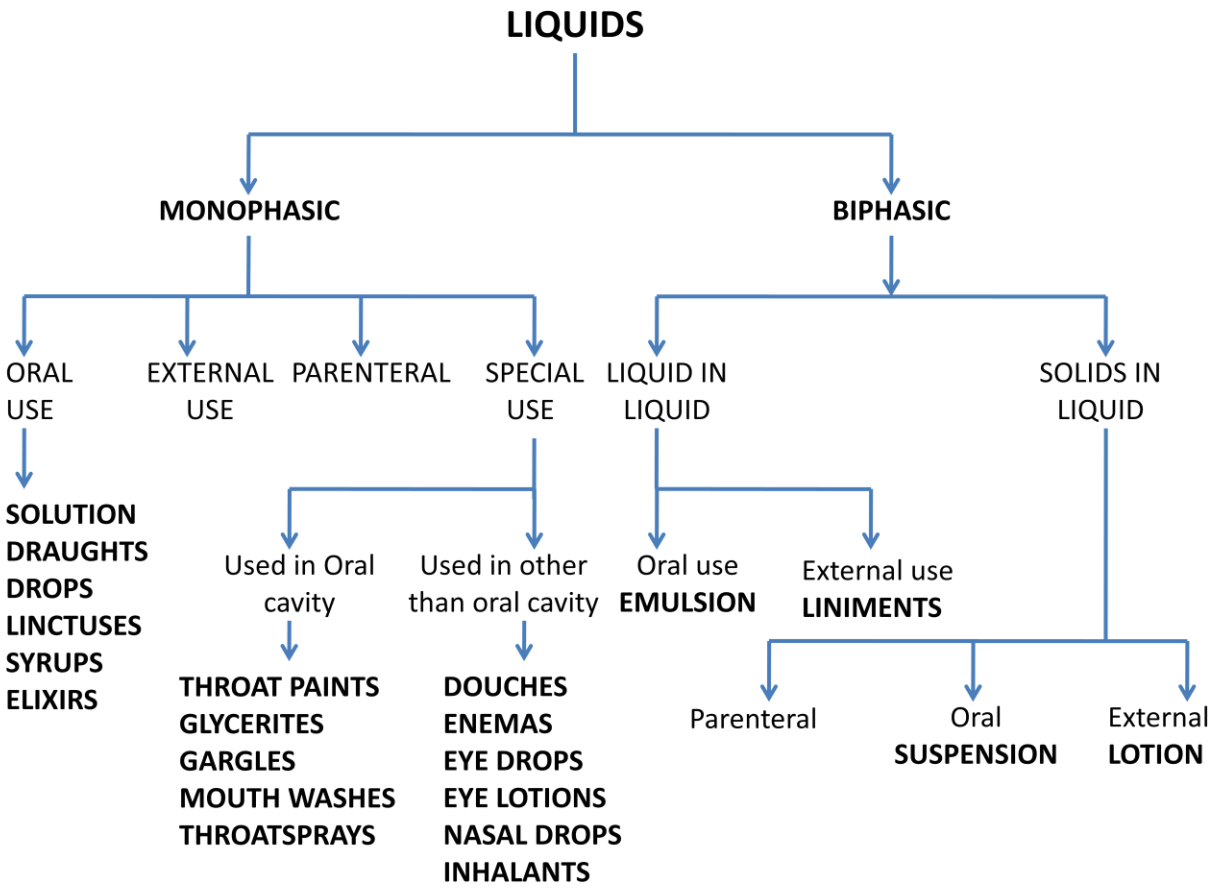
LIQUIDS

CLASSIFICATION OF LIQUIDS:-



RECENT INNOVATION IN SUSPENSION

Nanosuspensions in drug delivery

- More than 40 per cent of the drugs coming from high-throughput screening are poorly soluble in water. Obviously poorly water-soluble drugs show many problems in formulating them in conventional dosage forms. One of the critical problems associated with poorly soluble drugs is too low bioavailability and or erratic absorption.

- The problem is even more complex for drugs such as itraconazole and carbamazepine (belonging to BCS Class II) as classified by BCS System as they are poorly soluble in both aqueous and organic media, and for those drugs having a log P value of 2. The performance of these drugs is dissolution rate-limited (for Class II and III drugs) and is affected by the fed/fasted state of the patient. Dissolution rates of sparingly soluble drugs are related to the shape as well as the particle size. Therefore decrease in particle size results in an increase in dissolution rate.

- There are number of formulation approaches to resolve the problems of low solubility and low bioavailability. The approaches include micronization, solublization using co-solvents, use of permeation enhancers, oily solutions, surfactant dispersions, salt formation and precipitation techniques.
- Other techniques like liposomes, emulsions, microemulsions, solid-dispersions and inclusion complexes using Cyclodextrins show reasonable success but they lack in universal applicability to all drugs. These techniques are not applicable to the drugs, which are not soluble in both aqueous and organic medias. Hence there is need of some different and simple approach to tackle the formulation problems to improve their efficacy and to optimize the therapy with respect to pharmacoeconomics.

- Nanotechnology can be used to resolve the problems associated with these conventional approaches for solubility and bioavailability enhancement. Nanotechnology is defined as the science and engineering carried out in the nanoscale that is 10-9 meters. The drug microparticles/micronized drug powder is transferred to drug nanoparticles by techniques like Bottom Up Technology (precipitation) and Top Down Technologyor disintegration methods. Nano is a Greek word, which means 'dwarf'. Nano means it is the factor of 10-9 or one billionth.

★ Methods of preparation

- Mainly there are two methods for preparation of nanosuspensions. The conventional methods of precipitation (Hydrosols[25]) are called ‘Bottom Up technology’. In Bottom Up Technology the drug is dissolved in a solvent, which is then added to non-solvent to precipitate the crystals. The basic advantage of precipitation technique is the use of simple and low cost equipments. The basic challenge of this technique is that during the precipitation procedure the growing of the drug crystals needs to be controlled by addition of surfactant to avoid formation of microparticles. The limitation of this precipitation technique is that the drug needs to be soluble in atleast one solvent and this solvent needs to be miscible with nonsolvent. Moreover precipitation technique is not applicable to drugs, which are simultaneously poorly soluble in aqueous and nonaqueous media.

- The ‘Top Down Technologies’ are the disintegration methods and are preferred over the precipitation methods. The ‘Top Down Technologies’ include Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege). Few other techniques used for preparing nanosuspensions are emulsion as templates, microemulsion as templates etc

A) Media Milling (Nanocrystals or Nanosystems)

- The method is first developed and reported by Liversidge et.al. (1992) The nanosuspensions are prepared by using high-shear media mills. The milling chamber charged with milling media, water, drug and stabilizer is rotated at a very high shear rate under controlled temperatures for several days (at least 2-7 days). The milling medium is composed of glass, Zirconium oxide or highly cross-linked polystyrene resin. The high energy shear forces are generated as a result of the impaction of the milling media with the drug resulting into breaking of microparticulate drug to nanosized particles.

Advantages

1. Media milling is applicable to the drugs that are poorly soluble in both aqueous and organic media.

2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.

3. Nanosize distribution of final nanosize products.

Disadvantages

1. Nanosuspensions contaminated with materials eroded from balls may be problematic when it is used for long therapy.

2. The media milling technique is time consuming.

3. Some fractions of particles are in the micrometer range.

4. Scale up is not easy due to mill size and weight.

B) Homogenization In Water (Dissocubes)

- R.H.Muller developed Dissocubes technology in 1999. The instrument can be operated at pressure varying from 100 – 1500 bars (2800 –21300psi) and up to 2000 bars with volume capacity of 40ml (for laboratory scale). For preparation of nano suspension, we have to start with the micronized drug particle size less than 25µm to prevent blocking of homogenization gap hence it is essential to prepare a presuspension of the micronized drug in a surfactant solution using high speed stirrer.

Principle

In piston gap homogeniser particle size reduction is based on the cavitation principle. Particles are also reduced due to high shear forces and the collision of the particles against each other. The dispersion contained in 3cm diameter cylinder; suddenly passes through a very narrow gap of 25µm. According to Bernoulli's Law the flow volume of liquid in a closed system per cross

section is constant. The reduction in diameter from 3cm to 25µm leads to increase in dynamic pressure and decrease of static pressure below the boiling point of water at room temperature. Due to this water starts boiling at room temperature and forms gas bubbles, which implode when the suspension leaves the gap (called cavitation) and normal air pressure is reached. The size of the drug nanocrystals that can be achieved mainly depends on factors like temperature, number of homogenization cycles, and power density of homogeniser and homogenization pressure.

Advantages

1. It does not cause the erosion of processed materials.

2. Very dilute as well as highly concentrated nanosuspensions can be prepared by handling 1mg/ml to 400mg/ml drug quantity.

3. It is applicable to the drugs that are poorly soluble in both aqueous and organic media.

4. It allows aseptic production of nanosuspensions for parentral administration.

Disadvantages

1. Preprocessing like micronization of drug is required.

2. High cost instruments are required that increases the cost of dosage form.

C) Homogenisation In Nonaqueous Media (Nanopure)

- The drugs that are chemically labile can be processed in such nonaqueous media or water-miscible liquids like polyethyleneglycol-400 (PEG), PEG1000 etc. The homogenization can be done at room temperature, 0^{o} C and below freezing point (-20^{o} C).

D) Combined Precipitation And Homogenization (Nanoedege)

- The precipitated drug nanoparticles have tendency to continue crystal growth to the size of microcrystals. They need to be processed with high-energy forces (Homogenisation). The are in completely amorphous, partially amorphous or completely crystalline which create problems in long term stability as well as in bioavailability, so the precipitated particle suspension is subsequently homogenized which preserve the particle size obtained after the precipitation step.

E) Emulsification-solvent evaporation technique

- This technique involves preparing a solution of drug followed by its emulsification in another liquid that is a non-solvent for the drug. Evaporation of the solvent leads to precipitation of the drug. Crystal growth and particle aggregation can be controlled by creating high shear forces using a high-speed stirrer.

Hydrosol method

This is similar to the emulsification- solvent evaporation method. The only difference between the two methods is that the drug solvent is miscible with the drug anti-solvent. Higher shear force prevents crystal growth and Ostwald ripening and ensures that the precipitates remain smaller in size.

Characterization of nanosuspensions

The various essential parameters to be characterized for nanosusepnsions includes:

■Size and size distribution
■Particle charge (zeta potential)
■Crystalline status
■Dissolution velocity and saturation solubility.

For surface-modified nanosuspensions, a number of additional parameters have to be investigated to obtain a complete picture, especially with relevance for the in-vivo behavior:

■Adhesion properties (in case of mucoadhesive particles)
■Surface hydrophilicity/hydrophobicity
■Interaction with body proteins.

Nanosuspension technology applications

Nanosuspensions can play a critical role as an enabling technology for poorly water-soluble and/or poorly permeable molecules having significant in vitro activity. Such molecules pose problems at any or both of the following during new drug development activities:

■Formulation of an intravenously injectable product for preclinical in vivo evaluation of the new molecule to measure its toxicity and other pharmacokinetic characteristics.
■Poor absorption of the drug candidate from the GIT resulting into poor bioavailability during preclinical as well as clinical development studies.

Pure drug nanosuspensions can provide solutions to both of these problems. A pure drug nanosuspension contains pure drug particles suspended in an aqueous media. As the particle size (usually below 400 nm) is way below the minimum particle size that can be administered intravenously (ie, 5 µm), a nanosuspension can be administered intravenously to conduct exploratory study with the candidate drug molecules. Nanosuspension helps in administration of huge drug concentration of poorly water-soluble drugs to brain with decreased systemic effects. Thus nanosuspension has application to various route of administration like parenteral, oral topical, pulmonary and targeted drug delivery system.

★ Evaluation of nanosuspensions:–

A) In-Vitro Evaluations

1. Particle size and size distribution
2. Particle charge (Zeta Potential)
3. Crystalline state and morphology
4. Saturation solubility and dissolution velocity

B) In-Vivo Evaluation

C) Evaluation for surface-modified Nanosuspensions

1.Surface hydrophilicity
2. Adhesion properties
3. Interaction with body proteins

1) Mean particle size and size distribution

The mean particle size and the width of particle size distribution (called Polydidpersity Index) are determined by Photon Correlation Spectroscopy (PCS). Particle size and polydispersity index (PI) governs the saturation solubility; dissolution velocity and biological performance. It is proved that change in particle size changes saturation solubility and dissolution velocity. PCS measures the particle size in the range of 3nm- 3 µm only. PI governs the physical stability of nanosuspension and should be as low as possible for long-term stability. (Should be close to zero). PCS is a versatile technique but has low measuring range. In addition to PCS analysis nanosuspensions are analyzed by Laser Diffractometry (LD). LD measures volume size distribution and measures particles ranging from 0.05- 80µm upto 2000µm. Atomic Force Microscopy is used for visualization of particle shape.

2) Particle charge (Zeta Potential)

article charge determines the stability of nanosuspension. For electrostatically stabilized nanosuspension a minimum zeta potential of ±30mV and for combined steric and electrostatic stabilization it should be a minimum of ±20mV.

3) Crystalline state and particle morphology

Differential Scanning Calorimetry(DSC) determines the crystalline structure. When nanosuspensions are prepared drug particles get converted to amorphous form hence it is essential to measure the extent of amorphous drug generated during the production of nanosuspensions. The X-Ray Diffraction (XRD) is also used for determining change in physical state and extent of amorphous drug.

4) Saturation solubility and dissolution velocity

The nanosuspension increase the saturation solubility as well as dissolution velocity. Saturation solubility is compound specific constant depending upon temperature and the properties of dissolution medium. Kelvin equation and the Ostwald-Freundlich equations can explain increase in saturation solubility.

★ Conclusion

Drugs with poor solubility and low bioavailability are called 'brick dust' candidates once abandoned from formulation development work can be overcome by using novel approach called nanosuspensions technology. The transformation of any drug to drug nanoparticles leading to an increase in saturation solubility, dissolution velocity, and providing the general feature of an increased adhesiveness to surfaces is one of the most important achievement. A fusion of the novel nanosuspension technology with the traditional dosage forms, e.g. incorporating drug nanoparticles into pellets or tablets for oral delivery is also a note worthy advantage.

RECENT INNOVATION IN EMULSIONS

★ Microemulsions in drug delivery

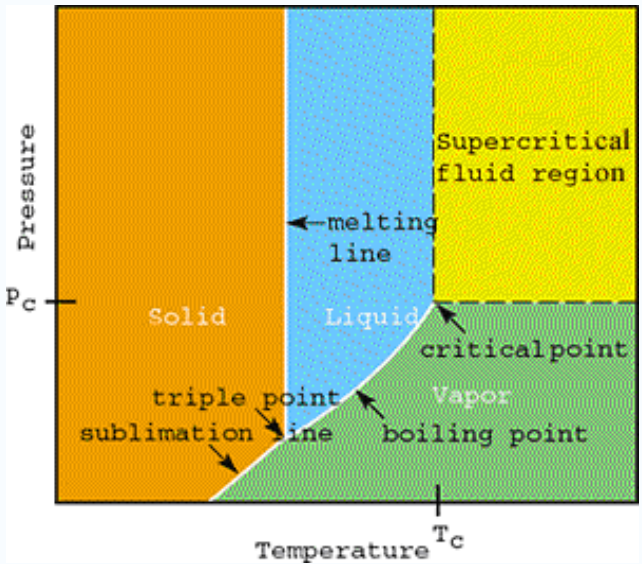
- **Microemulsions** are clear, stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt(s) and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins. In contrast to ordinary emulsions, microemulsions form upon simple mixing of the components and do not require the high shear conditions generally used in the formation of ordinary emulsions. The two basic types of microemulsions are direct (oil dispersed in water, o/w) and reversed (water dispersed in oil, w/o).
- In ternary systems such as microemulsions, where two immiscible phases (water and ‘oil’) are present with a surfactant, the surfactant molecules may form a monolayer at the interface between the oil and water, with the hydrophobic tails of the surfactant molecules dissolved in the oil phase and the hydrophilic head groups in the aqueous phase. As in the binary systems (water/surfactant or oil/surfactant), self-assembled structures of different types can be formed, ranging, for example, from (inverted) spherical and cylindrical micelles to lamellar phases and bicontinuous microemulsions, which may coexist with predominantly oil or aqueous phases.

Uses

- Microemulsions have many commercially important uses. The fluid used in some dry cleaning processes is a water-in-oil microemulsion. Some floor polishes and cleaners, personal care products, pesticide formulations, and cutting oils are actually microemulsions. Much of the work done on these systems have been motivated by their possible use to mobilize petroleum trapped in porous sandstone for enhanced oil recovery.
- A fundamental reason for the uses of these systems is that a microemulsion phase sometimes has an ultralow interfacial tension with a separate oil or aqueous phase, which may release or mobilize them from solid phases even in conditions of slow flow or low pressure gradients.

Phase Diagrams

- The microemulsion region is usually characterized by constructing ternary-phase diagrams.Three components are the basic requirement to form a microemulsion: an oil phase, an aqueous phase and a surfactant. If a cosurfactant is used, it may sometimes be represented at a fixed ratio to surfactant as a single component, and treated as a single "pseudo-component". The relative amounts of these three components can be represented in a ternary phase diagram. Gibbs phase diagrams can be used to show the influence of changes in the volume fractions of the different phases on the phase behavior of the system.



A typical phase diagram. The dotted line gives the anomalous behavior of water. The green lines mark the freezing point and the blue line the boiling point, showing how they vary with pressure.

- The three components composing the system are each found at an apex of the triangle, where their corresponding volume fraction is 100%. Moving away from that corner reduces the volume fraction of that specific component and increases the volume fraction of one or both of the two other components. Each point within the triangle represents a possible composition of a mixture of the three components or pseudo-components, which may consist (ideally, according to the Gibbs' phase rule) of one, two or three phases. These points combine to form regions with boundaries between them, which represent the "phase behavior" of the system at constant temperature and pressure.
- The Gibbs phase diagram, however, is an empirical visual observation of the state of the system and may, or may not express the true number of phases within a given composition. Apparently clear single phase formulations can still consist of multiple isotropic phases (e.g. the apparently clear heptane/AOT/water microemulsions consist multiple phases). Since these systems can be in equilibrium with other phases, many systems, especially those with high volume fractions of both the two imiscible phases, can be easily destabilised by anything that changes this equilibrium e.g. high or low temperature or addition of surface tension modifying agents.
- However, examples of relatively stable microemulsions can be found. It is believed that the mechanism for removing acid build up in car engine oils involves low water phase volume, water-in-oil (w/o) microemulsions. Theoretically, transport of the aqueous acid droplets through the engine oil to microdispersed calcium carbonate particles in the oil should be most efficient when the droplets are small enough to transport a single hydrogen ion (the smaller the droplets, the greater the number of droplets, the faster the neutralisation). Such microemulsions are probably very stable across a reasonably wide range of elevated temperatures.

1) Design and Development of Microemulsion Drug Delivery System of Acyclovir for Improvement of Oral Bioavailability

- The main purpose of this work was to develop an oral microemulsion formulation for enhancing the bioavailability of acyclovir.

- A Labrafac-based microemulsion formulation with Labrasol as surfactant and Plurol Oleique as cosurfactant was developed for oral delivery of acyclovir.
- Phase behavior and solubilization capacity of the microemulsion system were characterized, and in vivo oral absorption of acyclovir from the microemulsion was investigated in rats.
- A single isotropic region, which was considered to be a bicontinuous microemulsion, was found in the pseudoternary phase diagrams developed at various Labrasol:Plurol Oleique:Labrafac ratios. With the increase of Labrasol concentration, the microemulsion region area and the amount of water and Labrafac solubilized into the microemulsion system increased; however, the increase of Plurol Oleique percentage produced opposite effects.
- The microemulsion system was also investigated in terms of other characteristics, such as interfacial tension, viscosity, pH, refractive index, diffusion, and bioavailability.
- Acyclovir, a poorly soluble drug, displayed high solubility in a microemulsion formulation using Labrafac (10%), Labrasol (32%), Plurol Oleique (8%), and water (50%).
- The in vitro intraduodenal diffusion and in vivo study revealed an increase of bioavailability (12.78 times) after oral administration of the microemulsion formulation as compared with the commercially available tablets.

Materials and Methods

Labrasol (caprylocaproyl macrogol-8-glycerides), Plurol Oleique (polyglyceryl-6-dioleate), and Labrafac (medium-chain triglyceride, C8-C10 fatty acids),Double-distilled water was used throughout the study.

Preparation of Microemulsion Formulation

Liquid microemulsions were prepared by dissolving Labrasol in Plurol Oleique. Acyclovir and Labrafac were then dissolved, followed by gentle mixing with distilled water. The monophasic formulations were formed spontaneously at room temperature. The final concentration of acyclovir in the microemulsions was 5%.

Construction of Phase Diagrams

Pseudoternary phase diagrams were constructed to examine the formation of oil in water microemulsions using 4 components: oil, surfactant, cosurfactant, and aqueous phase system. Pseudoternary phase diagrams were constructed keeping the ratio of Labrasol and Plurol Oleique constant and varying the remaining 2 components. For convenience, the phase diagrams were constructed by drawing “water dilution lines” representing increasing water content and decreasing surfactant-cosurfactant levels. The water was titrated along dilution lines drawn from the surfactant-cosurfactant apex (100% surfactant-cosurfactant) to the opposite oil side of the triangle. The line was arbitrarily denoted as the value of the line intersection with the oil scale (eg, 20:80, 30:70). If turbidity appeared followed by a phase

separation, the samples were considered to be biphasic. If clear and transparent mixtures were visualized after stirring, the samples were considered monophasic. The samples were marked as points in the phase diagram. The area covered by these points was considered to be the microemulsion region of existence.

Results and Discussion

Phase Diagram Study

A pseudoternary phase diagram of the investigated quaternary system water/Labrasol/Plurol Oleique/Labrafac is presented in Figure 1. Formation of microemulsion systems (the shaded area) was observed at room temperature. Phase behavior investigations of this system demonstrated the suitable approach to determining the water phase, oil phase, surfactant concentration, and cosurfactant concentration with which the transparent, 1-phase low-viscous microemulsion system was formed.

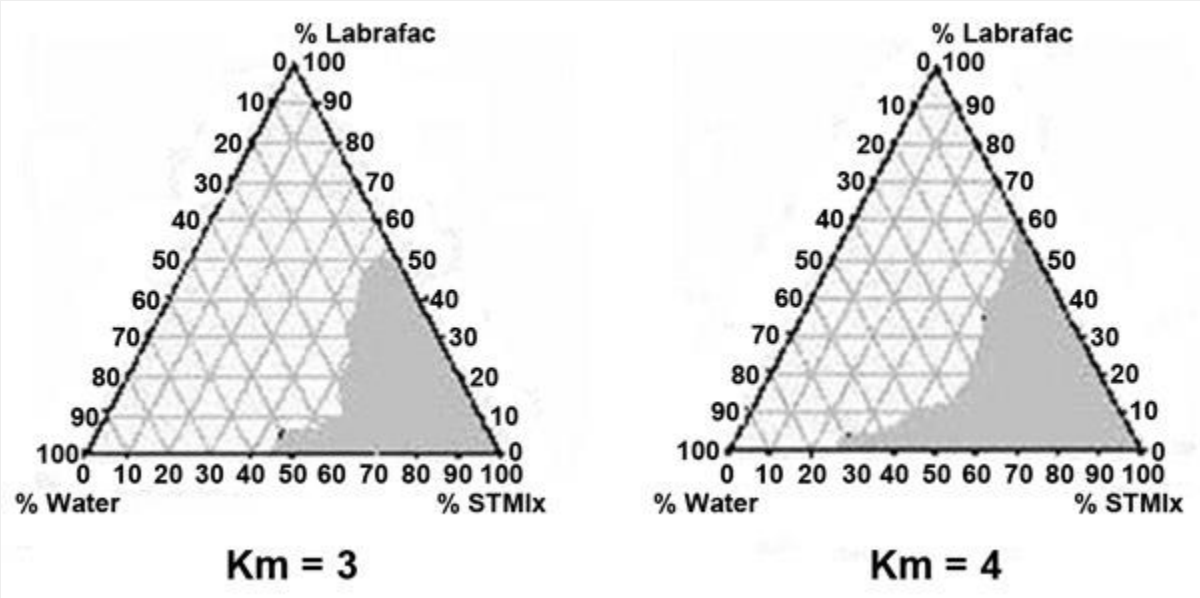


Figure 1. Pseudoternary phase diagram of Labrasol, Plurol Oleique, Labrafac, and water. (a) Km = 3, (b) Km = 4. Km indicates surfactant to cosurfactant ratio; STMix indicates surfactant + cosurfactant.

The phase study revealed that the maximum proportion of oil was incorporated in microemulsion systems when the surfactant-to-cosurfactant ratio (km) was 4:1. From a formulation viewpoint, the increased oil content in microemulsions may provide a greater opportunity for the solubilization of acyclovir. Moreover, when the composition (% wt/wt) of surfactant mixture (S_{mix}) in a microemulsion preparation was <40%, the formulation was less viscous. The optimum formulation of microemulsion contained Labrafac (10%), Labrasol (32%), Plurol Oleique (8%), and water (50%).

In Vitro Intestinal Permeability Study

In vitro intestinal permeability data are shown in Figure 2. The drug diffused at a faster rate from the microemulsion system than from the tablet dosage form. The total percentage diffusion was much higher for the microemulsion system than for the tablet dosage form. After 5 hours of diffusion, 85% of the drug was diffused from the microemulsion system, as compared with 69% diffused from the tablets.

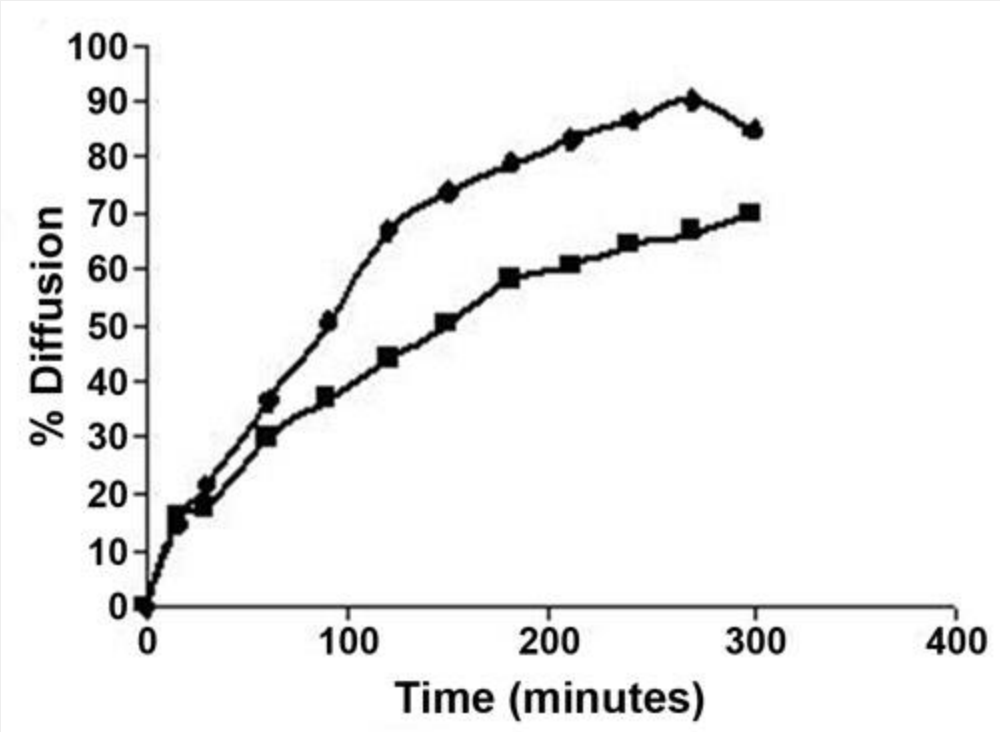


Figure 2. Comparative in vitro diffusion profile of acyclovir through rat duodenum (–♦–) for microemulsion (ME) and (–■–) for tablet.

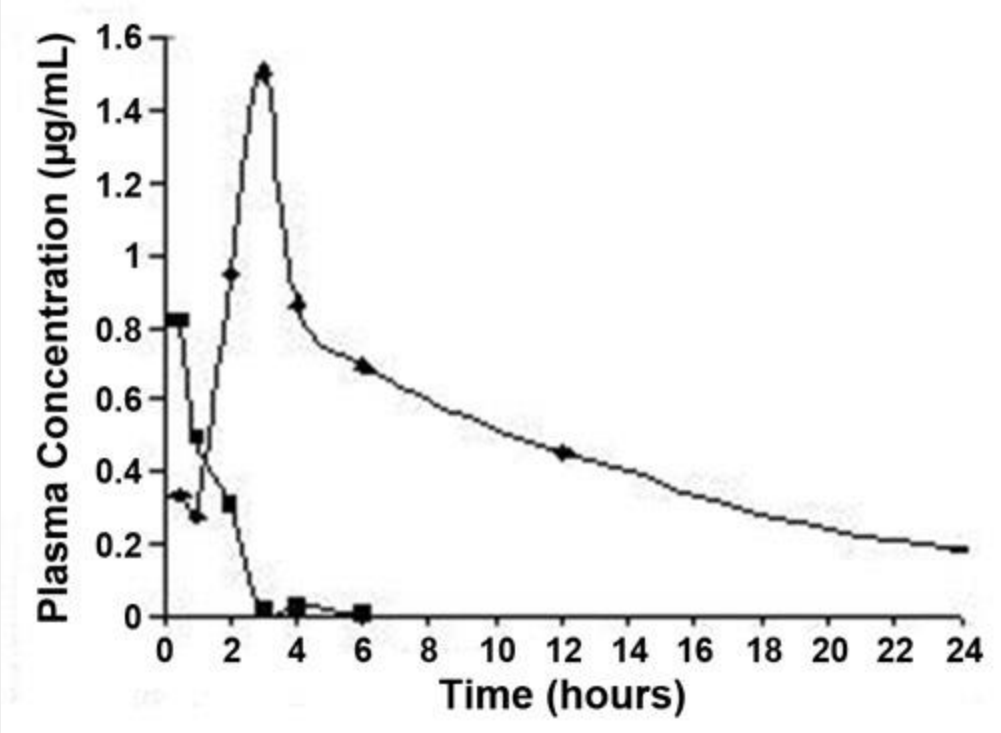


Figure 3. Comparative plasma concentration of acyclovir after oral administration of (–♦–) ME and (–■–) tablet. ME indicates microemulsion.

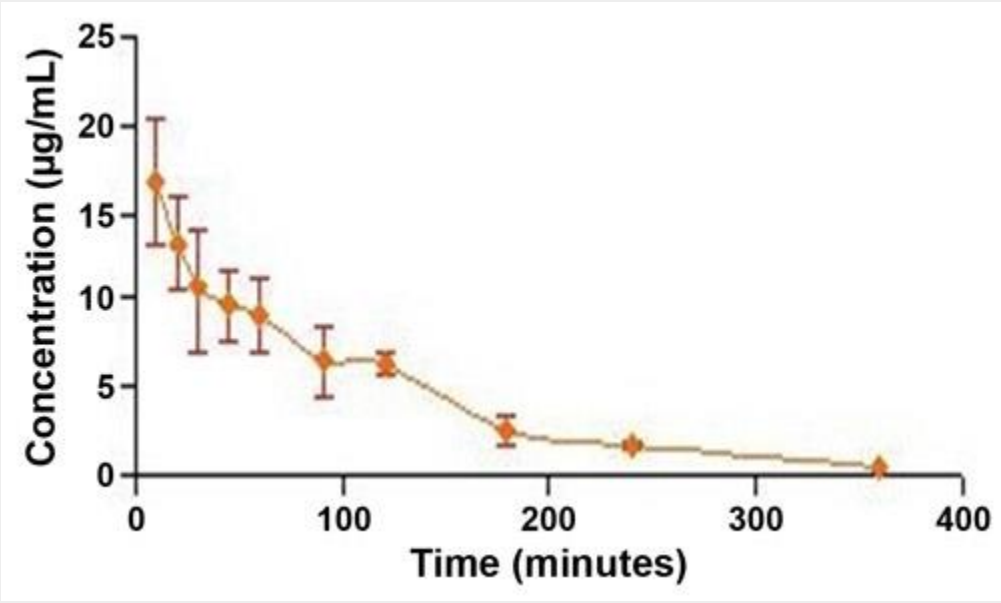


Figure 4. Plasma concentration of acyclovir after intravenous administration.

Conclusion

The study demonstrates that the microemulsion formulation can be employed to improve the bioavailability of a poorly absorbed drug. The ratio of Labrasol:Plurol Oleique:Labrafac played a major role in formulating the microemulsion. The optimum microemulsion formulation contained Labrafac (10%), Labrasol (32%), Plurol Oleique (8%), and water (50%), which was a transparent and less viscous system. After oral administration in rats, the microemulsion showed an absolute bioavailability of 27.83%, which is 12.78 times higher than that of commercially available tablets (Aquivir).

2) New vehicle based on a microemulsion for topical ocular administration of dexamethasone

Aim: Eye drops are the most used dosage form by the ocular route, in spite of their low bioavailability. Due to their properties and numerous advantages, microemulsions are promising systems for topical ocular drug delivery. They can increase water solubility of the drug and enhance drug absorption into the eye. The present study describes the development and characterization of an oil-in-water microemulsion containing dexamethasone and the evaluation of its pharmacokinetics in rabbits after topical ocular application.

Methods: The microemulsion was prepared by the titration technique. Its physico-chemical characteristics and stability were determined. The ocular irritation test and the pharmacokinetics of this system were studied in white rabbits.

Results: The developed system showed an acceptable physico-chemical behaviour and presented good stability for 3 months. The ocular irritation test used suggested that the microemulsion did not provide significant alteration to eyelids, conjunctiva, cornea and iris. This formulation showed greater penetration of dexamethasone in the anterior segment of the eye and also release of the drug for a longer time when compared with a conventional preparation. The area under the curve obtained for the microemulsion system was more than twofold higher than that of the conventional preparation ($P < 0.05$).

Conclusions: The microemulsion-based dexamethasone eye drop is advantageous for ophthalmic use because it is well-tolerated in the eye and seemed to provide a higher degree of bioavailability.

3) Study of Isopropyl Myristate Microemulsion Systems Containing Cyclodextrins to Improve the Solubility of 2 Model Hydrophobic Drugs

The objectives of this project were to evaluate the effect of alkanols and cyclodextrins on the phase behavior of an isopropyl myristate microemulsion system and to examine the

solubility of model drugs. Triangular phase diagrams were developed for the microemulsion systems using the water titration method, and the solubility values of progesterone and indomethacin were determined using a conventional shake-flask method. The water assimilation capacities were determined to evaluate the effective microemulsion formation in different systems. The alkanols showed higher microemulsion formation rates at higher concentrations. A correlation between the carbon numbers of the alkanol and water assimilation capacity in the microemulsions studied was observed; isobutanol and isopentanol produced the best results. The addition of cyclodextrins showed no effect or had a negative effect on the microemulsion formation based on the type of cyclodextrin used. Isopropyl myristate–based microemulsion systems alone could increase the solubility values of progesterone and indomethacin up to 3300-fold and 500-fold, respectively, compared to those in water. However, the addition of cyclodextrins to the microemulsion systems did not show a synergistic effect in increasing the solubility values of the model drugs. In conclusion, microemulsion systems improve the solubility of progesterone and indomethacin. But the two types of cyclodextrins studied affected isopropyl myristate–based microemulsion systems negatively and did not improve the solubilization of 2 model drugs.

Materials and Methods

Materials

Progesterone, indomethacin, IPM, 1-propanol, 1-butanol, 1-pentanol, Tween 20, Tween 40, Tween 80, and Span 20 ,Ethanol ,Methanol and acetonitrile ,Trappsol, Captisol ,Soybean oil Water used in the study was deionized and distilled.

Preparation of the Phase Diagram and ME Formulations

IPM and 1-butanol were selected as an oil component and cosurfactant, respectively, in the ME systems. The surfactants (a 1:1 mixture of Tween 80 and Span 20) were prepared separately. IPM and 1-butanol were added to the surfactant mixture. The pseudoternary phase diagrams of oil, surfactant/cosurfactant, and water were set up using the water titration method. The mixture of oil and surfactant/cosurfactant at predetermined weight ratios was diluted with water by sequential addition of 10 µL of water using a micropipette. No heating was necessary during the preparation. However, the system was stirred using a magnetic stirrer to ensure a thorough mixing. After each mixing, the sample was allowed to settle and its physical condition (clarity and flowability) was reviewed. If required, the sample was sonicated for 1 to 2 minutes to remove air bubbles and to enable a better visual examination. Mixtures that did not show a change in the meniscus after tilting to an angle of 90º were considered to be gels. Samples were examined under a microscope, if necessary.

The mixture compositions at different points in the phase diagrams were defined by the following equation:

$$\%A\ (\text{Tween 80} + \text{Span 20}) + \%B\ (\text{1-butanol} + \text{oil}) + \%C\ (\text{water}) = 100 \quad (1)$$

To study the effect of CDs on the formation of ME, a 50% wt/vol aqueous solution of each type of CD was prepared. The densities of 50% wt/vol Captisol and 50% wt/vol Trappsol aqueous solutions were 1.13 g/cc and 1.16 g/cc, respectively. Because the solutions were denser than water pipettes used in the experimentation were calibrated with CD solutions. The ME region was determined in the same way as it was determined for the ME system without CD.

Results and Discussion

Phase Behavior

The pseudoternary phase diagrams of the different ME systems are shown in Figures 1 and 2. Isobutanol concentration was kept constant with respect to the oil phase (8:1) to facilitate the construction of the phase diagram. The translucent and low-viscosity area is presented in the phase diagrams as an ME area. No distinct conversion from water/oil to oil/water ME systems was observed. Therefore, this single isotropic region was considered a bicontinuous ME. The emulsion region is an area in which a milky white heterogeneous system is formed. The gel area indicates the clear and high-viscosity region. The remainder of the phase diagram represents the turbid region, represented as 2 phases and conventional emulsions based on visual identification.

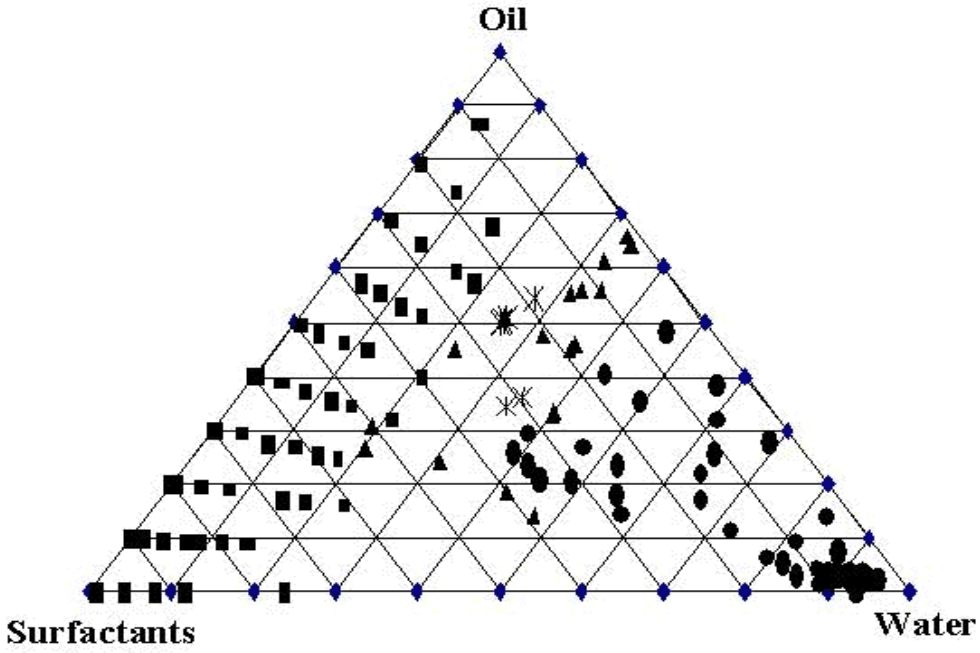


Figure 1. Pseudoternary phase diagrams of IPM-surfactant-water system at Tween 80:Span 20 ratios of 1:1, and IPM:1-butanol ratios of 8:1. ■ = ME, ● = emulsion, ▲ = gel, and ✳ = 2 phases.

Figure 1 shows the phase diagram of the IPM Tween 80:Span 20 pseudoternary system. The ME formation was favorable at high surfactant concentrations. At higher oil concentration, the system tended to separate into 2 phases.

The influence of CD on the ME isotropic region can be observed in Figure 2. The ME area decreased from about 30% in the blank ME to about 23% in the ME containing Captisol. These numbers were calculated manually by finding out the number of small triangles covered by the ME area in the phase diagram compared to the total number of small triangles in the phase diagram. On the other hand, Trappsol did not hamper the formation of ME (30% to 29%), but the shape of the ME region changed significantly. The results indicated that the formation of ME could be influenced negatively by the presence of ionic CD. Captisol has a high affinity for water, which might have affected the ME formation. The ME formation region improved at a 40% to 60% water level in the Trappsol system. The exact reason for this is not known at this time. The higher surface activity of Trappsol compared to Captisol may have played a role. Overall, from Figure 2, it was clear that ME could be formed in the presence of CDs, but the type of CD could alter the ME region either positively or negatively.

Conclusion

The ME system comprising IPM, Tween 80, Span 20, isobutanol, and water showed a high solubilization capacity for 2 model drugs, progesterone and indomethacin. The addition of CDs in general affected the ME formation negatively and did not improve the solubility of hydrophobic drugs in the ME systems tested.

RECENT ADVANCES IN SELF EMULSIFYING DRUG DELIVERY SYSTEM

- Self-emulsifying drug delivery systems (SEDDS) are usually used to improve the bioavailability of hydrophobic drugs.
- 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.
- From time to time many workers have claimed various rational applications of Self-emulsifying formulation for enhancing bioavailability and site-specific targeting of highly lipophilic drugs.
- SEDDS is ideally an isotropic mixture of oils and surfactants and sometimes co solvents.
- The multi-component delivery systems have optimized by evaluating their ability to self-emulsify when introduced to an aqueous medium under gentle agitation, and by determination of particle size of the resulting emulsion.
- Upon per oral administration,these systems form fine (micro) emulsions in the gastrointestinal tract (GIT) with mild agitation provided by gastric mobility.
- These articles give an overview of the recent advances in the development of SEDDS and the dosage forms along with the associated problems and the possible future research directions in this field.

Composition of SEDDSs

The self-emulsifying process is depends on:

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

a) **Oils.** Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract . Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified

or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium-chain triglyceride.

b) **Surfactant.** Nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

c) **Cosolvents.** Cosolvents like diehylene glycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactant in the microemulsion systems.

★ Formulation of SEDDSs

- With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water-soluble cosolvents, there are many different combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions
- The following should be considered in the formulation of a SEDDS:

✓ The solubility of the drug in different oil, surfactants and cosolvents. The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.

✓ The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and cosolvent. The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil–surfactant ratio. So, the design of an optimal SEDDS requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent.

★ Characterization of SEDDSs

- The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

- ✓ **Visual assessment.** This may provide important information about the self-emulsifying and microemulsifying property of the mixture and about the resulting dispersion.
- ✓ **Turbidity Measurement**. This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

- ✓ **Droplet Size.** This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. The reduction of the droplet size to values below 50 μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.

- ✓ **Zeta potential measurement**. This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

- ✓ **Determination of emulsification time.** Self-emulsification time, dispersibility, appearance and flowability was observed.

★ Application

- SEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation.
- SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism.

★ Conclusion

- Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

★ Drawbacks of SEDDS

- One of the advantages of SEDDS in relation to scale-up and manufacture is that they form spontaneously upon mixing their components under mild agitation and they are thermodynamically stable.

- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations. The large quantity of surfactant in self-emulsifying formulations (30-60%) irritates GIT. Consequently, the safety aspect of the surfactant vehicle had to be considered.
- Moreover, volatile cosolvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatin capsules, resulting in the precipitation of the lipophilic drugs.
- There is a long list of water soluble, insoluble and surfactants, whichcan be used as solubilizing excipients .
- Grinding is regularly used in the pharmaceutical industry to reduce particle size but it generates heat, sound and vibration energy . It must be performed at a temperature below the melting temperature. Cryogenic grinding is chosen because it is a process carried out at low temperature with frozen samples, used for different biological materials (plants, animal tissues)and unstable compounds (vitamins, volatile substances, etc.). However, grinding induces mechanical activation and generation of energy can lead to physical and chemical changes in crystalline solid which can affect its efficacy.

1) Preparation and In Vivo Evaluation of SMEDDS (Self-Microemulsifying Drug Delivery System) Containing Fenofibrate.

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

Materials

Fenofibrate ,Labrafac CM10 , Maisine 35-1 (glyceryl monolinoleate), Lauroglycol FCC (propylene glycol laurate), Labrafil 1944 CS (apricot kernel oil polyethylene glycol [PEG] 6 esters), and Labrafac PG (propylene glycol caprylate/caprate). Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil), Cremophor EL (polyethoxylated castor oil), and Solutol HS 15 (polyoxyethylene esters of 12-hydroxystearic acid, Gelucire 44/14 (PEG-32 glyceryl laurate) and 50/13 (PEG-32 glyceryl palmistearate) ,Span 20 (sorbitan monolaurate), Tween 80 (polyoxyethylene sorbitan monooleate), and PEG 400.Deionized water was prepared by a Milli-Q purification system .Acetonitrile and methanol used in the present study were of high performance liquid chromatography (HPLC) grade. All other chemicals were reagent grade.

Preparation of SMEDDS Formulations

A series of SMEDDS formulations were prepared using Tween 80 and PEG 400 as the S/CoS combination and Labrafac CM10 as the oil (Table 1). In all the formulations, the level of fenofibrate was kept constant (ie, 8.5% wt/wt of the total formulation weight). Briefly, accurately weighed fenofibrate was placed in a glass vial, and oil, surfactant, and cosurfactant were added. Then the components were mixed by gentle stirring and vortex mixing and were heated at 40ºC on a magnetic stirrer, until fenofibrate was perfectly dissolved. The mixture was stored at room temperature until further use.

Table 1. Developed Formulations With Their Compositions*

Components (% wt/wt)	Batch A	Batch B	Batch C	Batch D	Batch E	Batch F	Batch G	Batch H
Fenofibrate	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Labrafac CM10	28.5	29.5	30.5	31.5	32.5	31.5	31.5	31.5
S/CoS ratio	3:1	3:1	3:1	3:1	3:1	3.2:1	3.5:1	3.7:1
Tween 80	47.25	46.50	45.75	45.00	44.25	45.71	46.67	47.30
PEG 400	15.75	15.50	15.25	15.00	14.75	14.29	13.33	12.70

*S/CoS indicates surfactant/cosurfactant; PEG, polyethylene glycol.

Results and Discussion

1) Solubility Studies

- One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen in vivo.[1] Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. Results from solubility studies are reported in Figure 1. As seen from the figure, Maisine 35-1 and Labrafac CM10 showed the highest solubilization capacity for fenofibrate, followed by Tween 80 and PEG 400. Thus, for our study we selected Maisine 35-1 and Labrafac CM10 as oils and Tween 80 and PEG 400 as surfactant and cosurfactant, respectively.

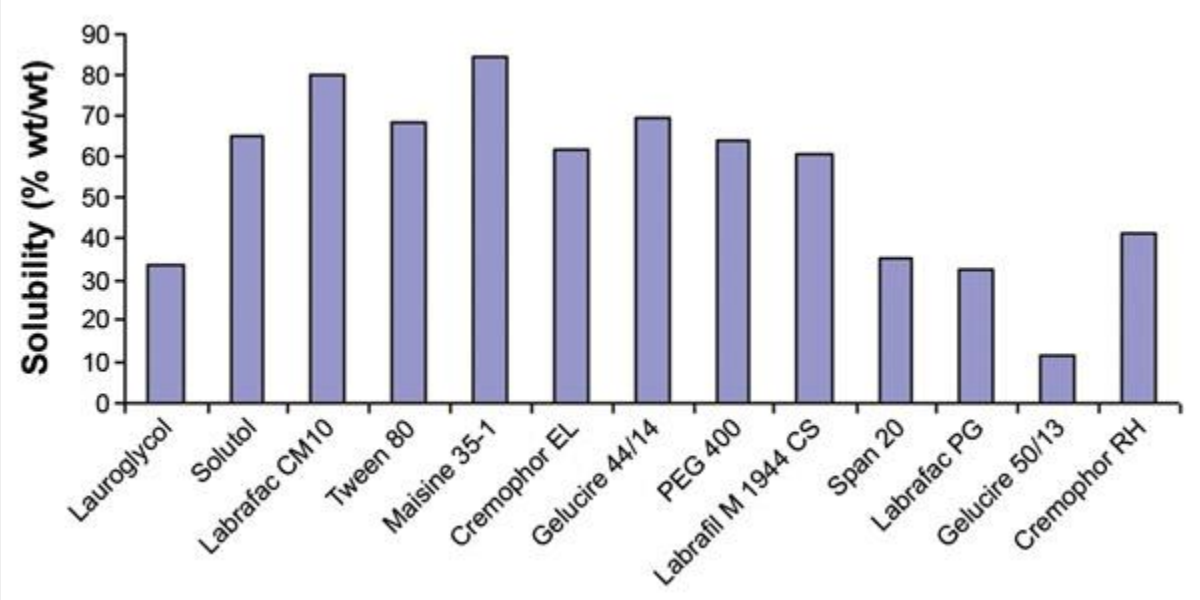


Figure 1. Solubility of fenofibrate in various components. PEG indicates polyethylene glycol.

2) Pseudoternary Phase Diagrams

- Self-microemulsifying systems form fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and cosurfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required

for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion.

- In the present study both Maisine 35-1 and Labrafac CM10 were tested for phase behavior studies with Tween 80 and PEG 400 as the S/CoS mixture. As seen from the ternary plot (Figures 2 and 3), Labrafac CM10 gave a wider microemulsion region than did Maisine 35-1 at all S/CoS ratios. Thus, Labrafac CM10 was selected as the preferred vehicle for the optimized formulation. The microemulsion existence area increased as the S/CoS ratio increased. However, it was observed that increasing the surfactant ratio resulted in a loss of flowability. Thus, an S/CoS ratio between 3:1 and 4:1 was selected for the formulation study.

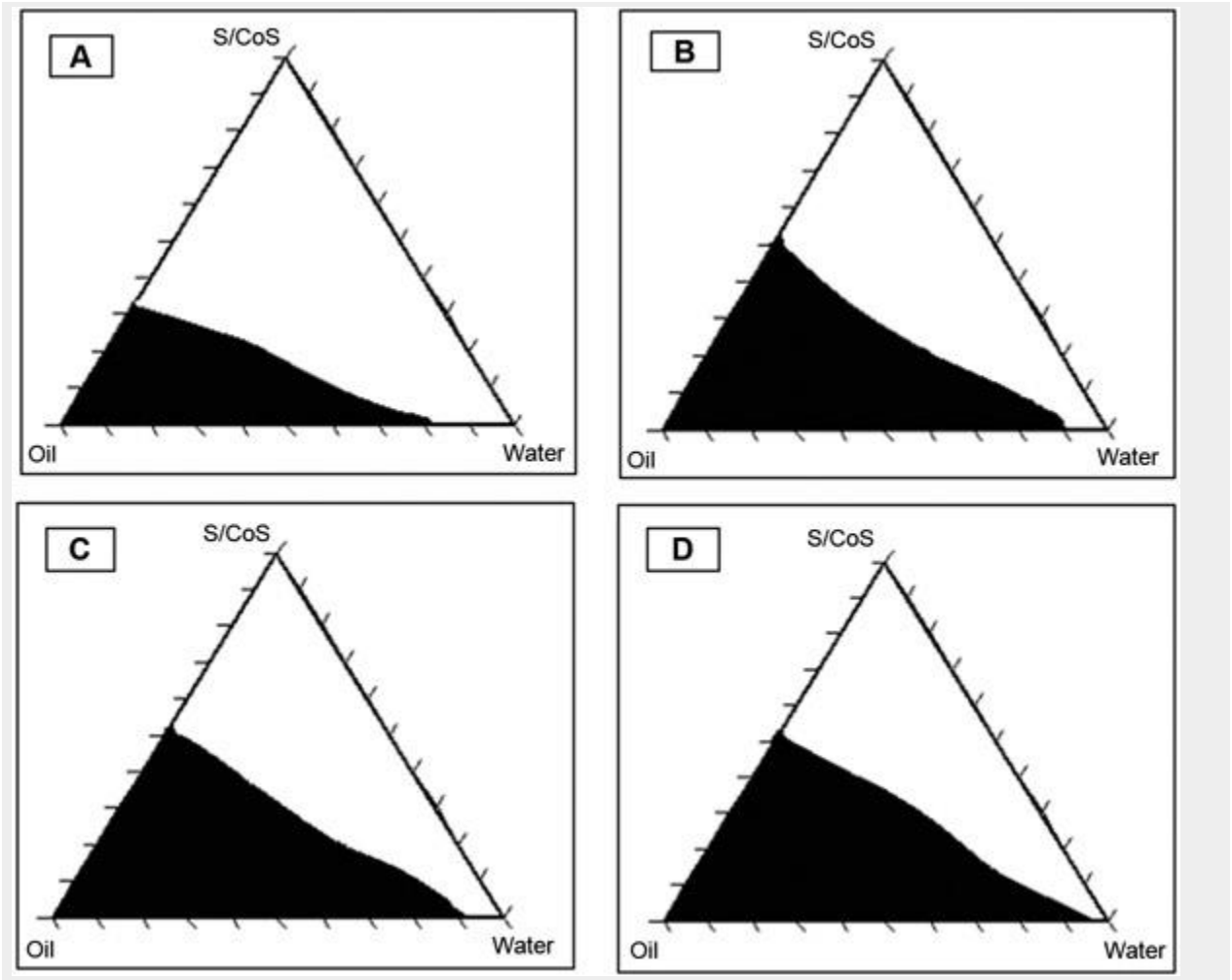


Figure 2. Pseudoternary phase diagram of system with the following components: oil = Labrafac CM10, surfactant = Tween 80, and cosurfactant = polyethylene glycol 400. S/CoS ratio

of A is 1:1, B is 2:1, C is 3:1, and D is 5:1. S/CoS indicates surfactant/cosurfactant.

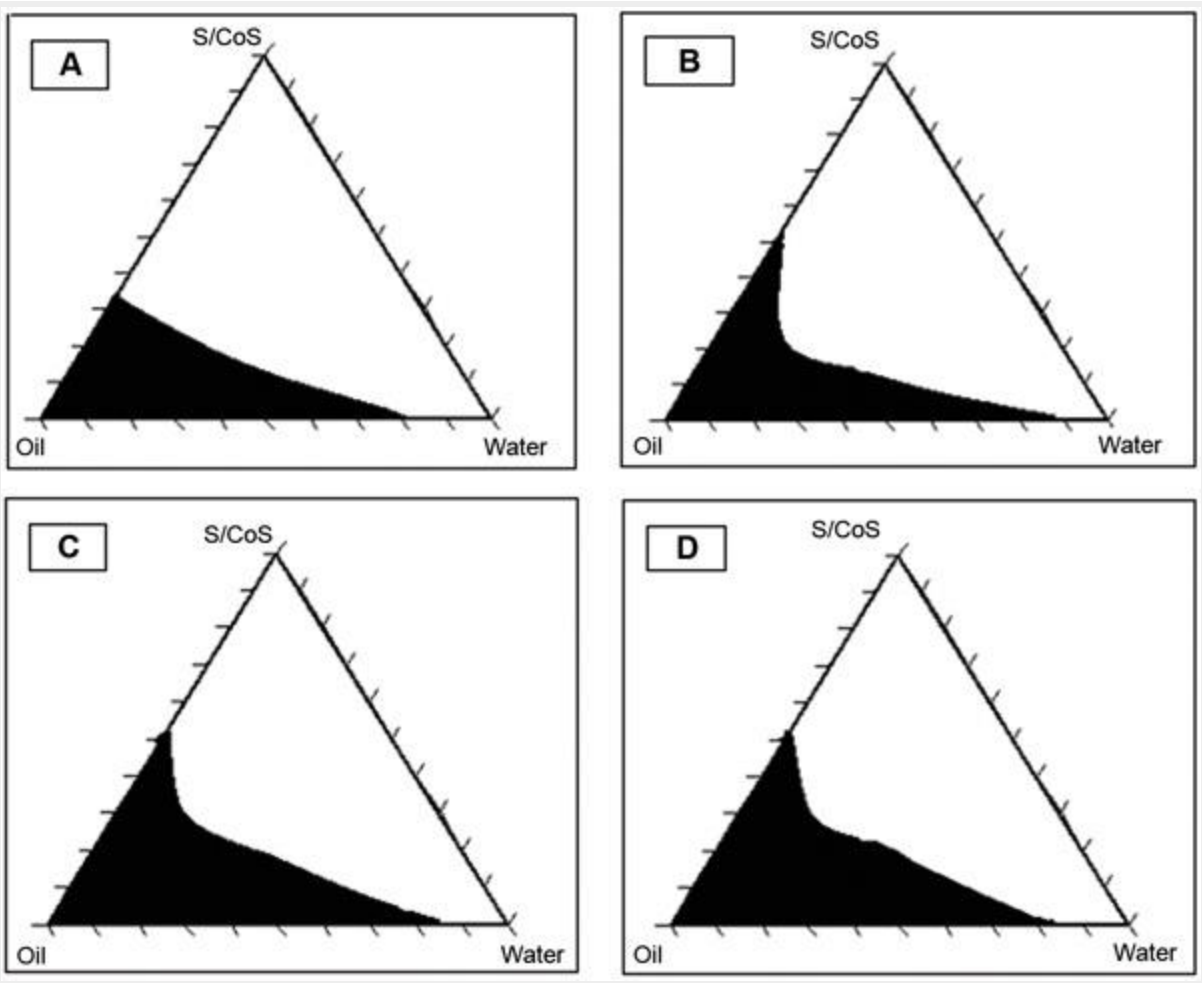


Figure 3. Pseudoternary phase diagram of system with the following components: oil = Maisine 35-1, surfactant = Tween 80, and cosurfactant = polyethylene glycol 400. S/CoS ratio of A is 1:1, B is 2:1, C is 3:1, and D is 5:1. S/CoS indicates surfactant/cosurfactant.

- PEG 400 is reported to be incompatible with hard gelatin capsules when used in high concentrations.[19] Thus, while optimizing the S/CoS ratio, we tried to keep the concentration of PEG 400 as low as possible (<15% wt/wt of total formulation), as we had a final aim of putting the SMEDDS formulations into liquid-filled hard gelatin capsules. Figure 4 shows phase diagrams in the presence of the drug. As seen from the figure, the inclusion of drug narrowed the microemulsion existence area, because

inclusion of the drug in the lipid phase led to expansion of the lipid phase and consequently a need for a higher S/CoS ratio for stabilization.

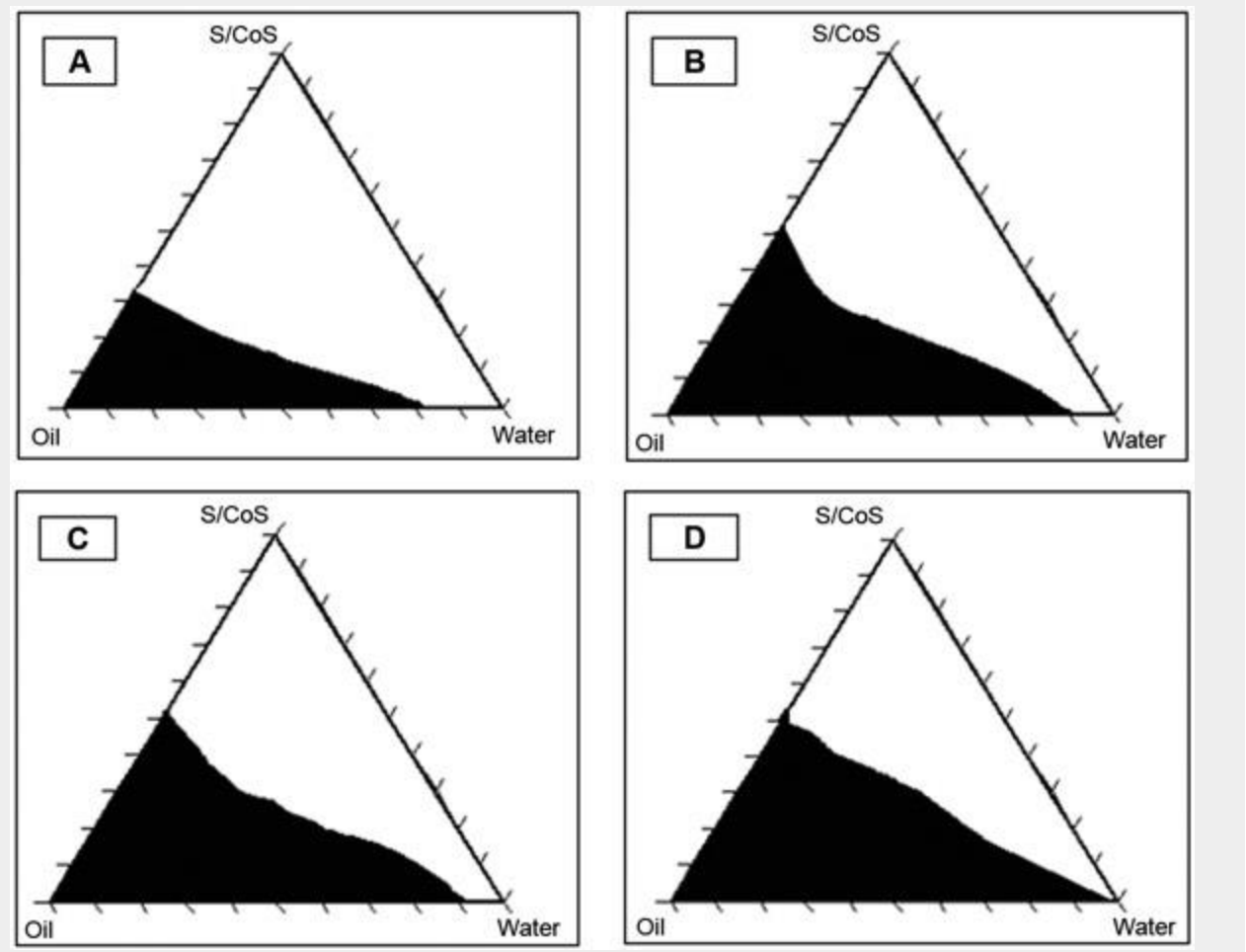


Figure 4. Pseudoternary phase diagram of system with the following components: oil = drug-enriched Labrafac CM10, surfactant = Tween 80, and cosurfactant = polyethylene glycol 400. S/CoS ratio of A is 1:1, B is 2:1, C is 3:1, and D is 5:1. S/CoS indicates surfactant/cosurfactant.

Conclusions

An optimized SMEDDS formulation consisting of Labrafac CM10 (31.5% wt/wt), Tween 80 (47.3% wt/wt), PEG 400 (12.7% wt/wt), and fenofibrate (8.5% wt/wt) was successfully developed with an increased dissolution rate, increased solubility, and, ultimately, increased bioavailability of a poorly water-soluble drug, fenofibrate. The developed formulation showed higher pharmacodynamic potential as compared with plain fenofibrate. Results from stability studies confirmed the stability of the developed formulation. Thus, our study confirmed that the SMEDDS formulation can be used as a

possible alternative to traditional oral formulations of fenofibrate to improve its bioavailability.

2) Development of prototype self-emulsifying lipid based formulations

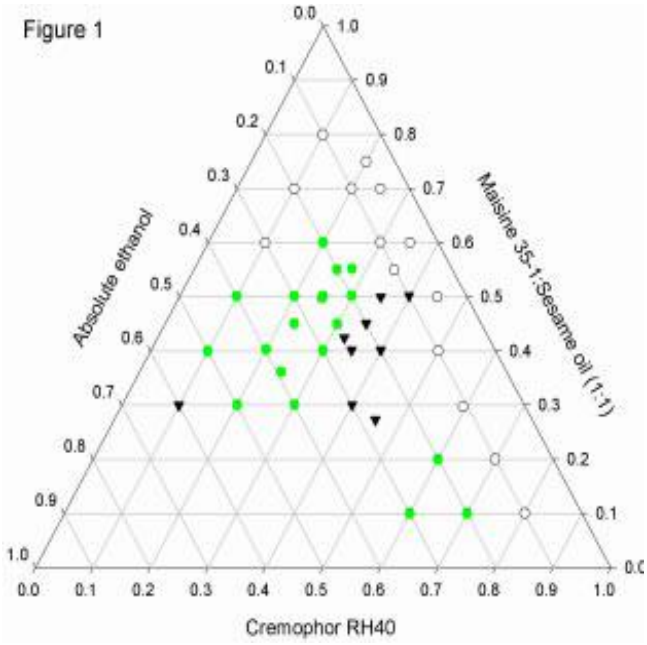
- It is well recognized that lipid-based formulations can enhance oral bioavailability of poorly water-soluble drugs. Lipid containing formulations can be an oil, an emulsion or SEDDS. SEDDS are isotropic mixtures of oil(s), surfactant(s), co-surfactant(s), co-solvent(s) and drug. They form fine oil-in-water emulsions when introduced into aqueous media under gentle agitation.The potential of SEDDS for enhancing the bioavailability of poorly soluble drugs has been evident for at least a decade.One of the working hypotheses in the present study is that particle size distribution of the emulsions can influence the bioavailability.

★ PURPOSE

To develop prototype lipid based selfemulsifying drug delivery systems (SEDDS) and self-microemulsifying drug delivery systems (SMEDDS) with the following characteristics:

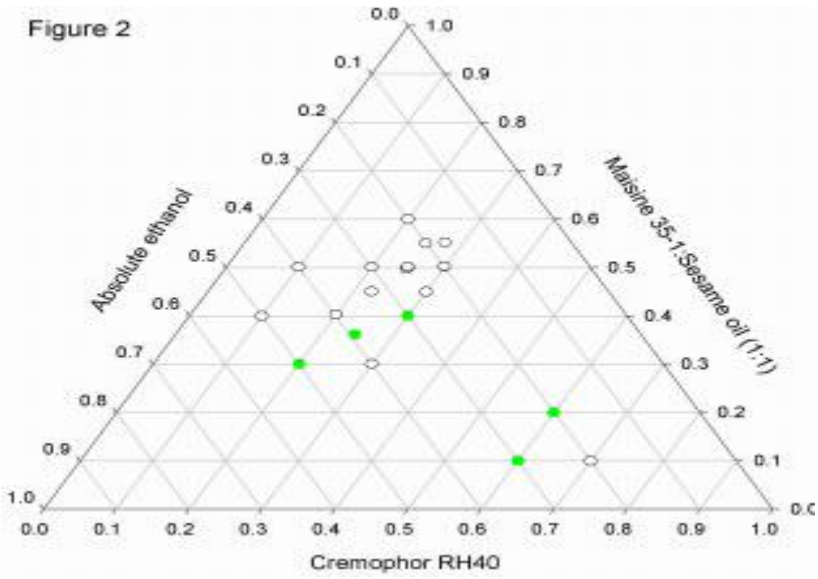
- ✓ Clear single-phase pre-concentrate
- ✓ Mono-modal particle size distribution
- ✓ Digestible lipid containing formulation with highest possible sesame oil content

★ RESULTS & DISCUSSION



A filled triangle indicates that the pre-concentrate is not single-phased. An open circle indicates a single-phased preconcentrate that do not self-emulsify. A filled circle indicates a single-phased and self-emulsifying system (S(M)EDDS).

Figure 1 presents the physical appearance of the pre-concentrate and its ability to selfemulsify as a function of the composition.Single-phased and self-emulsifying preconcentrates are only obtained in two distinct composition ranges. Furthermore it is shown that a concentration of ethanol higher than 10% is needed for the pre-concentrate to be self-emulsifying.



An open circle indicates a S(M)EDDS resulting in an (micro)emulsion with a bi-modal (poly-disperse) particle size distribution. A filled circle indicates S(M)EDDS resulting in an (micro)emulsion with a mono-modal particle size distribution.

- ✓ In figure 2 the particle size distribution of the resulting emulsions is presented as either bimodal or mono-modal as a function of the composition. The formulations with low Cremophor RH40 concentration correspond to a SEDDS and the formulations with high Cremophor RH40 concentration correspond to a SMEDDS.

★ CONCLUSIONS

- ✓ Different ratios of Maisine 35-1 and sesame oil have been tested but the ratio 1:1 afforded the most promising selfemulsifying systems.
- ✓ Self-emulsifying systems with monomodal particle size distribution and distinct different mean particle size have been developed.
- ✓ Mean particle size for the mono-modal self-emulsifying systems is dependent on the ratio between Cremophor RH40 and oil phase.

3) Self-microemulsifying Drug Delivery Systems (SMEDDS) of Nifedipine: Development and In Vitro - In Vivo Evaluation

★ Purpose

- ✓ To develop and characterize self-microemulsifying drug delivery systems (SMEDDS) of nifedipine and to evaluate their oral bioavailability in male Sprague-Dawley albino rats.

★ Methods

- ✓ Solubility of nifedipine was determined in different vegetable oils. Based on the solubility, sesame oil was selected and pseudo-ternary phase diagram was constructed using sesame oil, surfactants blend (Span 80 / Tween 80 at 3:7 ratio) and co surfactant (n-butanol) at surfactant / co surfactant mixture ratio of 9/1. Five SMEDDS were prepared

by selecting different proportions from the self-emulsifying region of pseudo-ternary phase diagram. The SMEDDS were characterized for the self-dispersibility, droplet size, drug content and Fourier transformed-infrared spectroscopy (FT-IR). The in vitro drug release from SMEDDS, pure drug and commercial products was compared. The selected SMEDDS and pure drug were orally administered to rats and blood concentrations of nifedipine at different time points were measured. T1/2, Tmax and AUC0-24 were compared. Relative bioavalilability of SMEDDS was caluclulated.

Results

- ✓ All the SMEDDS showed good self-dispersibility, formed clear microemulsions with very small droplet size (less than 0.2 µm) and drug content was found to be within the limits. FT-IR study showed that there is no incompatibility between the SMEDDS ingredients (sesame oil, Tween 80 and Span 80) and nifedipine. The prepared SMEDDS showed faster drug release compared to pure drug and the two selected commercial formulations. SMEDDS 4 and 5 gave the higher dissolution efficiency (DE) values DE10 and DE30 compared to pure drug, commercial formulations and the other prepared SMEDDS. All the prepared SMEDDS, pure drug and commercial formulations followed first order release. SMEDDS 4 and 5 were selected for the animal study, when compared to same dose of pure drug, Cmax was increased by 4- and 3.5- fold, AUC0-24 was increased by 2.7 and 2 fold respectively. Both the Tmax and T½ values were similar to the reported values. Relative % BA was found to be 267.81 and 196.99 for SMEDDS 4 & 5 respectively.

Conclusion

- ✓ These results indicate the usefulness of the SMEDDS for the improvement of the dissolution rate and thereby oral bioavailability of poorly water soluble drugs like nifedipine.

4) Self-nanoemulsifying drug delivery systems (SNEDDS) for oral delivery of protein drug

RECENT INNOVATION IN IN-SITU GELS

1) Formulation and Evaluation of pH Induced In-situ Nasal Gel of Salbutamol Sulphate

ABSTRACT: Nasal solutions of Salbutamol Sulphate were prepared for sustaining its release and improving its bioavailability.
Carbopol was used as a key ingredient to effect pH induced sol to gel conversion of the formulations.
Different formulations were prepared by varying the concentrations of Carbopol 934 and Hydroxyl Propyl Methyl Cellulose.
These formulations were evaluated for parameters like pH, drug content, viscosity, gel strength and drug release.

Release profile of some formulations showed rapid phase while some showed slow phase. At extreme low concentrations of the polymers, the formulations drained out due to poor viscosity while at higher concentrations of the same the formulations formed stiff gel and showed slow release of drug.
Finally optimized formulation with specific concentrations of carbopol 934 and Hydroxyl Propyl Methyl Cellulose showed pH induced sol-gel conversion, sustained release and higher bioavailability.

Ingredients

Salbutamol sulphate
Carbopol 934
HPMC K4M
NaCl
Benzalkonium chloride
Sodium metabisulphiteDistilled water (ml)

Evaluation of in Situ Gels

1. **Appearance**
2. **pH of the Gel**
3. **Gelation Studies**
4. **Drug Content**
5. **Viscosity Measurement**
6. **Measurement of Gel Strength**
7. **In Vitro Release Study**

2) Study of an alginate/HPMC-based in situ gelling ophthalmic delivery system for gatifloxacin.

- The poor bioavailability and therapeutic response exhibited by conventional ophthalmic solutions due to rapid pre-corneal elimination of the drug may be overcome by the use of in situ gel-forming systems that are instilled as drops into the eye and then undergo a sol-gel transition in the cul-de-sac. The present work describes the formulation and evaluation of an ophthalmic delivery system of an antibacterial agent, gatifloxacin, based on the concept of ion-activated in situ gelation. Alginate (Kelton((R))) was used as the gelling agent in combination with HPMC (Methocel E50Lv) which acted as a viscosity-enhancing agent. The rheological behaviors of all formulations were not affected by the incorporation of gatifloxacin. Both in vitro release studies and in vivo pre-corneal retention studies indicated that the alginate/HPMC solution retained the drug better than the alginate or HPMC E50Lv solutions alone. These results demonstrate that the alginate/HPMC mixture can be used as an in situ gelling vehicle to enhance ocular bioavailability and patient compliance.

3) DEVELOPMENT OF A NOVEL IN SITU GEL SYSTEM FOR ORAL DRUG DELIVERY

Purpose.

The aim of this investigation was to develop a novel chitosan-glyceryl monooleate

(GMO) gel system that can be used for sustained oral delivery of drugs.

Methods.

Ketoprofen and dexamethasone were used as the model hydrophilic and hydrophobic drugs, respectively. The optimal delivery system comprised of chitosan, 3% (w/v) and GMO, 3% (w/v) in 0.33 M citric acid containing 1% (w/v) ketoprofen or 0.03% (w/v) of dexamethasone. In vitro release of drug was carried out by adding 1.0 ml of the solution to 40ml of Sorensen¡¯s phosphate buffer (pH=7.4). The in situ gel formed was shaken in a water bath at 80 rpm and 37°C. Drugs were analyzed by HPLC. Effect of crosslinking (glutaraldehyde, 50% v/v) on the in vitro drug release was also evaluated.

Results.

Use of citric acid to dissolve the chitosan produced an optimal gel at pH 7.4 as compared to acetic, lactic, and tartaric acid. Incorporation of GMO into the gel minimized the initial burst effect of the drugs and enhanced its bioadhesive property.
The drug release from such a gel followed a matrix diffusion controlled mechanism.

Conclusion.

A novel in situ gel formulation containing chitosan and GMO was developed and tested. The in vitro release of ketoprofen and dexamethasone from such gel was found to be quick but could be controlled by incorporation of a crosslinker. This novel chitosan-GMO system, with its enhanced bioadhesive property, can be used for sustained and targeted delivery of a wide range of drugs.

RECENT INNOVATION IN LYOPHILIZED SUSPENSION

1) Lyophilized Lecithin Based Oil-Water Microemulsions as a New and Low Toxic Delivery System for Amphotericin B

- **Purpose**. To develop and investigate lecithin based oil-water microemulsions as potential amphotericin B (AmB) delivery systems and to evaluate their in vivo acute toxicity.

- **Methods**. AmB was added to the microemulsion and its location was evaluated by partitioning studies and UV-visible spectrophotometric analysis of the drug. Both, non-lyophilized and reconstituted microemulsions were characterised and assessed for their stability. Single-dose acute toxicity of the AmB microemulsion was studied on male albino Webster-derived CD-1 mice and compared with Fungizone®.

- **Results**. The studies performed showed that AmB was intercalated on the oil-water interface of the microemulsion as a complex formed with lecithin molecules. AmB addition did not seem to modify the rheological properties of the original system, but had an effect on its particle size distribution. Lyophilization of the microemulsion led to an oily cake, easily reconstituted and stable at the conditions studied. Single-dose acute toxicity studies proved that the LD_{50} of AmB microemulsions was of 4 mg kg^{-1} of animal weight, compared with 1 mg kg^{-1} found for Fungizone®.

- **Conclusions**. Lyophilized lecithin based oil-water microemulsions appear to be valuable systems for the delivery of AmB in terms of easy and low-cost manufacturing, stability and safety compared with the formulations already in market.

2) The ophthalmic lyophilisate carrier system (OLCS): development of a novel dosage form, freeze-drying technique, and in vitro quality control tests

- The ophthalmic lyophilisate carrier system (OLCS) is a novel dosage form for delivery of pharmacologically active ingredients or other substances improving the structure of the tear film to the eye.
- A drop of lyophilisate containing the drug and bulk forming water-soluble or swelling excipients is attached to a flexible hydrophobic carrier. Placebo OLCS and OLCS containing several drugs commonly used in ophthalmology were compared to conventional eye drops containing the same ingredients.

- A novel lyophilization procedure for the production of this dosage form is described, which allows stricter control of the freezing and drying conditions and shortens the production cycle by at least an order of magnitude.

- In clinical studies it was found that OLCS are easy to administer and well tolerated if the force of adhesion between lyophilisates and carrier strips and the structural firmness of the lyophilisates themselves are well controlled.

- These parameters are critical for convenient administration and complete delivery of the dose of active ingredients incorporated, therefore suitable in vitro tests were developed with which their values can be determined for the purpose of process validation.

- A study of fluorescein OLCS in humans indicated that concentration profiles in the cornea and anterior chamber are significantly higher than after administration of equal doses of the diagnostic in conventional eye drops.