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3.1 Review of work done on microemulsion and self-microemulsifying drug delivery system

3.1.1 Review of work done on Oral microemulsion

Solanki SS et al. (2012) enhanced the dissolution rate and bioavailability of Ampelopsin, one of the most common flavonoids by developing microemulsion. Capmul MCM-based ME formulation with Cremophor EL as surfactant and Transcutol as cosurfactant was developed for oral delivery of ampelopsin. The optimised microemulsion formulation containing ampelopsin, Capmul MCM (5.5%), Cremophor EL (25%), Transcutol P (8.5%), and distilled water showed higher in vitro drug release, as compared to plain drug suspension and the suspension of commercially available tablet. These results demonstrate the potential use of ME for improving the bioavailability of poor water soluble compounds, such as ampelopsin[1].

Gundogdu E et al. (2012) formulated imatinib (IM) loaded to oral water-in-oil (w/o) microemulsions as an alternative formulation for cancer therapy and evaluated the cytotoxic effect of microemulsions Caco-2 and MCF-7. Moreover, permeability studies were also performed with Caco-2 cells. According to cytotoxicity studies, all formulations did not exert a cytotoxic effect on Caco-2 cells. The permeability studies of IM across Caco-2 cells showed that permeability value from apical to basolateral was higher than permeability value of other formulations. In conclusion, the microemulsion formulations as a drug carrier, especially M3IM formulation, may be used as an effective alternative breast cancer therapy for oral delivery of IM[2].

Du H et al. (2012) reform the dosage forms of andrographolide to improve its aqueous solubility and oral bioavailability. An formulation of O/W microemulsion consisting of an oil phase of isopropyl myristate, a surfactant phase of Tween 80, a co-surfactant of alcohol, and water was found to be ideal, with mean droplet size of 15.9 nm, a high capacity of solubilisation for andrographolide. Such an andrographolide-loaded microemulsion was stable by monitoring the time, temperature and gravity-dependent change, and had a much better anti-inflammatory effect and a higher biological availability than andrographolide tablets[3].
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Park JH et al. (2011) investigated the effects of silymarin, on oral bioavailability of paclitaxel in rats, and to compare pharmacokinetic parameters of paclitaxel between a commercial formulation of paclitaxel and a paclitaxel microemulsion. Oral bioavailability of paclitaxel in a Taxol® formulation was enhanced in the combination with silymarin. In particular, the mean maximum plasma concentration and the mean area under the plasma concentration-time curve of paclitaxel in the formulation were significantly increased 3-fold and 5-fold compared with control, respectively, following oral co-administration with 10mg/kg of silymarin (p<0.01). When the paclitaxel microemulsion was co-administered with silymarin orally, it caused a maximum increase in the absolute bioavailability of paclitaxel [4].

Thakkar H et al. (2011) developed microemulsion and Self-Microemulsifying Drug Delivery System (SMEDDS) formulations of Raloxifene. The results indicated that high drug loading, optimum size and desired zeta potential and transparency could be achieved with both SMEDDS and microemulsion. The in vitro intestinal permeability results showed that the permeation of the drug from the microemulsion and SMEDDs was significantly higher than that obtained from the drug dispersion and marketed formulation[5].

Nagariya K et al. (2010) prepared oral microemulsion of Isotretinoin for improvement of bioavailability. A captex-355-based microemulsion formulation with cremophor EL as surfactant and ethanol as co-surfactant was developed for oral delivery of isotretinoin. The in vitro diffusion study revealed an increase of bioavailability (38.56 times) after in vitro drug diffusion analysis of the microemulsion formulation as compared with the commercially available soft gelatin capsules[6, 7]

Patel V et al. (2010) developed microemulsion for solubility enhancement of Clopidogrel. Solubility of Clopidogrel was successfully enhanced by 80.66 times, via capmul microemulsion, compared with distilled water[8].

Mandal S et al. (2010) formulated Carbamazepine mucoadhesive microemulsion. Carbamazepine microemulsion (CME) was prepared using labrafil M 1944 CS as oil, accenon CC as surfactant and transcutol P as co-surfactant by water titration method.
Mucoadhesive microemulsion containing Carbamazepine (CMME) was prepared using carbopol 934. Results from 8 hrs *ex-vivo* release study revealed that CME and CMME showed 29% and 17.6% higher drug release than that of plain drug solution of Carbamazepine (PDSC)\[^9\].

**Piao HM et al. (2010)** developed a microemulsion of Fexofenadine for intranasal delivery. Nasal absorption of Fexofenadine from these microemulsions was found to be fairly rapid. T\(_{\text{max}}\) was observed within 5 min after intranasal administration at 1.0 mg/kg dose, and the absolute bioavailability (0–4 h) was about 68% compared to the intravenous administration in rats\[^10\].

**Chaudhari SP et al. (2010)** formulated and evaluated thermoreversible mucoadhesive microemulsion based in-situ gel (TMMIG) of an anti-osteoporotic agent, Raloxifene (RLX). On the basis of results obtained TMMIG lead to increased in bioavailability of RLX when tested in suitable in vivo model\[^11\].

**Yin YM et al (2009)** prepared a microemulsion system of docetaxel and evaluated for its solubilization capacity and oral bioavailability improvement. Based on a solubility study and pseudo ternary phase diagrams, microemulsions of about 30 nm in mean diameter were formulated with improved solubilization capacity towards the hydrophobic drug, docetaxel. Both the ultrafiltration and dialysis studies revealed that the release of 80% of docetaxel from the microemulsions within 12 h in vitro. Compared to the commercial product Taxotere, the apical to basolateral transport of docetaxel across the Caco-2 cell monolayer from the Microemulsion formulation was significantly improved. Moreover, the oral bioavailability of the M-3 formulation in rats (34.42%) rose dramatically compared to that of the orally administered Taxotere (6.63%)\[^12\].

**Mandal S et al. (2009)** prepared microemulsion of Saquinavir for oral bioavailability enhancement. *In vivo* oral absorption of Saquinavir from the microemulsion containing labrafac CM10 (4.0%), tween 80 (36.0%), polyethylene glycol 400 (9.0%) and distilled water (51%) was investigated in rats. The *in vitro* intraduodenal diffusion and *in vivo* study revealed an increase of bioavailability (10.68 times) after oral administration of the microemulsion formulation as compared with the commercially available tablets\[^13\].
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Nornoo AO et al. (2009) developed cremophor-free oral microemulsions of paclitaxel (PAC) to enhance its permeability and oral absorption. Oral microemulsions of PAC were developed that increased both the permeability and AUC of PAC as compared to Control[14].

Karamustafa et al. (2008) prepared oral microemulsion formulation for Alendronate. The release of Alendronate from the microemulsion formulation was examined by dialysis method and found to be 97.2% at the end of 7 h. None of the parameters except refractive index changed significantly during the determined periods. This study succeeded in preparing a stable microemulsion formulation of Alendronate[15].

Date A et al. (2008) has investigated and evaluated the potential of the microemulsions to improve the parenteral delivery of propofol. The propofol microemulsions were evaluated for globule size, Physical and chemical stability, osmolarity, in vitro hemolytic, pain caused by injection using rat paw-lick test and in vivo anesthetic activity. The microemulsions exhibited globule size less than 25 nm and demonstrated good physical and chemical stability. Rat paw-lick test indicated that propofol microemulsions were significantly less painful as compared to the marketed propofol formulation[16].

Kantarci G et al. (2007) prepared and compared different W/O microemulsions containing Diclofenac sodium. The in vitro release rate of diclofenac sodium (DS) from microemulsion (M) vehicles containing soybean oil, nonionic surfactants (Brij 58 and Span 80), and different alcohols (ethanol [E], isopropyl alcohol [I], and propanol [P]) as co-surfactant. According to the release rate of DS, M prepared with P showed the significantly highest flux value (0.059±0.018 mg/cm2/h) among all formulations (P< 0.05). A skin irritation study was performed with microemulsions on human volunteers, and no visible reaction was observed with any of the formulations. In conclusion, M prepared with P may be a more appropriate formulation than the other 2 formulations studied as drug carrier for topical application[17].

Ghosh PK et al. (2006) developed microemulsion system of Acyclovir for improvement of oral bioavailability. A labrafac-based microemulsion formulation with labrasol as surfactant and plurol oleique as co-surfactant was developed for oral delivery of
3. Literature Review

Acyclovir. 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. 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\textsuperscript{[18]}.

Zhang Q et al. (2004) developed Nimodipine-loaded microemulsion for intranasal delivery. The optimal microemulsion formulation consisted of 8% labrafil M 1944CS, 30% cremophor RH 40/ethanol (3:1) and water, with a maximum solubility of NM up to 6.4 mg/ml, droplet size of 30.3 ± 5.3 nm, and no ciliotoxicity. After a single intranasal administration of this preparation at a dose of 2 mg/kg, the plasma concentration peaked at 1 h and the absolute bioavailability was about 32%. The uptake of NM in the olfactory bulb from the nasal route was three folds, compared with intravenous (i.v.) injection. The ratios of AUC in brain tissues and cerebrospinal fluid to that in plasma obtained after nasal administration were significantly higher than those after i.v. administration\textsuperscript{[19]}.

Kang BK et al. (2004) prepared SMEDDS for oral bioavailability enhancement of a poorly water soluble drug, Simvastatin. The release rate of Simvastatin from SMEDDS was significantly higher than the conventional tablet. Bioavailability was 1.5-fold higher compared to that of the conventional tablet\textsuperscript{[20]}.

Gao ZG et al. (1998) investigated microemulsion system for oral delivery of Cyclosporin A with improvement of solubility and bioavailability. Microemulsions with varying weight ratios of surfactant to co-surfactant were prepared using captex 355 as an oil, cremophor EL as a surfactant, transcutol as a co-surfactant and saline. The solubility of Cyclosporin A in microemulsion systems reached the maximum with 2:1 mixture of cremophor EL and transcutol. The maximal blood concentration (Cmax) of Cyclosporin A and the area under the drug concentration-time curve (AUC) after oral administration of this Cyclosporin A loaded microemulsion was 3.5 and 3.3 fold increased compared with
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Sandimmun. The absolute bioavailability of Cyclosporin A loaded in this microemulsion system was increased about 3.3 and 1.25 fold compared with Sandimmun and Sandimmun Neoral. The enhanced bioavailability of Cyclosporin A loaded in this microemulsion system might be due to the reduced droplet size of microemulsion systems\(^\text{[21]}\).

Table 3.1: Bioavailability enhancement of some drugs using microemulsion / SMEDDS technique\(^{[22]}\)

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Drug</th>
<th>Category</th>
<th>System</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Paclitaxel</td>
<td>Anticancer</td>
<td>Microemulsion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SMEDDS</td>
</tr>
<tr>
<td>2</td>
<td>Fenofibrate</td>
<td>Antihyperlipidemic</td>
<td>SMEDDS</td>
</tr>
<tr>
<td>3</td>
<td>Cholesterol ester transfer protein inhibitor</td>
<td></td>
<td>SMEDDS</td>
</tr>
<tr>
<td>4</td>
<td>Atorvastatin, Fluvastatin</td>
<td></td>
<td>SMEDDS</td>
</tr>
<tr>
<td>5</td>
<td>Rapamycin</td>
<td>Immunosuppressive</td>
<td>SMEDDS</td>
</tr>
<tr>
<td>6</td>
<td>Cyclosporine</td>
<td></td>
<td>SMEDDS</td>
</tr>
<tr>
<td>7</td>
<td>Nifedipine</td>
<td>Antihypertensive</td>
<td>Microemulsion</td>
</tr>
<tr>
<td>8</td>
<td>Indomethacin</td>
<td>Analgesic</td>
<td>SMEDDS</td>
</tr>
<tr>
<td>9</td>
<td>Ibuprofen</td>
<td></td>
<td>SMEDDS</td>
</tr>
<tr>
<td>10</td>
<td>Tipranavir</td>
<td>Anti HIV</td>
<td>Microemulsion</td>
</tr>
<tr>
<td>11</td>
<td>Progesterone, testosterone</td>
<td>Hormones</td>
<td>SMEDDS</td>
</tr>
<tr>
<td>12</td>
<td>Vit A, D, E, K</td>
<td>Nutrition supplement</td>
<td>Microemulsion</td>
</tr>
<tr>
<td>13</td>
<td>Acyclovir</td>
<td>Antiviral</td>
<td>Microemulsion</td>
</tr>
<tr>
<td>14</td>
<td>Melatonin</td>
<td>Immunomodulator</td>
<td>Microemulsion</td>
</tr>
</tbody>
</table>
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3.1.2 Review of work done on Self Microemulsifying drug delivery systems

Mezghrani O et al. (2011) designed an optimized self micro-emulsifying drug delivery system (SMEDDS) to enhance the bioavailability of the poor water soluble drug, astilbin. Pseudoternary phase diagrams were used to select the components and their ranges by evaluating the micro-emulsification area. In vitro drug release profile study was performed using the reverse dialysis method where 95% of the drug was released after 4 h. The developed astilbin SMEDDS was subjected to bioavailability studies in beagle dogs by LC-MS and showed a significant enhancement of bioavailability, indicating the possibility of using SMEDDS as possible drug carrier for astilbin.[23]

Cui J et al. (2009) prepared a self-microemulsifying drug delivery system to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened via solubility studies of curcumin and compatibility tests. The optimal formulation of SMEDDS was comprised of 57.5% surfactant, 30.0% cosurfactant and 12.5% oil (ethyl oleate). The solubility of curcumin (21 mg/g) significantly increased in SMEDDS. The average particle size of SMEDDS-containing curcumin was about 21 nm when diluted in water. No significant variations in particle size and curcumin content in SMEDDS were observed over a period of 3 months at 4 degrees C. The results of oral absorption experiment in mice showed that SMEDDS could significantly increase the oral absorption of curcumin compared with its suspension.[24]

Lee et al. (2009) Daewoong pharmaceuticals CO., Ltd. disclosed in WO Patent WO/2009/022 the SMEDDS composition containing coenzyme Q 10 and method for preparing the same. They claimed improvement in solubility and bioavailability using polyglucerine fatty acid ester as surfactants and polyethylene-sorbitan fatty acid ester as cosurfactant.[25]

Ofokansi KC et al. (2009) used Peanut oil and Tween 80 blends devoid of any cosurfactant and employed in the formulation of different batches of liquid SMEDDS and their suitability as vehicles for the delivery of a typical lipophilic drug griseofulvin was investigated. The release profile of griseofulvin from the optimized SMEDDS was
evaluated in citrate/phosphate buffer solutions of pH 2.0, pH 6.5, and pH 7.4. The release of griseofulvin from the SMEDDDS into aqueous media of pH 6.5 and pH 7.4 showed enhanced and controlled dissolution of the drug from the formulation. Incorporation of griseofulvin into this proposed formulation is suggested as a strategy to overcome the irregular dissolution and absorption behaviors often associated with conventional griseofulvin tablets\textsuperscript{(26)}.

**Mandawgadea SD et al. (2008)** has investigated SMEDDS of β-Artemether (BAM) using a novel, indigenous natural lipophile (N-LCT) as an oily phase. SMEDDS based on N-LCT and commercially available modified oil (capryol90) was formulated. Comparative \textit{in vivo} anti-malarial performance of the developed SMEDDS was evaluated against the (Larither) in Swiss male mice infected with lethal ANKA strain of Plasmodium berghei. Both the BAM–SMEDDS showed excellent self-microemulsification efficiency and released >98\% of the drug in just 15 min whereas Larither showed only 46\% drug release at the end of 1h. The anti-malarial studies revealed that BAM–SMEDDS resulted in significant improvement in the anti-malarial activity (P <0.05) as compared to that of (Larither) and BAM solubilized in the oily phases and surfactant\textsuperscript{(27)}.

**Zang Yao et al. (2008)** has prepared nobiletin SMEDDS and investigate its intestinal transport behavior using the single-pass intestinal perfusion (SPIP) method in rat. SPIP was performed in each isolated region of the small intestine over three concentrations of nobiletin and the effective permeability coefficients in rats were calculated. The intestinal permeability of nobiletin in SMEDDS, sub-microemulsions and micelles was compared. The \textit{Peff} in jejunum at 15 µg/ml was significantly higher than that at 60 µg/mL (p< 0.01). The estimated human absorption of nobiletin for the SMEDDS dilutions was higher than that for sub-microemulsions (p<0.01) and similar to that of the micelles (p>0.05)\textsuperscript{(28)}.

**Zhang P et al. (2008)** developed SMEDDS of ordonin to enhance its oral bioavailability. The influence of the oil, surfactant and co-surfactant types on the drug solubility and their ratios on forming efficient and stable SMEDDS were investigated in detail. The SMEDDS were characterized by morphological observation, droplet size and zeta-
potential determination, cloud point measurement and in vitro release study. In vitro release test showed a complete release of Oridonin from SMEDDS in an approximately 12h. The absorption of Oridonin from SMEDDS showed a 2.2-fold increase in relative bioavailability compared with that of the suspension\textsuperscript{[29]}.

**Patel AR et al. (2007)** formulated a SMEDDS of Fenofibrate and evaluated *in-vitro* and *in-vivo* potential. SMEDDS formulations were tested for microemulsifying properties, and the resultant microemulsions were evaluated for clarity, precipitation, and particle size distribution. The optimized SMEDDS formulation showed complete release in 15 minutes as compared with the plain drug, which showed a limited dissolution rate. The SMEDDS formulation significantly reduced serum lipid levels in phases I and II of the triton test, as compared with plain Fenofibrate\textsuperscript{[30]}.

**Liu L et al. (2007)** formulated SMEDDS in order to enhance the solubility, release rate, and oral absorption of the poorly soluble drug, Silymarine. *In vitro* release was investigated using a bulk-equilibrium reverse dialysis bag method. Differences in the release medium significantly influenced the drug release from SMEDDS and the release profiles of Silymarine from SMEDDS was higher than that for commercial capsules, and significantly higher than that for commercial tablets. The optimal formulation of SMEDDS is an alternative oral dosage form for improving the oral absorption of Silymarine\textsuperscript{[31]}.

**Lanlan Wei et al. (2005)** developed a new self-emulsifying drug delivery system and SMEDDS of carvedilol to increase the solubility, dissolution rate, and ultimately, oral bioavailability. The in vitro dissolution rate of carvedilol from SEDDS and SMEDDS was more than two-fold faster compared with that from tablets. The developed SEDDS formulations significantly improved the oral bioavailability of carvedilol significantly, and the relative oral bioavailability of SEDDS compared with commercially available tablets was 413\%\textsuperscript{[32]}.

**Lin J (2005)** in US20060275358 demonstrated increase in solubility and dissolution of poorly soluble active compounds like co-enzyme Q10 by SMEDDS comprising a
combination of a pair of hydrophilic and lipophilic surfactant. The formulations exhibited excellent storage stability\textsuperscript{[33]}

**Peracchia M et al. (2005)** in EP1498143 prepared Self microemulsifying formulation for oral administration of taxoids using cremophor EL as surfactant, and at least one oil and co-surfactant\textsuperscript{[34]}

**Benameur et al.(2004)** in US20036652865 have found that the incorporation of an active agent, particularly statins, into a self-microemulsifying system made it possible to reduce the first intestinal passage effect, and thus improve the systemic bioavailability of the active molecule\textsuperscript{[35]}

**Ghosal SK et al. (2004)** developed SMEDDS to improve the solubility and bioavailability and to get faster onset of action of celecoxib. Composition of SMEDDS was optimized using simplex lattice mixture design. Dissolution efficiency, t85%, absorbance of diluted SMEDDS formulation and solubility of celecoxib in diluted formulation were chosen as response variables. The SMEDDS formulation optimized via mixture design consisted of 49.5% PEG-8 caprylic/capric glycerides, 40.5% mixture of Tween20 and Propylene glycol monocaprylic ester (3:1) and 10% celecoxib, which showed significantly higher rate and extent of absorption than conventional capsule. The relative bioavailability of the SMEDDS formulation to the conventional capsule was 132\%\textsuperscript{[36]}

**Kanga BK et al. (2004)** prepared SMEDDS for oral bioavailability enhancement of a poorly water soluble drug, Simvastatin. The release rate of Simvastatin from SMEDDS was significantly higher than the conventional tablet. Bioavailability was 1.5-fold higher compared to that of the conventional tablet\textsuperscript{[20]}

**Kocheriakota C et al. (2004)** prepared a novel capsule SMEDDS formulations of etoposide for oral use (US 0220866). Self microemulsifying pharmaceutical compositions comprising Etoposide that are encapsulated comprising a a solvent; a co-solvent and an emulsifying base\textsuperscript{[37]}
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Annette M et al. (2003) has formulated SMEDDS to improve the lymphatic transport and the portal absorption of a poorly water-soluble drug, halofantrine. Two different structured triglycerides were incorporated in SMEDDS; (MLM) and (LML). A previously optimized SMEDDS formulation for halofantrine, comprising of triglyceride, Cremophor EL, Maisine 35-1 and ethanol was selected for bioavailability assessment. The extent of lymphatic transport via the thoracic duct was 17.9% of the dose for the animals dosed with the MLM SMEDDS and 27.4% for LML. The data indicate that the structure of the lipid can affect the relative contribution of the two absorption pathways. The MLM formulation produced a total bioavailability of 74.9%, which is higher than that of total absorption previously observed after post-prandial administration[^38].

Farah et al. (2000) in US Patent 6054136 provided a SMEDDS capable of forming a microemulsion in situ with the physiological fluid of the stomach and intestine for the enhancement of drug bioavailability[^39].

Crison et al (1999) in US5993858 taught a self-microemulsifying formulation for increasing the bioavailability of a drug which included oil/lipid material, a surfactant, and a hydrophilic co-surfactant. HLB of hydrophilic co-surfactant was greater than 8. The self-microemulsifying formulation could also include the addition of an aqueous solvent such as triacetin. They had found that a more hydrophilic co-surfactant not only increased the dissolution of poorly water-soluble drugs but, that it also increased their in vivo bioavailability[^40].
3. Literature Review

3.1.2.1 Review of work done on Solid Self Microemulsifying Drug Delivery System

Hu X et al. (2012) prepared self-microemulsifying pellets to enhance the dissolution and oral absorption of water insoluble drug sirolimus. The selected liquid SMEDDS formulations were prepared into pellets by extrusion-spheronization method and the optimal formulation of 1mg SMEDDS pellets capsule was finally determinated by the feasibility of the preparing process and redispersibility. The optimal SMEDDS pellets showed a significant quicker redispersion rate than the dissolution rate of commercial SRL tablets Rapamune in water. The droplet size and polydispersity index of the reconstituted microemulsion was almost unchanged after solidification, and pellet size and friability were all qualified. DSC, XRPD, and IR analysis confirmed that there was no crystalline sirolimus in the pellets. Pharmacokinetic study in beagle dogs showed the greater oral relative bioavailability of SMEDDS pellets to the commercial tablets\[41\].

Milovic M et al. (2012) investigated solid SMEDDS (S-SMEDDS), as potential delivery system for poorly water soluble drug carbamazepine. SMEDDS was formulated using the surfactant polyoxyethylene 20 sorbitan monooleate [Polysorbate 80] (S), the cosurfactant Cremophor RH40] (C) and the oil caprylic/capric triglycerides [Mygliol 812] (O). Four different adsorbents with high specific surface area were used: Neusilin UFL2, Neusilin FL2 (magnesium aluminometasilicate), Sylysia 320 and Sylysia 350 (porous silica). It was found that CBZ has great influence on rheological behaviour of investigated system upon water dilution. For SSMEDDS with different magnesium aluminometasilicate adsorbents, release rate of CBZ decreased with increasing specific surface area due to entrapment of liquid SMEDDS inside the pores and its gradual exposure to dissolution medium. With porous silica adsorbents no difference in release rate was found in comparison to physical mixtures. In physical mixtures at 12.5% (w/w) CBZ content, presence of amorphous CBZ led to high dissolution rate\[42\].

Oh DH et al. (2011) compared the effects of hydrophilic and hydrophobic solid carrier on the formation of solid SMEDDS. Two solid SMEDDS formulations were prepared by spray-drying the solutions containing liquid SMEDDS and solid carriers. Colloidal silica
and dextran were used as a hydrophobic and a hydrophilic carrier, respectively. The liquid SMEDDS, composed of Labrafil M 1944 CS/Labrasol/Transcutol HP with 2% w/v flurbiprofen, gave a z-average diameter of about 100 nm. Colloidal silica produced an excellent conventional solid SMEDDS in which the liquid SMEDDS was absorbed onto its surfaces. It gave a microemulsion droplet size similar to that of the liquid SMEDDS (about 100 nm) which was smaller than the other solid SMEDDS formulation. In the solid SMEDDS prepared with dextran, liquid SMEDDS was not absorbed onto the surfaces of carrier but formed a kind of nano-sized microcapsule with carrier. However, the drug was in an amorphous state in two solid SMEDDS formulations. Similarly, they greatly improved the dissolution rate and oral bioavailability of flurbiprofen in rats. They showed that except appearance, hydrophilic carrier (dextran) and hydrophobic carrier (colloidal silica) hardly affected the formation of solid SMEDDS such as crystalline properties, dissolution and oral bioavailability[43].

Kim DW et al. (2011) developed a novel flurbiprofen-loaded S-SMEDDS with improved oral bioavailability using gelatin as a solid carrier, the solid SMEDDS formulation was prepared by spray-drying the solutions containing liquid SMEDDS and gelatin. The liquid SMEDDS, composed of Labrafil M 1944 CS/Labrasol/Transcutol HP (12.5/80/7.5%) with 2% w/v flurbiprofen, gave a z-average diameter of about 100 nm. The flurbiprofen-loaded solid SMEDDS formulation gave a larger emulsion droplet size compared to liquid SMEDDS. It greatly improved the oral bioavailability of flurbiprofen in rats[44].

Huan D et al. (2011) studied the influences of silica on the absorption of S-SMEDDS. An in vitro lipolysis model was used to evaluate the influence of silica on self-microemulsifying drug delivery system digestion from intestinal tract. S-SMEDDS containing silica were prepared by extrusion/spheronization. The results showed that lipolysis rate and drug concentration in aqueous phase after intestinal lipolysis both increased by adding silica, which was benefit to drug absorption. And silica was not benefit to absorption for slowing drug release. Consistently, there was no significant influence of silica on intestinal absorption[45].
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**Ito Y et al. (2010)** formulated Oral gentamicin (GM) SMEDDS with PEG-8 caprylic/capric glycerides (Labrasol), and the mixture was solidified with several kinds of adsorbents. The used adsorbents were microporous calcium silicate (Florite RE), magnesium aluminometa silicate (Neusilin US2), and silicon dioxide (Sylysia 320). The in vivo rat absorption study showed that Florite RE 10 mg preparation had the highest $C_{(\text{max})}$ and AUC. These results suggested that an adsorbent system is useful as an oral solid delivery system of poorly absorbable drugs such as GM$^{[46]}$.

**Legen I et al. (2008)** in EP1961412 prepared free flowing and compressible powder comprising an admixture of drug containing SMEDDS and solid particle adsorbents$^{[47]}$. 
3.2 Review of work done on drugs used in the study

3.2.1 Felodipine

Bazzo GC et al. (2012) incorporated Felodipine into microparticles prepared with Eudragit E and it blended with poly(3-hydroxybutyrate) (PHB) using the emulsion-solvent evaporation technique, with the aim of improving the dissolution rate of the drug. The formulation prepared with Eudragit E showed irregular and fragmented microparticles, with a loading efficiency (LE) of 82.6%. When the microparticles were prepared with a blend of Eudragit E and PHB, they had a spherical form with a LE of 103.9%. X-ray diffraction and differential thermal analysis indicated a reduction in the crystallinity of felodipine after its incorporation into the microparticles, which caused a significant increase in the felodipine dissolution rate\[48\].

Basalious EB et al. (2011) applied quality by design (QbD) for pharmaceutical development of felodipine solid mixture (FSM) containing hydrophilic carriers and/or polymeric surfactants, for easier development of controlled-release tablets of felodipine. Not only did the ternary mixture of Pluronic, HPMC with Inutec SP1 enhance the dissolution rate and inhibit crystallization of felodipine, but also they aided Carbopol 974 in controlling felodipine release from the tablet matrix. It could be concluded that a promising once-daily CR tablets of felodipine was successfully designed using QbD approach\[49\].

Karavas E et al. (2011) prepared solid dispersion systems of felodipine with polyvinyl pyrrolidone (PVP) in order to enhance solid state stability and release kinetics. The dispersion of FEL was found to be in nano-scale particle sizes and dependent on the FEL/PVP ratio. The above dispersion shown a significant effect on the dissolution enhancement and the release kinetics of FEL, as it causes the pattern to change from linear to logarithmic. An impressive optimization of the dissolution profile is observed corresponding to a rapid release of FEL in the system containing 10% w/w of FEL, releasing 100% in approximately 20 min\[50\].
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**Alonzo DE et al. (2011)** prepared amorphous solid dispersions of Felodipine for bioavailability enhancement. The purpose of this research was twofold. First, the degree of supersaturation generated upon dissolution as a function of drug-polymer composition was investigated. Second, an investigation was conducted to correlate physical behavior upon dissolution with polymer loading. Hydroxypropylmethylcellulose (HPMC) and polyvinylpyrrollidone (PVP) were used to form the dispersions. The supersaturation generated upon dissolution may enhance the bioavailability of the drug.

**Sahu et al. (2011)** developed and evaluated mucoadhesive nasal gel of Felodipine. The aim of the present study was to prepare mucoadhesive nasal gels containing Felodipine from mucoadhesive substance isolated from fruits of *Dillenia indica* L to enhance absorption of the drug. The gels prepared from fruits of *Dillenia indica* L exhibited favourable mucoadhesive properties that caused them to adhere to the nasal mucosa for a long time and hence enhance the absorption of drugs administered intranasally.[51]

**Kulkarni et al. (2010)** formulated fast dispersible tablets of Felodipine by using super disintegrant croscarmellose sodium and solid dispersion with polyvinyl alcohol (PVA) as a carrier. Tablets prepared by solid dispersion having drug to carrier ratio of 1:4 (A3) yielded the best drug release in terms of dissolution rate. The formulation did not show any change in disintegration time, wetting time and drug content after stability period.[52]

**Patil PR et al. (2009)** developed a extended release Felodipine self-nanoemulsifying system (SNES) in which miglycol 840 as a oil, cremophore EL as surfactant and capmul MCM as a co-surfactant were used for nanoemulsion. The SNES showed good emulsification, median droplet size of 421 nm, and rapid FLD release (>90% release in 15 min). Gelling was induced in the SNES by addition of aerosil 200 (A 200). The hydrophobic gelucire 43/01 (GEL) coat to extend the release of FLD and caprol PGE-860 (CAP) was added to this coat as a release enhancer. 89.7% of the drug content were found to be released within 20 h in the in-vitro study.[53]

**Aboul-Einien et al. (2009)** formulated and evaluated of Felodipine in softgels with a solubilized core. In this study, softgels with a solubilized-drug core were used to improve the solubility and consequently the bioavailability of felodipine. Dissolution tests (under
3. Literature Review

sink or non-sink conditions) revealed a correlation between the composition of the softgel core fill liquid and drug dissolution parameters. The incorporation of water in the fill formula as well as the use of ingredients with low hygroscopicity was found to be essential to minimize water migration to the fill liquid during storage. In vivo studies showed rapid and enhanced absorption of Felodipine from solubilized core softgels compared with control drug powder filled in hard gelatin capsules. The total amount of drug absorbed over a 24-h period was markedly enhanced (1.6-fold) for softgels compared with control capsules\textsuperscript{[54]}.

Narkhede et al. (2007) investigated the effect of the presence of the water soluble polymers viz HPMC, PVP and PEG 6000 on aqueous solubility and complexation abilities of Felodipine with or without presence of β-cyclodextrin and HP βCD by phase solubility studies. All the polymers under study showed synergistic effect on Felodipine cyclodextrin solubilization by increasing complexation efficiency. The highest solubility improvement up to 81.8% was obtained for βCD ternary system when 0.25% w/v of PVP was used\textsuperscript{[55]}.

Karavas E et al. (2006) investigated Solid dispersion systems for the dissolution enhancement of Felodipine by polyvinylpyrrolidone (PVP). The intensity of interactions promoted the dissolution enhancement. Investigation of the solubility and the particle size distribution of felodipine in the binary system appeared to have similar behaviour indicating that the interactions affect the release profile through these two factors. The hydrophilicity of PVP does not significantly affect this enhancement as the contact angle was found to be linear to PVP concentration. Microscopic observation of the dissolution behaviour showed that felodipine remains in fine dispersion in aqueous solution, verifying the release mechanism\textsuperscript{[56]}.
3.2.2 Valsartan

Yan YD et al (2012) developed a novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes, various valsartan-loaded solid dispersions were prepared with water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS). The drug-loaded solid dispersion improved the drug solubility by about 43-fold. It gave a higher AUC, C(max) and shorter T(max) compared to valsartan powder and the commercial product. The solid dispersion improved the bioavailability of the drug in rats by about 2.2 and 1.7-fold in comparison with valsartan powder and the commercial product, respectively [57].

Cao QR et al (2012) formulated novel mucoadhesive pellets containing valsartan with enhanced oral bioavailability. The coated pellets displayed distinct mucoadhesive property in vitro and delayed gastrointestinal transit in vivo. Furthermore, the coated pellets exhibit significantly higher AUC (0-12h) and C(max), as compared to the core pellets and drug suspension. It was concluded that the mucoadhesive pellets could render poorly water soluble drugs like valsartan with a rapid drug release, delayed GI transit and enhanced oral bioavailability [58].

Ibrahim HK et al. (2011) improved the pH-independent solubility and dissolution characteristics of valsartan via the preparation of solid dispersions (SD) with poloxamer 407. The improved dissolution of valsartan via SD formulation appeared to be well correlated with the enhanced oral exposure of valsartan in rats. SDs increased C(max) and AUC(0-24) of valsartan by 2-7 folds in rats, implying that SDs should be effective to improve the bioavailability of valsartan [59].

Sung J et al (2011) developed a novel valsartan-loaded solid dispersion with enhanced bioavailability and no crystalline changes; various valsartan-loaded solid dispersions were prepared with water, hydroxypropyl methylcellulose (HPMC) and sodium lauryl sulphate (SLS). The bioavailability of the solid dispersions in rats was evaluated compared to valsartan powder and a commercial product.
(Diovan). The drug-loaded solid dispersion composed of improved the drug solubility by about 43-fold. It gave a higher AUC, \( C_{\text{max}} \) and shorter \( T_{\text{max}} \) compared to valsartan powder and the commercial product. The solid dispersion improved the bioavailability of the drug in rats by about 2.2 and 1.7-fold in comparison with valsartan powder and the commercial product, respectively\(^{57}\).

**Chowdary H et al. (2011)** prepared solid inclusion complexes of valsartan-\( \beta \)CD with and without Poloxamer 407 by kneading method as per \( 2^2 \)-factorial design and were evaluated for dissolution rate and efficiency. Poloxamer 407 alone gave higher enhancement in the dissolution rate of Valsartan (1.96 fold) than \( \beta \)CD alone and combination of \( \beta \)CD and Poloxamer 407. Drug- \( \beta \)CD- Poloxamer 407 inclusion complexes and their tablets also gave markedly enhanced dissolution rate when compared to those formulated employing \( \beta \)CD alone. As such Poloxamer 407 alone and in combination with \( \beta \)CD is recommended to enhance the dissolution rate of valsartan tablets\(^{60}\).

**Darira P et al. (2011)** prepared solid dispersion of a poorly soluble drug valsartan by using Soluplus as carrier material to enhance the solubility as well as dissolution rate. Five different formulations were prepared using hot melt extrusion technique in different ratios i.e., 1:1, 1:3, 1:5, 1:7, and 1:9. All the formulations showed a marked increase in the solubility behavior and improved drug release when tested for their In vitro studies. Formulation containing drug: polymer of 1:9 showed the best release with a cumulative release of 100%. Hence, it was concluded that soluplus as a carrier can be very well utilized to improve the solubility of poorly soluble drugs\(^{61}\).

**Mahapatra A et al. (2011)** have prepared solid dispersions (SDs) and physical mixtures of valsartan in \( \beta \)-cycloDEXtrin, HP \( \beta \)-CD, and polyvinyl pyrolidone (PVP K-30) to increase its solubility characteristics. The phase solubility behavior of valsartan in various concentrations of \( \beta \)-CD, HP \( \beta \)-CD, and PVP K-30 (0.25-1.0% w/v) in distilled water was obtained at 37 ± 2 °C. The dissolution of valsartan is increased with increasing amounts of the hydrophilic carriers. Compared with \( \beta \)-CD, HP \( \beta \)-CD showed better enhancement of dissolution rate; compared with HP \( \beta \)-CD, PVP K-30 showed better
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solubility and dissolution enhancement \cite{62}.

Youn SY et al. (2011) did the recrystallization of valsartan by ASES (Aerosol Solvent Extraction System), a supercritical micronization process, using compressed CO\textsubscript{2} to improve the bioavailability of valsartan through preparation of micro sized particles without excessive agglomeration. Fine valsartan particles from an ethyl acetate (EA) solution were precipitated using compressed CO\textsubscript{2} as an antisolvent at low temperature. The EA was considered a proper organic solvent to prevent agglomeration of the prepared valsartan associating to the solubility parameters of the solvents. Processed valsartan with compressed CO\textsubscript{2} at a low temperature improved its dissolution rate due to the small size of the particles attributing to low level of particle agglomeration \cite{63}.

Parmar B et.al. (2011) developed solid lipid nanoparticles of valsartan for improvement of bioavailability with poloxamer 188 by solvent evaporation technique. The nanoparticles were characterized by DSC, XRD and TEM analysis. The optimized formulation was found to have particle size 142.5nm, zeta potential of -14.3 mV and 84% drug entrapment. The optimized formulation showed better in-vitro and ex-vivo release profile than valsartan suspension. The Solid lipid nanoparticles of valsartan shown promise to improve bioavailability \cite{64}.

Sharma A et al., (2010) investigated the influence of Poloxamer 188 to increase the solubility and dissolution rate of Valsartan for enhancement of oral bioavailability. In this investigation solid dispersions with Poloxamer 188 were prepared by melting method and evaluated for physicochemical parameters and dissolution and reported that the solubility of drug increased with increasing polymer concentration. The dissolution rate was substantially improved for Valsartan from its solid dispersion compared with pure drug and physical mixtures \cite{65}.

Kshirsagar S et al. (2010) formulated solid dispersion of Valsartan using HPMC E5 LV as water soluble carrier. But film formation took place during solid dispersion formulation and was creating difficulty in releasing the drug from formulation; and those solid dispersions, were not free flowing. Thus such preparations are not useful
from the formulation development point of view. So to improve the flow properties, some inert materials were tried like microcrystalline cellulose (MCC) and Lactose and the incorporation of inert carriers improved the flow property of solid dispersion \[66\].

**Dixit AR et al. (2010)** prepared SMEDDS of valsartan with captex and tween 80. Diffusion of valsartan SMEDDS showed maximum drug release when compared to pure drug solution and marketed formulation. The area under curve and time showed significant improvement as the values obtained were 607 ng h/mL and 1 h for SMEDDS in comparison to 445.36 and 1.36 h for market formulation suggesting significant increase \((p < 0.01)\) in oral bioavailability of valsartan SMEDDS\[67]\.

**Kumar KV et al. (2009)** made another attempt to improve the solubility and dissolution rate of a poorly soluble drug, Valsartan by solid dispersion method using skimmed milk powder (SMP) as carrier. SMP is hydrophilic compound which combines with parent drug and change their physical properties. This hydrophilicity of carrier molecule markedly improved solubility of valsartan\[68]\.

**Agnivesh R et al. (2009)** prepared dispersion granules using a hot melt granulation technique which involved preparation of a homogenous dispersion of valsartan in gelucire-50/13 melt, followed by its adsorption on to the surface of aeroperl-300pharma, an inert adsorbent. DSC and XRD data indicated the retention of amorphous form of valsartan. The in-vitro dissolution rate of these tablets was significantly better in comparison with marketed formulation. In conclusion the statistical model enabled us to understand the effects of formulation variables on the dispersion granules of Valsartan\[69]\.

**Kumar KV et al. (2009)** prepared solid dispersion method using skimmed milk powder as carrier. Four different formulations were prepared with varying drug: carrier ratios viz.1:1, 1:3, 1:5 and 1:9 and the corresponding physical mixtures were also prepared. All the formulations showed marked improvement in the solubility behavior and improved drug release. Formulation containing drug: polymer ratio of 1:9 showed the best release with a cumulative release of 81.60% as compared to 34.91 % for the pure
drug. The interaction studies showed no interaction between the drug and the carrier. It was concluded that skimmed milk powder as a carrier can be very well utilized to improve the solubility of poorly soluble drugs [68].

**Cifter U et al. (2008)** in WO 9524901 A1 directed to the use valsartan for the treatment of diabetic nephropathy. WO 9749394 A2, discloses compressed solid oral dosage forms, e.g., by compaction of valsartan optionally combined with HCTZ. In patent no having WO 0038676 A1, it has been found surprisingly that it is possible to improve the bioavailability characteristics of known solid formulation of valsartan by increasing the proportion of microcrystalline cellulose [70]

**Cappello B et al. (2006)** developed co-formulation of drug with cyclodextrins (CD). Hydroxypropyl-b-cyclodextrin (HP-b-CD) was used due to its higher solubility to improve the solubility in water and dissolution of Valsartan. This work also reveals the potential of HP-b-CD from the stability point of view, since the inclusion complex VAL/HP-b-CD exhibits a greater thermal stability than the neat drug [71]

**Vrbinc M et al. (2005)** tried to overcome the problem of poor dissolution of valsartan by formulation of tablet containing valsartan particles having size ($D_{50}$) 150 µm or below [72].
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3.3 Review of work done on excipients used in the study

3.3.1 Capmul MCM

Solanki SS et al. (2012), enhanced the dissolution rate and bioavailability of Ampelopsin, one of the most common flavonoids by developing microemulsion. Capmul MCM-based ME formulation with Cremophor EL as surfactant and Transcutol as cosurfactant was developed for oral delivery of ampelopsin. The optimised microemulsion formulation containing ampelopsin, Capmul MCM (5.5%), Cremophor EL (25%), Transcutol P (8.5%), and distilled water showed higher in vitro drug release, as compared to plain drug suspension and the suspension of commercially available tablet. These results demonstrate the potential use of ME for improving the bioavailability of poor water soluble compounds, such as ampelopsin\cite{1}.

Bajaj A et al. (2012) developed self-nanoemulsifying drug delivery to the solubility, permeability and oral bioavailability of cefpodoxime proxetil, ß-lactam antibiotic. It is BCS Class IV drug having solubility 400 µg/ml. Various surfactant and co-surfactants such as tween 80, tocopheryl polyethylene glycol succinate (TPGS), propylene glycol and Capmul MCM as oil phase were used and ternary phase diagrams were constructed to identify stable microemulsion region. Capmul MCM as oil phase were found to produce stable nanoemulsions\cite{73}.

Cho HJ et al. (2012) achieved rapid onset of action and improved bioavailability of udenafil, by microemulsion system for its intranasal delivery. A single isotropic region was found in pseudo-ternary phase diagrams developed at various ratios with Capmul MCM as an oil, Labrasol as a surfactant, and Transcutol or its mixture with ethanol (1:0.25, v/v) as a co-surfactant. Optimized microemulsion formulations with a mean diameter of 120-154 nm achieved enhanced solubility of udenafil (>10mg/ml) compared with its aqueous solubility (0.02 mg/ml)\cite{74}.

Prajapati HN et al. (2012) compared physiochemical properties of mono-, di- and triglycerides of medium chain fatty acids for development of oral pharmaceutical dosage
forms of poorly water-soluble drugs using phase diagrams, drug solubility, and drug dispersion experiments. The monoglyceride gave microemulsion (clear or translucent liquid) and emulsion phases, whereas di- and triglycerides exhibited an additional gel phase. Among individual mono-, di- and triglycerides, the oil-in-water microemulsion region was the largest for the diglyceride. Dispersion of drug in aqueous media from mixtures of mono- and diglyceride or mono- and triglyceride was superior to individual lipids\[^{75}\].

**Du H et al. (2012)** reform the dosage forms of andrographolide to improve its aqueous solubility and oral bioavailability. The formulation, characterisation, stability, anti-inflammatory effect, pharmacokinetics and oral toxicity of andrographolide-loaded microemulsion, were studied. An formulation of O/W microemulsion consisting of an oil phase of capmul, a surfactant phase of Tween 80, a co-surfactant of alcohol, and water was found to be ideal, with mean droplet size of 15.9 nm, a high capacity of solubilisation for andrographolide\[^{3}\].

**Kadu PJ et al. (2011)** formulated a self-emulsifying drug delivery system of atorvastatin calcium. The solubility of atorvastatin calcium was determined in various vehicles such as Captex 355, Captex 355 EP/NF, Ethyl oleate, Capmul MCM, Capmul PG-8, Gelucire 44/14, Tween 80, Tween 20, and PEG 400. Pseudoternary phase diagrams were plotted on the basis of solubility data of drug in various components to evaluate the microemulsification region. In vivo performance of the optimized formulation was evaluated using a Triton-induced hypercholesterolemia model in male Albino Wistar rats. The formulation significantly reduced serum lipid levels as compared with atorvastatin calcium\[^{76}\].

**Nornoo AO et al. (2009)** developed cremophor-free oral microemulsions of paclitaxel (PAC) to enhance its permeability and oral absorption. The microemulsion region on the phase diagrams utilizing surfactant-mycacet oil combinations was in decreasing order: lecithin: butanol: myvacet oil (LBM, 48.5%)>centromix CPS: 1-butanol: myvacet oil (CPS, 45.15%)>capmul MCM: polysorbate 80: myvacet oil (CPM, 27.6%)>capryol 90: polysorbate 80: myvacet oil (CP-P80, 23.9%)>capmul: myvacet oil (CM, 20%). The area-under-the-curve of PAC in CM was significantly larger than LBM, CPM and CE.
Oral microemulsions of PAC were developed that increased both the permeability and AUC of PAC as compared to CE\textsuperscript{[14]}.

**Kale AA et al (2008)** developed lorazepam (LZM) microemulsions as an alternative to the conventional cosolvent based formulation. Solubility of LZM in various oils and Tween 80 was determined. Capmul MCM demonstrated highest solubilizing potential for LZM and was used as an oily phase. LZM microemulsions were compatible with parenteral dilution fluids and exhibited mean globule size less than 200 nm. The LZM microemulsions containing amino acids exhibited good physical and chemical stability when subjected to refrigeration for 6 months\textsuperscript{[77]}.

**Fricker et al. (1999)** used a microemulsion preconcentrate carrier medium for their effective oral delivery. A lipophilic component selected from the group consisting of fatty acid triglycerides (Miglyol, Captex, Capmul, etc.), mixed mono-, di-, and tri-glycerides and transesterified ethoxylated vegetable oils (e.g. Maisine), and a surfactant which was selected from the group consisting of polyethylene glycol, natural or hydrogenated castor oils (Cremophor EL\textsuperscript{®}, Cremophor RH40\textsuperscript{®}), polyethylene-sorbitan fatty acid esters (Tweens), polyoxyethylene fatty acid esters (Myrj), polyoxyethylene-polyoxypropylene co-polymers, and block co-polymers (Pluronic, Polaxamers). The composition on dilution with water gave a microemulsion having an average particle size of <150 nm\textsuperscript{[78]}.

**Constantiides PP et al. (1994)** developed self-emulsifying water-in-oil (w/o) microemulsions incorporating medium-chain glycerides and measured their conductance, viscosity, refractive index and particle size. Formulation of Calcein (a water-soluble marker molecule, MW = 623), or SK&F 106760 (a water-soluble RGD peptide, MW = 634) in a w/o microemulsion having a composition of Captex 355/Capmul MCM/Tween 80/Aqueous (65/22/10/3, % w/w), resulted in significant bioavailability enhancement in rats relative to their aqueous formulations. \textsuperscript{[79]}.
3.3.2 Polysorbate 20 and Polysorbate 80

Mahdi Es et al. (2012) studied the effect of Nonionic surfactant blends of Tween and Tween/Span series based on their solubilization capacity with water for palm kernel oil esters. Tween 80 and five blends of Tween 80/Span 80 and Tween 80/Span 85 in the hydrophilic-lipophilic balance (HLB) value range of 10.7-14.0 were selected to study the phase diagram behavior of palm kernel oil esters using the water titration method at room temperature. High solubilization capacity was obtained by Tween 80 compared with other surfactants of Tween series. High HLB blends of Tween 80/Span 85 and Tween 80/Span 80 at HLB 13.7 and 13.9, respectively, have better solubilization capacity compared with the lower HLB values of Tween 80/Span 80[^80].

Edris AE et al. (2012) investigated the solubilization behaviour of a number of essential oils (EOs) containing volatile phenolic constituents in five different micellar solutions. These oils include clove bud (Eugenia caryophyllata), thyme (Thymus serpyllum) and oregano (Thymus capitatus). Ternary and pseudo-ternary phase diagrams were constructed to assess the ability for microemulsion formation and dilutability of each system using non-ionic surfactants. Results showed that Tween 20 (T20) was more suitable to solubilize these oils compared with Tween 80 (T80)[^81].

Xu Sx et al. (2012) developed a food-grade water-dilutable microemulsion system with cassia oil as oil, ethanol as cosurfactant, Tween 20 as surfactant and water and its antifungal activity in vitro and in vivo against Geotrichum citri-aurantii was assessed. The phase diagram results confirmed the feasibility of forming a water-dilutable microemulsion based on cassia oil. One microemulsion formulation, cassia oil/ethanol/Tween 20 = 1:3:6 (w/w/w), was selected with the capability to undergo full dilution with water[^82].

Saha R et al. (2012) prepared an edible microemulsion (ME) composed of Tween 80/butyl lactate/isopropyl myristate (IPM)/water. Pseudoternary phase diagram of the system contains a large single isotropic region. The study finds strong correlation in the relaxation dynamics of water with the structure of host assembly and offers an edible ME
system which could act as a potential drug delivery system and nontoxic nanotemplate for other applications\textsuperscript{[83]}.

**Franzini CM et al (2012)** investigated anionic microemulsions containing soya phosphatidylcholine, Tween-20, sodium oleate as surfactant, and cholesterol as oil phase were investigated as drug carriers for amphotericin B. They suggested that for both amphotericin B-loaded and amphotericin B unloaded microemulsions, the increase in the O/S ratio led to the formation of ordered structures with lamellar arrangements\textsuperscript{[84]}.

**Panapisal V et al (2012)** studied the potential of several microemulsion formulations for dermal delivery of silymarin was evaluated. The pseudo-ternary phase diagrams were constructed for the various microemulsion formulations which were prepared using glycercyl monooleate, oleic acid, ethyl oleate, or isopropyl myristate as the oily phase; a mixture of Tween 20, Labrasol, or Span 20 with HCO-40 (1:1 ratio) as surfactants; and Transcutol as a cosurfactant. Oil-in-water microemulsions were selected to incorporate 2\% w/w silymarin. The silybin remainings depended on the type of surfactant and were sequenced in the order of: Labrasol > Tween 20 > Span 20. In vitro release studies showed prolonged release for microemulsions when compared to silymarin solution. Microemulsions containing Labrasol also were found to enhance silymarin solubility. Other drug delivery systems with occlusive effect could be further developed for dermal delivery of silymarin\textsuperscript{[85]}.

**Tian Q et al. (2012)** investigated the skin permeation microemulsion with high content of naproxen for transdermal delivery and its solubilization mechanism was studied. Naproxen micoremulsions composed of 4\% isopropyl myristate, 18\% Tween 80, 18\% ethanol and water were prepared and phase inversion temperature (PIT) method was used to increase drug content. The powerful permeation enhancing ability of microemulsion induced by the solubilization of PIT method makes it a promising vehicle for the transdermal delivery of naproxen\textsuperscript{[86]}.

**Ryu JK et al (2012)** prepared oral microemulsion to overcome problems associated with the poor solubility and low oral bioavailability of bicyclool and evaluated in vitro and in
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vivo. The optimized premicroemulsion concentrate consisted of transcutol, Tween 20, Cremophor RH 40, propylene glycol monocaprylate and bicyclol (ratio, 50:150:100:150:3)\textsuperscript{[87]}.\n
**Zheng G et al (2011)** investigated the solubilization of organochlorine pesticides (DDT or gamma-HCH) in oil-in-water (Winsor I) microemulsions (microE) composed of non-ionic surfactant (Tween 80 or Triton X-100), plant oil (linseed oil or soybean oil), and the cosurfactant (1-pentanol). Results show that the cosurfactant to surfactant ratio (C/S ratio, w/w) is the major factor influencing the microemulsion formation, and C/S ratios of 1:3 and 1:6 are superior to 1:1 for microemulsion formation. The solubilization of gamma-HCH also increased by 40.6-57.5% in microemulsion formed with Tween 80\textsuperscript{[88]}.

**Zeng Z. et al. (2010)** developed an elemene oil/water (o/w) microemulsion and evaluated its characteristics and oral relative bioavailability in rats. Elemene was used as the oil phase and drug, polysorbate 80 as a surfactant along with ethanol, propylene glycol, and glycerol as the cosurfactants. The study demonstrated the elemene microemulsion as a new formulation with ease of preparation, high entrapment efficiency, excellent clarity, good stability, and improved bioavailability\textsuperscript{[89]}.

**Mehta SK et al (2010)** studied the microemulsion composed of oleic acid, phosphate buffer, ethanol, and Tween (20, 40, 60, and 80) in the presence of antitubercular drugs of extremely different solubilities, viz. isoniazid (INH), pyrazinamide (PZA), and rifampicin (RIF). The phase behavior showing the realm of existence of microemulsion has been delineated at constant surfactant/co-surfactant ratio \((K_{(m)} = 0.55)\) with maximum isotropic region resulting in the case of Tween 80. To compare the release of RIF, PZA, and INH from Tween 80 formulation, the dissolution studies have been carried out. It shows that the release of drugs follow the order INH>PZA>RIF. The results have given a fair success to predict that the release of PZA and INH from Tween 80 microemulsion is non-Fickian, whereas RIF is found to follow a Fickian mechanism\textsuperscript{[90]}.

**Kale AA et al (2008)** developed lorazepam (LZM) microemulsions as an alternative to the conventional cosolvent based formulation. Solubility of LZM in various oils and
3. Literature Review

Tween 80 was determined. The ternary diagram was plotted to identify area of microemulsion existence and a suitable composition was identified to achieve desired LZM concentration. Capmul MCM demonstrated highest solubilizing potential for LZM and was used as an oily phase along with tween 80 as surfactant. LZM microemulsions were compatible with parenteral dilution fluids and exhibited mean globule size less than 200 nm. The LZM microemulsions containing amino acids exhibited good physical and chemical stability when subjected to refrigeration for 6 months\cite{77}.

Pather SI et al (2001) in US2008077823 showed enhancement in the solubility of pharmaceutical ingredients comprising a polyoxyethylene sorbitan fatty acid ester emulsifier, a fatty acid ester co-emulsifier and an oil\cite{91}.

3.3.3 Polyethylene Glycol 400

Dora CL et al (2012) developed oil-in-water nanosized emulsions by the hot solvent diffusion method, using castor oil as oily phase and poly(ethylene glycol) (400)-12-hydroxystearate (PEG 660-stearate) and lecithin as surfactants. The effect of the PEG concentration on the droplet size of the nanosized emulsions and on the ability of these systems to load quercetin was investigated. They demonstrated that a critical concentration of PEG 400-stearate (2.5 wt%) was needed to obtain colloidal dispersions displaying microemulsion characteristics\cite{92}.

Senhao L et al. (2011) prepared microemulsion gel formulation by a self-microemulsifying system for transdermal topical delivery of ilomastat. Ilomastat microemulsion gel was prepared by drawing a ternary phase diagram with PEG 400 and Pluronic F127 was added as gel matrix for the formulation. The optimal formulations had wide microemulsion existent field and good self-microemulsifying efficiency. The droplet size was within 100 nm\cite{93}.

Li G et al (2012) developed an oil-free o/w microemulsion, composed of pluronic F68, propylene glycol 400 and saline, which solubilized poorly soluble anesthetic drug propofol for intravenous administration. The ternary diagram was constructed to identify the regions of microemulsions, and the optimal composition of microemulsion was
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determined by in vitro evaluation such as globule size upon dilution and rheology. The droplet size of the diluent emulsion corresponding to oil-in-water type ranged from 200 to 300nm in diameter. Stability analysis of the microemulsions indicated that they were stable upon storage for at least 6 months[94].

Ngawhirunpat T et al. (2011) prepared novel microemulsion for transdermal drug delivery of ketoprofen (KP). The microemulsion composed of ketoprofen as model drug, isopropyl myristate (IPM) as oil phase, surfactant mixture consisting of polyoxyl 40 hydrogenated castor oil (Cremophor RH40) as surfactant and polyethylene glycol 400 (PEG400) as co-surfactant at the ratio 1:1, and water were prepared. The viscosity, droplet size, pH, conductivity of microemulsions, and skin permeation of KP through shed snake skin were evaluated. The particle size, pH, viscosity and conductivity of microemulsions were in the range of 114-210 nm, 6.3-6.8, 124-799 cPs and 1-45 µS/cm, respectively. The ratio of IPM, and surfactant:PEG 400 mixture played the important role in the skin permeation of KP microemulsions.[95].

Cui J et al. (2009) prepared a new self-microemulsifying drug delivery system to improve the solubility and oral absorption of curcumin. Suitable compositions of SMEDDS formulation were screened via solubility studies of curcumin and compatibility tests. The optimal formulation of SMEDDS was comprised of 57.5% surfactant (emulsifier OP:Cremorphor EL = 1:1), 30.0% co-surfactant (PEG 400) and 12.5% oil (ethyl oleate). The solubility of curcumin (21 mg/g) significantly increased in SMEDDS. The average particle size of SMEDDS-containing curcumin was about 21 nm when diluted in water. No significant variations in particle size and curcumin content in SMEDDS were observed over a period of 3 months at 4 degrees C. The results of oral absorption experiment in mice showed that SMEDDS could significantly increase the oral absorption of curcumin compared with its suspension[24].

Following is a list of microemulsion based drug formulations available in market. But very few of them are available in India.
The exhaustive literature has revealed few important points which made us to understand and investigate our research work systematically. We have analyzed critically a segment of a published body of knowledge through summary, classification, and comparison of prior research studies, reviews of literature, and theoretical articles to solve the problems associated with poorly water soluble drugs through concept of microemulsion based drug delivery systems. It helped us to build a solid background for selection of drugs and excipients to be used for formulating microemulsion and SMEDDS systems. We came to know that there has been no study till reported for formulating Solid SMEDDS of Valsartan using adsorption on solid hydrophilic and hydrophobic carrier approach. Also no efforts were reported for stable Felodipine Microemulsion formulation. We could also not found any information about effect of dynamic surface tension on stability of microemulsion system.

### Table 3.2: Marketed Lipid- based and Surfactant-based Drug Formulation[^96]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Product</th>
<th>Components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amprenavir</td>
<td>Agenerase</td>
<td>TPGS, PEG 400, propylene glycol</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Norvir</td>
<td>Ethanol, oleic acid, cremphor EL, BHT</td>
</tr>
<tr>
<td>Ritonavir/lopinavir</td>
<td>Kaletra</td>
<td>Oleic acid, Cremophor EL, propylene glicol</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Fortovase</td>
<td>Medium chain mono-diglycerides, povidone, α-tocopherol</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Aptivus</td>
<td>Ethanol, polyoxyl 35 castor oil, propylene glycol, mono-diglycerides of caprylic/capric acids</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Neoral</td>
<td>Corn oil mono-di glycerides, cremophor RH40, ethanol, propylene glycol, α-tocopherol</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sandimmune</td>
<td>Corn oil, labrafil, ethanol, glycerol</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Gengraf</td>
<td>Ethanol, PEG, Cremophor EL, polysorbate 80, sorbitan monooleate</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Rapimmune</td>
<td>Phosal 50 PG, polysorbate 80</td>
</tr>
<tr>
<td>Doxecalciferol</td>
<td>Hectoral</td>
<td>Medium chain triglycerides, ethanol, BHA</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Prometrium</td>
<td>Peanut oil, glycerin, lecithin</td>
</tr>
</tbody>
</table>
3.4 References


3. Literature Review


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3. Literature Review


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3. Literature Review


