Novel Delivery Systems for the Treatment of Vitiligo

Chapter 2

Literature Review
The literature related to novel delivery systems for the treatment of vitiligo have been extensively reviewed and compiled as follows.

2.1. Patents on Treatments of Vitiligo:

WO/2005/011676 made a composition that can be used as cosmetic medicine and which is useful for the treatment of lesions caused by vitiligo. The inventive composition contains L-proline amino acid as active ingredient, which can stimulate the synthesis of melanic pigment of the skin as well as the reproduction of melanocytes and has no severe side effects as shown in the toxicological and clinical tests (Miyares et al., 2004). The technical aim of the invention was to provide a synthetic product which is useful for the treatment of vitiligo, has no toxic effects and shows the absence of relapse of the disease.

WO/2001/062205 invented a method of treating vitiligo by using an excimer laser which emits light in the UVB range and also disclosed a method of increasing exposure of affected areas to restore pigmentation. This approach was attempted to overcome the drawbacks of topical preparations, topical PUVA treatment, oral PUVA treatment and UVB phototherapy. Topical preparations tend to rub-off and have limited value in areas such as the lower neck, wrists and hands. Moreover they do not attempt to treat vitiligo, but simply mask the affected areas with the surrounding skin (Freedberg et al., 1999). Another treatment for vitiligo attempts to increase the effect of UVA light is PUVA in which the patient applies psoralen topically to the affected areas, and then stands inside the phototherapy unit for exposure to the UVA light emitted by conventional tube-style bulbs to gain the combined actions of psoralen and UVA (Spencer et al., 2001). Major drawbacks of PUVA treatment is that the exposure of whole body rather than vitiligo areas which may lead to the risk of skin cancers, erythema, blistering and hyperpigmentation of the surrounding unaffected areas also. Regimenation is seen in only about half of treated patients (Westernof et al., 1997). The present invention, however, treats only those skin areas afflicted with vitiligo and thus minimizes the risk of skin cancers and other side effects. It is less time consuming, and has higher success rate. Phototherapy with UV-A radiation and oral psoralens is another known treatment. UV-A irradiation occurs at intervals of two to three times weekly and is generally maintained for months to greater than a year (Elliott et al., 1959, Farah et al., 1969 and Ortonne.,
1989). Moreover, side effects of this type of PUVA include burning, nausea, erythema, lentigenes, pruritus, and cataracts. UVB phototherapy is much more effective at stimulating melanocytes than PUVA. However, regular UVB light cannot penetrate the skin deeper than the epidermis, and hence is completely ineffective in stimulating the deep melanocytes underneath patches of vitiligo. The present invention overcomes this problem in the prior art through the use of an excimer laser which emits laser light in the ultraviolet range and provides higher energy thereby decreasing the treatment time (Yu et al., 1999). This method of treating vitiligo is confined to segmental-type vitiligo, which is vitiligo caused by dysfunction of nerves. Lasers have also been used to treat vitiligo to aid in skin grafting.

DE 102006042529A1 had studied about the UV irradiator, which has a miniaturized lamp with electrodes serves simultaneously as reflector, operating electronics for operating the lamp, and an adapter that was arranged in front of a radiation outlet window, where the irradiator is so handy that the irradiator is suitable as tool holder for manual application to the patient (Ernesti Karsten., 2008). The electronics is integrated into the tool holder, where the waveguide was adapted as an easily replaceable adapter to the radiation outlet window for the treatment of vitiligo.

US 20070278880A1 explained about the synergistic effects of basic fibroblast growth factor for the treatment of vitiligo. A hypothesis, postulated that deficiency of mitogen like basic fibroblast growth factor (bFGF) in the skin could result in the loss of melanocytes (melanin producing cells) which leads to vitiligo. Basic fibroblast growth factor (bFGF) or FGF2 is a potent mitogen for variety of cell types including melanocytes and also contains large number of basic amino acid residues (Lysine, Arginine and Histidine). It was found in a wide variety of tissue types including placenta, keratinocytes and fibroblasts. The bFGF or its agonist peptides were tested on human volunteers in the various phases of clinical trials in India and found to be successful in repigmenting about 80% of volunteers with stable generalised vitiligo and segmental vitiligo. The major therapies for the treatment of vitiligo are Psoralen plus UV-A which is effective in about 50% of cases, steroids has certain effects in the case of fast spreading vitiligo and often
reoccurs on stoppage of treatment. Surgical treatment is the last resort for vitiligo, when all other option fails. Basic fibroblast growth factor peptide(s) lotion was developed as a new mode of therapy for the treatment of vitiligo (US 2007027080A1). The combinatorial treatment of vitiligo by local application of bFGF peptide(s) lotions in association with psoralen and UV-A, or steroids or surgical procedures produce synergistic response and that the rate of repigmentation increases synergistically and more effective results are obtained than with any of them alone.

WO/2006/088310 explained an invention related to a pharmaceutical composition for the prevention and treatment of vitiligo comprising retinoid as an effective ingredient. Retinoic acid has been used as an anti-acne drug. In addition, retinoic acid works well in lightening of pigment by reducing adhesion of melanocytes, inhibits proliferation of melanocytes (Fligiel et al., 1992) and reduces dendrites of melanocytes, so that it is also used for the treatment of melasma (Ortonne, 1992). Retinoic acid can reduce skin atrophy caused by corticosteroid, it is expected for retinoic acid to inhibit side effects carried by corticosteroid. Therefore, a pharmaceutical composition containing retinoid as an active ingredient was prepared. The preparation not only prevents skin atrophy by corticosteroid but also proliferates human keratinocytes and inhibits apoptosis to upregulate SCF and other melanocyte growth factors, so that it is effectively used for the treatment of vitiligo by increasing melanocytes with restoring pigment. It can also induce melanocytes proliferation and increase coloring effect of the cells (Chey et al., 2006). It was claimed that pharmaceutical composition of this invention containing retinoid as an effective ingredient not only prevents skin atrophy caused by corticosteroid, a conventional treatment agent of vitiligo, but also inhibits apoptosis of melanocytes and thus improving pigmentation, so that it can be effectively used for the prevention and treatment of vitiligo.

Young et al in WO/2005/067405 described an invention related to methods and kits for screening responsiveness to drugs effective in treatment or prevention of vitiligo. It was claimed that methods and kits for screening active ingredients effective in treatment or prevention of vitiligo, and methods and kits for prognosis of vitiligo using eukaryotic
translation initiation factor 4A1 (eIF4A1) gene, ribosomal protein L13 (L13) gene and mediator of RNA polymerase to transcription (MRT) gene (Lee et al., 2005). The responsiveness to drugs used for treatment or prevention of skin diseases which requires the administration of corticosteroids was investigated. Preferably, drugs are selected from the group consisting of all- trans-retinoic acid (ATRA), vitamin C, trichloroacetic acid, and calcipotriol. Most preferably, the drug is ATRA.

US 5690966 claimed a process for the preparation of an extract from human placenta containing glycosphingolipids and endothelin-like peptides useful for the treatment of vitiligo which comprises extracting the whole triturated human placenta by heating in a phased manner, first at about 40-50°C for about 20-40 minutes and then at about 60-70°C for about 5-15 minutes, avoiding the application of direct heat (Bhadra et al., 1997).

US 6451358 invented a compositions and methods for the treatment of vitiligo. The composition consists of one or more herbal ingredients like *Eclipta prostrata* L., *Angelica dahurica* (Fish. ex. Hoffm), *Polygonum multiforum* Thumb, *Astragalus complanatus*, *Tribulus terrestris* L., *Lithospermum erythrorhizon* sieb et zucc, *Paris petiolata* (Bak. ex Forb), *Salvia multiiorrhiiza* Bge, *Sophora flavescens* Ait, *Atractylodes lancea* (Thumb) Do, or their mixtures. The method comprises treating the vitiligo by giving this composition to the patient through oral route (Huiping Zhao., 2002). The treatment may be further improved by applying topically to the affected areas, any one of the following preparations such as, sulfur and kerosene, *Nevillum oporum solund* and alcohol, a preparation of *Cinnamomum cassia* presl, *Psoralea corylifalia* L., alcohol and water and a preparation of *Portulaca oleracea* L., brown sugar, and vinegar.

EP 1747786A2 proved the effect of natural ingredients with anti-vitiligo properties by applying it in white patches of depigmentation present in the skin. There are evidences states about the pathogenic association between vitiligo and the increase in epidermal oxidative stress, mechanism underlying the functional alterations in the melanocytes and vitiligo development (Paleo and Rojas., 2007). This treatment does not allow any synthetic drugs to be incorporated in the formulation other than natural products with
anti-vitiligo properties. It contains the water extract of *Pimienta racemosa* as active ingredients, this inhibits neutrophil chemotaxis and superoxide anion production and acts as antioxidant on the skin with vitiligo, promoting the restoration of the affected area. Moreover, it contains watery extract of melon, which supplies antioxidant enzymes like catalase and superoxide dismutase, these antioxidant enzymes are free radicals scavengers present in melanocytes. Coenzyme Q-10 is other active ingredient, which helps these enzymes to develop their function besides having antioxidant properties, and plays an important role in the production of cell energy, and therefore it is an important mitochondrial and immunological stimulator. It also contains pyridoxine, which is necessary for the metabolism of amino acids like tyrosine and phenylalanine which participate in melanin production and the lemon terpene which contains ascorbic acid which also acts as an antioxidant inhibiting free radicals. Its formula is given by 1:1 of watery extract of *Pimienta racemosa; 1:2 of watery extract of Cucumis melo, 100 ml of extract of Citrus aurantifolia, 100 mg Coenzyme Q-10 and 100 mg Pyridoxine Chlorhydrate and also contains 100 g of excipients which contains unibase cream, eucalyptus essential oil, propyleneglycol, glycerine, cetylic alcohol, nipagin and nipazol.

WO/2008/098325 described the use of one or many parts of plants or extracts of plants or pure isolated compounds of plants from the species of *Stachytarpheta cayensensis*, *S. jamaicensis* and *S. eliottis* (Verbenaceae family) in different ratios incorporated together in the form of tablets and capsules for oral route or in the form of emulsions, creams, gels, liposomes, microcapsules, nanoparticles, aerosols, ointments and slow release implants for topical application which can be used for the treatment of vitiligo (Queiroz Ferreira., 2008). Through pre-clinical and clinical tests, it has been proven that the identified compounds are used as part of formulae to treat vitiligo, used by oral route when in tablets or capsules, and by topical route as dyes, creams, gels, aerosols or similar others used as adjuvant. This invention also extends to the pharmaceutical compositions containing, besides the referred extracts, fractions or components of those extracts (natural or synthetic), used to formulate medications applied on the treatment or prophylaxis of vitiligo.
Table 2.1: Summary of Patents:

<table>
<thead>
<tr>
<th>Patents</th>
<th>Actives</th>
<th>Benefits</th>
<th>Draw backs</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO/2005/011676</td>
<td>L-proline amino acid</td>
<td>No toxic effects, absence of relapse of vitiligo</td>
<td>Rub off, tedious to apply in areas like eye lid.</td>
</tr>
<tr>
<td>WO/2001/062205</td>
<td>Psoralen and UVB</td>
<td>Exposed only to the affected skin</td>
<td>Risk of side effects</td>
</tr>
<tr>
<td>DE 102006042529A1</td>
<td>UV irradiator</td>
<td>Patient compliance</td>
<td>Risk of side effects</td>
</tr>
<tr>
<td>US 2007027080A1</td>
<td>Basic fibroblast growth factor</td>
<td>Synergistic effect</td>
<td>Rub off, tedious to apply in areas like eye lid.</td>
</tr>
<tr>
<td>US 6590966</td>
<td>Glycosphingolipids and endothelin-like peptides</td>
<td></td>
<td>Formulation stability</td>
</tr>
<tr>
<td>WO/2006/088310</td>
<td>Retinoid (retinoic acid)</td>
<td></td>
<td>Formulation stability</td>
</tr>
<tr>
<td>EP 1747786A2</td>
<td>Pimenta racemosa, watery extract of melon, Coenzyme Q-10, pyridoxine and lemon terpene</td>
<td></td>
<td>No risk of side effects</td>
</tr>
<tr>
<td>WO/2008/098325</td>
<td><em>Stachytarpheta cayensensis</em>, <em>S. jamaicensis</em> and <em>S. eliotis</em> (Verbenaceae family)</td>
<td></td>
<td>No risk of side effects</td>
</tr>
</tbody>
</table>

2.2. Recent Developments in Sustained Release Drug Delivery

Mohsen et al., (2012) formulated sustained release matrix tablets of aceclofenac with Eudragit® RSPO and Eudragit® RLPO were prepared using three techniques; direct compression, wet granulation and solid dispersion. The most optimum matrix formula was manipulated by addition of an immediate release layer for prompt release of the drug. All tablets were evaluated regarding their physical properties and in-vitro release.
over 24 hours. In-vitro release studies revealed that Eudragit RSPO retarded the release more than Eudragit RLPO and solid dispersion was the most suitable preparation technique. The double layer tablet was successful in prolonging drug release up to 24 hours. Pharmacokinetic studies in albino rabbits were conducted for the optimized formula (Registration No. PI-260). The results of pharmacokinetic studies showed that double layer tablet exhibited longer MRT when compared to the commercial brand of aceclofenac immediate release tablet (Bristaflam®), demonstrating the sustained release properties.

Nataraj et al., (2011) formulated a control release oral delivery system and investigated the influence of different diluents, Carbopoi 934P concentration and granulation technique in the release of poorly water-soluble drug (Ibuprofen) from Carbopoi 934P matrix tablets. Matrix tablets were prepared by direct compression, wet granulation and dry granulation method at different polymer concentration using lactose, dibasic calcium phosphate (DCP), microcrystalline cellulose (MCC) and starch as diluents. Dissolution studies were carried out in 900 ml phosphate buffer pH 7.4 using USP-apparatus I. At 5% Carbopoi 934P concentration, the $t_{50\%}$ was found in the rank order of tablets containing starch<MCC<DCP<lactose. Granulation technique had appreciable effect on drug release profile which was in the rank order of direct compression<dry granulation<wet granulation (alcohol)<wet granulation (water). There was a significant effect of granulation technique, polymer concentration in the drug (Ibuprofen) release rate from Carbopoi 934P matrix based tablets (ANOVA, $p<0.05$). Diluents have appreciable effect on drug release rate only at low polymer concentration.

Ahammad et al., (2011) described the effect of different percentages of a hydrophilic polymer and impact of granulation technique on the release profile of gliclazide from matrix system. In their study, matrix tablets of Gliclazide were prepared by both direct compression and wet granulation process using methocel K15M CR. Release kinetics of gliclazide matrix tablets were determined using USP paddle method at Phosphate buffer (pH 7.4). They found that, at lower concentration of polymer (15%) most of the formulation tends to Higuchi release kinetics and at higher concentration (30%), the
release fits well with Zero order kinetics. 30% of polymeric content in the matrix tablets decreased the rate of the drug due to increased tortuosity and decreased porosity. The effect of granulation process on drug release were also studied and they found that wet granulation extend the release more than that of the direct compression technique.

Zaid et al., (2011) compared the quality of Valzan R tablet (160 mg, valsartan immediate release test formulation) and its pharmacokinetic parameters with Diovan R tablet (160 mg, valsartan reference formulation). Valzan R tablets were prepared according to a dry granulation method (roll compaction). To assess the bioequivalence of Valzan R tablets a randomized, two-way, crossover, bioequivalence study was performed in 24 healthy male volunteers. The selected volunteers were divided into two groups of 12 subjects. One group was treated with the reference formulation (Diovan R) and the other one with the generic Valzan R, with a cross-over after the drug washout period of 14 days. Blood samples were collected at fixed time intervals and valsartan concentrations were determined by a validated HPLC assay method. The pharmacokinetic parameters AUC0.48, AUC0, Cmax, Tmax, Ke and T1/2 were determined for both the tablets and were compared statistically to evaluate the bioequivalence between the two brands of valsartan, using the statistical model recommended by the FDA. The analysis of variance (ANOVA) did not show any significant difference between the two formulations and 90% confidence intervals (CI) fell within the acceptable range for bioequivalence. Based on their statistical evaluation it was concluded that the test tablets (Valzan R) exhibits pharmacokinetic profile comparable to the reference brand Diovan.

Sunitha et al., (2011) investigated, hydroropic solution of sodium citrate (0.01M) as solubilizing agent to solubilize valsartan (poorly water soluble drug) fine powder and its tablet dosage form for spectrophotometric determination in UV region. Valsartan showed maximum absorbance at 250 nm and followed Beer's law in concentration range of 5-30 mcg/mL. Results of analysis were statistically validated for linearity, precision, LOD, and LOQ. The proposed method was new, simple, accurate, reliable, economic and can be employed in routine to analyze Valsartan tablets. Either hydroropic agent or commonly used tablet additives did not interfere in analysis.
Mahajan et al., (2011) developed antihypertensive sustained release matrix tablets of valsartan Angiotensin II receptor antagonist, using hydroxypropylmethylcellulose alone and in combination with ethyl cellulose as the matrix material in different proportion by wet granulation method. The granules showed satisfactory flow properties, compressibility and all the tablet formulations showed acceptable pharmacotechnical properties. In vitro dissolution studies indicate that EC significantly reduced the rate of drug release compared to HPMC. But no significant difference was observed in the release profile of matrix tablets made by higher percentage of EC. The result of dissolution study indicate that the formulation prepared by low viscosity grade HPMC showed maximum drug release up to 8 hrs and high viscosity grade HPMC and EC formulation showed up to 12 hrs. Mathematical treatment of the in vitro drug release data suggests that, optimized formulation fitted in to Korsmeyer and Peppas release kinetic shows R² value 0.9930. Drug release from the matrix occurred by combination of two mechanism, diffusion and erosion of tablet.

Raju et al., (2011) developed a rapid, precise, accurate, specific and sensitive reverse phase liquid chromatographic method for the estimation of valsartan in pure and tablet formulation. The chromatographic method was standardized using a Xterra C18 column (100x4.6 mm I.D., 5 µm particle size) with UV detection at 210 nm and flow rate of 1 ml/min. The mobile phase consisting of a mixture of phosphate buffer pH 3 and acetonitrile in the ratio of 50:50 v/v was selected. The proposed method was validated for its sensitivity, linearity, accuracy and precision. The retention time for valsartan was 4.450 min. The % recovery was within the range between 98.6 % and 101.2 %. The percentage RSD for precision and accuracy of the method was found to be less than 2 %. This method can be employed for routine quality control analysis of valsartan in tablet dosage forms.

Kumar et al., (2011) developed a simple method for the estimation of Valsartan in bulk and pharmaceutical dosage forms. Methanol was chosen as the solvent system. The λmax was found to be 249nm and all absorbance values were carried out at 249nm. The responses were linear in the range of 5-100µg/ml. The regression equation of the
calibration graph and correlation coefficient were found to be \( y = 0.028x - 0.001 \) and 0.999 respectively. The %RSD values for both intraday and interday precision were less than 1%. The recovery of the drug from the sample was ranged between 97.77% and 101.4%. The proposed method was validated for accuracy, precision, robustness, ruggedness, LOD and LOQ. Commercial tablets containing 40mg and 80mg of valsartan were analysed by the proposed method and the results were well within the claimed limits. Furthermore stability studies of valsartan were carried out under acidic, alkaline, hydrolytic, thermolytic, oxidation, photolytic and UV degradation conditions as per SIAM (Stability Indicating Assay Methods).

Raman et al., (2011) prepared nifedipine solid dispersions in cross carmellose sodium (CCS) and sodium starch glycholate (SSG) and were investigated with a view to design sustained release tablets. As nifedipine is practically insoluble in water and aqueous fluids, its solid dispersions in CCS and SSG has markedly enhanced the dissolution rate of nifedipine. Matrix tablets formulated employing nifedipine dispersion in CCS and SSG with gum olibanum alone and in combination with methocel KM. The matrix tablets followed first order kinetic and the release was diffusion controlled.

Afsar et al., (2011) developed once daily sustained release tablets of Aceclofenac by wet granulation using HPMC K-100. The tablets were subjected to physicochemical studies, in vitro drug release, kinetic studies and stability studies. FTIR studies shown there were no interaction between drug and polymers. The drug release from optimize formulation was extended for period of 24 hrs. The kinetic release follows zero order models. Stability studies for optimize formulation for one month at 45° C with RH 75 ± 5% and showed there was no significant change in drug content. Their study indicated the suitability of hydrophilic polymers in the preparation of matrix based sustained release formulation of Aceclofenac.

Gande et al., (2011) investigation efforts were made to improve the bioavailability of baclofen by increasing the residence time of the drug through sustained-release matrix
tablet formulation via gastroretentive mechanism. Tablets were prepared by wet granulation technique. The influence of gas generating and gel forming agents, amount of baclofen and total weight of tablet on physical properties, in vitro buoyancy, floating lag time, drug release, DSC, X-ray studies were investigated. The release mechanisms were explored and explained by applying zero order, first order, Higuchi and Korsmeyer equations. The selected formulations were subjected to stability study for the period of three months. For all formulations, kinetics of drug release from tablet followed Higuchi's square root of time kinetic treatment heralding diffusion as predominant mechanism of drug release: X-ray imaging in six healthy human volunteers revealed a mean gastric retention period of 5.50 ± 0.7 hrs for the selected formulation. Stable, sustained release effervescent floating matrix tablets of baclofen could be prepared by wet granulation technique.

Jothiswari et al., (2011) described a new, simple, accurate and sensitive UV-spectrophotometric absorption correction method has been developed for simultaneous determination of amlodipine besylate, valsartan and hydrochlorothiazide in bulk and in combined tablets dosage form. The stock solutions were prepared in methanol followed by the further required dilution with distilled water. The method was based upon direct estimation of amlodipine besylate at 365 nm, as at this wavelength hydrochlorothiazide and valsartan have zero order absorbance and show no interference. For estimation of hydrochlorothiazide, corrected absorbance was calculated at 315 nm due to the interference of amlodipine besylate and valsartan has zero absorbance at this wavelength. At 250 nm, these three drugs showed absorbance. To estimate the amount of valsartan, the absorbance of amlodipine besylate and hydrochlorothiazide were corrected for interference at 250 nm by using absorptive values. Beer's law obeyed the concentration range of 1 -32 mcg/ mL, 4 - 40 mcg / mL and 2 - 20 mcg / mL for amlodipine besylate, valsartan and hydrochlorothiazide, respectively. The developed method was validated according to ICH guidelines and it found to be accurate and precise. Thus the proposed method can be successfully applied for simultaneous determination of amlodipine besylate, valsartan and hydrochlorothiazide in bulk and in combination tablets dosage form.
Krishnamoorthy et al., (2011) enhanced the aqueous solubility of olanzapine by using the solid dispersion technique. Solid dispersions of olanzapine were prepared by the dispersion method using using PGS and SSG as carriers. Characterization was done by phase solubility, in-vitro release, saturation solubility, permeation, wettability, XRD and FTIR analysis. Solid dispersions showed higher solubility and an improved drug release profile than the pure drug. Solid dispersion and physical mixture with a drug-polymer ratio of 1:10 showed the best release profile in comparison with the other samples. Phase solubility results verified the solubilization effect of the carrier. XRD and NIR analysis confirmed the reduction of crystallinity in the samples. The release study findings were well supported by the results of wettability, saturation solubility and permeability studies. IR analysis substantiated the inertness of the carrier. It was concluded that pregelatinised starch (PGS) and sodium starch glycolate (SSG) could be utilized as effective carriers to improve the aqueous solubility of poorly soluble drugs.

Wadher et al., (2011) formulated an oral sustained release metformin tablet prepared by direct compression method, using hydrophilic Eudragit RSPO and RLPO alone or in combination with hydrophobic ethyl cellulose polymer as rate controlling factor. All the batches were evaluated for thickness, weight variation, hardness, and drug content uniformity and in vitro drug release. Mean dissolution time is used to characterize drug release rate from a dosage form and indicates the drug release retarding efficiency of polymer. When Eudragit RSPO and RLPO were used alone as the only retarding polymer, a sustained drug release pattern were not observed while, Inclusion of ethylcellulose in the matrix almost doubled (12 h) the time required for releasing the drug. Kinetic modeling of in vitro dissolution profiles revealed the drug release mechanism ranges from diffusion controlled to anomalous type. Fitting the data to Korsmeyer equation indicated that diffusion along with erosion could be the mechanism of drug release.

Vidyadhara et al., (2011) formulated solid dispersions of Glimepiride with sodium starch glycolate (SSG) were prepared and further compressed as tablets by using diluents such as lactose, dicalcium phosphate and microcrystalline cellulose. The solid dispersions
of Glimepiride with SSG at different ratios were prepared by physical mixing, solvent evaporation and kneading methods. The rapid release of poorly soluble Glimepiride from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. Among the three methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of Glimepiride. The release was found to follow the first order kinetics. Some of the dispersions prepared by the solvent evaporation method and kneading method were formulated into tablets with diluents such as lactose, DCP and MCC. All the tablet preparations containing diluents were found to release the drug in the order of DCP > MCC > Lactose.

Ramana et al., (2011) prepared nifedipine solid dispersion in carbamolose sodium (CCS) and sodium starch glycolate (SSG) and were investigated with a view to design sustained release tablets of nifedipine. As nifedipine is practically insoluble in water and aqueous fluid; its solid dispersion in CCS and SSG has markedly enhanced the dissolution rate of nifedipine. Matrix tablets formulated employing nifedipine dispersions in CCS and SSG with gum arabic alone and in combinations with methocel K4 M. The matrix tablets gave slow, controlled and complete release over a period of 12 hrs. Drug release from these tablets followed first order kinetics and the release was diffusion controlled. The (n) values obtained from Peppas plots were within the range of 0.45 to 0.9, indicates the drug release by both diffusion coupled with erosion. The DSC studies were also indicating the absence of strong interactions between the components and suggesting drug – excipient compatibility in all the formulations examined.

Mullaicharam et al., (2010) developed once-daily sustained release matrix tablets of metoprolol tartrate with inlay hydrochlorothiazide tablet as an immediate release formulation. The inlay tablets were prepared by wet granulation method using hydroxy propyl methylcellulose in various percentages. The drug-excipient incompatibility studies were performed by Differential Scanning Calorimetry(DSC).The granules showed satisfactory flow properties and compressibility. The in vitro and the in vivo release studies in rabbit were performed. The mechanism of drug release was diffusion coupled with erosion.
Shanthi et al., (2010) stated the Captopril provides effective treatment for hypertension and congestive heart failure. Development of a prolonged action dosage form for captopril will bring many benefits. The development of oral controlled or sustained captopril formulations has been a challenge for a long period of time. The reason being the drug is highly water soluble, unstable in alkaline intestinal pH and decrease in bioavailability in presence of food. Various attempts have been made to regulate the release and increase the bioavailability of the drug.

Anoop et al., (2010) stated The Hydroxy propyl methyl cellulose (HPMC) is generally combined with hydrophobic polymers in fabricating oral controlled solid dosage forms. This study evaluated the utility of diverse grades of HPMC in developing a controlled release formulation for a hydrophilic drug, enalapril maleate. Two grades of HPMC (K100 and K4M) in different proportions were used to prepare the tablets, all the formulations demonstrated good physical integrity and the drug content were in the official limits.

Kumar1 et al., (2010) designed and evaluated sustained-release matrix once-daily formulation of Stavudine, to increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release tablets were prepared by Direct Compression and formulated using different drug: polymer ratios, formulations such as F1 to F15. Hydrophilic polymers like Hydroxy Propyl Methyl Cellulose (HPMC), Carboxymethyl Cellulose (CMC) and Starch 1500 were used.

Kumar2 et al., (2010) worked on sustained release dosage forms which are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects.

Sankar, et al., (2010) studied the effect of Hydrophilic and Hydrophobic polymers on Losartan Potassium matrix tablet and investigated the possibility of sustaining the Losartan Potassium release from matrix tablet, prepared by Hydrophilic and Hydrophobic polymer. The preformulation studies were carried out the interaction between the drug.
and polymers. The granules were punched into tablet, which was evaluated for physical parameters.

Kumar3 et al., (2010) formulated and Evaluated Didanosine enteric coated sustained release tablet. Enteric coated tablets of Didanosine were developed to get resistance from gastric juice when it presents in stomach, because Didanosine is incompatible with gastric juice. The tablets are prepared by using Wet Granulation Technique using polymer Ethyl Cellulose STD 100 FP, Ethyl Cellulose Med 70 P, Ethyl Cellulose MED 50 P and other excipients are Povidone Micro Crystalline Cellulose in different ratios.

Pal et al., (2010) formulated a sustained release matrix tablet containing micronized carvedilol phosphate. Phosphate salt of carvedilol possesses better aqueous solubility than it’s free base. Hydroxy propyl substituted β cyclodextrin and poly ethylene oxide are used as release modifying polymer to develop the matrix tablet. The comparative in vitro evaluation between the developed micronized sustained release and non-micronized sustained release matrix tablet of carvedilol are done. A significant increase in in vitro drug release rate is observed in case of the micronized product over the non micronized one. The sustained release matrix tablet of micronized carvedilol may be used as a once daily formulation after relevant pharmacokinetic studies.

Ankit et al., (2010) introduced a validated method for the determination of valsartan and hydrochlorothiazide in tablets. Calibration curves for valsartan and hydrochlorothiazide over concentration range of 2-20 µg/ml were plotted and molar absorptivity for both the drugs were calculated at both the wavelengths of 270.5 nm (I-max of hydrochlorothiazide) and 231.5 nm (iso- absorptive point). The results of analysis have been validated statistically followed by recovery studies. The value of recovery studies were ranging from 99.05-102.23% for valsartan and 97.42-100.22% for hydrochlorothiazide and were indicative for accuracy and precision of the proposed method. The results of the assay are in good agreement with the labeled amount.
Nikam et al., (2010) developed a simple first order derivative spectrophotometric method for simultaneous estimation of valsartan, amlodipine besylate and hydrochlorothiazide in combined dosage form. The method employed was multi-wavelength method for analysis using methanol: water (70:30) as a solvent. The three wavelengths 245, 265 and 279 nm were selected for estimation of valsartan, amlodipine besylate and hydrochlorothiazide respectively. Linearity was observed in the concentration range of 8-80 µg/ml, 1-10 µg/ml and 2-20 µg/ml for valsartan, amlodipine besylate and hydrochlorothiazide respectively. The recovery studies ascertained the accuracy of the proposed method and the results were validated as per ICH guidelines.

Prabakaran et al., (2010) formulated a sustained release matrix dosage form of Nifedipine, by using different polymers to achieve better bioavailability and also to reduce dosing frequency and side-effects employing response surface methodology by incorporating a 3-factor, 3-level Box-Behnken statistical design. Dependent variables are the release retardant polymers such as HPMC K15M), HPMC E10 CR Prem., and Sodium Alginate and Independent variables are the percentage drug release at 1 h, percentage drug release at 8 h and hardness were studied. Box-Behnken response surface plots were drawn, statistical validity of the second order and quadratic models were established and the optimized formulations was chosen based on feasibility and grid search. The physical evaluation and in-vitro release studies were performed on all the formulations and the data were fitted to different release kinetic equations such as zero order, first order, Higuchi, Hixson Crowell and Korsemayer-peppas in terms of $r^2$ and n-value. Validation of the optimization study with 13 confirmatory runs indicated high degree of prophetic ability of response surface methodology. From the confirmatory runs, the optimized formulation showed gradual sustained release (best fit model—peppas, n=0.44) by Fickian diffusion process. Their design facilitated the optimization of Nifedipine sustained release matrix dosage form to achieve better bioavailability.

Shantveer et al., (2010) described sustained release matrix tablets of anti-hypertensive drug propranolol hydrochloride. Hydroxy propyl methyl cellulose was used as a rate retarding polymer where as lactose and dibasic calcium phosphates are used as diluent.
The results of study show that the rate of propranolol hydrochloride release from HPMC matrices is mainly controlled by the drug – HPMC ratio. When the influence of excipients on the release of drug was examined, the excipients lactose enhanced the release rate of propranolol hydrochloride, however the dibasic calcium phosphate (DCP) demonstrated slower release rate. The prepared sustained release matrix tablets were evaluated for various parameters like hardness, friability, uniformity of weight, uniformity of drug content, in vitro drug release and short term stability studies. The dissolution t\(_{50}\)% and t\(_{90}\)% values for the co-excipients were in the order of lactose>dibasic calcium phosphate.

Pal et al., (2009) established a correlation between in vitro dissolution and in vivo absorption data of prepared sustained release Leflunomide microcapsules and compare with conventional tablets of Leflunomide( EravalOmg ).they took New-Zealand white rabbit species for performing this study. The correlation ship was established according to Drewe and Guitard basing on (degree A). Comparison of cumulative in vitro dissolution profile, in vitro dissolution constant ( K ) Vs AUC, Mean dissolution time Vs mean residence time. The plasma drug concentration was measured with standard curve equation and compared with the standard tablet data which showed all the formulations have 1 hr to 4 hr extended T-max value confirming their sustained action. All formulated micro spheres show identical pharmacological effect in comparison to standard Leflunomide tablet. The parameters like dissolved fraction absorbed, MDT Vs MRT andT85% revealed a significant in vitro in vivo correlation which substantiate the success of correlation study.

Uddin et al., (2009) designed oral sustained release matrix tablets of Ranolazine using hydroxypropyl methylcellulose (HPMC) as the retardant polymer and to study the effect of formulation factors such as polymer proportion and polymer viscosity on the release of drug. In vitro release studies were performed in 0.1N HCl for 12 hours. The release kinetics was analyzed using the zero-order, first order, Higuchi and Korsmeyer-Peppas equations to explore and explain the mechanism of drug release from the matrix tablets. In vitro release studies revealed that the release rate decreased with increase in polymer
proportion and viscosity grade. The release kinetics indicated that the nature of drug release from the matrix tablets was dependent on drug diffusion and polymer relaxation and therefore followed non-Fickian or anomalous release.

Deshmukh et al., (2009) developed Formulation and Evaluation of sustained release Metoprolol Succinate tablet using Hydrophilic gums as release modifiers. The objective of this study was to design and evaluate oral sustained drug delivery system for Metoprolol Succinate using Natural hydrophilic gums such as Karaya gum and Xanthan gum as a release modifier. Matrix tablets were prepared by wet granulation method and were evaluated physical & chemical parameters, and Stereo Photography.

Smith et al., (2009) developed sustained release matrix tablets of Ondansetron hydrochloride [5mg] formulated employing Hydroxy Propyl Methyl Cellulose polymer and the sustained release behavior of the tablets was investigated. Tablets were prepared by wet granulation methods. The granules were evaluated for angle of repose, bulk density and drug content. The tablets were subjected to thickness, diameter, weight variation test, hardness, friability, drug content and in vitro release studies. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release.

Agnivesh et al., (2009) has designed, optimized, prepared and evaluated the dispersion granules of valsartan and formulation into tablets and the present work undertaken was to enhance the solubility and dissolution rate of valsartan an poorly water soluble antihypertensive, by preparation of solid dispersion granules which would additionally allow easy compression into tablets.

Sayed et al., (2009) have incorporated Metoclopramide hydrochloride (MCP) in sustained release formulations by using different polymer ratios. These polymers were hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose (CMC) and ethyl cellulose (EC). Sodium starch glycolate (SSG) was added to some formulae in different amounts in order to soften and/or disintegrate the tablets. Both direct compression and granulation techniques were used to prepare the tablets. The dissolution profiles of the
tablets were constructed using the change-over method. The drug release involved a combination of both diffusion and polymer-chain relaxation mechanisms. The time required to release 50% of MCP ranged from 1.2 to more than 8 hours. Direct compression and dry granulation techniques produced sufficient sustaining of the drug release. However, the pellets made by wet granulation released MCP in about 2 hrs, i.e., Pelletization spheronization technique was not effective in sustaining the drug.

Roni et al., (2009) discussed about their in vitro evaluation of their controlled release dosage form containing alfuzosin hydrochloride. Binary mixer of one hydrophilic polymer (hydroxypropyl methylcellulose) and one hydrophobic polymer (ethyl cellulose) was used in tablets prepared by direct compression, 32 factorial designs were chosen and the amount of two polymers was taken as independent variables. The percent drug released at 1, 6, 12, and 20 h were selected as response. The main effect and interaction terms were quantitatively evaluated using mathematical model. Dissolution data were fitted to zero order, first order, and Higuchi’s release kinetics to evaluate kinetic data. According to Korsmeyer's equation drug release followed both diffusion and erosion mechanism in all cases.

Rahman et al., (2009) initiated in the formulation of Metoclopramide hydrochloride (MCP) in sustained release formulations. Metoclopramide hydrochloride (MCP) was incorporated in 12 formulae containing different polymers and/or different polymer ratios. These polymers were hydroxypropylmethyl cellulose (HPMC), carboxymethylcellulose (CMC) and ethyl cellulose (EC). Sodium starch glycolate (SSG) was added to some formulae in different amounts in order to soften and/or disintegrate the tablets. Both direct compression and granulation techniques were used to prepare the tablets. The physical properties were found to be satisfactory for all the formulae. The dissolution profiles of the tablets were constructed using the change-over method. The drug release involved a combination of both diffusion and polymer-chain relaxation mechanisms. The time required to release 50% of MCP ranged from 1.2 to more than 8 hours. Direct compression and dry granulation techniques produced sufficient sustaining
of the drug release. However, the pellets made by wet granulation released MCP in about 2 hrs, i.e., Pelletization spheronization technique was not effective in sustaining the drug.

Basak et al., (2008) benefited of a sustained release dosage form, compared to a conventional dosage form, is the uniform drug plasma concentration and therefore uniform therapeutic effect. Over the past two decades, sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Matrix devices, due to their chemical inertness, drug embedding ability and drug release character, have gained steady popularity for sustaining the release of a drug.

Preettha et al., (2008) described the effect of mode of incorporation of superdisintegrants like croscarmellose sodium, sodium starch glycolate and crospovidone (polyplasdone XL and XL-10) on dissolution of three model drugs with varying aqueous solubility, like carbamazepine (poorly soluble), acetaminophen (sparingly soluble) and cetirizine HCl (soluble) from their respective tablet formulations prepared by wet granulation. The disintegrants were incorporated extragranularly or intragranularly or distributed equally between the two phases. The dissolution test demonstrated that Crospovidone in general was effective in improving the in vitro drugs release used in the study and generally extragranular mode of addition seemed to be the best mode of incorporation, irrespective of the solubility of the main tablet component.

Jaberemami, et al., (2008) prepared and evaluated in-vitro of sustained - release matrix tablets of Flutamide using synthetic and naturally occurring polymers. The sustained-release matrix tablets of Flutamide were prepared by direct compression method using different polymers. Cellulose ethers (HPMC and NaCMC), Natural gums (Guar and Xanthan gums) and compressible Eudragits (RSPO and RLPO) and their combinations were used in different ratios to examine their influence on tablet properties and drug release profile.

Bhalekar et al., (2008) studies the influence of hydrophilic polymer (HPMC) and hydrophobic polymer (Ethyl cellulose) on Nicorandil matrix sustained release tablet
which can release the drug up to time of 24 hrs in predetermined rate. The formulation of Nicorandil matrix tablet was prepared by the polymer combination in order to get required theoretical release profile. The influence of hydrophilic and hydrophobic polymer and granulation technique on Nicorandil was studied. The formulated tablet were also characterized by physical and chemical parameters. The in-vitro release rate profile should the higher concentration of F2 polymer in tablet, the combination of hydrophilic and hydrophobic combination showed less result than use of alone. The in-vitro release data was well fit to Peppas and Hixon crowel release kinetics.

kumar et al., (2006) designed Eudragit-S100 coated pellets for chronotherapeutic delivery of diltiazem hydrochloride by aqueous extrusion spheronization technique using microcrystalline cellulose as a spheronizing aid and PVP K 30 as a binder. The friability with glass spheres was below 1.0%, signifying the core pellets produced were sufficiently hard. In vitro dissolution studies showed that the drug release from the coated pellets depended on the coat weights applied and pH of the dissolution media. Since, diltiazem hydrochloride is a drug, which exhibits a high solubility, it would be possible to minimize drug release from the coated pellets below pH 7.0, and effectively release the drug at colonic pH only with higher coat loads (15-20% weight gain).

Shoaib et al., (2006) developed a once-daily sustained release matrix tablet of ibuprofen using hydroxypropyl methylcellulose (HPMC) as release controlling factor and to evaluate drug release parameters as per various release kinetic models. In order to achieve required sustained release profile tablets were directly compressed using Avicel pH 101 and Magnesium stearate. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Criteria for selecting the most appropriate model were based on linearity (coefficient of correlation). The drug release data fit well to the Higuchi expression. Drug release mechanism was found as a complex mixture of diffusion, swelling and erosion.
Mishra et al., (2005) formulated and evaluated hydrophilic matrix tablets of diltiazem hydrochloride to achieve a controlled and sustained drug release with reduced frequency of drug administration, reduced side effects and improved patient compliance. Matrix tablets of diltiazem hydrochloride were prepared using polymers like hydroxypropylmethyl cellulose (HPMC K15, HPMC K4), sodium carboxymethyl cellulose (SCMC) and Guar gum. All the batches were evaluated for thickness, weight variation, hardness, drug content uniformity and in vitro drug release. The drug release rates from matrix tablets were compared with marketed SR formulations. Matrix erosion and swelling studies were also carried out. The release kinetics and mechanism of drug release by regression coefficient analysis and Peppas exponential release model equation were also investigated. SCMC matrix tablets showed more hydration and erosion than other matrix tablets. Tablets having HPMC K15 gave more sustained release than other hydrophilic polymers studied and it was comparable with marketed SR tablets. Amount of HPMC K15 and presence of different diluents significantly affected the drug release. They observed that all the fabricated tablets delivered the drug following Higuchi diffusion mechanism.

Ojoe et al., (2005) developed tablets containing theophylline (66.67%) based on a Eudragit® RS 30D and NE 30D matrices containing 10% to 30% of either of the polymer were produced by compression method. The influence of the different proportions of methacrylic esters, the use of lactose and tribasic calcium phosphate as diluents and also the effects of the addition of magnesium stearate as a lubricant on the theophylline release, were studied. Physicochemical analyses and drug content was evaluated. In vitro drug release studies were carried out in simulated gastric fluid without pepsin (pH1.2) and simulated intestinal fluid without pancreatin (pH7.5). A relatively prolonged release of theophylline from the polymer matrices for a 7 hr release period was detected. Magnesium stearate at 0.5% and Eudragit® NE 30D at 10% was considered a better sustained release matrix compressed theophylline tablets comparing with Eudragit® RS 30D in the same conditions (USP). Results from physicochemical analyses were in accordance with specifications. Higuchi was the model that better fitted theophylline kinetic, and diffusion controlled was involved.
Tabandeh et al., (2003) prepared matrix aspirin (acetylsalicylic acid) tablets with ethylcellulose (EC), Eudragit RS100 (RS), and Eudragit S100 (S) were prepared by direct compression. The release behaviors were then studied in two counterpart series of tablets with hardness difference of three Kp units, and compared by non-linear regression analysis. The release pattern for both the S-containing and RS-containing formulations fitted best in Higuchi model, and the proper equations were suggested. In the EC-containing formulation, Higuchi and also zero-order models were probable models for the release, and a combination equation for the release was suggested. In the S-containing formulation, the release profile was completely sensitive to the hardness change. In RS-containing series, the slope of the release graph did not change due to the hardness decrease, but the y-intercept or the lag time in release was decreased. In EC-containing matrix tablets, both the slopes and the y-intercepts did not change by the decrease in hardness. In conclusion, EC with an amount as little as 10 percent in formulation could make sustained-release aspirin tablets in which the release profile is not sensitive to moderate changes in hardness.

Saravanan et al., (2003) Developed hydroxypropyl methylcellulose (HPMC) based cephalixin extended release tablet, which can release the drug for six hours in predetermined rate. The influences of HPMC, microcrystalline cellulose powder (MCCP), granulation technique, wetting agent and tablet hardness on cephalixin release from HPMC based extended release tablets were studied. The dissolution results showed that a higher amount of HPMC in tablet composition resulted in reduced drug release. Addition of MCCP resulted in faster drug release. Tablets prepared by dry granulation was released the drug slowly than the same prepared with a wet granulation technique. Addition of wetting agent in the tablets prepared with dry granulation technique showed slower release. An increase in tablet hardness resulted in faster drug release. The in vitro release data was well fit in to Higuchi and Korsmeyer- Peppas model. The effect of storage on in vitro release and physicochemical parameters of successful batch was studied and was found to be in acceptable limits.
Kubo et al., (2003) developed an oral sustained delivery of paracetamol from in situ gelling gellan and sodium alginate formulations. The potential for the oral sustained delivery of paracetamol of two formulations with in situ gelling properties was evaluated. In-vitro studies demonstrated diffusion-controlled release of paracetamol from the gels over a period of six hrs. The bioavailability of paracetamol from the gels formed in situ in the stomachs of rabbits following oral administration of the liquid formulations was similar to that of a commercially available suspension containing an identical dose of paracetamol.

Mitchell et al., (2003) developed a technique to enhance the dissolution rate of poorly soluble drugs with hydroxypropyl methylcellulose (HPMC) without the use of solvent or heat addition. Polymer and drug were blended, compressed into slugs on a tablet press or into ribbons on a roller compactor, and then milled into a granular powder. Dissolution testing of the milled powder was performed on 900 ml deionized water, 37 \( ^\circ \)C. Drug distribution vs. particle size was also studied. The compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging methods produced comparable dissolution enhancement. They claim that the compaction methods in their study may provide a lower cost, quicker, readily scalable alternative for formulating poorly water-soluble drugs.

Silvina et al., (2002) formulated and developed uncoated HPMC matrix tablets and evaluated the relationship and influence of different content levels of microcrystalline cellulose (MCC), starch, and lactose, in order to achieve a zero-order release of Diclofenac Sodium. In their study, HPMC matrix tablets of Diclofenac Sodium using microcrystalline cellulose (MCC), starch, and lactose were prepared by wet granulation process. The dissolution profiles carried out in 900 mL 0.1 N HCl, and phosphate buffer. They found no significant difference in drug release between the hydrophilic matrices when the HPMC concentration was modified in low percentage. Release kinetics of Diclofenac Sodium from these swollen matrices was principally regulated by starch (17 \%) or lactose (17 %), even on the presence of MCC. Additionally, when starch (8.5 %)
and lactose (8.5%) were mixed at lower concentration in a ratio 1:1, MCC (5% or 7, 5 %) appeared to control the drug release. The best-fit release kinetics was achieved with the zero-order plot, followed by the Higuchi and first-order equations. The data obtained proved that the formulations are useful for a sustained release of Diclofenac, due to the percentage released after 8 hours is nearly to 70%. Compared to conventional tablets, release of the model drug from these HPMC matrix tablets was prolonged; as a result, an oral release dosage form to avoid the gastrointestinal adverse effects was achieved.

Nataraj et al., (2001) targeted a simple precise accurate UV Spectroscopic method as their objective and validated for estimation of valsartan in pure and pharmaceutical dosage form. UV Spectroscopic method is based on measurement of absorption of UV light, the spectra of valsartan in methanol showed maximum wave length at 250nm and calibration graphs were plotted over the concentrations ranging from 2-20 μg/ml of valsartan with correlation coefficient 0.996 validation was performed as per ICH Q2 (R1) guidelines for linearity, accuracy, precision and recovery. The limit of detection (LOD) and limit of quantification (LOQ) were found to be 0.15 and 0.449 respectively by simple UV Spectroscopy.

Tahara et al., (1995) studied sustained release tablet matrices prepared using HPMC of different viscosity and three different drugs of different solubility: methylparaben (MP), propylparaben (PP) and U-78875. The tablets were prepared by granulating the active compound with cornstarch and purified water, and blending the granulated material with HPMC and lactose. The weight change of the tablets during release was monitored. Solubility results indicated that MP was soluble, PP was reasonably soluble and U-78875 was poorly soluble in the test medium. Increased with time indicating infiltration of medium into intersperse of the tablet matrix. This was followed by swelling and erosion of the matrix tablet. Surface erosion of the tablet was also observed. The drug release also depended on the amount of drug loaded and the solubility of drug in the matrix.

Gudsoorkar et al., (1993) sustained release preparations provide an immediate dose required for the normal therapeutic response, followed by the gradual release of drug in
amounts sufficient to maintain the therapeutic response for a specific extended period of time. The major advantage of this category is that, in addition to the convenience of reduced frequency of administration, it provides blood levels that are devoid of the peak-and-valley effect which are characteristic of the conventional intermittent dosage regimen.

Carmella et al., (1984) studied the role of disintegrants in the swelling process, which was carried out by studying a number of disintegrants available in the market. They used various methods like X-ray analysis, microscopic observation, particle volume increases and hydration or salvations capacity. It was suggested that swelling could happen in ways like capillary swelling and molecular swelling. So capillary and pore wet ability are important in the development of the swelling force. The whole process involved the steps of disintegration in the sequence of water penetration, particle swelling of the disintegrant, force development and bond disruption. Nevertheless, swelling is the governing factor regarding the kinetics of the whole process.

US Patent 0132839 and 0152620; compared and discussed that their pharmaceutical composition of valsartan tablets dosage form is at 1.2 times more bioavailable than the conventional valsartan capsule. The tablet formulation according to the invention contains a disintegrant at concentration level of 10-18% based on total weight of the composition. The higher amount of disintegrant ensures that the hydrophobic valsartan is wetted well during the granulation stage. The tablet is readily dispersed as granules in the dissolution medium resulting in a better dissolution and improved bioavailability over the normal formulation. The invention does not, however, described methods to increase solubility of the valsartan itself in the gastric milieu; and therefore, the dissolution of valsartan in 0.1N HCl still remains low which results in low bioavailability (Ganter, Sabina Maria 2002).

2.3. Recent Developments in Nano and Microemulsion Drug Delivery

Kotta et al., (2012) gives a brief description about how oral nanoemulsions act as tool for improvement of bioavailability of BCS class 2 and class 4 drugs. It also summarizes
the theory behind the formation of nanoglobules. This review clears the difference
between nanoemulsion and lyotropic 'microemulsion' phase. It also covers the definition
of nanoemulsion according to different authors. It gives a clear cut idea about all possible
methods for the preparation of nanoemulsion and the advantages and disadvantages of
each method. It gives a brief description of the stability problems of nanoemulsion and its
prevention methods. This review also describes the most important and useful
characterization methods for nanoemulsion. It also presents a comprehensive update on
the patents and research works done in the arena of oral nanoemulsion.

Bali et al., (2011) developed an optimal and stable nanoemulsion of ezetimibe. The
release of drug from the nanoemulsion was highly significant as compared to the drug
suspension. The value of total cholesterol in the group administered with the optimized
nanoemulsion formulation was highly significant with respect to the group administered
with the suspension of the drug. The plasma concentration time profile of ezetimibe from
nanoemulsion represented greater improvement of drug absorption than the marketed
formulation and simple drug suspension. The shelf life of the nanoemulsion was found to
be 5.94 years at room temperature. So the present study established nanoemulsion to be a
possible alternative for minimizing variation in bioavailability of ezetimibe.

Shah et al., (2010) described that the nanoemulsion possesses various advantages such as
they do not show the problems of inherent creaming, flocculation, coalescence and
sedimentation which are commonly associated with macroemulsions, NEs have a much
higher surface area than macroemulsions that make them an effective transport system.
Since NEs are formulated with surfactants, which are approved for human consumption,
they can be used orally. In the world of nanomaterials, nanoemulsions hold great promise
since they can typically be formulated using considerably less surfactant than is required
for nanostructured lyotropic microemulsion phases.

Mustafa et al., (2009) investigated oil-in-water (o/w) nanoemulsion of atorvastatin for
enhancing its oral bioavailability. The area under the curve and maximum plasma
concentration of atorvastatin nanoemulsion were found 9-fold and 5-fold higher,
respectively when compared to simple atorvastatin suspension. The present study illustrated the potential of nanoemulsion dosage form in improving biopharmaceutic performance of atorvastatin.

Tagne et al., (2008) formulated a water-soluble nanoemulsion of the highly lipid-soluble drug tamoxifen by microfluidization technique. The results suggested that nanoemulsions of tamoxifen, having mean particle sizes of 47 nm, inhibited cell proliferation 20-fold greater and increased cell apoptosis 4-fold greater in the HTB-20 breast cancer cell line.

Alves et al., (2007) studied the in vitro skin penetration of a drug model (nimesulide) from semisolid topical formulations containing nanospheres, nanocapsules or nanoemulsion. They used nanoprecipitation, interfacial deposition and spontaneous emulsification methods for preparation of nanostructured suspension. They incorporated these nanocarrier systems in the hydrophilic gels and investigated in vitro skin permeation through human skin using stripping technique and Franz-type diffusion cells. They found that amount of nimesulide released into the stratum corneum (SC) from the gel containing nanocapsules (GNM-NC) and the gel containing nanospheres (GNM-NS) was similar. On the other hand, for the gel containing nanoemulsion (GNM-NE), the nimesulide was not quantified in SC, but it had directly permeated in the dermis.

Biruss et al., (2007) investigated the permeation and the chemical stability of 17-β-estraadiol, progesterone, cyproterone acetate and finasteride incorporated in an eucalyptus oil containing microemulsion system. The formulations contained 1% (w/w) of the steroid hormones. From these results a bicontinuous structure was proposed for the multicomponent system. However a correlation between the self diffusion of the hormones in the vehicle and the transdermal flux was not indicated. By addition of certain polymers the skin permeation rates was improved with exception of cyproterone acetate.

Chan et al., (2007) evaluated microemulsion-based phase transition systems for ocular delivery of pilocarpine hydrochloride. They used two non-ionic surfactants, sorbitan mono laurate and polyoxyethylene sorbitan mono-oleate with ethyl oleate (oil
component) and water. These systems underwent a phase change from ME to liquid crystalline (LC) and to coarse emulsion (EM) with a change in viscosity depending on water content. They found that phase transition microemulsion is promising for ocular drug delivery as it provides the desired fluidity.

Ichikawa et al., (2007) evaluated the effects of the formulation and particle composition of gadolinium (Gd) containing lipid nanoemulsion on the biodistribution of Gd after its intravenous (IV) injection in D(1)-179 melanoma-bearing hamsters for its application in cancer neutron-capture therapy. Biodistribution data revealed that Brij 700 and HCO-60 prolonged the retention of Gd in the blood and enhanced its accumulation in tumors.

Khandavilli and Panchagnula, (2007) investigated in vivo pharmacokinetic performance of paclitaxel (PCL) nanoemulsion in order to achieve penetration of PCL into deeper skin layers. Further, the same formulation was explored for per oral bioavailability enhancement of PCL. They concluded that developed nanoemulsion formulation was safe and effective for both per oral and dermal delivery of PCL.

Kuo et al., (2007) investigated whether a subcutaneous injection and/or transdermal application of a nanoemulsion preparation of antioxidant synergy formulation (ASF) would reduce tumor growth rate in a neuroblastoma xenograph mouse model. They found that subcutaneous and/or transdermal application of an ASF nanoemulsion preparation was effective in reducing tumor growth rate in this neuroblastoma mouse model.

Reis et al., (2007) prepared insulin-loaded alginate-dextran nanospheres by nanoemulsion dispersion followed by triggered in situ gelation. Nanospheres were characterized for mean size and distribution by laser diffraction spectroscopy and for shape by transmission electron microscopy. They found that alginate-dextran particles suppressed insulin release in acidic media and promoted a sustained release at near neutral conditions. Nanoencapsulated insulin was bioactive as demonstrated by both in vivo and in vitro bioassays.

Bouchemal et al., (2006) investigated the role of the polymeric membrane in the protection of the active drug against damaging caused by external agents and to select the monomer which helps in formulation of a stable formulation with the highest possible
payload of the active drug. The colloidal suspensions of nanocapsules were obtained using the combined interfacial polycondensation and spontaneous emulsification. They concluded that the polyurethane based on HD offers good protection of alpha-tocopherol against damage caused by the temperature and UV irradiation.

Chen et al., (2006) constructed microemulsion-based hydrogel formulation for topical delivery of ibuprofen. Various microemulsions were prepared and evaluated for their skin permeation through franz diffusion cell. The results indicated that microemulsion-based hydrogel may be a promising vehicle for topical delivery of ibuprofen.

Cruz et al., (2006) established models to differentiate the kinetic release behavior of drug models from nanocapsules, nanoemulsion and nanospheres by physico-chemical characterization and release experiments. Mathematical modeling of the release profiles was conducted, showing that the presence of the polymer increased the half-lives of the burst phases (5.9, 4.4 and 2.7 min) while the presence of the oil increased the half-lives of the sustained phases (288.8, 87.7 and 147.5 min) for nanocapsules, nanospheres and nanoemulsion, respectively.

Freitas et al., (2006) developed a novel concept for the continuous, contact and contamination-free treatment of fluid mixtures with ultrasound. It was based on exciting a steel jacket with an ultrasonic transducer, which transmitted the sound waves via pressurised water to a glass tube installed inside the jacket. They concluded that this novel technology offers a pharmaceutically interesting platform for nanodroplet and nanoparticle production and is well suited for aseptic continuous processing.

Fu et al., (2006) enhanced the bioavailability and antimicrobial activity of poorly water-soluble glycerol monolaurate (GML) by loading it in microemulsion system. Microemulsions were prepared with GML as oil, tweens as surfactant, and medium-and-short chain alcohols at different ratio as cosurfactants. The effect of the ratio of surfactant to cosurfactant on the stability of microemulsion was tested. The results showed that the microemulsion was most stable when the ratio of surfactant to cosurfactant was 3:2, the suitable cosurfactant was pentanol to dodecane at 2:1. The area of o/w microemulsion region in pseudo-ternary phase diagram increased with increasing content of potassium
sorbate. They concluded that GML loaded in microemulsion had much higher antimicrobial activity.

Garti et al., (2006) constructed U-type phase diagrams for celecoxib and formulated reverse microemulsions that were progressively and fully dilutable with aqueous phase. Results indicated the enhanced solubilization of celecoxib in U-type nonionic microemulsions.

Kogan and Garti, (2006) reviewed selected studies of various microemulsions containing certain drugs including retinoic acid, 5-fluorouracil, triptolide, ascorbic acid, diclofenac, lidocaine, and prilocaine hydrochloride in transdermal formulations. In conclusion, they found microemulsions as an effective vehicle for the solubilization of certain drugs and as protecting medium for the entrapment of drugs from degradation, hydrolysis, and oxidation. It also provide prolonged release of the drug and prevented irritation despite the toxicity of the drug. Yet, in spite of all the advantages, the present formulations lacked several key important characteristics such as cosmetic-permitted surfactants, free dilution in water capabilities, stability in the digestive tract and sufficient solubilization capacity.

Lv et al., (2006) investigated chloramphenicol microemulsion, composed of Span 20, Tween 20, isopropyl myristate (IPM) and water as potential drug delivery systems for eye drops. Chloramphenicol in the common eye drops hydrolyzes easily. Here, the chloramphenicol was trapped into the o/w microemulsions free of alcohols. Its stability was investigated by the HPLC method in the accelerated experiments of 3 months. They revealed that the content of the glycols in the microemulsion formulation was much lower than that in the commercial eye drops at the end of the accelerated experiments. It implied that the stability of the chloramphenicol in the microemulsion formulations was increased remarkably.

Pattani et al., (2006) prepared and evaluated lipid nanoparticles and nanoemulsion of polymyxin B sulphate. They compared antimicrobial activity of lipid nanoparticles and nanoemulsion against a sensitive strain of E. Coil. They concluded that the developed lipid nanoparticles and nanoemulsion are promising delivery vectors for the antimicrobial
drugs.

Poulsen et al., (2006) examined w/o microemulsions typically used for preparation of sensors. The cores of the microemulsion droplets were constituted by an aqueous component consisting of water, reagent monomer mixture, buffer salts, and the relevant dyes and/or enzymes. The cores were encapsulated by a mixture of the surfactants Brij30 and AOT and the resulting microemulsion droplets were suspended in a continuous hexane phase. They tested and investigated how the monomers and the ratio between the two surfactants affect the size of the microemulsion droplets and the microemulsion domain. They found that the monomers in water had a profound effect on the microemulsion domain as well as on the size of the microemulsion droplets.

Sintov and Botner, (2006) evaluated the transdermal delivery potential of diclofenac-containing microemulsion system in vivo and in vitro. They found that the transdermal administration of the microemulsion to rats resulted in 8-fold higher drug plasma levels than those obtained after application of Voltaren Emulgel. The transdermal fluxes of diclofenac were measured in vitro using skin excised from different animal species. In three rodent species, penetration fluxes of 53.35±8.19 (furry mouse), 31.70±3.83 (hairless mouse), 31.66±4.45 (rat), and 22.89±6.23 μg/cm²/h (hairless guinea pig) were obtained following the application of the microemulsion. These fluxes were significantly higher than those obtained by application of the drug in aqueous solution.

Spernath et al., (2006) demonstrated the feasibility of constructing phase diagrams with a large isotropic regions capable of being fully diluted with water. The microemulsions were stabilized with mixtures composed of phosphatidylcholine (PC) and nonionic surfactant (polyoxyethylene-40 hydrogenated castor oil, HECO40) and short-chain organic acid as cosurfactant/cosolvent. The presence of a blend of PC and HECO40 seemed to have a synergistic effects, forming an isotropic region comprising 72% of the area of the phase diagram, in comparison to 20 and 50% in systems stabilized by PC and HECO40, alone, respectively. The role of the PC molecules in the formation of those microemulsions was demonstrated by comparing three soy lecithins. Lecithin with a high PC content formed larger isotropic regions with more "free dilution" lines. Several nonionic surfactants were investigated, yet only HECO40 seemed to have a packing
parameter suitable for the formation of large isotropic U-type systems.

Tomsic et al., (2006) used small-angle X-ray scattering technique to study the structural properties of the quaternary microemulsion. They prepared microemulsion for ketoprofen using Tween 40/Imwitor 308/isopropyl myristate/water. The present results indicated that in the samples with the moderate to high concentration of water, the addition of smaller amounts of the ketoprofen did not change their inner structure significantly. They found that all these changes in the inner structure of the studied systems did not affect the trend of the drug release rates in this regime of water concentrations.

Yilmaz and Borchart, (2006) evaluated the effect of positively charged oil/water nanoemulsions (PN) containing ceramide 3B and naturally found SC lipids (PNSC) such as ceramide 3, cholesterol, and palmitic acid on skin hydration, elasticity, and erythema. Creams of PNSC were compared to PN creams. The formulations (PN, PNSC, and NNSC) were prepared by high-pressure homogenization. After adding Carbopol 940 as thickener, particle size and stability of the creams were not significantly changed as compared to the nanoemulsions. The studies were carried out on three groups, each with 14 healthy female test subjects between 25 and 50 years of age, using Corneometer 825, Cutometer SEM 575 and Mexameter 18 for measurements of skin hydration, elasticity, and erythema of the skin, respectively. All formulations increased skin hydration and elasticity. There was no significant difference between PNSC and Physiogel. However, PNSC was significantly more effective in increasing skin hydration and elasticity than PN and NNSC indicating that phytosphingosine induced positive charge. It was also concluded that SC lipids and ceramide 3B are crucial for the enhanced effect on skin hydration and viscoelasticity.

Zhao et al., (2006 a) prepared and characterized gelatin-containing microemulsion-based organogels (MBGs) composed of isopropyl myristate (IPM), AOT, Tween 85 and H₂O, loaded with and without a model drug (butenafine hydrochloride) by rheological measurements and environmental scanning electron microscope (ESEM). Transparent and homogeneous MBGs were formed when the concentration of gelatin in the selected w/o microemulsion was in the range of 7.0–12.0 % v/v. The rheological properties such as the yield stress, storage and loss moduli of the MBGs samples increased and the
network structures of the MBGs became more compact with increasing concentration of gelatin in the formulations. Furthermore, the addition of butenafine hydrochloride to the MBGs weakened the interconnected network structures of the MBGs systems. These results showed that MBGs could be used as potential transdermal drug delivery vehicles.

Zhao et al., (2006 b) studied a microemulsion vehicle as a possible matrix for transdermal delivery of theophylline. The existence of microemulsion regions were investigated in pseudo-ternary phase diagrams, and various microemulsion formulations were prepared using oleic acid, Cremophor RH 40/Labrasol (1:2) and water. The results showed that microemulsion system of theophylline might be a promising vehicles for the transdermal delivery of theophylline.

Bidyut and Rajib, (2005) studied solubilization of water in mixed reverse micellar systems with anionic surfactant (AOT) and nonionic surfactants (Brijs, Spans, Tweens, Igepal CO 520), cationic surfactant (DDAB)—nonionic surfactants (Brijs, Spans, Igepal CO 520), and nonionic (Igepal CO 520)—nonionics (Brijs, Spans) in oils of different chemical structures and physical properties (isopropyl myristate, isobutyl benzene, cyclohexane) at 303 K. The maximum water solubilization capacity in mixed reverse micellar systems occurred at a certain mole fraction of a nonionic surfactant.

Carli et al., (2005) applied nanoemulsified composite (NECTM) delivery system on a very water insoluble ubidecarenone drug. The resulting composite powder showed good technological properties such as flowability; also good stability was observed. The sizes of the nanodroplets released from the systems were maintained same as the starting size and also after a long storage. Furthermore very good biopharmaceutical properties were originated, with water solubility concentrations up to 50-fold higher than pure ubidecarenone and oral absorption in rats up to three-fold greater than standard commercial products in terms of plasma levels and AUC.

Djordjevic et al., (2005) studied the influence of both formulation parameters and vehicle structure on in vitro release rate of amphiphilic drug diclofenac diethylamine (DDEA) from microemulsion vehicles containing PEG-8 caprylic/capric glycerides (surfactant), polyglyceryl-6 dioleate (cosurfactant), isopropyl myristate and water. Low
water/isopropyl myristate apparent partition coefficient for DDEA as well as elevated electrical conductivity and apparent viscosity values for the investigated microemulsion formulations containing 1.16% (w/w) of DDEA, suggested that the drug molecules predominantly partitioned in the water phase and most likely self aggregated and interacted with interfacial film. Release of DDEA from the selected water-continuous (W/O), oil-continuous (O/W) and balanced microemulsions was investigated using rotating paddle dissolution apparatus modified by addition of enhancer cell. A linear diffusion of DDEA through regenerated cellulose membrane was observed for the W/O and O/W formulations with the low content of dispersed phase. Non-linearity of the drug release profile in the case of bicontinuous formulations was related to the more complex distribution of DDEA including interactions between the drug and vehicle. Moreover, the obtained flux values for balanced microemulsions suggested that bicontinuous microstructure hampered the release of the amphiphilic drug.

Gupta et al., (2005) studied transdermal permeation of 5 fluorouracil (5FU), a hydrophilic drug encapsulated in AOT/water/IPM w/o microemulsions using a modified keshary chein diffusion cell. Results revealed that the microemulsion interacted with a component of the stratum corneum and perturbed its architectural structure. Preliminary toxicity studies indicated that the AOT/water/IPM w/o microemulsion were safe for the transdermal permeation of 5-FU.

Lee et al., (2005) developed an o/w microemulsion system to enhance the skin permeability of aceclofenac. Pseudoternary phase diagrams were constructed to obtain the concentration range of oil (Labrafil), surfactant (Cremophor-ELP) and cosurfactant (ethanol) for microemulsion formation. Terpenes were added to the microemulsion at a level of 5% and their effects on skin permeation of aceclofenac were investigated. Limonene showed the best permeability enhancing capacity amongst all the terpenes tested.

Shiokava et al., (2005) reported a novel microemulsions formulation for tumor-targeted drug carrier of lipophilic antitumor antibiotics, aclacinomycin A (ACM). Their findings suggested that a folate-linked microemulsion was feasible for tumor-targeted ACM
delivery. This study showed that folate modification with a sufficiently long PEG chain on emulsions was an effective way of targeting emulsion to tumor cells.

Solans et al., (2005) reviewed and summarized the formation, properties and applications of nanoemulsions (also referred to as miniemulsions, ultrafine emulsions, submicron emulsions). Although most of the publications on either O/W or W/O nanoemulsions reported their formation by dispersion or high-energy emulsification methods, an increased interest was observed in the study of nanoemulsion formation by condensation or low-energy emulsification methods (based on the phase transitions that take place during the emulsification process). Phase behaviour studies showed that the size of the droplets was governed by the surfactant phase structure (bicontinuous microemulsion or lamellar) at the inversion point induced by either temperature or composition. Studies on nanoemulsion formation by the phase inversion temperature (PIT) method showed a relation between minimum droplet size and complete solubilization of the oil in a microemulsion bicontinuous phase independent of the initial phase equilibria which was either single or multiphase. The interesting application which was derived was an active development in the use of nanoemulsions as formulations, for controlled drug delivery and targeting.

Subramanian et al., (2005) developed and investigated microemulsion system (isopropyl myristate/medium chain glyceride/polysorbate 80/water) for topical delivery of celecoxib. The in vitro permeation rate of celecoxib through rat skin was determined for microemulsions, microemulsion gel and cream by using the modified Franz diffusion cell. Microemulsions enhanced the permeation rate of celecoxib up to 5 and 11 times as compared to microemulsion gel and cream respectively.

Yilmaz and Borchart, (2005) focused on the preparation and characterisation of phytosphingosine (PS) containing PN (PPN) which served as colloidal carriers for the dermal application of ceramide IIIIB (CIIIIB) and the stratum corneum (SC) lipids (PPNSC) such as ceramide III (CIII), cholesterol, and palmitic acid. The investigations were conducted using appropriate emulsification and homogenisation processing conditions to optimise PPNSC with regard to droplet size, physical stability, and solubility of PS, CIII and CIIIIB. A decrease in droplet size was observed through eight
homogenisation cycles at a pressure of 500 bars and a temperature of 50 °C. Above these optimal values, an increase in droplet size was observed. When Lipoid E-80 (LE80) was added to the oil phase, the solubility of PS and ceramides increased, indicating some interactions shown by DSC measurements. It was shown that PS was responsible for the positive charge and thus supported the high physical stability of PPNSC.

Alvarez-Romana et al., (2004) evaluated how confocal laser scanning microscopy may contribute to the determination of the mechanisms of diverse skin penetration enhancement strategies.

Amnon et al., (2004) studied new microemulsion vehicle for lidocaine which was composed of glyceryl oleate and polyoxy 40 fatty acid derivatives (surfactants)/tetraglycol (co-surfactant)/isopropyl palmitate/water by constructing pseudo-ternary phase diagrams at fixed co-surfactant/surfactants (CoS/S) ratios. Percutaneous penetration studies using rat skin showed that the transdermal flux of lidocaine was significantly improved by microemulsion composed of the glyceryl oleate–PEG-40 stearate combination rather than glyceryl oleate–PEG-40 hydroxylated castor oil. By analyzing skin layers (epidermis and dermis) for lidocaine content, significant higher concentrations were found after rats were treated in vivo with liquid microemulsions (CoS/S = 1.8, 30 wt.% water) or patches compared to those measured after application of EMLA cream.

Aubrun et al., (2004) prepared nanoemulsions with a high shear device, which was less constraining than spontaneous emulsification procedures. They found that nanoemulsions were easily acceptable in skin care due to their good sensorial properties (rapid penetration and merging textures) and their biophysical properties (especially their hydrating power).

Boinpally et al., (2004) attempted to deliver cyclosporine A (CsA) across human cadaver epidermis in vitro using colloidal systems like microemulsion, lecithin vesicles and iontophoresis. Although, passive diffusion did not result in permeation of quantifiable amounts of CsA, a nodal iontophoresis of the negatively charged colloidal systems facilitated the permeation. Lecithin vesicles were better than microemulsion for the
iontophoretic delivery of CsA and appeared to have potential in site-specific immunosuppression.

Brine et al., (2004) studied deoxycholate-AmB (D-AmB) in an immunocompetent and neutropenic murine model of systemic candidiasis through microemulsions. D-AmB was administered at the maximum tolerated dose of 1 mg/kg whereas M-AmB was given at the doses of 1, 2 and 3 mg/kg. Doses were well tolerated due to their reduced toxicity. Kaplan-Meier survival curves showed that the M-AmB treated group had a better survival time than infected mice without treatment used as a control group. The Mann-Whitney W statistical test indicated that it reduced the percentage of mortality and fungal load in the most representative organs.

Bajaj and Eastoe, (2004) studied the electrical conductivity of D$_2$O-in-n-heptane microemulsions stabilized by cationic/nonionic surfactant mixtures as a function of D$_2$O content, surfactant concentration and surfactant mixture composition. Qualitative structural information was drawn from a comparison between the measured conductivity and that predicted by the charge fluctuation model for spherical droplets. The conductivity versus water content curves were found to be typical for water-in-oil systems composed of spherical droplets. From the effect of blending nonionic surfactant with DDAB on the measured conductivities, it was concluded that microemulsion conductivity was independent of the concentration of cationic surfactant (DDAB).

Deen et al., (2004) synthesized a piperazine-based cationic surfactant, N, N dimethyl-N-acryloyloxyundecyl piperazinium bromide (DAOUPB) by a two-step procedure. The monomer was polymerised in two new microemulsion systems: (i) DAOUPB / water / methyl Methacrylate (MMA):hydroxyethylmethacrylate (HEMA) and (ii) DAOUPB /water / acrylonitrile with ethyleneglycol dimethacrylate (EGDMA) as the crosslinking agent. Transparent solid polymeric materials were obtained by photo-initiated polymerisation of some of these microemulsion compositions. Most of the bicontinuous microemulsions investigated gelled within 10 minutes resulting in transparent solid polymers. The swelling of the gels was highly sensitive to pH.
Desai, (2004) studied microemulsion gels (MEGs) containing rofecoxib and rofecoxib solid dispersion with PEG-4000 for rapid percutaneous absorption. Topical MEGs were prepared by using neat rofecoxib as well as its solid dispersion to compare the efficacy of individual MEG with conventional gel (CG). MEGs containing rofecoxib-PEG 4000 solid dispersion exhibited higher drug permeation when compared to MEG containing neat rofecoxib. MEGs containing rofecoxib-PEG 4000 solid dispersion exhibited faster anti-inflammatory activity than CG.

Podlogar et al., (2004) prepared and examined pharmaceutically usable microemulsion systems from water and isopropyl myristate with a constant amount of Tween 40 and Imwitor 308 at a mass ratio of 1:1. Results of conductivity, viscosity, density and surface tension measurements confirmed the prediction of a percolation transition to a bicontinuous structure. DSC detected the degree of water interaction with surfactants thus identifying the type of microemulsion.

Porrasa et al., (2004) studied the formation of w/o nanoemulsions in water/mixed nonionic surfactant/oil system by a condensation method. The appropriate ratio between two surfactants was studied. The existence of microemulsion, nanoemulsion and emulsion regions was investigated by studying samples stability using backscattering with time multiple light scattering technique. These studies allowed determination of zones where nanoemulsions were formed. For low water concentration, nanoemulsions breakdown was attributed to ostwald ripening and for high water concentration, nanoemulsions breakdown was attributed to coalescence.

Richter and Keipert, (2004) investigated the in vitro permeability of androstenedione as a highly lipophilic drug in excised bovine nasal mucosa, porcine cornea and the artificial cellulose membrane Nephrophan. Results showed that structure and character of different membranes were considered to be mainly responsible for the different permeation behaviour.

Sari et al., (2004) found that the solubilities of the levamisole HCl and abamectin were higher in the isotropic MCMDG/sesame oil/water formulations than in equivalent MCMDG/water formulations. In some formulations, the solubility of levamisole HCl was
higher in the absence of abamectin than in combination with abamectin. Isotropic MCMDG/oil/water systems were obtained without the use of co-surfactants. Increasing water content in the system did not proportionally increase the solubility of hydrophilic drug. Solubilization of hydrophilic drug was affected by lipophilic drug in the presence or absence of SO and lipophilic drug solubility was affected by hydrophilic drug in the absence of SO. These systems were found to be suitable vehicles to deliver both hydrophilic and lipophilic drugs and could be of interest for pharmaceutical formulations.

Yuksel, (2004) investigated the influence of chain length of the alkanes and alcohols on water solubilization behavior of microemulsions. Microemulsions were produced by mixing different combinations of the non-ionic surfactants Triton X-100 and Triton X-405, n-alkanes (C6, C7, C8 and C10) and benzene as oils, n-alcohols (C5 and C7) as cosurfactants with water. The solubilization of water in a particular microemulsion was governed by the partitioning of alcohols among oil, water and interfacial phases, depending on the chain length and nature of oil and alcohol, and their interaction with the surfactant.

Blanks et al., (2003) investigated the phase behaviour of microemulsions stabilized by mixtures containing a strongly amphiphilic double chain cationic surfactant with a weakly amphiphilic short chain alcohol and found that microemulsions stabilized by mixtures of hydrogenated tallow di-methyl ammonium bromide (2HT) and weak propan-2-ol (IPA) amphiphile, showed monolayer curvature and the extent of microstructure could be tuned.

Bisceglia and Acosta, (2003) measured layer bending rigidities for an AOT- water- iso-octane microemulsion by electric deformation and temperature dependent fluctuation mode analysis. The values of rigidity obtained by electric deformation method were lower when computed with the fluctuation mode analysis. The dependence of the rigidity values on the methods of calculation suggested that the mathematical approach based on static method was more reliable than the dynamical one.

Escribano et al., (2003) studied transdermal permeation of four liquid formulations of 1% (w/w) sodium diclofenac: three ternary solvent systems (M4, M5, M6) and one
microemulsion (M3) through human skin. A 1% (w/w) solution of sodium diclofenac and a commercially available semisolid preparation were tested as reference formulations. The highest values of permeability parameters were obtained with formula M4, which contained transcutol 59.2%, oleic acid 14.9% and d-limonene 5% (w/w) as permeation enhancers.

He et al., (2003) prepared paclitaxel microemulsions with small particle size and evaluated its hypersensitivity reaction. They found that paclitaxel microemulsions caused less toxicity and had a longer circulation time in rats as compared to Taxol.

Jumping et al., (2003) evaluated injectable microemulsions of vincristine (M-VCR) for its pharmacokinetics, acute toxicity and antitumor effects and found that M-VCR was a useful tumor targeting microemulsion drug delivery system.

Jurkovic et al., (2003) investigated the effectiveness of amphiphilic antioxidant ascorbyl palmitate against free radical formation in porcine skin. In this study, three different radicals were identified in UV irradiated porcine ear skin: two originated from sulphur centred radicals, while the third was the carbon-centred acyl radical. Ascorbyl palmitate applied on the skin decreased the level of formation of free radicals. O/W microemulsions delivered ascorbyl palmitate to the skin significantly better than W/O microemulsions.

Mei et al., (2003) developed controlled release delivery systems such as solid lipid nanoparticle (SLN) and microemulsion for triptolide and evaluated their transdermal delivery capacity and anti-inflammatory activity. The results indicated that these SLN dispersions and microemulsions could serve as efficient promoters for the triptolide penetrating into skin. The anti-inflammatory activity of SLN dispersion was stronger than that of microemulsion in carrageenan induced rat paw edema.

Nandi et al., (2003) reported the effect of alkanols and cyclodextrins on the phase behavior of an isopropyl myristate microemulsion system and studied the solubility of model drugs, progesterone and indomethacin. A correlation between the carbon numbers of the alkanol and water assimilation capacity in the microemulsions studied was observed. Isobutanol and isopentanol produced the best results. The addition of
cyclodextrins showed no effect or had a negative effect on the microemulsion formation based on the type of cyclodextrin used. Isopropyl myristate-based microemulsion systems alone could increase the solubility values of progesterone and indomethacin up to 3300-fold and 500-fold, respectively, compared to that in water. However, the addition of cyclodextrins to the microemulsion systems did not show a synergistic effect in increasing the solubility values of the model drugs.

Peltola et al., (2003) investigated microemulsions as delivery systems for estradiol. Transdermal flux of estradiol was determined using Franz-type diffusion cells and the samples were analyzed by HPLC. The permeation data showed that microemulsion formulations increased estradiol flux 200–700 fold over the control, but permeability coefficients were decreased by 5–18 times. The superior transdermal flux of estradiol was due to 1500-fold improvement in solubilization of estradiol by microemulsions. The results suggested the use of microemulsions as potential vehicles for improved topical delivery of estradiol.

Rodriguez et al., (2003) investigated the phase behavior and structure of sucrose ester/water/oil systems in the presence of long-chain cosurfactant (monolaurin) and small amounts of ionic surfactants by phase study and small angle X-ray scattering. In a water / sucrose ester / monolaurin / decane system at 27°C, instead of a three-phase microemulsion, lamellar liquid crystals were formed in the dilute region. The addition of small amounts of ionic surfactant increased the solubilization of water in w/o microemulsions. The solubilization of oil in o/w microemulsions was not much affected, but structuring was induced and a viscous isotropic phase was formed.

Spicoli et al., (2003) selected o/w and w/o microemulsions as carrier systems for topical delivery of sodium ascorbyl phosphate. They showed that sodium ascorbyl phosphate was stable in both types of microemulsion with no significant influence of its location in the carrier system. They obtained liquid microemulsions for topical application by adding thickening agents. They found that presence of thickening agent and the location of sodium ascorbyl phosphate in the microemulsion influenced the in vitro drug release profiles. When incorporated in the internal aqueous phase, sustained release profiles were
observed. This study confirmed microemulsions as suitable carrier systems for topical application of sodium ascorbyl phosphate.

Trotta et al., (2003 a) determined the significance of ion pairing on the topical permeation of retinoic acid (R.A) using microemulsions as delivery vehicles. Results of diffusion studies through polydimethylsiloxane membrane (PDMS) indicated that retinoic acid permeation from ethanol-pH 6.4 buffer mixture significantly increased in the presence of counter ions. In order to develop alternative formulations for topical administration of R.A, microemulsions were evaluated as delivery vehicles. Experiments with PDMS membranes showed decreasing permeabilities of R.A from microemulsions in the presence of counter ions. This was related to the increased lipophilicity and different vehicle membrane affinity of the ion pairs. The results suggested that O/W microemulsions containing a counter ion can be used to optimise drug targeting without a concomitant increase in systemic absorption.

Trotta et al., (2003 b) prepared and evaluated nanoparticles of gresiofulvin from dilutable microemulsions by the solvent diffusion technique. Solvent-in-water microemulsions were investigated by construction of pseudoternary phase diagrams. The displacement of butyl lactate with an excess of water from the internal phase of microemulsions containing drug into the external phase, lead to successful fabrication of drug nanosuspensions. They found increased dissolution rate of gresiofulvin from nanosuspensions.

El-iaithy and El-Shaboury, (2002) evaluated the influence of vehicle on the release and permeation of fluconazole from cutina lipogels and gel microemulsion. They found better antifungal activity with gel microemulsion as compared to cutina lipogels and concluded that gel microemulsion were an excellent vehicle for fluconazole topical drug delivery.

Kreilgaard, (2002) reviewed that microemulsion vehicles have been frequently employed over recent years to increase cutaneous drug delivery. He also reviewed that microemulsion formulations have been shown to be superior for both transdermal and dermal delivery of particularly lipophilic compounds, but also hydrophilic compounds.
appear to benefit from application in microemulsions compared to conventional vehicles, like hydrogels, emulsions and liposomes.

Paolino et al., (2002) investigated the potential application of highly biocompatible o/w microemulsions as topical drug carrier systems for the percutaneous delivery of ketoprofen. The topical carrier potentialities of lecithin-based o/w microemulsions were compared with respect to conventional formulations, i.e. a w/o emulsion, a o/w emulsion and a gel. The percutaneous adsorption of the various topical formulations was evaluated through healthy adult human skin. Ketoprofen-loaded microemulsions showed an enhanced permeation through human skin with respect to conventional formulations. The human skin tolerability of various microemulsion formulations was evaluated on human volunteers. Microemulsions showed a good human skin tolerability.

Pitaksuteepong, (2002) studied the effect of drug properties and method of loading (sorption and encapsulation) on entrapment within poly(alkyl cyanoacrylate) nanocapsules prepared by interfacial polymerisation of biocompatible water-in-oil microemulsions. Entrapment efficiency within the negatively charged nanocapsules (zeta potential approximately 230 mV) was in the decreasing order of cationic compound, neutral compound and anionic compound. Only minimal differences for entrapment efficiency were noted between sorption (addition of the compound 4 h after initiation of the polymerisation) and encapsulation (addition of the compound to microemulsion prior to polymerisation).

Taha et al., (2002) utilized data mining, computer-aided molecular modeling, descriptor calculation and multiple linear regression techniques to produce statistically significant and predictive models for o/w and w/o microemulsions. The generated models were statistically cross-validated and were found to be of significant predictive power. Furthermore, the resulting models allowed better understanding of the process of microemulsion formation.

Yang et al., (2002) developed a novel transdermal formulation, microemulsion for aceclofenac to increase its skin permeability. Microemulsion was prepared by
spontaneous emulsification method. Skin permeation of microemulsion from microemulsion formulation was higher than that of cream.

Acharya et al., (2001) investigated microemulsification of eucalyptol / polyoxyethylene (4) lauryl ether (Brij-30) / ethanol / water. The phase behaviours of the mixed system in pseudoternary and tetrahedral representations were examined to understand the topological nature of the multicomponent mixtures. Phase volumes of the heterogeneous combinations were estimated to understand the mixing efficacy of the combinations.

Alvarez-Figueroa et al., (2001) investigated the effectiveness of transdermal administration of methotrexate (MTX) by iontophoretic delivery from two type of hydrogel and passive delivery from two types of microemulsions. The results showed that both hydrogels and microemulsions may be of value for the topical administration of MTX in the treatment of psoriasis.

Hamouda et al., (2001) tested a novel non-ionic surfactant nanoemulsion designated 8N8 for its biocidal activity. One percent 8N8 produced effective bactericidal activity, virucidal activity and fungistatic activity against all tested strains of bacteria, virus and fungi respectively in 15 minutes. The rapid and non-specific inactivation of vegetative bacteria and enveloped viruses, made 8N8 a potential candidate for use as a topical biocidal agent.

Wu et al., (2001 a) prepared a variety of w/o nanoemulsions using Span80, Tween80, olive oil and water. The nanoemulsions were tested for their ability to facilitate transport of a model hydrophilic solute, inulin, across hairless and hairy mouse skin and hairy rat skin following topical in vitro application. The rate and extent of inulin transport across hairy mouse skin was found to be highly dependent on HLB of the surfactant mixture in the nanoemulsion. Nanoemulsions prepared using mixtures with lower HLB exhibited significantly higher rate and extent of transport. More importantly, transport of inulin from nanoemulsions was independent of animal skin characteristics such as stratum corneum thickness and follicle-type.

Wu et al., (2001 b) formulated expression plasmids encoding chloramphenicol acetyltransferase (CAT) or human interferon-α2 cDNA in w/o nanoemulsions and
applied to murine skin. The results suggested that w/o nanoemulsions can be used to facilitate transfection of follicular keratinocytes in vivo.

Baroli et al., (2000) evaluated microemulsions as delivery vehicles for the topical administration of 8-MOP. The ability of the systems to deliver 8-MOP into and through the skin was evaluated in vitro using newborn pig-skin. The in vitro permeation data showed that the novel microemulsions increased the 8-MOP total penetration through the skin by order of 1.9–4.5, as compared with IPM. These results suggested that the studied microemulsion systems may be appropriate vehicles for the topical delivery of 8-MOP.

Ceschel et al., (2000) investigated the diffusion and permeation of Salvia desoleana Atzei & Picci (S. desoleana) essential oil through porcine buccal mucosa. Topical formulations (microemulsions, hydrogels and microemulsion hydrogels) were prepared for application to the buccal mucosa. The diffusion of the oil through the membrane was determined by evaluating the amount of essential oil components present in the receiving solution, the flux and the permeation coefficient (at the steady state) in the different formulations at set intervals. Qualitative and quantitative determinations were done by gas chromatographic analysis. All the formulations allowed a high permeability coefficient in comparison with the pure essential oil. In particular, the components with a terpenic structure (b-pinene, cineole, a-terpineol and linalool) had the highest capacity to pass through the porcine buccal mucosa when compared to the other components (linalyl acetate and a-terpinil acetate).

Kreilgaard et al., (2000) investigated the influence of structure and composition of microemulsions (Labrasol/Plurisol Isostearique/isostearic isostearate/water) on their transdermal delivery potential of a lipophilic drug (lidocaine) and a hydrophilic model drug (prilocaine hydrochloride), and compared the drug delivery potential of microemulsions to conventional vehicles. Self-diffusion coefficients determined by pulsed-gradient spin-echo NMR spectroscopy and $T_1$ relaxation times were used to characterise the microemulsions. Transdermal flux of lidocaine and prilocaine hydrochloride through rat skin was determined in vitro using Franz-type diffusion cells. Microemulsions increased transdermal flux of lidocaine up to 4 times compared to a conventional oil-in-water emulsion, and that of prilocaine hydrochloride almost 10 times.
compared to a hydrogel. The increased transdermal drug delivery from microemulsion formulations was found to be mainly due to the increased solubility of drugs and appeared to be dependent on the drug mobility in the individual vehicle.

Scherlund et al., (2000) investigated environmentally responsive drug delivery systems as interesting development. Example of such development involved the use of thermosetting microemulsions as delivery systems for periodontal anesthesia. In this case, a block copolymer liquid microemulsion containing lidocaine and prilocaine was designed to form a gel after in vivo administration to the periodontal pocket.

Chung et al., (1999) produced thermoresponsive polymeric block copolymer micelles based on poly (N isopropylacrylamide) and poly (butylmethacrylate) containing adriamycin.

Park et al., (1999) investigated the possibility for parenteral delivery of flurbiprofen without chemical modification using a phospholipid-based microemulsion system. They concluded that the microemulsion system might be applicable to formulate the parenteral dosage form of poorly water-soluble flurbiprofen without chemical modification.

Soderman and Nyde, (1999) investigated microemulsions prepared by mixing the double chained surfactant didodecyldimethylammonium sulfate (DDAS), water, dodecane and hexadecane using NMR self-diffusion approach. At low surfactant-to-oil ratios the aggregates were discrete and spherical in shape. As the surfactant-to-oil ratio was increased, the surfactant aggregates changed shape and the structure evolved into a bicontinuous microemulsion. In extracting this information from the experimentally determined self-diffusion coefficients, authors made use of reduced diffusion coefficients, which were obtained by dividing the observed diffusion coefficients with the values pertaining to diffusion in a system. The observation that the reduced diffusion coefficients for the surfactant and oil were equal at high surfactant-to-oil ratios indicated that the structure was truly bicontinuous over distances on the order of mm.

Trotta, (1999) reported the release rates of indomethacin from microemulsions containing water, isopropyl myristate, lecithin, lysolecithin and alcohol. Depending on the composition, the microemulsions transformed on contact with the release medium.
into emulsions, liquid crystals, or remained as microemulsions. The release rates were found to be dependent on the size of the disperse phase after dilution with the release medium, and on the alcohol used in the formulation. Microemulsions that remained transparent after dilution produced rate constants lower than those that transformed into emulsions. The rate constant for the microemulsion that transformed into liquid crystals were not calculated because of the broad dispersion, but the percentage of drug released was much lower than those from the others systems.

Malcolinson et al., (1998) reported that microemulsions prepared from ethyl esters and triglyceride oils exhibited a significant increase in solubilization over the corresponding micellar solution. Light scattering and phase inversion temperature studies suggested that the structure of the microemulsion was sensitive to the oil being used. The smaller molecular volume oils generally permitted the interfacial surfactant monolayer in much the same way as a cosurfactant, causing an alteration, presumably a dilution, of the relatively concentrated polyoxyethylene region close to the hydrophobic core, thereby destroying one of the main loci of drug solubilization and counteracting any advantages encountered due to the high solubility of the drug in the bulk oil.

Cortesi et al., (1997) reported that the microemulsion formulation for Camptothecin (CPT) was optimal when Labrasol, Plurol isostearate and isostearyl isostearate was used as surfactant, cosurfactant and oil components respectively. CPT solubility in microemulsion was, in fact, at least five-fold higher with respect to that displayed by the micellar solution of polysorbate and almost 23 fold higher than that in water.

2.4. Commercial preparations of psoralen:

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Composition</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manademi tab</td>
<td>Psoralen 10 mg</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Manaderm oint</td>
<td>Psoralen 10 mg/g</td>
<td>Wyeth</td>
</tr>
<tr>
<td>Melanocyl tab</td>
<td>Psoralen 10 mg</td>
<td>Franco India</td>
</tr>
<tr>
<td>Chromalin tab</td>
<td>Psoralen 10 mg</td>
<td>Smith stanistreet</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pharmaceuticals Ltd.</td>
</tr>
</tbody>
</table>