Novel Delivery Systems for the Treatment of Vitiligo

Chapter 1
1. Introduction

Vitiligo (leukoderma) is a pigmentation disorder in which melanocytes, the cells that make pigment and give color to the skin, are destroyed. This results in smooth, white patches in the midst of normally pigmented skin. The term vitiligo is probably derived from the Latin word *Vitilus* — meaning calf and was first named by Roman physician Celsus of first century AD. People with vitiligo may also have eye abnormalities and have a higher incidence of thyroid disease, diabetes mellitus, and pernicious anemia. 1–2% of the world's population seeks treatment for this autoimmune disorder. White patches appear on the skin in different parts of the body. Similar patches also appear on both the mucous membranes (tissues that line the inside of the mouth and nose), and the retina (inner layer of the eyeball). The hair that grows on areas affected by vitiligo sometimes turns white. It can begin at any age but in about 50% it starts before the age of 20 (Njoo and Westerhof, 2001).

1.1. Factors

Vitiligo is a disorder with complex causes. The emergence of white patches can be brought on by a variety of impulsive causes. Many people report that their vitiligo first appeared following a stressful event, such as an accident, job loss, death of a family member, severe sunburn, or serious illness (Bystryn J C, 1997). There are mainly three theories about the underlying mechanism of vitiligo. One theory states that nerve endings in the skin release a chemical that is toxic to the melanocytes. A second theory states that the melanocytes simply self-destruct. The third theory is that vitiligo is a type of autoimmune disease in which the immune system targets the body's own cells and tissues.

1.1.1. Autoantibody responses

Antibodies to melanocytes are in the blood of patients with vitiligo. These antibodies are related to the extent of the disease being detected in 50% of patients with minimal vitiligo compared with 93% of patients with greater depigmentation. Immunofluorescence has detected that the binding of vitiligo patient Immunoglobulin G to cultured melanocytes increased with disease extent and activity. Some vitiligo autoantigens appear to be
expressed on cells other than melanocytes. The most valuable contribution is that studies on anti-melanocyte antibody reactivity can make help in identifying relevant target antigens (Kemp et al., 2007).

1.2. Treatments

1.2.1. Autoimmune vitiligo T cells

The skin is made up of keratinocytes and melanocytes. The keratinocytes make up the bulk of the skin. The melanocytes are the cells that make the skin color. In people with vitiligo, the immune cells which fight infection, attack the melanocytes and damage them (Bystryn J C, 1997). When the melanocytes in a certain area die, the skin turns white. Vitiligo sometimes runs in families, meaning that a genetic factor may be involved. Vitiligo sometimes occurs at the site of an old injury. Even though the condition cannot be cured drastically, medical treatments target the immune system, and try to reverse the destruction (Kovacs S O, 1998). The goal is to restore the skin's color by restoring healthy melanocytes to the skin (repigmentation) allowing the skin to regain its normal appearance (Schallreuter K U, 2004). T cells are more common in vitiligo skin and remains in lesional area but most of the infiltrate appears to migrate with the depigmenting epidermal border. The infiltrate consists not only of CD8 but also of CD4 T cells. Skin infiltrating T cells can be isolated and propagated without antigen selection in the presence of IL-2 and anti-CD3/anti-CD28 antibody coated beads. T cells have been isolated from perilesional skin of a vitiligo patient. These T cells were found to have similar reactivity towards vitiligo patient melanocytes. Autoimmune response may be allowed to grow and develop in the absence of functional T regulatory cells. These cells actively mediate suppression of the immune system generally by secreting IL-10 and TGF-β to prevent autoimmunity. Polyclonal cytotoxic T cells derived from vitiligo skin are highly reactive towards melanoma cells and may serve as a superior source of high affinity TCR genes to treat melanoma (Valencia et al., 2006).

1.2.2. Steroids

Steroid creams are the first line of treatment. They are usually applied twice daily, and results require three to six months. Side effects are observed when overdosed, which
include local skin damage, and glaucoma or cataracts when used around the eyes (Kwinter et al., 2007). Regular monitoring and adjusting the potency of the creams to be appropriate for the location can avoid these side effects.

1.2.3. PUVA

For extensive vitiligo, oral medications of psoralen and phototherapy by ultra violet rays (PUVA) can be tried. It takes at least 2–3 months or about 200 treatment sessions required to have an effect. PUVA is partially successful in those treated, but complete repigmentation occurs in only 15–20%. Repigmentation occurs slowly as the cells creep back in over months to years.

1.2.4. Water bath PUVA

The most recent model in phototherapy is water bath PUVA, in which the patient lies in a bath tub containing psoralen water for 15 min so that the drug gets absorbed on the skin and then goes for light therapy. This kind of therapy is especially beneficial in children for whom oral medicines are not safe (Aragane et al., 2001). Another method of psoralen treatment, used rarely for pediatric patients with small, scattered vitiligo patches, involves the application of a very dilute solution of the drug directly to the affected skin area. This is then exposed to sunlight. Such topical treatment makes a person very liable to severe burn and blisters following too much sun exposure whereas water bath PUVA has the advantages of being done at home, and does not damage the entire skin surface.

1.2.5. Narrow band UVB therapy

Narrow band UVB therapy or TL-01 therapy is the latest in phototherapy for the treatment of vitiligo. In this therapy there is no need to take oral psoralen or apply psoralen. The therapy is very safe and can be safely administered even to children. Narrow band UVB light is at a wavelength of 311 nm. Narrow band UVB is much safer than full spectrum UVB. Narrow band UVB is the faithful wavelength that vitiligo responds to best (Kanwar and Dogra, 2005). It's a fact that if exposure to natural sunlight is equal to 100% UV radiation exposure, using a narrow band UV light is roughly 1% UV radiation exposure.
1.2.6. Tissue grafts

The grafts will be implanted into perforations made at the recipient site using a biopsy punch under local anaesthesia. The grafts should be placed 4–8 mm apart because apparently pigment cells seem not to migrate beyond 5 mm. The grafted area will then be covered with petrolatum gauze or a transparent adhesive tape and secured with bandages to give compression and fixation for at least one week. The success rate of this technique depends upon the individual skin type (Khunger et al., 2009, Parsad and Gupta, 2008). Difficult areas like lips can also be treated using this technique. Repigmentation is based on the pigment spread phenomena by the grafted piece of normal skin. Pigment spread occurs gradually after grafting within 1 month and full repigmentation can be achieved in 3–6 months (Van Geel et al., 2001).

1.2.7. Split thickness skin grafts

This technique has a high success rate of 78–91%. After obtaining a split thickness skin graft using a dermatome it can be applied directly to the derma braded recipient area. Temporary small epithelial milia like cysts can be observed in the recipient area during the first months, especially on the face and neck. Scar or keloid formation at the donor site is reported in 12% of the patients treated with split thickness grafts. As donor tissue is limited more than one split skin grafting session can be necessary (Ozdemir et al., 2002).

1.2.8. Suction blister grafts

Grafts are carefully removed with sharp scissors and forceps after harvesting the graft. This epidermal sheet is then grafted onto the denuded recipient site. The success rate is 73–88%. Pigment spread after epidermal blister grafting can be enhanced by pre operative radiation therapy of the donor site using PUVA. Temporary hyper pigmentation can be seen in the grafted sites in 2–65% (Ozdemir et al., 2002).

1.2.9. Non cultured keratinocytes and melanocytes

Transplantation technique with a suspension of non cultured keratinocytes and melanocytes in the treatment of depigmented lesions is effective. Donor skin is obtained
from the occipital area and immersed for 18 h in 0.25% trypsin solution. The following day the epidermis of the donor skin can be separated from the dermis in vitro using fine forceps. After several procedures a cellular suspension is obtained (Mysore and Salim, 2009). Liquid nitrogen is used to induce blisters in the recipient area. The cellular suspension from the donor site is injected into each blister at the recipient area after aspiration of the viscous blister fluid. The intact blister top is a natural dressing that holds the transplanted cells in place. It is important not to separate keratinocytes from melanocytes before grafting because factors furnished by keratinocytes sustain melanocyte growth (Ozdemir et al., 2002).

1.2.10. Transplantation of cultured melanocytes

Lerner and coworkers, first described the use of cultured pure autologous human melanocytes. They explained pigment cells of a shave biopsy from normally pigmented skin in vitro with the addition of several growth factors and chemical media (Lerner et al., 1987).

1.2.11. Cultured epidermal grafts

A shave biopsy of normally pigmented skin is the source for epidermal cell culture. After separating the epidermis from the dermis the cells are seeded in a medium that allows co-cultivation of melanocytes and keratinocytes. After a week a cultured sheet is obtained, released by treatment with dispase and attached to petrolatum gauze as support. Subsequently the gauze to which the epithelium adheres will be applied onto the dermabraded recipient site and covered with occlusive dressing (Barclay L, 2003). The greatest advantage of this technique is the potential expansion of the cells in culture, which permits treatment of a wide area of hypomelanosis with a small sacrifice donor skin. Because only superficial derm abrasion is performed, the procedure is non scaring (Barclay L, 2003).

1.2.12. Stability in surgical repigmentation of vitiligo

Even after almost thirty years of implementing surgery in vitiligo, there seems to be little consensus among workers regarding the optimal required period of stability. After several
years of experience in surgical repigmentation of vitiligo, some interesting observations are raising up. The observation is that even after grafting, the pigment spread from successive sessions of grafting can be unpredictable; perigraft spread of pigment may be minimal or absent and in some cases even depigmentation of grafts is noted (Lahiri K, 2009).

1.2.13. Autologous skin grafts

This type of skin grafting is often used for patients with small, stable patches of vitiligo (recipient sites). Normal unaffected skins from the thigh or buttocks area of a patient's body (donor sites) were taken and fixed it to an area of vitiligo. The treated area responds almost 90% of the time, but may develop a cobblestone appearance, or a spotty pigmentation, or may fail to re-pigment at all (Lahiri K, 2009).

1.2.14. Fake tanning products

Cover creams or self tanning products are special drug cosmetics that can be used to match most skin patches when medical treatment is not successful. All patients with vitiligo should always protect their depigmented skin against excessive sun exposure by wearing protective clothing. Tattooing is rarely recommended. It works best for the lip area, particularly in people with dark skin. However, it is difficult to perfectly match the skin, and tends to look worse over time. The remaining skin will be an even white color, which can then be covered with the cosmetics. Cosmetics can be used to improve the appearance of the white areas not covered by clothing. Sunscreens give coolness to the affected areas and also prevent the normal skin around the patches from becoming darker. Bleaching or depigmentation of the normal skin and autologous transplantation of skin are an option for those who are severely affected (Berti et al., 2008).

1.2.15. Vitamin D analogues

Combination of PUVA (psoralen-sun therapy) and calcipotriol is highly effective and may be used for shortening the therapy with PUVA in the treatment of patchy areas of vitiligo depigmentation (Parsad et al., 1998). Topical calcipotriol appeared to be an
effective and well tolerated treatment for vitiligo and it can be safely used in conjunction with PUVA (Ameen M, 2001).

1.2.16. Pseudocatalase

It has been shown that patients with vitiligo have an extremely low catalase activity (Ameen M et al., 2001). Topical application of pseudocatalase (a low molecular weight inorganic complex of unknown formula with catalase activity) used in combination with short term UVB light exposure has been reported in an open study to show repigmentation. Complete repigmentation on the face and dorsum of the hands appeared in 90% of those treated (Ameen M, 2001).

1.2.17. Herbal products

1.2.17.1. Anti-vitiligo® (True Herbals, Lahore, Pakistan)

Anti-vitiligo® (True Herbals, Lahore, Pakistan) is a traditional herbal formulation which was available internationally since November 2003. It is effective both in disease of recent onset as well as long standing established cases. Formulation contains the following ingredients.

Psoralea corylifolia

It is a rich source of naturally occurring psoralen. It sensitizes human skin to the tanning effect of UV and sun light. *P. corylifolia* has been traditionally used both orally as well as in the form of topical preparations. Oxidative stress is widely believed to be one of the likely causative factors in the initiation of white skin patches of vitiligo. Hence, the protective, anti-oxidative and anti stress properties of *P. corylifolia* may contribute to the improvement in the hypo-pigmented white skin patches of vitiligo.

Black cumin

Seeds of *Nigella sativa* have also been having an immunomodulatory as well as anti cancer effect, which is due to augmentation of T cell and natural killer cell mediated immune responses (Tahir et al., 2010).
Barberry root

Barberry root or the root of *Berberis vulgaris* contains numerous chemicals and bioactive compounds of medical significance. It contains for example the alkaloids like berbamine, berberine, and oxyacanthine. Other compounds include tannins, chelidonic acid and resins. It is also quite rich in B-vitamin thiamine, lutein, vitamin C, beta-carotene, zeaxanthin, zinc, chromium, and cobalt. This herb has also been shown in scientific studies to possess antioxidant and cytoprotective properties (Tahir et al., 2010).

1.2.17.2. Kalawalla® (American Life Style, New York, USA)

Kalawalla® (American Life Style, New York, USA) is a herbal product that works as a natural immunomodulator with proven immunomodulating effect. The product contains *Polypodium leucotomos* standardized extracts. *P. leucotomos* is a fern plant extract that has been used in Europe to treat vitiligo for over 10 years with encouraging results. Vitiligo is characterized by skin depigmentation and is commonly associated with the immune system. The extract can help to regulate the immune system bringing it to its healthiest, strongest and balanced levels. Repigmentation results can be seen within the first month of taking the product. *P. Leucotomos* standardized extract has been known to increase the lymphocyte levels. It is also known to regulate the CD4/CD8 ratios to their normal values (Tahir et al., 2010). This product contains (per capsule): *P. leucotomos* extract 120 mg and *P. leucotomos* rhizome 280 mg.

1.2.17.3. Piperine

The synthetic derivatives of piperine can stimulate pigmentation in the skin especially when combined with UVR treatment (Tahir et al., 2010). The studies have compared the effects of piperine and its analogues tetrahydropiperine (THP), cyclohexyl analogue of piperine (CHP) and reduced CHP (rCHP) when applied to the skin of mice, either alone or followed by UV treatment. CHP did not show significant results while piperine, THP and rCHP did induce pigmentation in the skin. When used alone, the compounds stimulated pigmentation to an even, light brown color within six weeks. However, by accompanying the use of piperine or THP with UV, the skin became significantly darker,
and within only seven weeks as compared to other treatments which take a year or so (Tahir et al., 2010).

1.3. Current and future developments

It is clear that vitiligo is a common disease. It spares no sex, age, or race. Vitiligo remains a challenging disease to researchers and clinicians. The pathogenesis is still unknown and constitutes a huge research innovation for those interested in melanocyte biology and pigmentation disorder. Education, support groups, counseling and psychotherapy can be implemented in the management of many patients, as can cosmetic camouflage of the myriad therapies reported to repigment vitiliginous skin lesions, maximal results are most often achieved with oral or topical PUVA. The route of administration of PUVA therapy should be adjudicated by age, severity and progression of disease. Significant cosmetically acceptable repigmentation can be achieved in many vitiligo patients treated with PUVA. Topical steroids are probably first line therapy for most patients. In selected cases depigmentation with monobenzyl ether of hydroquinones gives excellent cosmetic results. There are a number of other therapies such as surgical techniques that seem promising; however, further studies are both necessary and eagerly awaited.

Vitiligo is one of several dermatologic disorders that are easy to minimize because it is often dismissed as a cosmetic problem. In this era of medical cost containment, vitiligo is in danger of being left behind. While it is easy to reassure patients that vitiligo will not shorten their lives or lead to physical disability, it is very difficult to fix the problem. Often patients endure extreme psychological stress as a result of their illness. Therapy has not been satisfying for vitiligo patients. But now the time has come to offer patients therapy and hope. However the treatment of vitiligo remains a challenge.

1.4. Novel drug delivery systems

Drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. Thus the method by which a drug is delivered can have a significant effect on its efficacy. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the
delivery of therapeutics to target in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. These strategies are called as drug delivery systems (DDS) and are based on interdisciplinary approaches (Kaparissides et al., 2006; Santini et al., 2000).

Controlled drug release and subsequent biodegradation are important for developing successful formulations. Potential release mechanisms involve desorption of surface-bound/adsorbed drugs, diffusion through the carrier matrix, diffusion (in the case of nanocapsules) through the carrier wall, carrier matrix erosion and a combined erosion/diffusion process. The mode of delivery can be the difference between a drug’s success and failure, as the choice of a drug is often influenced by the way the medicine is administered (Kaparissides et al., 2006; Reddy and Swarnalatha, 2010; Torchilin, 2001).

Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature) (Kaparissides et al., 2006).

One of the primary objectives in the design of novel drug delivery systems (NDDS) is the controlled delivery of the pharmacological agent to its site of action at a therapeutically optimal rate and dosage regimen. This site specific or targeted delivery combined with delivery at an optimal rate will improve the efficacy of the drug and reduce the possibility of unwanted toxic side effects. Thus the therapeutic index of the drug could be enhanced (Kreuter, 1994). Colloidal drug delivery systems are the most promising systems to achieve this goal.

Colloidal drug carrier systems (Muller-Goymann, 2004; Reddy and Swarnalatha, 2010) such as micellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticulate dispersions show great promise as drug delivery systems. When developing these formulations, the goal is to obtain systems with optimized drug loading and release properties, long shelf-life and low toxicity. The incorporated drug participates in the microstructure of the system, and may even influence it due to molecular...
interactions (Reddy and Swarnalatha, 2010). For over 20 years, researchers have appreciated the potential benefits of nanotechnology in providing vast improvements in drug delivery and drug targeting. Improving delivery techniques that minimize toxicity and improve efficacy offer great potential benefits to patients, and opens up new markets for pharmaceutical and drug delivery companies. Other approaches to drug delivery are focused on crossing particular physical barriers, in order to target the drug and improve its effectiveness (Kaparissides et al., 2006).

Colloidal drug delivery systems include the drug carrier systems liposomes, niosomes, nanoparticles, and micro/nanoemulsions. Liposomes, niosomes, nanoparticles, and micro/nanoemulsions are very similar in their size, shape and mode of administration, and for this reason they may be used alternatively. Colloidal drug delivery systems can provide site specific or targeted drug delivery combined with optimal drug release profiles.

1.4.1. Sustained Release Tablets

The oral route of drug administration is the route of choice for the formulators and continues to dominate the area of drug delivery technologies. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. When a new drug is discovered, one of the first questions a pharmaceutical company asks is whether or not the drug can be effectively administered by the oral route, for its intended effect. Tablets are the ruling dosage forms since years mainly because of patient acceptance, convenience in administration, and cost effective manufacturing process. We can administer 0.01 mg of a drug dose to 1 g of a drug dose by formulating as a tablet. In the immediate release (IR) dosage form, there is little or no control of drug release from the dosage form, which often results in constantly changing, unpredictable, and often sub- and supra-therapeutic plasma concentrations (Hui et al., 1987). Sustained release (SR) systems have been introduced to overcome the drawback associated with IR dosage forms.

The sustained delivery attempts to;
1) Sustain drug action at a pre determined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a saw tooth kinetic pattern.

2) Localize the drug action by spatial placement of a controlled release system (usually rate controlled) adjacent to or in the diseased tissue or in the organ.

3) Target drug action by using carriers or chemical derivatization to deliver drugs to a particular “target” cell type.

In order to maintain a constant drug level in either plasma or target tissue, release rate from controlled system should be equal to the elimination rate from the plasma or target tissue.

1.4.1.1. Factors influencing the design and performance of sustained release products

1) Drug properties: the physicochemical properties of a drug, including stability, solubility, partitioning characteristics, charge, and protein binding propensity, play a dominant role in the design and performance of sustained release systems.

2) Route of drug delivery: the area of the body in which the drugs will be applied or administered can be restrictive on the basis of technological achievement of a suitable sustained release mechanism or device.

3) Target site: in order to minimize unwanted side effects, it is desirable to maximize the fraction of applied dose reaching the target organ or tissue.

4) Acute or chronic therapy: consideration of whether one expects to achieve cure or control of a condition and expected length of drug therapy are important factors in designing sustained release systems.

5) The disease: pathological changes during the course of a disease can play a significant role in the design of a suitable drug delivery system.

6) The patient: whether the patient is ambulatory or bedridden, young or old, obese or gaunt, etc. can influence the design of a sustained release product (Staniforth J, 2002).
Sustained release tablets are often classified according to the mechanism of drug release. The following are the most common means used to achieve a slow, controlled release of the drug from tablets:

- Drug transport control by diffusion
- Dissolution control
- Erosion control

1.4.1.2. Diffusion-controlled extended release systems

In Diffusion-controlled extended release systems the transport by diffusion of dissolved drugs in pores filled with gastric or intestinal juice or in a solid (normally polymer) phase is the release controlling process. Depending on the part of the release unit in which the drug diffusion takes place, diffusion controlled release systems are divided into matrix systems (also referred to as monolithic systems) and reservoir systems. In both cases the release unit should stay more or less intact during the course of the release process. In matrix systems diffusion occurs in pores located within the bulk of the release unit, and in reservoir systems diffusion takes place in a thin water insoluble film or membrane, often about 5-20 μ thick, which surrounds the release unit. Diffusion through the membrane can occur in the pores filled with fluid or in the solid phase that forms the membrane (Speers and Bonnano, 1999).

Drug is released from a diffusion controlled unit in two steps:

1. The liquid that surrounds the dosage form penetrates the release unit and dissolves the drug. A concentration gradient of dissolved drug is thus established between the interior and the exterior of the release unit.

2. The dissolved drug will diffuse in the pores of the release unit or the surrounding membrane and thus be released, or, alternatively, the dissolved drug will partition into the membrane surrounding the dose unit and diffuse in the membrane.

A dissolution step is thus normally involved in the release process, but the diffusion step is the rate controlling step. The rate at which diffusion will occur depends on four variables: the concentration gradient over the diffusion distance, the area and distance
over which diffusion occurs, and the diffusion coefficient of the drug in the diffusion medium. Some of these variables are used to modulate the release rate in the formulation (Verma et al., 2003).

1.4.1.3. Reservoir systems

In a reservoir system the diffusion occurs in a thin film surrounding the release unit. The diffusion distance will be constant during the course of the release and as long as a constant drug concentration gradient is maintained, the release rate will be constant, i.e. a zero-order release (Jaleh Varshosaz et al., 2006). One possible process for the release of the drug from a reservoir system involves partition of the drug dissolved inside the release unit to the solid membrane, followed by transport by diffusion of the drug within the membrane. Finally, the drug will partition to the solution surrounding the release unit. The driving force for the release is the concentration gradient of the dissolved drug over the membrane.

1.4.1.4. Matrix systems

In a matrix system the drug is dispersed as solid particles within a porous matrix formed of a water-insoluble polymer. Initially drug particles located at the surface of the release unit will be dissolved and the drug released rapidly. Thereafter the drug particles at successively increasing distances from the surface of the release unit will be dissolved and release by diffusion in the pores to the exterior of the release unit. Thus, the diffusion distance of dissolved drug will increase as the release process proceeds (Jaleh Varshosaz et al., 2006). The main formulation factors, by which the release rate from a matrix system can be controlled, are the amount of the drug in the matrix, the porosity of the release unit, the length of the pores in the release unit and the solubility of the drug. The characteristics of the pore system can be affected by the addition of soluble excipients and by the compaction pressure during tabletting.

1.4.1.5. Dissolution-controlled release systems

In Dissolution-controlled extended release systems, the rate of dissolution in the gastrointestinal juices of the drug or another ingredient is the release controlling process.
It is obvious that a sparingly water soluble drug can form a preparation of a dissolution controlled extended release type. Reduced drug solubility can be accomplished by preparing poorly soluble salts or derivatives of the drug. In practice, this approach is a less common way, an alternative means to achieve extended release based on dissolution is to incorporate the drug in a slowly dissolving carrier (Sandip et al., 2006). It can also be obtained by covering drug particles with a slowly dissolving coating. The release of the drug from such units occurs in two steps:

1. The liquid that surrounds the release unit dissolves the coating (rate-limiting dissolution step).
2. The solid drug is exposed to the liquid and subsequently dissolves.

1.4.1.6. Erosion controlled release systems

In erosion controlled extended release systems, the rate of drug release is controlled by the erosion of a matrix in which drug is dispersed. The matrix is normally a tablet and the system can thus be described as a single unit system. The erosion in this simplest form can be described as a continuous liberation of matrix material (both drug and excipient) from the surface of the tablet, i.e. surface erosion. The consequence will be a continuous reduction in the tablet weight during the course of the release process. Drug release from an erosion system can thus be described in two steps:

1. Matrix material, in which the drug is dissolved or dispersed, is liberated from the surface of the tablet.
2. The drug is subsequently exposed to the gastrointestinal fluids and mixed with (if the drug is dissolved in the matrix) or dissolved in (if the drug is suspended in the matrix) the fluid.

In the last two decades, sustained-release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug-embedded matrix tablet that involves the direct compression of a blend of drug, retardant material and additives is one of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is commonly used for...
manufacturing sustained-release dosage forms because it makes such manufacturing easy (Pratap Kumar et al., 2009). A wide array of polymers has been employed as drug retarding agents each of which presents a different approach to the matrix concept. They are

- Plastic matrix systems
- Hydrophobic
- Hydrophilic matrices.

Polymers forming insoluble or skeleton matrices constitute the first category of retarding materials, also classed as plastic matrix systems. The second class represents hydrophobic and water-insoluble materials, which are potentially erodible, while the third group includes polymers those form hydrophilic matrices. Plastic matrix systems, due to their chemical inertness and drug embedding ability, have been widely used for sustaining the release of drug. Liquid penetration into the matrix is the rate-limiting step in such systems unless channeling agents are used. The hydrophobic and waxy materials, on the other hand, are potentially erodible and control the release of drug through pore diffusion and erosion Polymers belonging to hydrophilic matrix systems, when exposed to an aqueous medium, do not disintegrate, but immediately after hydration develops a highly viscous gelatinous surface barrier which controls the drug release and the liquid penetration into the centre of the matrix system.

1.4.2. Nanoemulsion

The nanoemulsions can thus be defined as thermodynamically stable, transparent (or translucent) dispersions of oil and water stabilized by an interfacial film of surfactant molecules having the droplet size less than 100 nm (Shafiq et al., 2007). The observed transparency of these systems is due the fact that the maximum size of nanoemulsion droplets is less than the one-fourth of the wavelength of visible light (approximately 150 nm). Droplet size in thermodynamically stable nanoemulsions is usually 10-100 nm (Sintov and Shapiro, 2004). The surfactant may be pure, a mixture, or combined with other additives. The homogeneous systems that can be prepared over a wide range of surfactant concentrations and oil to water ratios (20-80%) are all fluids of low viscosity.
Nanoemulsions have potential applications whenever it is necessary to mix oil and water, and where a large oil-water interface is required. Nanoemulsion provides ultra low interfacial tension and large o/w interfacial areas. Nanoemulsions being colloidal nanodispersions of oil in water (or water in oil) and thermodynamically stabilized by an interfacial film of surfactant(s) and co-surfactant(s) have revealed tremendous potential in nanoengineering of various inorganic materials (Date and Patravale, 2004). The design of effective formulation for drugs has long been a major challenge, because drug efficacy can be severely limited by instability or poor solubility in the vehicle. Nanoemulsions have a higher solubilization capacity than simple micellar solutions and their thermodynamic stability offers advantages over unstable dispersions, such as emulsions and suspensions, because they can be manufactured with little energy input (heat or mixing) and have a long shelf life. The nanosized droplets leading to enormous increase in interfacial areas associated with nanoemulsions can influence the transport properties of the drug, an important factor in sustained and targeted drug delivery (Eccleston, 1994; Lawrence and Rees, 2000). The attraction of o/w nanoemulsion systems lies in their ability to incorporate hydrophobic drugs into the oil phase thereby enhancing their solubility (Lawrence and Rees, 2000). Nanoemulsions have been reported to make the plasma concentration profiles and bioavailability of drugs more reproducible (Constantinides, 1995; Lawrence and Rees, 2000; Kommuru et al., 2001; Kawakami et al., 2002a; Kawakami et al., 2002b).

1.4.2.1. Structure of Nanoemulsions

Fig. 1.1: An example of the surfactant molecule (Manisha Mishra et al., 2009)
Conventional surfactant molecules comprise a polar head group region and an apolar tail region (Fig. 1.1), the latter having the larger molecular volume particularly in the case of ionic surfactants. On dispersion in water, surfactants self-associate into a variety of equilibrium phases (Fig. 1.2 and 1.3), the nature of which stems directly from the interplay of the various intra and intermolecular forces as well as entropy considerations. Nanoemulsions are the simple, spherical or cylindrical structures formed by the aggregates of micelles that are formed by surfactants (Lawrence and Rees, 2000; Ghosh and Murthy, 2006).

Another nanoemulsion structure is the lamellae in which the water and oil consecutive layers are separated by surfactant layers conveniently oriented. The lamellar structure is similar to the thermotropic phase (Fig. 1.4). It presents birefringence and maintains the
order even at diluted concentrations. This structure is related with the spherulite structure (onion structure) (Fig. 1.4). It is possible that spherulites are only out-of-equilibrium transient lamellar phases induced by mechanical work (yet to be proved) or by other stimulus (Ghosh and Murthy, 2006). The thermodynamic stability of spherulites is still under study.

The bicontinuous structure or sponge phase is quite an intricate structure (Fig. 1.5). As its name suggests, in this structure water and oil are continuous phases. The sponge structure is a good example: the sponge has a continuous structure, but it is possible to "fill" the sponge with a liquid. The liquid forms a continuous phase and the material of sponge also forms a continuous phase. Thinking that the sponge surface is the surfactant of a bicontinuous structure below is given in Fig. 1.5.

Fig. 1.4: The lamellae (L) and the spherulite (S) structures (Manisha Mishra et al., 2009)

Fig. 1.5: Bicontinuous structure (Manisha Mishra et al., 2009)
1.4.2.2. Theories of Nanoemulsion formation

Many approaches have been used to explore the mechanisms of nanoemulsion formation and stability. Some emphasize on the formation of an interfacial film and the production of ultra low interfacial tension (mixed film theories); others emphasize on the monophasic nature of many nanoemulsions (solubilization theories). Thermodynamic theories take into consideration the free energy of formation of the nanoemulsions and the bending elasticity of the film. Eccleston J, 1994 reviewed the various approaches that have been postulated for nanoemulsion formation. Although not a single approach alone covers all aspects of nanoemulsion structure and stability but all have a place in the overall understanding of nano or microemulsions.

1.4.2.3. Mixed film Theories

The early scientific treatment of nanoemulsions was developed by Schulman's school and emphasized the importance of the interfacial film and ultralow interfacial tension (Schulman et al., 1959; Prince LM, 1967). The spontaneous formation of nanoemulsion droplets were considered due to the formation of a complex film at the oil-water interface by the surfactant and cosurfactant. This caused a reduction in the oil-water interfacial tension to a very low value (from close to zero to negative). The mixed interfacial film in equilibrium with both oil and water was considered to be liquid and duplex in nature (i.e., showing different properties at the oil and water sides) with a two dimensional spreading pressure, \( \pi_i \), which determined the interfacial tension \( \gamma_i \) by equation

\[
\gamma_i = \gamma_{o/w} - \pi_i
\]

Where \( \gamma_{o/w} \) represents the oil/water interfacial tension without the film present. When large amounts of surfactant and cosurfactants are adsorbed to form the interface, the spreading pressure, \( \pi_i \), may become larger than \( \gamma_{o/w} \). A negative interfacial tension results and energy is available to increase the interfacial area, thereby effectively reducing droplet size. This negative interfacial tension produced by the mixing of the components is a transient phenomenon, and at equilibrium, it becomes zero or a very small positive value.
A major drawback to Schulman's concept was the high value of the spreading pressure which was necessary to give the transient negative interfacial tension. Prince (Prince, 1967) later postulated that the negative interfacial tension could be a result of the depression of $\gamma_{o/w}$, rather than the unrealistically high initial pressure in the original model. The alcohol cosurfactant partition between the oil phase and the interface, with the fraction in the oil phase was able to significantly depress the $\gamma_{o/w}$ from its normal value of approximately 50 mN/m to a new value ($\gamma_{o/w}$) of around 15 mN/m.

The interfacial film must be curved to form small droplets, and the concept duplex film was used to explain both the stability of the system and the bending of the interface. A flat duplex film would be under stress because of the different tension and spreading pressure on either side of it. The reduction of this tension gradient by equalizing the two surface pressures and tensions is the driving force for the film curvature. Both sides of the interface expand spontaneously with penetration of oil and cosurfactant until the two pressures become equal. The side with the higher tension would be concave and would envelope the liquid on that side, making it the internal phase. The pressure gradients, and hence the type of nanoemulsion, are influenced by the molecular structures of the oil, surfactant and cosurfactant and the concentrations of each. Since it is generally easier to expand the oil side of an interface (by penetration of the oil or cosurfactant into the hydrocarbon chain area) than the water side, it is easier to form w/o rather than o/w nanoemulsion (Tadros, 1984). A short to medium chain length cosurfactant ensures that the film is flexible enough to readily deform around the droplets.

The early theories described above considered interfacial aspects of nanoemulsion formation, stability, and structure and did not distinguish between thermodynamically stable systems and very fine kinetically stable emulsions. Later investigators emphasized on the monophasic nature and thermodynamic stability of many of the transparent fluids considered by Schulman to be microemulsion, and discussed the systems in terms of solubilization and micellization rather than microemulsification.

1.4.2.4. Solubilization Theories

The group of Shinoda (Shinoda and Kunieda, 1973; Shinoda and Friberg, 1975) and Friberg (Friberg, 1978) considered nanoemulsions to be thermodynamically stable
monophasic solutions of water-swollen (w/o) or oil-swollen (o/w) spherical micelles. The relationship between reverse micelles and w/o nanoemulsions was illustrated by Ranee and Friberg (Ranee and Friberg, 1977) with the aid of phase diagrams. The inverse micellar region of the ternary system water, pentanol, and sodium dodecyl sulphate (SDS) is shown as the base triangle of Fig. 1.6. The region is composed of water solubilized in reverse micelles of SDS in pentanol. The addition of up to 50% p-xylene gives rise to transparent w/o regions containing a maximum of 28% water with 16% pentanol and 6% surfactant (i.e., nanoemulsion). The quaternary phase diagram constructed on addition of hydrocarbon clearly shows the relationship of these areas to the isotropic inverse micellar phase. These four-component systems could be prepared by adding hydrocarbon directly to the inverse micellar phase or by the titration method of Schulmann and co-workers. Thus these systems were identical to Schulman's microemulsions and they were an extension of the inverse micellar region rather than small emulsion droplets (Shinoda and Kunieda, 1973; Ranee and Friberg, 1977).

Similar diagrams were presented to explain the relationship between o/w nanoemulsions and the isotropic aqueous micellar region. The solubilization of oil in normal micelles is small and the molecular characteristics and concentration of all the components are critical for an aqueous micelle to solubilize large amounts of hydrocarbon and swell directly into an oil droplet without forming a large number of intermediate structures of low curvature.

![Fig. 1.6: The base triangle, water, surfactant, SDS and cosurfactant pentanol](Rance and Friberg, 1977)
1.4.2.5. Thermodynamic Treatments

The free energy of nanoemulsion formation can be considered to depend on the extent to which surfactant lowers the surface tension of the oil-water interface and the change in entropy of the system such that (Overbeek J, 1978; Ruckenstein and Chi, 1978; Ruckenstein and Krishnan, 1980)

\[ \Delta G_f = \gamma \Delta A - T \Delta S \]

Where \( \Delta G_f \) is the free energy of formation

- \( \gamma \) is the surface tension of the oil water interface
- \( \Delta A \) is the change in interfacial area on nanoemulsification.
- \( T \) is the temperature
- \( \Delta S \) is the change in the entropy of the system which is effectively the dispersion entropy.

When a nanoemulsion is formed the change in \( \Delta A \) is very large due to the large number of nanosized droplets formed. Originally, workers proposed that in order for a nanoemulsion to be formed, a (transient) negative value of \( \gamma \) was required, but it is now recognized that while value of \( \gamma \) is positive at all times, it is very small (of the order of fractions of mN/m), and is offset by the entropic component. The dominant favourable entropic contribution is the very large dispersion entropy arising from the mixing of one phase in the other in the form of large numbers of small droplets. However, there are also expected to be favourable entropic contributions arising from other dynamic processes such as surfactant diffusion in the interfacial layer and monomer-micelle surfactant exchange. Thus, a negative free energy of formation is achieved when large reduction in surface tension is accompanied by significant favourable entropic change. In such cases, nanoemulsification is spontaneous and the resulting dispersion is thermodynamically stable.

Ruckenstein and Chi (Ruckenstein and Chi, 1978) considered the free energy of formation of nanoemulsions \( \Delta G_f \) to consist of three main contributions as shown in equation

\[ \Delta G_f = \Delta G_1 + \Delta G_2 + \Delta G_3 \]

Where \( \Delta G_1 \) is the interfacial free energy, including a positive term due to the formation of an uncharged interface and a negative term due to the formation of an electric double
layer. $\Delta G_2$ is the free energy of interdroplet interactions, composed of a negative term due to Van der Waals attraction and a positive term due to repulsive double layer interaction, and $\Delta G_3$ is an entropy term for dispersion of droplets into the continuous medium. Later it was shown the accumulation of the surfactant and cosurfactant at the interface results in a reduction of bulk concentration and a decrease in chemical potential, generating an additional negative free-energy change, the so-called dilution effect. Nanoemulsions form because the negative free energy changes due to the adsorption of the surfactant and cosurfactant on the generated interface plus the entropy of the dispersion of the droplets in the continuous phase overcome the positive product of the small interfacial tension and the large interfacial area.

The role of the cosurfactant cannot be entirely reconciled to its effect on packing. A highly flexible film is required to form small droplets (Overbeek J, 1978). The bending of an interface requires work against both interfacial tension and the bending stress of the interface. The bending stress, which is particularly important for very low interfacial tension and highly curved interfaces, is represented by $K$, the rigidity (i.e., elastic) constant. The interplay between bending and thermal energies plays an important role in these systems, because thermal fluctuations produce large undulations in surfactant layers when their elastic energy is comparable to the thermal energy. This interplay is expressed in terms of persistence length, which represents the average length of the straight part of the film. The persistence length increases exponentially with $K$, in such a way that a small reduction of $K$ would drastically decrease the persistence length of the film toward a very curved phase. A large value of $K$ represents a rigid interface for which large energy is required to bend the interface, and a lamellar birefringent phase often forms near the nanoemulsion region of the phase diagram. The rigidity constant is lowered by a cosurfactant and can cause a transition from lamellar phases to isotropic nanoemulsions phases. A small value of $K$ represents a fluid interface for which little energy is necessary for bending, and the interface can become extremely wrinkled to give bicontinuous structures.

1.4.2.6. Advantages of Nanoemulsions

Nanoemulsions exhibit several advantages as a drug delivery system. They are listed as:
1. Nanoemulsions are thermodynamically stable systems and the stability allows self-emulsification of the system whose properties are not dependent on the process followed.

2. They act as supersolvent of the drug. They can solubilize hydrophilic and lipophilic drugs and improve the bioavailability of the poorly soluble drugs. This is due to the existence of nanodomains of different polarity within the same single-phase solution.

3. The dispersed phase, lipophilic or hydrophilic (o/w or w/o nanoemulsions) can behave as a potential reservoir of lipophilic or hydrophilic drugs respectively. The drug partition between dispersed and continuous phase, when the system comes into contact with a semipermeable membrane, the drug can be transported through the barrier. Drug release with pseudo zero order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport of the drug.

4. The mean diameter of droplets in nanoemulsion is below 0.1 μm and therefore they can be sterilized by filtration. The small size of droplets in nanoemulsion e.g., below 100 nm, yields very large interfacial area, from which the drug can quickly be released into the external phase, when absorption (in vitro or in vivo) takes place, maintaining the concentration in the external phase close to the initial levels.

5. Same nanoemulsion can carry both lipophilic and hydrophilic drugs.

6. Because of thermodynamic stability, nanoemulsions are easy to prepare and require no significant energy contribution during preparation.

7. Nanoemulsions have low viscosity compared to other emulsions.

8. The use of nanoemulsion as drug delivery systems can improve the efficacy of drug, allowing the total dose to be reduced and thus minimizing side effects.

9. The formation of nanoemulsions is reversible. They may become unstable at low or high temperature, but when temperature returns to the stability range, the nanoemulsion reforms.

10. Hydrophilic peptide drugs which are susceptible to proteolysis in the GI tract can be successfully incorporated into the dispersed aqueous phase of w/o
nanoemulsion droplets where they are afforded some protection from enzymatic degradation when administered orally.

11. Water in oil nanoemulsions can be employed as intramuscular injections.

12. Nanoemulsions and nanoemulsion gels have found application as topical agents where the surfactants and in some cases the oil phase itself acts as penetration enhancer to facilitate topical delivery.