reference
1	Paclitaxel	Anticancer	13
2	Fenofibrate	Antihyperlipidimic	14
3	Cholesterol ester transfer protein (CETP) inhibitors	Antihyperlipidimic	15
4	Atorvastatin, Fluvastatin	Antihyperlipidimic	16
5	Rapamycin	Immunosuppressive	17
6	Cyclosporine	Immunosuppressive	18
7	Felodipine	Antihypertensive	19
8	Nifedipine	Antihypertensive	20
9	Indomethacin	Analgesic	21
10	Naproxen	Analgesic	22
11	Tipranavir	Analgesic	23
12	Progesterone, Testosterone	Hormones	24

CHARACTERIZATION OF SMEDDS:

Zeta potential: The charge of the oil droplets of SMEDDS is another property that should be assessed. The charge of the oil droplets in conventional SMEDDS is negative due to the presence of free fatty acids; however, incorporation of a cationic lipid, such as oleylamine at a concentration range of 1.0-3%, will yield cationic SMEDDS. Thus, such systems have a positive n-potential value of about 35-45 mV. This positive n-potential value is preserved following the incorporation of the drug compounds.[25]

Self-Emulsification

The emulsification time of SMEDDS was determined according to USP 22, dissolution apparatus 2. 300 mg of each formulation added drop wise to 500ml purified water at 37ºC. Gentle agitation was provided by a standard stainless steel dissolution paddle rotating at 50 rpm. Emulsification time was assessed visually.[26]

Drug Precipitation Assessment:

The ability of SMEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If the surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant, hence it is very important to determine stability of the system after dilution. This is usually done by diluting a single dose of SMEDDS in 250ml of 0.1N HCl solution. This solution is observed for drug precipitation if any. Ideally SMEDDS should keep the drug solubilized for four to six hours assuming the gastric retention time of two hours.[27]

Freeze-thaw cycles (Accelerated ageing):

It is done to monitor accelerated stability testing of microemulsions formulation. In this study we place the formulation at two different temperatures i.e. -21ºC and 21ºC. For the better estimation of accelerated stability studies three such cycles should be run for each batch of formulation.[28]

Transmittance Test

Stability of optimized microemulsion formulation with respect to dilution was checked by measuring Transmittance through U.V. Spectrophotometer (UV-1700 SHIMADZU). Transmittance of samples was measured at 650nm and for each sample three replicate assays were performed**.**[29]

In vitro release

The quantitative *in vitro* release test was performed in 900 ml purified distilled water, which was based on USP 24 method. SMEDDS was placed in dialysis bag during the release period to compare the release profile with conventional tablet. 10 ml of sample solution was withdrawn at predetermined time intervals, filtered through a 0.45 µ membrane filter, dilute suitably and analyzed spectrophotometrically. Equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percent drug dissolved at different time intervals was calculated using the Beer Lambert's equation.[30]

Applications of SMEDDS

Solubilization in SMEDDS

Owing to their frequently high content oil, as well as of surfactant, SMEDDS are usually efficient solubilizers of substances of a wide range of lipophilicity. Thus, the solubilizing capacity of a w/o microemulsion for water soluble drugs is typically higher than that of an o/w microemulsion, while the re-

verse is true for oil soluble drugs. Furthermore, the solubilization depends on the SMDDS composition.[30]

Sustain release from SMEDDS

Due to the wide range of structures occurring in them, SMEDDS display a rich behavior regarding the release of solubilized material. Thus in. case of O/W microemulsion, hydrophobic drugs solubilized mainly in the oil droplets, experience hindered diffusion and are therefore released rather slowly (depending on the oil/water partitioning of the substance). Water soluble drugs, on the other hand, diffuse essentially without obstruction (depending on the volume fraction of the dispersed phase) and are release fast. For balanced microemulsions, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinuous nature of microemulsion "structure".[4] Apart from the microemulsion structure, the microemulsion composition is important for the drug release rate.

Increase the bioavailability of drug

Many of drugs were lipophilic in nature so, it should be insoluble in water. Lipophilic drug should have low bioavailability. In SMEDDS, drugs should be combining with the oil and make a complex. Oil is easily absorbed from the gut and increase the solubility of drugs. So increase the bioavailability of the drug. Ex. Julianto et al, was increase the 3 fold bioavailability from SEDDS which is composed of the Tween 80 and palm oil. [31]

REFERENCES

1. Tang J: Self-Emulsifying Drug Delivery Systems: Strategy for Improving Oral Delivery of Poorly Soluble Drugs. Current Drug Therapy 2007; 2: 85-93.
2. Neslihan GR and Benita S: Self-Emulsifying Drug Delivery Systems (SEDDS) for Improved Oral Delivery of Lipophilic Drugs. Biomedicine and Pharmacotherapy 2004; 58: 173–182.
3. Khoo SM, Humberstone AJ, Porter CJ, Edwards GA and Charman WN: Formulation Design and Bioavailability Assessment of Lipidic Self-Emulsifying Formulations of Halofantrine. International Journal of Pharmaceutics 1998; 167: 155-164.
4. Kawakami K, Yoshikawa T, Moroto Y, Kanakao E, Takahuani K, Nishihara Y and Masuda K: Microemulsion Formulation for Enhanced Absorption of Poorly Soluble Drugs. I .Prescription design. Journal of Controlled Release 2002; 81: 75-82.
5. Cortesi R, Espositi E, Maietti A, Menegatti E and Nastruzzi C: Formulation Study for the Antitumor Drug Camptothecin: Liposomes, Micellar Solutions and a Microemulsion. International Journal of Pharmaceutics 1997; 159: 95-103.
6. Tolle S, Zuberi T and Lawrence MJ: Physiochemical and Der-Solubilisation Properties of N, N-dimethyl-N-(3-dodecyloxy propyl) amine oxide: a Biodegradable Nonionic Surfactant. Journal of Pharmaceutical Sciences 2000; 89: 798-806.

7. Kimura M, Shizuki M, Miyoshi K, Sakai T, Hidaka H, Takamura H and Matoba T: Relationship between the Molecular Structures and Emulsification Properties of Edible oils. Bioscience Biotechnology and Biochemistry 1994; 58: 1258–1261.
8. Murdandea SB and Gumkowskia MJ: Development of a Self-Emulsifying Formulation that Reduces the Food Effect for Torcetrapib. International Journal of Pharmaceutics 2008; 351: 15-22.
9. Lawrence MJ and Rees GD: Microemulsion-based Media as Novel Drug Delivery System, Advanced Drug Delivery Reviews 2000; 45: 89-121.
10. Hauss DJ, Fogal SE, Ficorilli JV, Price CA, Roy T, Jayaraj AA and Keirns JJ: Lipid-based Delivery Systems for Improving the Bioavailability and Lymphatic Transport of a Poorly Water-Soluble LTB4 Inhibitor. Journal of Pharmaceutical Sciences 1998; 87: 164- 169.
11. Karim A, Gokhale R, Cole M, Sherman J, Yeramian P, Bryant M and Franke H. HIV Protease Inhibitor SC-52151: A Novel Method of Optimizing Bioavailability Profile via a Microemulsion Drug Delivery System. Pharmaceutical Research 1994;11: S368.
12. Georgakopoulos E, Farah N and Vergnault G. Oral Anhydrous non-ionic Microemulsions Administered in Soft gel Capsules. Gattefossé Bulletin Technique 1992; 85: 11-20.
13. Gao, P., Morozowich, W.: US20067115565 (**2006**).
14. Liang, L., Shojaei, A.H., Ibrahim, S.A., Burnside, B.A.: US20067022337 (**2006).**
15. Gumkowski, M.J., Franco, L., Murdande, S.B., Perlman, M.E.: US20056962931 (**2005**).
16. Benameur, H., Jannin, V., Roulot, D.: US20036652865 (**2003**).
17. Fricker, G., Haeberlin, B., Meinzer, A., Vonderscher, J.: US20067025975 (**2006**).
18. Ward, M.V., Cotter, R.: US4678808 (**1987**).
19. Rudnic, E., McCarty, J., Burnside, B., McGuinness, C., Belenduik,G.: US5952004 (**1999**).
20. Farah, N., Denis, J.: US20006054136 (**2000**)
21. Gao, P., Morozowich, W.: US20016231887 (**2001**).
22. Bauer, K., Neuber, C., Schmid, A., Volker, K.M.: US20026426078 (**2002**).
23. Mulye, N.: US20026436430 (**2002**).
24. Gao, P., Morozowich, W.: US20036531139 (**2003**).
25. Benita S, Microencapsulation: Methods and Industrial Applications, CRC Press, Florida, Edition 3, Vol. 158, 2006: 447-448
26. Wei L, Li J, Guo L, Nei S and Pan W: Preparation and Evaluation of SEDDS and SMEDDS Containing Carvedilol. Drug Dev Ind Pharm. 2005; 31: 785-794.
27. Charman WN, Noguchi T and Stella VJ: An experimental System Designed to Study the *in situ* Intestinal Lymphatic Transport of Lipophillic Drugs in Anesthetized Rats. International Journal of Pharmaceutics 1986; 33:155-164.

28. Shen H and Zhong M: Preparation and Evaluation of Self-microemulsifying Drug Delivery Systems SMEDDS) Containing Atorvastatin. Journal of Pharm pharmacol. 2006; 58(9): 1183-1191.
29. Kang B, Lee J, Chon S, Jeong S, Yuk S, Khang G, Lee H, and Hang Choc S: Development of Self microemulsifying Drug Delivery Systems (SMEDDS) for Oral Bioavailability Enhancement of Simvastatin in Beagle Dogs. International Journal of Pharmaceutics 2004; 274: 65-73.
30. Rajesh BV, Reddy TK, Srikanth G, Mallikarjun V and Nivethithai P: Lipid Based Self-Emulsifying Drug Delivery System (SEDDS) for Poorly Water- Soluble Drugs: A Review. J Global Pharma Tech. 2010; 2(3): 47-55.
31. Julianto T, Yuen K, and Noor A: Improved Bioavailability of Vitamin E with a Self-Emulsifying Formulation. International Journal of Pharmaceutics 2000; 200: 53–57.

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