"Formulation and Characterization of A self Micro Emulsifying Drug Delivery System for Poorly Water Soluble Drugs"

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Abstract

The current study's objective was to create a self-micro emulsifying drug delivery system (SMEDDS) for cardiovascular medications like verapamil hydrochloride in order to increase solubility, dissolution rate, which may improve therapeutic performance, and drug loading capacity in order to create an alternative to conventional oral formulations and increase bioavailability. Oleic acid, Tween 80, PEG 400, Castor oil, Labrasol, and Transcutol P were chosen as the oil, surfactant, and co-surfactant for VPH, respectively, in this study. The three formulations, designated VLM1, VLM2, and VLM3 for VPH, were successfully prepared after being chosen from the ternary phase diagram at Km value 3. A variety of criteria were assessed for prepared liquid SMEDDS. It was discovered from this investigation that all liquid SMEDDS formulations had globule size in the nanometric range, good stability with no phase separation, creaming, or cracking, and swiftly created micro emulsion that was clear with a faint blue tint.

Keywords: Verapamil hydrochloride, Oleic acid, Labrasol, Transcutol P, smedds

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INTRODUCTION

Drugs are introduced in to the body by several routes. They may be taken by mouth (orally); given by injection into a vein (intravenously), into a muscle (intramuscularly), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously); placed under the tongue (sublingually); inserted in the rectum (rectally) or vagina (vaginally); instilled in the eye (by the ocular route); sprayed into the nose and absorbed through the nasal membranes (nasally); breathed into the lungs, usually through the mouth (by inhalation); applied to the skin (cutaneously) for a local (topical) effect; or delivered through the skin by a patch (transdermally) for a systemic effect. Each route has specific purposes, advantages, and disadvantages. [1]

But the oral route is the preferred route for the chronic drug therapy. It has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach. Usually, however, most of the drug is absorbed from the small intestine. The drug passes through the intestinal wall and travels to the liver before it is transported via the bloodstream to its target site. [1]

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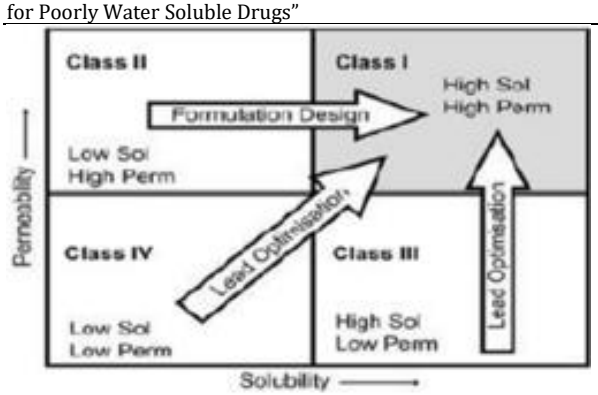


Figure 01. A typical representation of the biopharmaceutical classification system

Class 1 contains drugs with a high solubility and permeability. Those drugs are well absorbed and their absorption rate is usually higher than excretion. Class 2 contains drugs with a low solubility and high permeability. The bioavailability of those drugs is limited by their dissolution rate. In addition, Class 3 drugs are highly soluble, although permeability is limitedby the permeation rate but the drug is dissolved very fast. Finally, Class 4 drugs have poor bioavailability because of low solubility and permeability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected. In comparison with marketed The solubility and permeability issues (Class 2 & 4) that the new molecular entities in pharmaceuticals exhibit reduce the huge pharmaceutical and biopharmaceutical industry's output further. [2-4] The absorption number for BCS Class II medications is high, but the dissolution number is low. The rate-limiting phase for absorption is hence in vivo drug dissolution, with the exception of very high dose numbers. Class II medications often take longer to absorb than Class I drugs and do so at a slower rate. For Class I and Class II medications, in vitro-in vivo correlation (IVIVC) is typically acknowledged. These items' solvation rates restrict the bioavailability of certain substances. Consequently, a link between in vivo bioavailability and in vitro solvation can be established. [4].To promote the therapeutic effectiveness of lipophilic medicines, efforts are being made to improve their oral bioavailability. The bioavailability of class II medications can be increased using a variety of formulation techniques, including enhancing the rate of dissolution or delivering the drug in solution and keeping it there throughout the intestinal lumen.

Figure 3 shows how paying enough attention to the formulation can significantly increase the absorption of a class II medication. Class IV medicines' limited membrane permeability is likely to make them less bioavailable despite formulations that may increase their bioavailability.

SELF-MICROEMULSIFYING SYSTEM:

Self-microemulsifying drug delivery systems (SMEDDS) are combinations of oils and surfactants that are ideally isotropic and occasionally incorporate co-solvents. When injected into an aqueous phase while being gently stirred, SMEDDS spontaneously emulsify to generate fine oil-in-water emulsions. SMEDDS have recently been created using nonionic surfactants, which are less hazardous, and medium chain triglyceride oils. Following oral route delivery, these systems cause modest stomach movement and the formation of fine emulsions (or micro-emulsions) in the GIT. These systems could have a number of advantages, such as improved oral bioavailability that allows for a dose reduction, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, and protection of drug(s) from the hostile environment in gut. [10, 11, 17].

Potential advantages of these systems include; [21]

1. Increased oral bioavailability allowing dosage decrease,
2. More reliable temporal patterns of medication absorption,
3. Selective medication targeting for a certain GIT absorption window,
4. Protection against the harmful environment in the gut for the drug(s).
5. Delivery profile control.
6. Less variation, including food-related effects.
7. Safeguards sensitive medicinal ingredients.
8. Significant drug payloads.
9. Oral or injectable dosing types.

MECHANISM OF SELF-EMULSIFICATION:

When the energy required to expand the surface area of the dispersion is larger than the

entropy change that favours dispersion, self-emulsification happens. Additionally, Equation [22] can be used to show how the free energy of a traditional emulsion formation is directly related to the energy needed to construct a new interface between the two phases.

Where N is the number of droplets with radius r and s is the interfacial energy, G is the process-related free energy (ignoring the free energy of mixing). In order to decrease the interfacial area and subsequently the free energy of the systems, the two phases of the emulsion will tend to separate throughout time.

Various liquid crystal (LC) or gel phases generated on the surface of the droplet could be related to the ease of emulsification. When an oil/nonionic surfactant binary mixture is added to water, an interface between the oil and aqueous-continuous phases forms, which is followed by water solubilization in the oil phase as a result of aqueous penetrating through the contact. This will continue until the interface is near to the solubilisation limit. The dispersed LC phase will arise as a result of further aqueous penetration. All material near the interface will eventually be LC as the aqueous penetration progresses; the precise amount depends on the amount of surfactant present in the binary mixture. Once created, droplet production is brought on by the quick infiltration of water into the aqueous cores, which is facilitated by the self-emulsification process' mild agitation. These self-emulsified systems' exceptional stability to coalescence is thought to be a result of the LC interface that surroundsthe oil droplets. [23, 24]

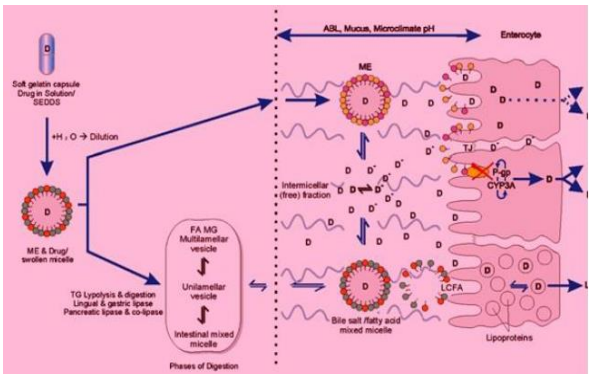


Figure 02. Mechanism of self-emulsification & Absorption.

The capacity of lipids and/or meals to increase the bioavailability of weakly water soluble medicines is well established. This is one of the formulation-mediated mechanisms of improved drug absorption. Despite being poorly understood, it is currently believed that lipids may increase bioavailability through a variety of possible pathways, such as. [19, 25]

a) Modifications (decrease) in gastric transit, which lengthen the time before dissolution and slow transport to the absorption site. [26]

b) A rise in the drug's effective luminal solubility. The creation of intestinal mixed micelles and an increase in the GI tract's solubilization capacity are both influenced by the presence of lipids in the GI tract, which also encourages an increase in the secretion of bile salts and endogenous biliary lipids such phospholipids and cholesterol. But when supplied (exogenous) lipids intercalate into these BS structures, either directly (if sufficiently polar) or as a result of digestion, the micellar structures inflate and their solubilization capacity is further increased. [26]

c) Stimulation of lymphatic transport in the intestine. Lipids may increase the amount of lymphatic transport and increase bioavailability for highly lipophilic medicines either directly or indirectly by lowering first-pass metabolism. A hydrophilic medication may diffuse directly into the portal supply rather than through the lymphatic system (chylomicron) for absorption. Hence in this case, increased dissolution from the large surface area afforded by emulsion may be a contributing factor to enhanced absorption of drugs. [27]

d) Modifications to the GI tract's biochemical barrier function. According to the p glycoprotein efflux pump, it is evident that some lipids and surfactants may lessen the activity of intestinal efflux transporters, which would decrease the amount of enterocyte-based metabolism. [27]

COMPONENTS OF SMEDDS

The self-emulsifying process depends on:

- The nature of the oil–surfactant pair

• The surfactant concentration
• The temperature at which self-emulsification occurs. [18]

The characteristics of the oil-surfactant pair and the concentration of the surfactant are key factors in the self-emulsifying process.
• The temperature where self-emulsion takes place. [18]

Excipient selection

At room temperature, the oily/lipid component is typically a fatty acid ester or a medium- to long-chain saturated, partially unsaturated, or unsaturated hydrocarbon. Examples include lanolin, refined animal oil, silicon oil, vegetable oil, mineral oil, mono-, di-, and tri-glycerides. [29] Non-ionic surfactants with a reasonably high hydrophilic-lipophilic balance (HLB) VPHue are the ones that are most frequently advised. To create stable SMEDDS, the surfactant concentration must be between 30% and 60% (w/w). [7] Other places provide more thorough descriptions, which might be a helpful reference for choosing an excipient. [7, 11]

Oils:

A certain number of oils can solubilize the lipophilic medication. Depending on the triglyceride's molecular structure, it can accelerate self-emulsification, raise the proportion of lipophilic drugs carried by the intestinal lymphatic system, and increase absorption from the GI tract. For these reasons, it is the most significant excipient. [30] For the creation of self-emulsifying formulations, long and medium chain triglyceride (LCT and MCT) oils with various saturation levels have been employedrational and desirable lipid excipient choice for the production of SMEDDS, are not usually used.

Surfactants

For the design of self-emulsifying systems, a variety of compounds with surfactant capabilities may be used, but the options are constrained because so few surfactants are suitable for oral use.
The non-ionic surfactants with a comparatively high hydrophilic-lipophilic balance are the ones that are most frequently advised (HLB). Since natural emulsifiers are thought to be safer than synthetic surfactants, they are recommended. [30] These surfactants can only partially self-emulsify, though.
The type of hydrophilic group that exists within a surfactant molecule can be used to categorise the molecule. The following are definitions of the four major surfactant groups:

1. Anionic Surfactants
2. Cationic surfactants
3. Ampholytic surfactants.
4. Nonionic surfactants

Co-surfactants

The production of an optimum SMEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants, thus the concentration of surfactant can be reduced by incorporation of co surfactant. Role of the co-surfactant together with the surfactant is to lower the interfacial tension to a very small even transient negative VPHue. At this VPHue 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.
El-Nokaly et al summarized the role of a Co-surfactant as following:[36]

1. Increase the fluidity of the interface.
2. Destroy liquid crystalline or gel structure which would prevent the formation of microemulsion.
3. Adjust HLB VPHue and spontaneous curvature of the interface by changing surfactant partitioning characteristic.

Biopharmaceutical issues

It is important to note that lipids (e.g. triglycerides) affect the oral bioavailability of drugs by changing biopharmaceutical properties, such as increasing dissolution rate and solubility in the intestinal fluid, protecting the drug from chemical as well as enzymatic degradation in theoil droplets and the formation of lipoproteins promoting lymphatic transport of highly lipophilic drugs. [22]

Specificity

Self-emulsification depends on the nature of the oil/surfactant pair, surfactant concentration

and oil/surfactant ratio, and the temperature at which self-emulsification occurs. The following should be considered in the formulation of a SEDDS

1. The solubility of the drug in different oil, surfactants and cosurfactant/co-solvents.
2. The selection of oil, surfactant and co-solvent based on the solubility of the drug and the preparation of the phase diagram.
3. The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and co-surfactant/co-solvents.

Verapamil hydrochloride (Indian Pharmacopoeia, 1996, The United State Pharmacopoeia 2000 and Tripathi K. D. 2003):-

Chemical Formula $C_{13}H_{12}F_2N_6O$ Molecular weight 491.07 g/mol Chemical Structure

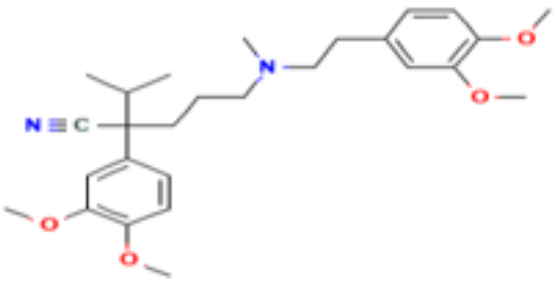


Fig.03: Structure of Verpamil

Category:- Calcium channel blocker Description White, crystalline powder.

Melting range:- 140 - 144 ^{0}C

Pharmacokinetic parameters:-
Pharmacokinetic parameters

Oral bioavailability:- 20 - 35 %

Plasma half-life mean:- 2.8 - 7.4 h

Volume of distribution:- 5.0 L/Kg

Plasma protein binding:- 90 %

Plasma clearance:- 0.9 L/h/kg

Onset of action:- < 1.5 minutes (i.v.), 30 minutes (oral)

Disposition:- About 90% bound to plasma protein. 70% eliminated by kidney; 15% by gastrointestinal tract.

Mechanism of action:- It dilates arterioles and has some a adrenergic blocking activity – decreases total peripheral resistance but BP is only modestly lowered. The heart rate generally decreases, A-V conduction is slowed, but cardiac output is maintained by

ADVANTAGES OF SMEDDS

- Improvement in oral bioavailability
- Ease of manufacture and scale-up.
- Reduction in inter-subject and intra-subject variability and food effects
- Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT
- Increased drug loading capacity

FACTORS AFFECTING SMEDDS [28]

Nature and dose of the drug. Polarity of the lipophilic phase

INFLUENCE OF SELF-MICRO EMULSIFYING LIPID-BASED FORMULATIONS ONFOOD EFFECT

The effect of food on the bioavailability of poorly water-soluble, hydrophobic drugs is determined by multiple factors, including the physicochemical properties of the drug substance, the dose, the nature of the formulation and the amount and composition of the ingested food. Since food effect can lead to exaggerated pharmacologic responses or unexpected toxicity, clinical trial guidelines routinely require studies comparing drug exposure in fed and fasted subjects. [45]

RATIONALE FOR SELECTION OF DRUG (VERAPAMIL)

The drug belongs to BCS Class I, hence exhibit high solubility and permeability but employing SMEDDS technology enhances the member drugs bioavailability and efficacy thereby my reduce the required dose of drug.

OBJECTIVES OF RESEARCH WORK

1) It is needed to develop SMEDDS of nonselective NSAID drug VERAPAMIL to enhance solubility, dissolution rate which may improve therapeutic performance and drug

loading capacity so as to develop alternative to traditional oral formulations to improve bioavailability.

2) Self microemulsifying drug delivery system is lipid-based formulations, which release the drug from an oily solution which is often immiscible with water. This would bypass the step of solubilization of poorly soluble drugs.

3) Increase in solubility will result in increase in rate of in vitro dissolution of VERAPAMIL SMEDDS formulation.

4)Release and absorption of drugs from oily dispersions in vivo is thought to occur subsequent to lipid digestion and micellization or possibly, via direct transfer from the oil droplets to the intestinal epithelia, the efficiency of both processes being proportional to the total oil droplet surface area.

EXPERIMENTAL WORK

PLAN OF WORK

Development & characterization of Self Emulsifying drug delivery system for poorly water soluble drug

Drug Preformulation Study

- VPH

Preparation of Self Microemulsifying Drug delivery System

- Drug Solubility Study in Oils, Surfactant &Cosurfactant
- Construction of Psuedo Ternary Phase Diagram & optimization of Combination

Formulation Compatibility study

- Emulsification time
- Dilution study
- Thermodynamic stability studies

(Centrifugation time & freeze thaw study)

Characterization SMEDDS

- Refractive index &
- % transmittance
- pH
- Electro conductivity test
- Drug content
- Dissolution Testing

Material and Methods:-

PROCUREMENT OF DRUG AND EXCIPIENTS

Drugs, excipients, chemicals/ reagents and instruments used for various experiments are enlisted in Table.1 and 2

Table 1. Drug, Excipients used for Various Experiments

Materials Gifted/Supplied By	Materials Gifted/Supplied By
VERAPAMIL	Zydus Healthcare Ltd
Capmul MCM C8 Abitec Pvt Ltd, USA	Capmul MCM C8 Abitec Pvt Ltd, USA
Capmul PE 8 Abitec Pvt Ltd, USA	Capmul PE 8 Abitec Pvt Ltd, USA
Captex 355 Abitec Pvt Ltd, USA	Captex 355 Abitec Pvt Ltd, USA
Triacetin Sigma Aldarich , Mumbai	Triacetin Sigma Aldarich , Mumbai
Labrafill M 1944 CS	Gattefosse Pvt Ltd, Mumbai
Acrysol K 140	Corel Pharma, Ahmedabad
Acrysol EL 135	Corel Pharma, Ahmedabad
Castor oil	S. D. fine chem Mumbai
Spearmint oil	S. D. fine chem Mumbai
Cotton seed oil	D. fine chem Mumbai
Oilve oil	S. D. fine chem Mumbai
Sesame oil	S. D. fine chem Mumbai
Kolliphore RH 40	BASF India Ltd., Mumbai

PREFORMULATION STUDY METHODS

Preformulation research is a necessary phase in the formulation and development of pharmaceutical products in order to make the optimal choices for the dosage form and excipients. The preformulation study for drugs (VPH) and excipients was carried out in the planned study. The following parameters for VPH were done in the drug preformulation studies: [19, 23,150]

Organoleptic properties & VPH were tested for organoleptic properties such as appearance, colour, taste, etc.

Physicochemical Properties

FTIR spectroscopy

Appearance of solution:

Loss on drying [151]

Micromeritical properties

- Bulk density [153]
- Tapped density [153]

• Purity

PREPARATION, CHARACTERIZATION & OPTIMIZATION OF SMEDDS OF VPH

PREPARATION OF DRUG DELIVERY SYSTEM METHODS

Determination of solubility of Drugs in Oils, Surfactants & Co-surfactants

The solubility of drug (VPH) in various oils, surfactants, and cosurfactants was determined by supersaturation method. An excess amount of drug (VPH) was added into each vial containing 2 ml of selected vehicle. After sealing the mixture was vortexed using a cyclomixer for 10 minutes in order to facilitate proper mixing of drug with the vehicles. Then, the formed suspensions were shaken for 24 h in a mechanical shaker (Remi, India) maintained at 37±1ºC. After reaching equilibrium, the mixtures were centrifuged at 5000 rpm for 5 minutes to remove undissolved drug, followed by filtration through a 0.45-µm millipore membrane filter paper.

Table 2. List of various Oils, Surfactants &Cosurfactants used for VPH Solubility

Sr no.	Oils	Surfactants & co-Surfactants
1	Capmul MCM	Kolliphore RH 40
2	Capmul PE 8	Solutol HS 15
3	Captex 355	Tween 80
4	Triacetin	Tween 20
5	Acrysol K 140	Span 80

Construction of Psuedoternary phase diagram

Psuedoternary phase diagrams of oil, surfactant/Cosurfactant (Smix) and water were developed using the water titration method. On basis of the solubility studies oil, surfactants and cosurfactants were grouped in different combinations for phase studies. Distilled water was used as an aqueous phase for the preparation of microemulsions. For each phase diagram at a specific ratio (example: 1:1, 1:2, 2:1) of Surfactant and cosurfactant (Smix) were mixed. Mixtures of the oil and Smix were prepared at ratios (w/w) of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10 in vials. A transparent and homogenous mixture of oil and Smix was formed by vortexing for 5 min. The resultant mixture titrated with distilled water dropwise and observed for transparency and flowability.

RESULTS & DISCUSSION

Physicochemical and micromeritical preformulation

The results of physicochemical and micro-meritical studies are depicted in Table 5

Table 5. Physiochemical & derived data for VPH

Sr No	Description	Experimental observation	Specification
	Organoleptic Properties		
1.	Colour	White to off white crystalline powder	White to off white crystalline powder
2	**Taste**	Bitter	Bitter
	Physicochemical Properties		
3	FTIR Spectra	Complies with COA	The Absorption maxima in the spectrum obtained with sample correspond in position and relative size to those in the spectrum obtained with VPH working Standard.
4	Loss on Drying	0.30%	Maximum 0.5 %
5	Appearance of solution	Complies with COA	It is not more intensely coloured than reference solution.
6	Melting range	142-144ºC	**140-144ºC**
7	Solubility	Soluble in water, freely soluble in chloroform, sparingly soluble in alcohol, practically insoluble in ether	Soluble in water, freely soluble in chloroform, sparingly soluble in alcohol, practically insoluble in ether
8	pH of 5 % solution	**4.6**	**4.5 -6.5**
9	Clarity and colour of solution	Clear and colourless	Clear and colourless
	Saturation Solubility(mg/mL)		
10	D. M water Practically	0.0002	insoluble
11	0.1 N HCl	2.21	Sparingly soluble
12	pH 4.5 acetate buffer	0.0004	Practically insoluble
13	pH 6.8 phosphate buffer	0.0012	Practically insoluble
	Derived Properties		
14	Bulk density (g/mL)	0.25	Not more than 0.3
15	Tapped Density (g/mL)	0.36	Not more than 0.5
16	Compressibility Ratio	38.88	.....
17	Hausner's Ratio	1.63	...

Spectroscopic study for VPH

A. UV Spectroscopy (Determination of λmax) Wavelengths of maximum absorption (λmax) of VPH in different solvent are shown in Table 4.

Table 3: Wavelength of maximum absorption (λmax) in different solvents.

Solvent	λmax (nm)
Methanol	278
Acid buffer of pH 1.2	278
Phosphate buffer of pH 6.8	278

FTIR spectrum of VPH

The characteristic absorption peaks of VPH were obtained. Table 5 shows the characteristic functional groups of the drug along with their wave numbers in cm-1. The FTIR spectrum of VPH is shown in Figure 5.1. (Indian Pharmacopoeia, 2007)

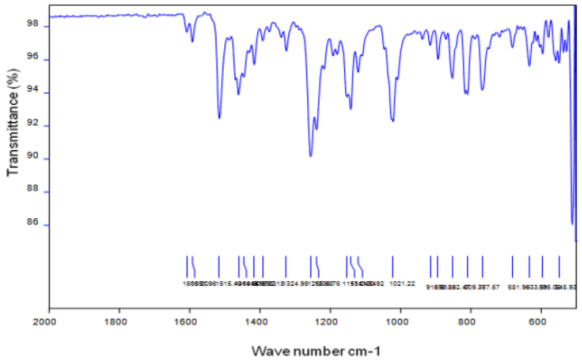


Figure 04: FTIR spectrum of VPH Table

Table No.4: Wave number and respective functional group (VPH)

Wave number (cm-1)	Functional group
1515.91	C-N
1259.43	Asymmetric C-O-C
1027.99	Symmetric C-O-C
1325.07	OCH3

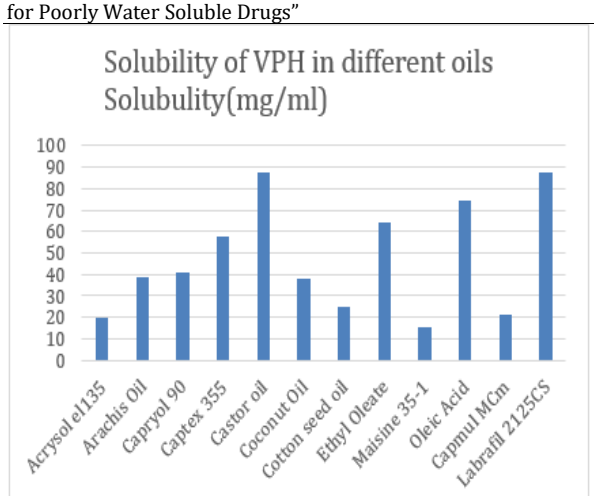
Determination of solubility of Drugs in Oils, Surfactants & Co-surfactants

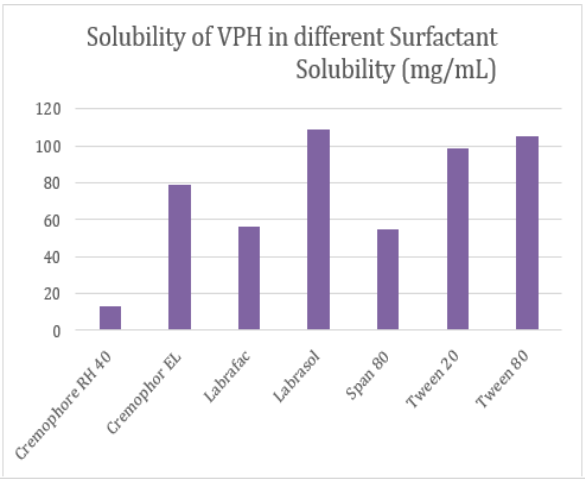
Determination of solubility of VPH in Oils, Surfactants &*Co*-surfactants

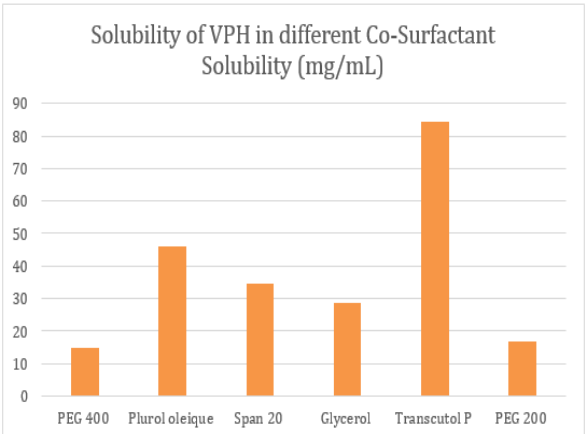
The solubility of VPH in various oils, surfactants, and cosurfactants was determined by supersaturation method. The concentration of VPH was quantified by UV spectrophotometrically (UV-1900i, Shimadzu Corporation, Japan). Solubility data results are shown in Table 6 and graphically presented in Figure 5, 6 and 7.

Table 5: Solubility Data of VPH in various Oils, Surfactants &Cosurfactants

Oil	Solubility (mg/mL)	Surfactant	Solubility (mg/mL)	Co-surfactant	Solubility (mg/mL)
Acrysol EL 135	24.25	Cremophore RH 40	12.89	PEG 400	14.73
Arachis oil	37.84	Cremophor EL	79.12	Plurololeique	46.14
Capryol 90	40.98	Labrafac	56.10	Span 20	34.45
Captex 355	57.04	Labrasol	109.01	Glycerol	28.48
Castor oil	98.15	Span 80	55.12	Transcutol P	84.54
Coconut oil	39.32	Tween 20	98.37	PEG 200	16.87







Construction of Psuedoternary phase diagram

Construction of Psuedoternary phase diagram for VPH SMEDDS

Components used for construction of pseudo ternary phase diagram for VPH are Castor oil (oil phase), Labrasol (surfactant), Transcutol P (co-surfactant) and bi-distilled water (aqeous phase). Composition of Castor oil, Labrasol, Transcutol P and water at each Km values are shown in Table 5.4,5.5,5.6,5.7& 5.8 and pseudo ternary phase diagram at respective Km values are shown in Figure 5.5,5.6,5.7,5.8,5.9 and 5.10.

Table 6: Composition of Castor oil, Labrasol, Transcutol P and water at Km=1

Smix: Oil	Composition expressed as % W/W		
	Smix	Oil	Water
1:9	5.85	75.65	18.5
2:8	16.93	66.7	16.37
3:7	28.55	45.95	25.5
4:6	32.47	38.41	29.12
5:5	35.78	32.44	31.78
6:4	40.69	28.99	30.32
7:3	47.65	22.47	29.88
8:2	53.41	13.64	32.95
9:1	52.74	3.17	44.09

Figure 05: Pseudo ternary phase diagram of Castor oil, Labrasol, Transcutol P and water at Km=1

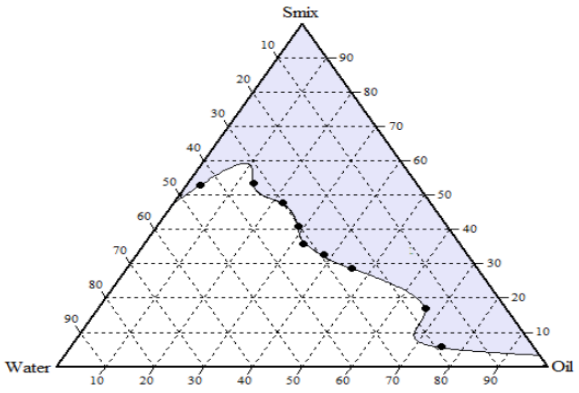


Table 7: Composition of Castor oil, Labrasol, Transcutol P and water at Km=2

Smix: Oil	Composition expressed as % W/W		
	Smix	Oil	Water
1:9	8.38	76.21	15.41
2:8	12.45	70.64	16.91
3:7	19.37	60.21	20.42
4:6	25.35	53.21	21.44
5:5	30.42	45.25	24.33
6:4	35.41	35.68	28.91
7:3	38.25	20.35	41.4
8:2	42.26	10.47	47.27
9:1	14.15	5.56	80.29

Figure 06: Pseudo ternary phase diagram of Castor oil, Labrasol, Transcutol P and water at Km=2

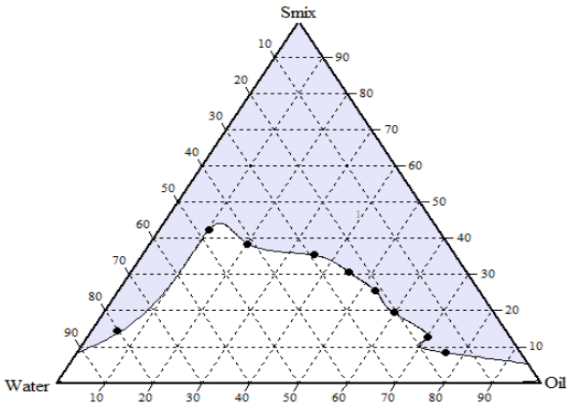


Table 8: Composition of Castor oil, Labrasol, Transcutol P and water at Km=3

Smix: Oil	Composition expressed as % W/W		
	Smix	Oil	Water
1:9	8.54	77.25	14.21
2:8	15.75	72.51	11.74
3:7	21.73	52.41	25.86
4:6	26.35	43.54	30.11
5:5	30.42	35.58	34
6:4	35.41	25.68	38.91
7:3	27.81	15.42	56.77
8:2	22.35	12.85	64.8
9:1	14.15	4.56	81.29

Figure 07: Pseudo ternary phase diagram of Castor oil, Labrasol, Transcutol P and water at Km=3

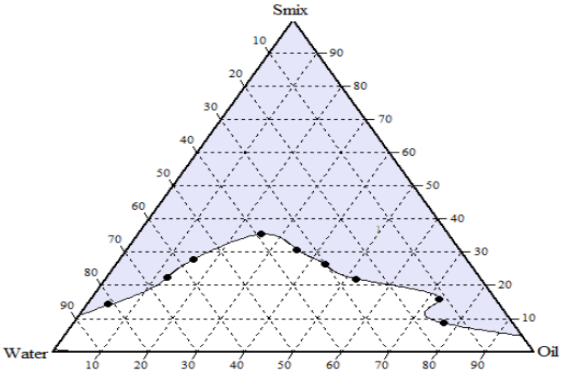


Table 9: Composition of Castor oil, Labrasol, Transcutol P and water at S/Coratio 1:1

Smix: Oil	Composition expressed as % W/W		
	Smix	Oil	Water
1:9	5.84	78.51	15.65
2:8	12.59	70.81	16.6
3:7	19.47	55.31	25.22
4:6	24.58	46.84	28.58
5:5	28.35	38.42	33.23
6:4	32.54	28.65	38.81
7:3	25.54	18.54	55.92
8:2	20.45	15.36	64.19
9:1	13.45	6.32	80.23

Figure 08: Pseudo ternary phase diagram of Castor oil, Labrasol, Transcutol P and water at S/Co ratio 1:1

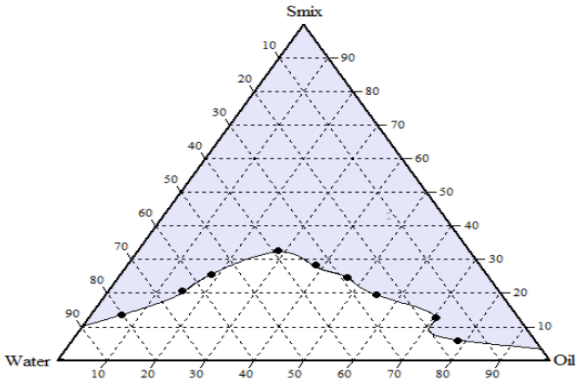
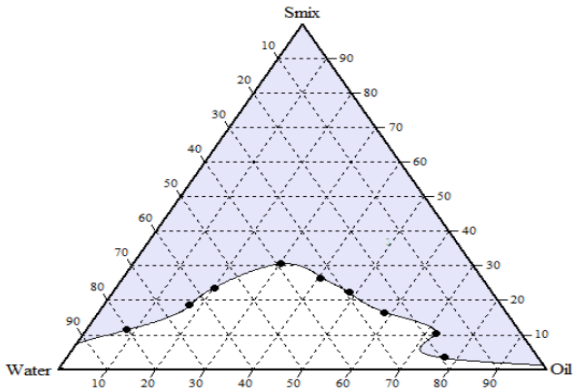


Table 10: Composition of Castor oil, Labrasol, Transcutol P and water at S/Co ratio 1:2

Smix: Oil	Composition expressed as % W/W		
	Smix	Oil	Water
1:9	3.57	77.38	19.05
2:8	10.22	72.36	17.42
3:7	16.35	58.69	24.96
4:6	22.15	48.65	29.2
5:5	26.38	40.59	33.03
6:4	30.54	30.39	39.07
7:3	23.51	20.36	56.13
8:2	18.54	17.58	63.88
9:1	11.45	8.35	80.2

Figure 09: Pseudo ternary phase diagram of Castor oil, Labrasol, Transcutol P and water at S/Co ratio 1:2



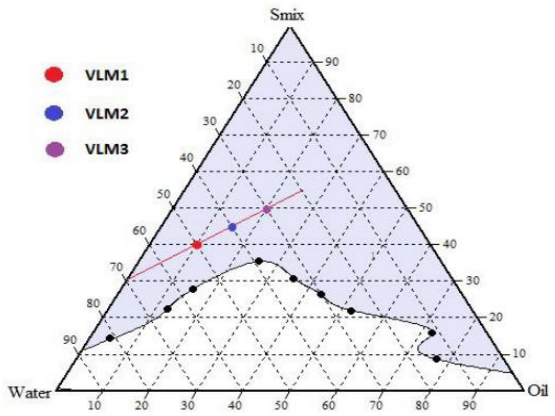
Formulation of Liquid SMEDDS of VPH

Same criteria were used here to select pseudo ternary phase diagram as that of for TEL for the preparation of liquid SMEDDS of VPH. Pseudo ternary phase diagram at Km value 3 was selected for preparation of liquid SMEDDS. The three formulations were selected from phase diagram at Km value 3, named as VLM1, VLM2, and VLM3 as shown in Figure 3.26. Quantitative unit compositions of selected formulation of SMEDDS are presented in Table 3.24 with the composition selected from phase

diagram, micro emulsion was prepared by titration with distilled water to characterize in liquid state.

Figure 10: Composition of Liquid SMEDDS of VPH

Formulation	% Composition (w/w)					
	VPH (mg/10g)	Castor oil	Labrasol	Transcutol P	Smix	Water
VLM1	120	10	30	10	40	50
VLM2	120	15	33.75	11.25	45	40
VLM3	120	20	37.5	12.5	50	30



Evaluation of Liquid SMEDDS

Thermodynamic stability studies

Robustness to dilution

From results of robustness of dilution study, it was observed that there was no any sign of phase separation or drug precipitation.

Table 12: Thermodynamic stability studies, robust to dilution and dispersibility tests

Formulation	Observations based on the thermodynamic stability studies, robust to dilution and dispersibility tests					Inference
	H/C	Cent.	Friz. Thaw	Robust	Disperse.	
VLM1	✓	✓	✓	✓	Grade B	Passes
VLM2	✓	✓	✓	✓	Grade A	Passes
VLM3	✓	✓	✓	✓	Grade A	Passes

H/C: Heating cooling cycle, Cent.: Centrifugation, Friz. Thaw: Freeze thaw cycle, Robust.: Robustness to dilution Disperse.: Dispersibility test

Transmittance, globule size, PDI, zeta potential and viscosity

Results of % Transmittance, globule size, PDI, zeta potential and viscosity are summarized in Table 14. % Transmittance of all formulations of liquid SMEDDS of TEL and VPH was found in between 90.7 ±0.67 to 97.36±0.28. This indicates that prepared liquid SMEDDS are clear and no turbid

Assessment of Efficiency of self-emulsification

From the results of assessment of efficiency of self-emulsification study, it was found that, formulation VLM2 and VLM3 rapidly formed micro emulsion within 1 min which was clear and slightly bluish in appearance as per grade A and VLM1 rapidly formed, slightly less clear emulsion which had a bluish white appearance as per grade B. From results it was found that all formulations of liquid SMEDDS of VPH passed preliminary thermodynamic stability studies, robustness to dilution test and assessment of efficiency of self-emulsification test.

Table 13: Results of % transmittance, globule size, PDI, zeta potential and viscosity

Formulation	% Transmittance*	Viscosity* (cP)
VLM1	97.36±0.28	20.47±0.24
VLM2	93.47±0.48	8.31±0.51
VLM3	90.14±0.68	15.28±0.12

Discussion:-

VPH SMEDDS were successfully synthesised, characterised, and optimised in this study. In contrast to commercial formulations, VPH SMEDDS, which contains components of Castor oil (oil phase), Labrasol (surfactant), and Transcutol P (co-surfactant), showed faster and more drug dissolution. Given that SMEDDS

was available in concentrate form, its stability may have increased. The potential ability of medium chain triglycerides to pre-dissolve drugs before they are introduced into the body and the production of microemulsions with particles smaller than 100 nm both contributed to an increase in drug dissolution by increasing surface area.

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