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Micro-Formulations: IntegratingMicro-Sponges, Micro-Spheres, Micro-Needles, and Micro-Emulsions in Advanced Drug Delivery

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Abstract

Microformulations are the emerging innovative advancements in the field of novel drug delivery systems, which have shown immense potential in enhancing patient compliance, improving therapeutic efficacy, and minimizing side effects. This comprehensive review explores various micro-formulation technologies, including microsponges, microspheres, microneedles, and microemulsions, providing an in-depth analysis of their types, mechanisms of action, methods of preparation, and evaluation, as well as their prospects in various fields, including pharmaceuticals, cosmetics, biotechnology, and others. By highlighting the advantages, benefits, and challenges associated with microformulations, this review aims to provide a comprehensive understanding and perception of their potential in transforming drug delivery systems and processes.

Keywords: micro-formulation, novel drug delivery technologies, patient compliance, micro-sponges, micro-spheres, micro-needles, micro-emulsions.

Introduction

Throughout the years, the drug industry has seen great progress in the administration of medicine in the body. One of the critical developments is microformulation. This is a process where active drug contents are covered with thin protective polymer layers to create small particles with sizes between 1 and 1000 micrometers (μm) [1]. The primary objective of microformulation is to address some of the typical issues related to conventional drug delivery systems, including instability of the drug, low solubility, and poor release of the medicine in the body [2].

Microformulation facilitates the creation of diverse pharmaceutical products that can transport active ingredients possessing diverse physical and chemical attributes. The products, such as soft and hard capsules, tablets, emulsions, lotions, gels, and injections, were successfully produced under controlled conditions and were therefore appropriate for mass industrial production [3]. Micro-formulations are specifically formulated for controlled drug delivery, improved bioavailability, and localized effect. Examples:- microsponges, microspheres, microcapsules, micelles, lipid-based microparticles, microemulsions, microneedles [1].

Historical Development of Micro-formulation

The concept of time-controlled drug release started in the 1940s when Dr. Harold A. Clymer started research work in this field [3].

From the year 1952 onwards, there have been tremendous advancements in drug delivery technology, starting with the innovation of the Spansule sustained-release capsule. This technology promotes a drug release over 12 hours postoral ingestion through the administration of an immediate dose followed by the slow release of the rest of the medication with the assistance of micro-formulation [4].

In 1987, Won came up with Microsponges technology, and Advanced Polymer Systems was awarded the first patents on it.Traditional methods of drug delivery are usually confronted with multiple drawbacks, such as drug instability in the body, reduced bioavailability, poor solubility, and less efficient absorption [5].

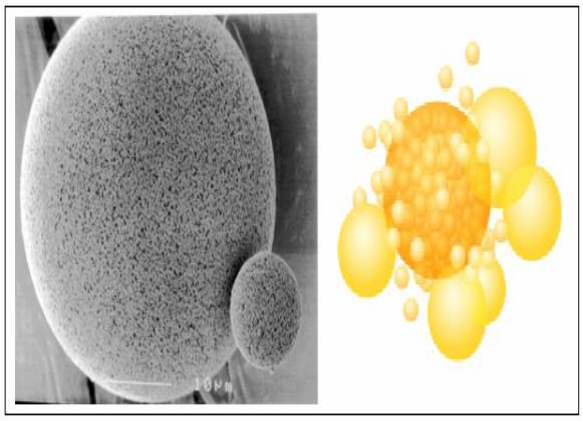

Figure 1: Micro-sponge Technology [6]

All these issues can result in compromised therapeutic effects, non-target-specific action, and unwanted side effects. Advanced drug delivery systems like microformulations have been studied to overcome all these limitations [7].

Micro-formulation methods are applied in numerous industries, such as the pharmaceutical industry for targeting drug delivery, food and beverages for maintaining nutrients and flavor, agriculture to release agrochemicals under controlled conditions, cosmetics for stable delivery of active compounds, and textiles for providing functional properties like fragrance or heat regulation [8].

This review indicates the potential of microformulation to enhance the action of bioactive substances, as derived from in vitro and in vivo research [1].

By creating microparticles through various methods and incorporating certain structural components (e.g., polymers, lipids) into their composition, microformulation is able to alter the physical and chemical characteristics of the substances.These alterations usually occur as a result of the interaction between various ingredients being employed [1].

One of the most important advantages of micro formulation is particle size reduction. This results in smaller particles that are more easily soluble, easier to absorb in the body, and more capable of passing through cell membranes. Such improvements enhance their overall bioavailability and aid in processes

such as excretion. The review also discusses the present drug market, citing some drugs that already employ microparticle-based systems. These are examples of how such sophisticated formulations are superior to conventional ones [1].

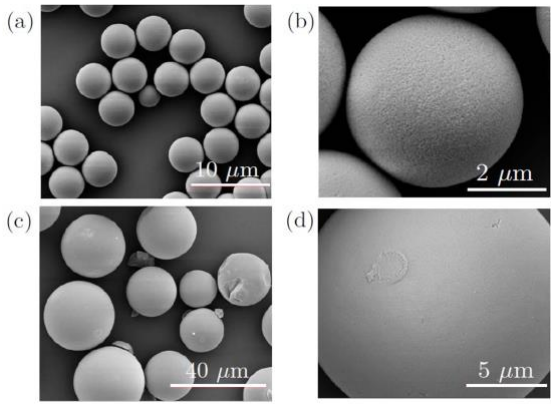

Figure 2: Microspheres Images (a) and (b) show particles with an average radius of about 2.5 μm, while (c) and (d) show particles with an average radius of about 10 μm [9]

Micro-formulation systems are determined by numerous factors such as the physicochemical nature of the active ingredient to be encapsulated, the pharmaceutical form, and the route of administration. Structural components, i.e., synthetic, semi-synthetic, and natural polymers or lipids, and the manufacturing process are also significant factors. Microparticulate systems can be employed in various pharmaceutical forms such as solids, liquids, or semi-solids. Depending on the size and release properties, these systems can be delivered by different routes, oral, inhalation, intravenous, intramuscular, or subcutaneous [1].

Micro-formulation systems are influenced by various factors like the physicochemical properties of the active ingredient being encapsulated, the type of pharmaceutical form, and the method of administration. Other important considerations include the choice of structural components, such as synthetic, semi-synthetic, and natural polymers or lipids, as well as the production process. These microparticulate systems can be used in different pharmaceutical forms, including solids, liquids, or semi-solids. Depending on their size and release characteristics, these systems can be administered through various routes, including orally, via inhalation, intravenously, intramuscularly, or subcutaneously [1].

Advantages of Micro-formulations

Micro-formulations have various advantages, such as:

1. They possessa high Loading capacity as well as predictable release kinetics [10].
2. They are compatible with diverse therapeutic modalities [10].
3. Micro-formulations are expected to be used in a traditional micro-dosing [10].
4. They are also used as a medium for alternative delivery techniques, such as controlled [10], sustained, and localized release [11].
5. Micro-formulations provide high efficacy and also give a high target delivery effect. prolonging systemic circulation of the drug for the lifetime,and alsoenhancing the bioavailability of the drug [12].
6. They are also known to protect the drugs from metabolic degradation [12].
7. Reducing particle size boosts effectiveness by increasing the surface area, making even hard-to-dissolve materials more potent [13].

8. Polymer-based packaging protects drugs from enzymatic breakdown, making them compatible with targeted delivery systems and ensuring their effectiveness [13].

Benefits of micro-formulations

Micro-formulations can effectively encapsulate drugs, delivering and protecting them over a period of time while increasing their local concentration and reducing their toxicity in the remaining tissues [11]. Thus, traditional prolonged action products may be well formulated by the use of nano- and micro-particles. Capsule long-acting dosage forms have two main benefits over traditional tablet or capsule types [11].

1. Controlled Release

Non-disintegrating tablets can remain in the stomach for some time and may delay absorption or maintenance dose levels. Capsulated formulations release particles more slowly through the pyloric sphincter at a rate sufficient to ensure controlled release of the active ingredient [14].

2. Targeted Drug Delivery

The disturbance of capsule shells in gastric juices triggers the release of the granules, which in turn release a significant amount of the drug. The highly targeted delivery process eliminates the loss of the entire maintenance dose, which is a drawback of conventional tablets. Furthermore, the application of micro particles also ensures a sustained release for maximum therapeutic efficacy.

This means that the use of nano and micro-particles in long-acting capsule dosage forms allows pharmaceutical companies to develop new-generation formulations that exhibit improved controlled release and targeted drug delivery compared to their classical counterparts [14].

Types of Micro-formulations [1]

The types of micro-formulations can be broadly classified by their structure and the manufacturing method used, but the general types include the following:

1. Micro-sponges
2. Micro-spheres
3. Micro-needles
4. Micro-emulsions

1. Micro-sponges

1.1 Introduction

Micro-sponge technology is a novel drug delivery system preparation method that offers several benefits in drug delivery. Micro-sponge systems are porous biocompatible microspheres with 10- to 25-micrometer particle size. The quasi-emulsion solvent diffusion method is one of the most popular methods applied for micro-sponge preparation, by which potent controlled-release dosage forms can be prepared. Micro-sponge carriers are programmed to deliver active pharmaceutical components in a site-specific and controlled manner so that the drug reaches a specific site in the body. This control over delivery increases the efficacy of treatment, minimizes side effects, and extends the action of the drug. There have been dozens of patents filed on micro-sponge systems over the years, attesting to the innovative nature of the technology and greater use in pharmaceutical research. In delivering the drug with high precision in

duration, micro-sponge technology presents a new and exciting method for quickly and efficiently maximizing therapeutic effect [15].

1.2 Mechanism of action [16]

Micro-sponges are made such that they respond to various environmental stimuli by delivering therapeutic compounds in a slow and controlled manner. The extremely porous structure and tailored polymer matrix allow for diffusion or expulsion of the drug as a function of the stimulus. The predominant release mechanisms areas follows:

1. Temperature-Responsive Release

Drug mobility in micro-sponges is modified by temperature fluctuations. When the surroundings heat up, the kinetic energy of the molecules is higher, and hence delivery of the drug through the porous channels is accelerated. This attribute is particularly useful for heat-sensitive topical and transdermal products.

2. Mechanically Triggered Release (Pressure-Activated)

On exposure to external forces such as rubbing or skin contact, the physically entrapped drug materials are pushed out of the pores. Such a delivery mechanism can behighly beneficial for cosmetic and dermatological uses where release at application is desirable.

3. Solubility-Governed Release

For water-soluble drugs, entry into an aqueous environment triggers release. The liquid penetrates the inner sponge matrix, dissolves the active ingredient, and forces its outward diffusion in a sustained manner.This renders the system suitable for applications such as antiseptics or deodorants.

4. pH-Dependent Release

In modification of the polymer content or by application of specialized coatings, micro-sponges can be designed to release their products in environments of specific acidity or alkalinity. This enables site-specific targeting, for instance, to deliver drugs at different sites in the gastrointestinal tract.

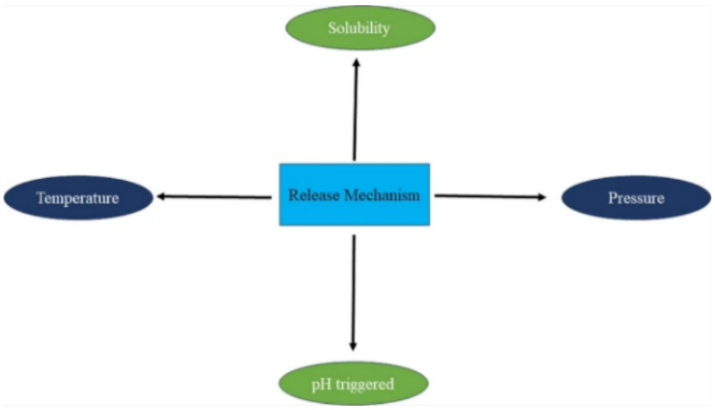

Figure 3: Mechanism of action [17]

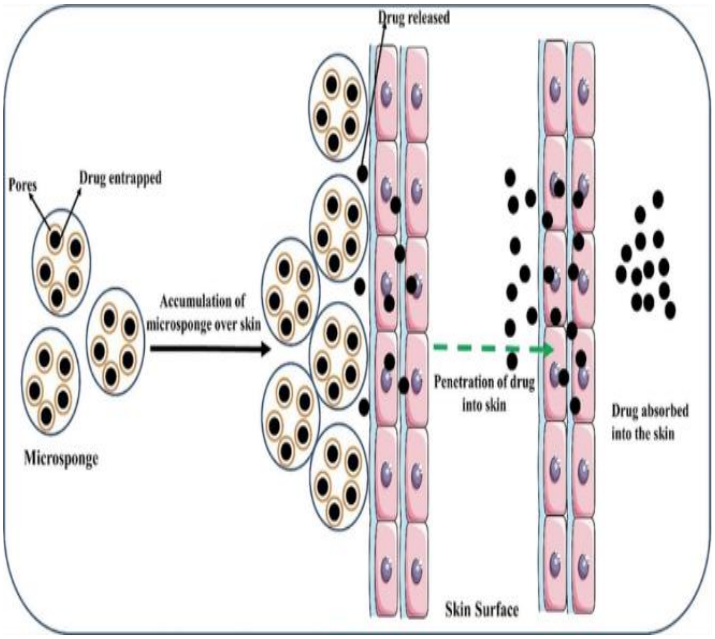

Figure 4: Hypothetical mechanism of action [17]

1.3 Micro sponge preparation methods [18]

1. Quasi-Emulsion Solvent Diffusion Method

For this method, a polymer is dissolved in an appropriate solvent, like ethanol, first to produce the internal phase. The drug is added to this solution and kept under ultrasonic mixing at a temperature of approximately 35 °C for about 15 minutes to produce a homogeneous dispersion. Meanwhile, the external phase is prepared by dissolving polyvinyl alcohol (PVA) in distilled water at room temperature. The internal phase is added incrementally to this aqueous medium under constant stirring at 500 rpm for about two hours. This step enhances solvent diffusion and micro-sponge formation. The product formed is filtered, extensively washed, and dried in an oven at 40 °C to provide stable micro-sponges.

2. Quasi-Emulsion Solvent Evaporation Method

This method is found to be an easy and versatile process for the production of micro-sponges. Here, the internal phase consists of the drug, ethyl cellulose, and an organic solvent like dichloromethane (DCM). The blend is mixed for approximately 15 minutes to be made homogeneous. It is slowly dropped into an aqueous phase with a surfactant and a plasticizer, stabilizing the emulsion. Following emulsification, the emulsion is maintained under constant stirring for about one hour, during which time the solvent gradually evaporates, causing micro-sponge formation. The suspension is filtered to harvest the particles, and these are dried at 40 °C for 24 hours.

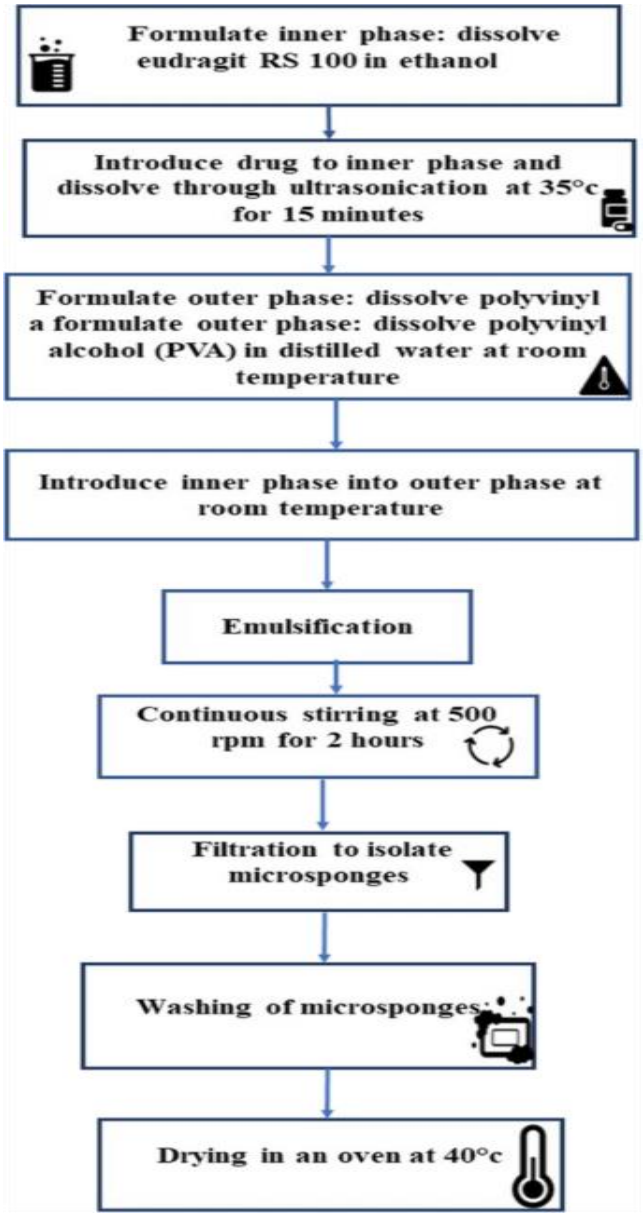

Figure 5: Quasi-Emulsion Solvent Evaporation Method [18]

3. Liquid–Liquid Suspension Polymerization Method

In this technique, a mixture of monomers, an active component, and a surfactant is dissolved in a suitable solvent. The mixture is dispersed into fine droplets by the addition of a suspending agent. After stabilizing the suspension, polymerization is activated by adding a catalyst, applying heat, or by the use of radiation. The process produces spherical polymeric particles with a porous reservoir-like structure. Sometimes, a liquid that is immiscible with water but miscible with the monomer is used in the course of polymerization to encourage pore development. After polymerization is complete, the inert liquid is removed, leaving behind micro-sponges that can encapsulate and release active ingredients slowly. If the drug that is to be encapsulated is unstable under polymerization conditions, then a two-step approach is utilized to prevent degradation. This approach is highly useful for incorporating therapeutic and cosmetic agents like antifungal drugs, anti-acne agents, anti-inflammatories, and rubefacients.

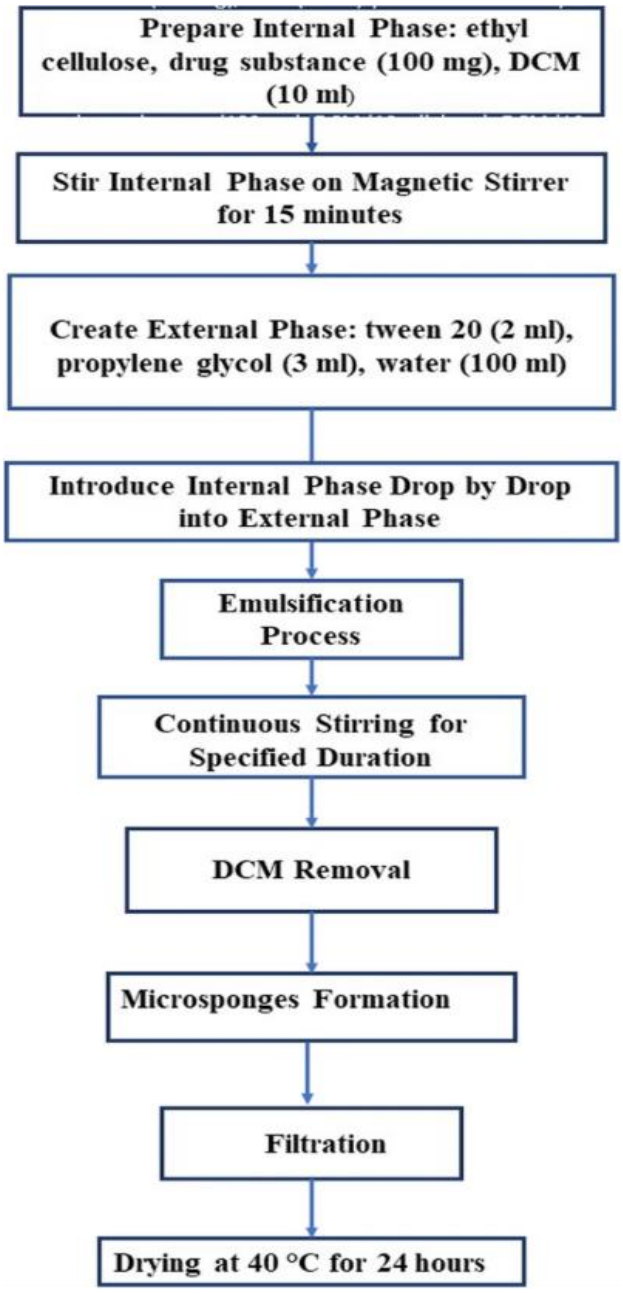

Figure 6: Liquid–Liquid Suspension polymerization Method [18]

The preparation process generally progresses through the following stages as mentioned below: [18]

1. Selection of proper monomers or a mixture of monomers.
2. Initiation of polymerization for the formation of linear chains
3. Cross-linking of chains for the formation of ladder-like structures.
4. Formation of spherical microspheres.
5. Agglomeration of microspheres into clusters.
6. Clusters assemble into micro-spongenetworks.

1.4 Evaluation of Microsponges [18]

1. Particle Size and Distribution

Loaded or unloaded micro-sponge particle size can be identified by laser diffraction methods, which give a precise determination of size distribution. Together with conventional optical microscopy (LM) and scanning electron microscopy (SEM), these are often utilized for visualization purposes. These tools are especially valuable in determining the shape, uniformity, and outer surface of the microparticles.

2. Morphology and Surface Characteristics

For the study of surface properties, micro-sponge samples are typically prepared under argon conditions and coated with a thin layer of gold–palladium for increased conductivity.

SEM imaging can be employed to analyze the outer morphology and inner structure when fractured particles are inspected. This method provides high-resolution information regarding porosity and surface topology of the micro-sponges.

3. Polymer and Monomer Composition

The ratio of polymer in the micro-sponge system is a main factor in controlling drug release. Differences in polymer composition change the partition coefficient between drug and polymer matrix, thus affecting the diffusion rate. Release behavior can be examined by graphing cumulative percentage drug release versus time, which gives valuable information for kinetic modeling.

4. Production Yield and Drug Loading

The yield of production is determined by dividing the real weight of micro-sponges recovered bythe theoretical polymer and drug weight used for formulation. For analysis of drug content, a definite weight of microspheres is dissolved in an appropriate solvent, and the solution is sonicated to extract it completely. After filtration, the sample absorbance is determined at the drug-specific wavelength by a UV–VIS spectrophotometer, through which the concentration can be measured.

5. Entrapment Efficiency

The entrapment efficiency reveals how well the drug has been entrapped into the micro-sponge system and is measured as:

Entrapment Efficiency(%) = Amount of drug entrapped in microsponges / Total amount of drug used x 100

2. Microspheres

2.1 Introduction

Microspheres are small, solid, roughly spherical particles with diameters typically ranging from 1 to 1000 micrometers.They are usually made from one or more types of biocompatible and miscible polymers. The active drug or therapeutic substance can be uniformly distributed throughout the entire structure, either in the form of fine particles or at the molecular level. Microspheres can either be of microcrystalline material or as drug-carrying particles in a particular solution. In brief, microspheres are very tiny polymer balls that are made to deliver medicine, and their delivery can be prolonged or controlled in the body [19-21].

Microspheres are generally categorized under micro-matrices and micro-capsules.In micro-matrices, the active agent (e.g., a drug) is evenly dispersed throughout the whole polymer matrix. This implies that the drug is dispersed in the material itself, not within an independent compartment. Microcapsules, by

contrast, consist of a well-characterized active core with an independent external coating or shell. The outer coat is also a barrier with release control over the core material. Separation is necessary as it controls drug release, formulation stability, and in vivo performance [19].

2.2 Types of Microspheres [20]

They are prepared in different forms based on the mode of action and material composition as mentioned below:

1. Bio-adhesive Microspheres

They adhere to the body surfaces such as the mouth, nose, eyes, or rectum with water-soluble polymers. They are more stable on the site of application, with better absorption and improved therapeutic action.

2. Magnetic microspheres

Targeting drugs is achieved through the application of a magnetic field that guides medicines to precise sites in the body by means of magnetic microspheres. The amount is minimized because they specify the administration of medicine to the disease site. Therapeutic Magnetic Microspheres: Deliver chemotherapy within tumors, specifically liver tumors. Diagnostic Magnetic Microspheres: Employed in medical imaging for visualization of internal organs, e.g., in the detection of liver disease or differentiation of bowel segments.

3. Floating Microspheres

They are retained in suspension in gastric fluids because of their low density. They stay longer in the stomach and gradually and continuously release the drug, which enhances its action and reduces the frequency of administration of the dose.

4. Polymeric Microspheres

They are produced using natural or synthetic polymers and used to regulate drug release.

Biodegradable Polymeric Microspheres are produced from native materials such as starch and are biodegradable and slowly release the drug in a safe manner. But they may be challenging to load drugs and control drug release.

Synthetic Polymeric Microspheresare produced from synthetic polymers and are employed extensively in drug and cosmetic therapy. But they may migrate from the point of administration and become harmful in the form of blockage or organ injury.

2.3 Mechanism of Action (MOA) of microsphere [21]

Microspheres enclose the drug initially to avoid its degradation. The drug comes out in a controlled fashion by diffusion, dissolution, or polymer erosion later. After release, it is distributed and absorbed in the blood or tissues. Targeted delivery to a site can be made possible by microspheres if they are so designed. This leads to sustained therapeutic action, minimal side effects, and improved compliance by patients.

Microspheres deliver drugs by a variety of mechanisms based on structure and composition [21]

In diffusion-controlled systems, drug molecules slowly move out either through a surrounding membrane or through tiny water-filled pores in the polymer matrix. Indissolution-controlled systems, the drug is surrounded by a core or combined with a polymer and dissolves gradually into the surrounding fluid.

Slowly diffuse drug molecules out either through a membrane around them or tiny water-filled pores in the polymer matrix in diffusion-controlled systems.Osmotic systems use water entry and pressure from the inside to expel the drug out through a tiny pore.erosion-controlled release, the carrier polymer itself breaks down either from the outside inwards or along the entire particle, releasing the medication in a controlled fashion.In prodrug systems, the medication is chemically attached to a carrier and released after some chemical or enzymatic action. Externally controlled systems are designed to respond to stimuli such as pH change, temperature, light, or magnetic fields in a way that on-demand release at the targeting site is achieved.

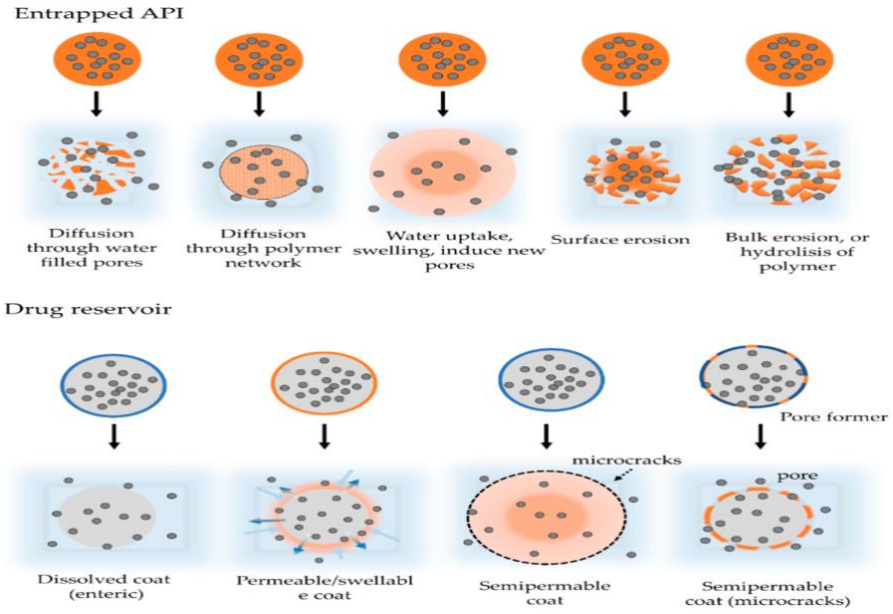

Figure 7: Release mechanisms in microencapsulated products [21]

2.4 Method of preparation

Microspheres can be prepared by various methods according to the drug and polymer type as mentioned below:

1. Spray Drying

The polymer and the drug are dissolved, aerosolized in hot air, and instantly dried into microspheres,swift, economical, but incompatible with heat-sensitive drugs [22].

2. Solvent Evaporation

Drug and polymer dissolved in solvent are emulsified in water; slowly, the solvent evaporates, forming microspheres. Widely used for both hydrophilic and hydrophobic drugs [22].

3. Wet Inversion Technique

A solution of polymer-drug is dissolved in a non-solvent, and it becomes hard in the form of microspheres. Used for the preparation of biodegradable microspheres [22].

4. Complex Coacervation

Two oppositely charged polymers segregate and enclose the drug to form microspheres upon hardening. Suitable for fragile drugs like proteins [23].

5. Hot Melt Method (Hot Melt Microencapsulation)

Polymer is melted with the drug and then rapidly cooled to provide solid microspheres. The solvent-free method is ideal for drugs that are moisture sensitive [22].

6. Single Emulsion

The solution of the drug and polymer is emulsified in water; microspheres are formed as the solvent evaporates. Ideal for drugs insoluble in water [22].

7. Double Emulsion Technique A

Water-in-oil-in-water (W/O/W) emulsion is used; evaporation of solvent produces microspheres, ideal for water-soluble drugs. Ideal for proteins, peptides, and vaccines [22].

8. Polymerization Techniques

Polymerization is done throughout the solution to entrap the drug in solid microspheres. Excellent size and drug loading controlare achieved. There are two types of polymerization techniques as mentioned below [22].

A] Normal polymerization.

B] Interfacial Polymer.

9. Phase Separation (Coacervation) Method

The Polymer separates from the solution and encloses the drug particles in microspheres. Effective in slow-release preparations [22].

10. Spray Congealing

The drug and polymer are melted and sprayed into cold air, where they solidify into microspheres. No solvent required, safe and easy [23].

11. IonicGelation

Microspheres are formed by transferring an alginate-drug solution into a solution of calcium and chitosan, where crosslinking ionic is formed. Release of the drug is pH-dependent and occurs mainly at pH 7.4 [20].

12. Quasi-Emulsion Solvent Diffusion

A solution of drug-polymer-ethanol is combined with water that contains PVA. Solvent exchange results in the precipitation of the polymer and forms porous microspheres. These support drug release over a long period of time [20].

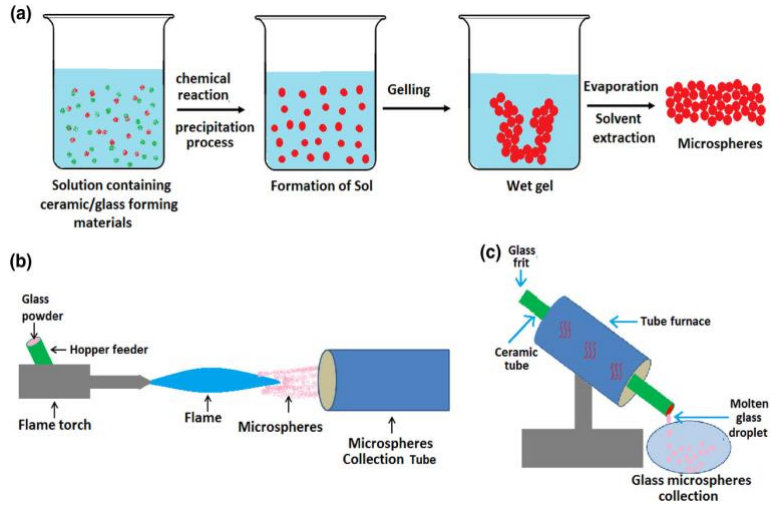

Figure 8: Scheme of production of glass microspheres via a sol–gel, b flame spheroidization, and c tubefurnace methods [24]

Evaluation Methods for Microspheres

1. Optical Microscopy

Optical microscopy is utilized for the approximate measurement of the particle size of microspheres. A compound microscope (e.g., Meizer OPTIK) is utilized at 450x magnification (10x eyepiece and 45x objective lens), and around 100 particle sizes are noted manually. This method is simple and useful for obtaining a general impression in terms of particle size distribution [19].

2. Scanning Electron Microscopy (SEM)

SEM is useful in studying the surface microstructure and morphology of microspheres. Double-sided adhesive tapes are used to hold microspheres in an SEM stub, and a gold conductive coating is used in case of charging. Photography is carried out in a low vacuum for the study of surface properties such as smoothness, porosity, or cracks [19].

3. Thermal Analysis

Thermal analytical methods such as Thermogravimetric Analysis (TGA) and Differential Scanning Calorimetry (DSC) are used for the measurement of thermal properties. Tests measure such values as heat flow, weight loss, or heat transitions (glass transition, melting point) by applying controlled heat to microspheres. It is also used for drug-polymer compatibility as well as for stability [19].

4. Entrapment Efficiency

Entrapment efficiency is also used as a means of determining the amount of drug that is truly entrapped in the microspheres. Here, a predetermined amount of microspheres is ground into powder, mixed with distilled water, and sonicated for homogeneity. Drug content is calculated after filtration using UV-Visible spectroscopy. Percentage calculation is done by comparing the actual drug content with the theoretical content [19].

5. Flow Properties

Flow behavior of microspheres is quantified by parameters including the Hausner ratio, Carr's compressibility index, and angle of repose. Bulk and tapped densities are measured in a graduated cylinder.Good flowability is required for effective handling, filling, and processing during production [19].

6. Swelling Index

The swelling index measures the capability of absorptive microspheres and their swelling. It is determined by the equation:

Swelling Index(%)= (Swollen microspheres weight – Dry microspheres weight) / (Dry microspheres weight) x 100

This property is very important in controlled-release products [19].

7. Dissolution Apparatus

To study how the drug is released from the microspheres in the lab (in vitro), a dissolution test apparatus was utilized, which is routine as specified by USP or BP guidelines. Two paddle and basket models of stirring devices were utilized throughout the experiment. The liquid volume (termed as the dissolution medium) ranged from 100 to 500 ml, while the stirring speed was varied between 50 to 100 revolutions per minute (rpm), as a function of the requirements of the studies [22].

8. Determination of Density

The density of microspheres is measured in a multi-volume pycnometer. The weighted sample is added to the device, and helium gas is used to fill the chamber. When the gas gets expanded, the pressure decrease is calculated. Two pressures are taken, through which the density of microspheres is calculated accurately [22].

9. Isoelectric Point

The isoelectric point of microspheres is defined by a microelectrophoresis apparatus, which indicates the velocity with which the particles travel upon the imposition of an electric field. The movement velocity is acquired at different pH levels (3–10). From these, the electrical mobility is calculated, and the pH value that makes the particles immobile (zero mobility) represents the isoelectric point [22].

10. Attenuated Total Reflectance FT-IR (ATR-FTIR) Spectroscopy

ATR-FTIR is used in examining the surface composition of microspheres and to confirm if the structure of the polymer has degraded or not. The technique is useful in understanding what happens in changes in production by investigating the surface without destroying the sample [22].

11. Animal Models

Animal models also aid in establishing how microspheres deliver medicine in the body. Microsphere formulation is given to an anesthetized animal, and for certain studies, the esophagus is also tied off so that absorption through the lining of the mouth can be examined. Blood samples are taken at different times to measure drug concentration and how effectively the microspheres are working [22].

12. Drug Content

The microspheres for estimation of drug content are suspended in a solvent (0.1 N NaOH), and then it is diluted in a volumetric flask. The solution is filtered after it is left to settle with any residue. Drug

concentration is then estimated by spectrophotometry. This ensures drug loading and drug content uniformity and accuracy [19].

13. Stability Studies (for Microsphere Evaluation)

Stability studies verify whether microspheres retain drug content in the long run under various storage conditions. Microspheres in screw-capped glass vessels are stored for 60 days under the following conditions:

a. Room temperature (27±2°C
b. Oven (40 ± 2°C)
c. Refrigerator (5–8°C)
d. Humid climate

After the storage time, the drug content is determined to find the stability of the microspheres [22].

2.5 Applications

Medical and Pharmaceutical Applications, Biotechnology and Research, Industrial Applications, Environmental Applications, Cosmetics and Personal Care [21].

3. Microneedles

3.1 Introduction

Microneedle-based drug delivery systems hold great potential for enabling vaccine and therapeutic delivery through the skin, as well as biofluid sampling for point-of-care diagnostics—an approach known as theranostics [25].

The concept of employing microneedle structures to painlessly puncture the outermost layer of the skin, the stratum corneum (SC), was initially conceived in 1976. Nonetheless, with the unavailability of adequate microfabrication technologies, experimental studies on this concept lagged until the 1990s, when improvements in microfabrication tools made it possible to fabricate microstructures and microelectromechanical systems (MEMS), thereby providing a basis for designing compact, miniaturized medical devices for health screening, monitoring, and diagnostic purposes [25].

Microneedles (MNs), whose lengths are generally in the range of 25 μm to 2000 μm, have far sharper tips than hypodermic needles. They can, therefore, penetrate the stratum corneum (SC) and open micro-scale channels for drug delivery without extending to the epidermal nerve fibers and dermal blood vessels. As a result, the efficiency of drug delivery is significantly enhanced, and the number of drugs accessible through transdermal drug delivery (TDD) is significantly increased, all in a nonpainful and minimally invasive manner [25].

The last four decades have witnessed tremendous development in microneedle (MN) technologies. There are many preclinical experiments and a few clinical trials that have confirmed their capacity to transport oligonucleotides, desmopressin, DNA, vaccines, insulin, and human growth hormone across the skin. Beyond this, MNs have been studied in great detail for devices that involve blood sampling, signal monitoring, intrascleral drug delivery, microneedle-mediated gene transfer, and biosensing. This suggests that MNs can not only address the $32 billion transdermal drug delivery market and the $25 billion worldwide vaccine market but also the worldwide biologics market, which is more than $120 billion [26].

3.2 Mode of action

Microneedles (MNs) can deliver relatively large therapeutic agents across the stratum corneum (SC) by mechanically creating microchannels in the skin. The easy and self-help nature of this medical procedure has also enabled the creation of many skin-based treatments. When used in combination with other treatment modalities, including chemotherapy, radiotherapy, phototherapy, and immunotherapy, MNs have shown improved clinical efficacy against many indications [27].

3.3 Types of microneedles [27]

1. Solid microneedles
2. Coated microneedles
3. Dissolving microneedles
4. Hollow microneedles

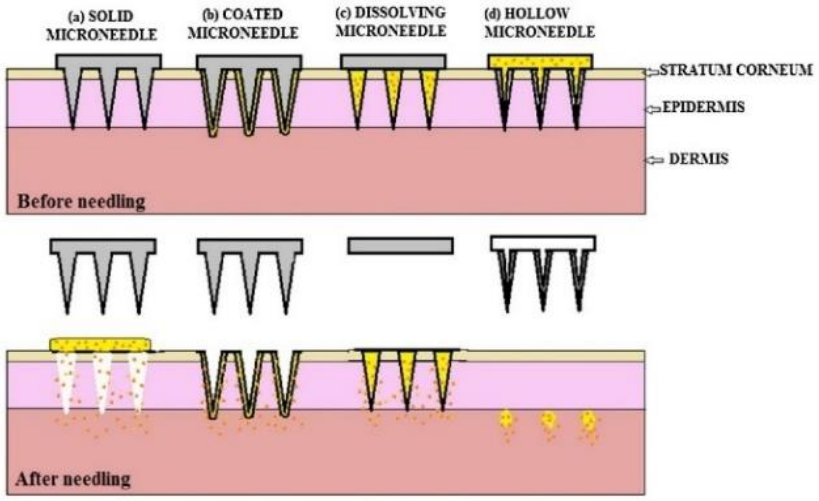

Figure 9: Various types of microneedles (a) solid microneedles adopt poke with patch technique, applied for pre-treatment of skin; (b) coated microneedles adopt a coat and poke technique, a drug solution coating is applied on the surface of the needle; (c) dissolving microneedles are constructed of biodegradable polymers; (d) hollow microneedles contain the drug solution and deliver the drug to the dermis [27].

1. Solid microneedles

Solid microneedles (MNs) facilitate the delivery of high-molecular-weight substances through microchannels that are created instantly upon application. When utilized in an array, they generate numerous microchannels that temporarily enhance skin permeability, which then naturally close as the skin heals, presenting no risk of infection. Research has shown the self-healing process, indicating that the recovery of the barrier is influenced by the dimensions of the MNs, while occlusion can slow it down; consequently, removing the MNs after application promotes restoration. The effectiveness of drug delivery through these channels is influenced by their physicochemical characteristics, such as molecular weight, partition coefficient, melting point, and permeability coefficient, suggesting that the fundamental principles of skin permeation are also applicable to MN-based transdermal systems [27].

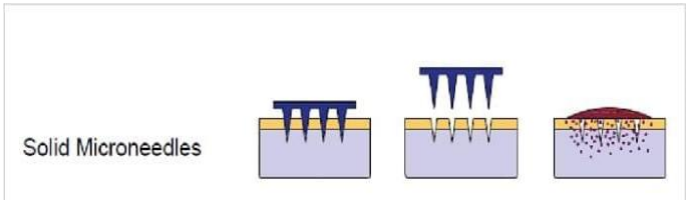

Figure 10: Solid microneedles [25]

2. Coated microneedles

Coated microneedles (MNs) deliver drugs deposited on their surface rather than being embedded during their fabrication, enabling subdermal release during insertion. Different coating techniques include dip coating, gas-jet drying, spray coating, electrohydrodynamic atomization (EHDA), and piezoelectric inkjet printing. Although dip coating is easy, it tends to produce non-uniform films; gas-jet and spray coating improve uniformity through controlled drying and optimum solution properties. EHDA employs an electric field to selectively apply polymeric drug formulations to the tips of MNs, whereas piezoelectric inkjet printing accurately places ultra-low-viscosity solutions on MN tips, guaranteeing consistent coating [27].

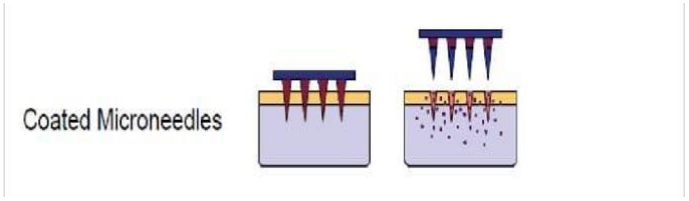

Figure11: Coated microneedles [25]

3. Dissolving microneedles

Dissolving microneedles (MNs) have attracted considerable attention due to their user-friendly “poke and release” mechanism. To enable complete dissolution, these MNs are generally fabricated from polysaccharides or other polymers. They are generally manufactured by charging molds with polymeric solutions blended with therapeutic substances, which are then vacuum-dried at ambient temperature. On application, the MNs slowly disintegrate in the skin, liberating the drug as the polymer dehydrates or swells. One major benefit of dissolving MNs is that they can be used to deliver drugs in a single application without inducing occlusion that may otherwise impede micro channel healing [27].

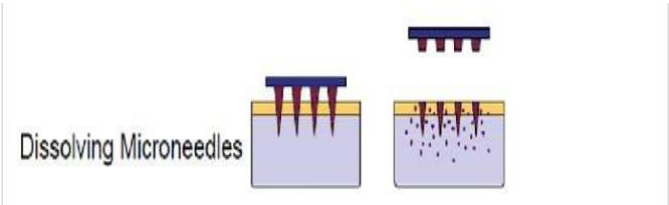

Figure 12: Dissolving microneedles [25]

4. Hollow microneedles

Hollow microneedles (HMs) are arrays of micron-scale hypodermic needles that are useful in the delivery of therapeutic agents. As opposed to ordinary hypodermic needles, which can lead to trypanophobia or the risk of infections by pathogenic agents, HMs are safer and more patient-friendly. For example, pre-filled insulin in HMs can be used as a convenient and effective way of delivering insulin in type 1 diabetes [27].

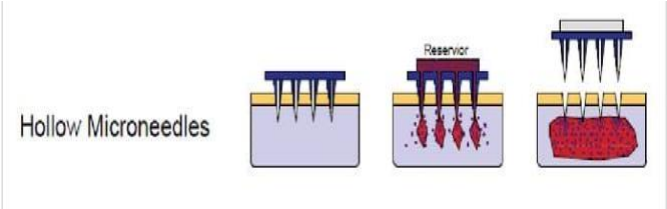

Figure 13**:** Hollow microneedles [25]

3.4 Fabrication of microneedles [25]

Microneedles have been fabricated from a variety of materials, beginning with silicon, and designed in different shapes and sizes for diverse applications. Materials used include metals such as titanium and stainless steel, silicon, ceramics, biodegradable polymers like polylactic acid (PLA), PLGA, and polyglycolic acid (PGA), as well as non-degradable polymers such as photolithographic epoxy.

Fabrication of microneedles using silicon [25]

The most commonly used microneedle structures, Silicon microneedles, are currently produced by microfabrication methods that take the form of intricate multistep processes and expensive equipment borrowed from the microelectronics industry. Of these, subtractive processes in the form of wet and dry etching are most widely utilized.

Wet etching involves suspending a single-crystal silicon wafer in chemical etchant baths to produce either isotropic etching, where the etch rate is the same in all directions, or anisotropic etching, where the rate depends on the crystal planes. Anisotropic etching cannot be used to create cylindrical microneedles but rather produces faceted pyramid-like micro-protrusions due to its tendency to selectively expose certain crystal planes. For both isotropic and anisotropic processes, an optical lithography is first used to pattern a silicon nitride hard mask. Isotropic etching involves a very corrosive HNA solution (hydrofluoric, nitric, and acetic acids), which results in the unwanted mask undercutting that needs to be compensated for in the pattern design. Anisotropic etching is generally done with EDP (ethylenediamine pyrocatechol), hydrazine-based solutions, or most frequently, potassium hydroxide.

Deep reactive ion etching of silicon is now a widespread process, performed in a low-pressure chamber in which reactive ion plasma acts upon the material surface. The etching can be isotropic at high gas pressures or anisotropic at low pressures. The most commonly used silicon etchant is sulfur hexafluoride ($SF_6 + O_2$) in an inductively coupled plasma system.High aspect ratio structures are produced in the Bosch process using alternating $SF_6 + O_2$ for etching and C_4F_8 sidewall passivation.

3.5 Evaluation of microneedles

A. In vitro evaluation

1. Skin Penetration (In Vitro)

(Puncture Efficiency)It is a critical test to ensure that the microneedles are capable of making channels through the skin. It is typically done on surrogate materials like Parafilm or on excised human or animal cadaver skin.The holes and depth so formed are quantified [28].

2. Dye or Fluorescent Probe Test

A fluorescent dye or a fluorescent marker is loaded in the microneedles and used on a skin sample. The skin is examined under a microscope to see the channels formed behind the needles [28].

3. Drug Release/Permeation

In Vitro Drug Release: Drug release from the patch, with reference to time and released amount by the patch, is measured using a Franz diffusion cell, as a simulation of drug transport through the skin [29].

4. Bioavailability

The proportion of the drug delivered becomes available to the systemic circulation, commonly expressed in terms of a normal route of administration of the drug [29].

B. In Vivo Evaluation

Efficacy and Pharmacokinetics/Pharmacodynamics

1. Drug Delivery Efficacy

The realized amount of drug delivered into the circulation and skin is quantified to ensure that the patch delivers a therapeutic dose [30].

2. Pharmacokinetics (PK)

This is the process of quantifying the amount of drug in the bloodstream over a period to define its absorption, distribution, metabolism, and excretion [30].

3. Pharmacodynamics (PD)

This quantifies the physiological or biological action of the drug to ensure that it is causing the intended therapeutic effect [30].

4. Patient Compliance (User-friendliness)

Ease of use, comfort, and patient acceptability are assessed using user questionnaires and interviews. This is an important consideration in terms of commercial success because microneedle patches must be user-friendly [31].

4. Microemulsions

4.1 Introduction

Schulman et al, in the year 1943, discussed the topic of Microemulsions [32]. Microemulsions, referred to as μE and further described as swollen micelles or solubilized micellar solutions [33], are highly adjusted, transparent, thermodynamically stable [32] dispersed systems comprised of oil, surfactant, co-surfactant, isotropic liquid, or aqueous phase in the right proportions. They have a diameter typically below 100 nm [34]. In contrast to coarse emulsions micronized through external energy, microemulsions are founded on

low interfacial tension [35]. Microemulsions constitute a mixture of water, hydrocarbons, and amphiphilic compounds [32].

4.2 Mechanism of action

1. Microemulsion formation

Knowing how microemulsions are structured is central to knowing how they behave. Several theories or models describe the structural basis and formation, as mentioned below:

2. Interfacial tensions in microemulsions

Temporary interfacial tension facilitates spontaneous water/oil incorporation in microemulsions. Transient negative tension must be present for emulsification. Surfactant diffusion and the addition of components affect this process. Extremely low interfacial tensions are needed for stability [32].

3. Double-layer interaction and interfacial charge

Schulman et al demonstrated that interfacial charge regulates phase continuity in microemulsions. Compressing the double layer with higher concentrations of counterions results in w/o microemulsions, whereas lower concentrations reverse to o/w microemulsions. Microemulsions demonstrate special properties, e.g., isotropy and optical anisotropy. Total interfacial tension is given by $\gamma T = \gamma p - \gamma d$ [32].

4. Instantaneous (or negative) interfacial tension theory

Surfactants and co-surfactants can lower oil-water interfacial tension (IFT) to ultralow or even negative values, allowing spontaneous dispersion of small droplets and stabilizing microemulsions [36].

5. Interfacial adsorption film (or dual-membrane) theory

The Structure of the microemulsion (O/W, W/O, or bi-continuous) is determined by the film formed at the oil-water interface by surfactants and cosurfactants, depending on its flexibility, bending properties, and adsorption behavior [36].

6. Micelle solubilization theory:

Certain microemulsions can be regarded as extended micelles, where, at high surfactant concentrations, micelles can form, and the oil or water phase can be accommodated within them. Cosurfactants make this possible by lowering interfacial tension, hence enabling extension of micelles [36].

4.3 Mechanism of their working

Microemulsions deliver enhanced penetration and controlled drug release due to their minute droplet size and high interfacial area, favoring close interaction with biological barriers. The ingredients of microemulsions can destabilize barrier lipids, enhance fluidity, and promote permeation. In addition, microemulsions can be designed to control drug release by diffusion, composition of surfactant and oil, and inner structure to facilitate sustained release and better delivery. In addition, Microemulsions have shown intrinsic antimicrobial activity, disrupting microbial cell membranes by surfactant and cosurfactant insertion into lipid bilayers. The disruption causes disturbance in the membrane, leakage of cellular material, alteration in the cell wall, and finally, cell death. Microemulsions' antimicrobial action is influenced by their composition and time of contact, with some of them showing self-preserving properties that inhibit microbial growth [37].

4.4 Types of microemulsions

Three major types of microemulsions are as mentioned below:

1. Oil-in-water (O/W) microemulsions

In which surfactant molecules cover the droplets protectively,with their hydrophilic head in the water phase and their hydrophobic tail in the oil droplets. It is widely applied in the food, cosmetics, and pharmaceutical industries due to its stability and simple formulation [38].

2. Water-in-oil (W/O) microemulsions

Water-in-oil (W/O) microemulsions, however, consist of water droplets suspended in a bulk oil phase with surfactant molecules surrounding the water droplets having hydrophobic tails facing towards the oil phase and hydrophilic heads facing towards the water droplets.Though less frequently occurring, W/O microemulsions find use in enhanced oil recovery and controlled release products [38].

3. Bicontinuous microemulsions

Bicontinuous microemulsions, or middle-phase microemulsions, share a distinct structure in which oil and water phases are closely interwoven, with no discernible boundary. The interfaces between the networked oil and water phases are occupied by surfactant molecules. The distinctive organization provides special properties, such that bi-continuous microemulsions can be applied to drug delivery, emulsion polymerization, and environmental cleanups. Every type of microemulsion possesses certain advantages, such as increased solubilization, regulated release, and better stability, based on the desired application. Through judicious choice of surfactants, co-surfactants, and adjustment of the composition of the oil and water phases, microemulsion compositions can be formulated to possess certain properties and functionalities [38].

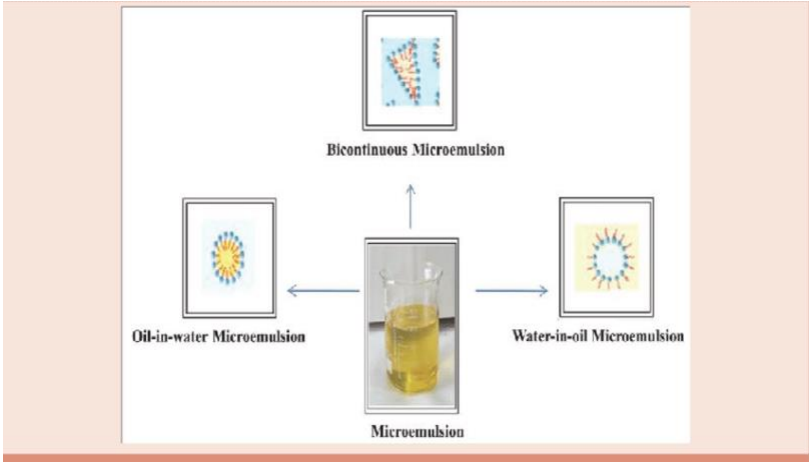

Figure 14: Types of Microemulsions [39]

4.5 Method of Preparation [38]

1. Phase Titration Method

Spontaneous emulsification can be used to prepare microemulsions and phase diagrams to characterize them, allowing for the exploration of intricate interactions between components. Phase diagrams show the appearance of microemulsions and other association structures, including emulsions, micelles, and liquid

crystalline phases, as a function of the chemical composition and concentration of components. Phase equilibria and phase boundaries are key features of microemulsion studies. Because quaternary phase diagrams are difficult to interpret, pseudo-ternary phase diagrams are used to mark various zones, the corners of each being a pure component. From the composition, microemulsion regions are categorized into oil-rich or water-rich, which differentiates between water-in-oil (w/o) and oil-in-water (o/w) microemulsions. Metastable systems must be carefully avoided by observation

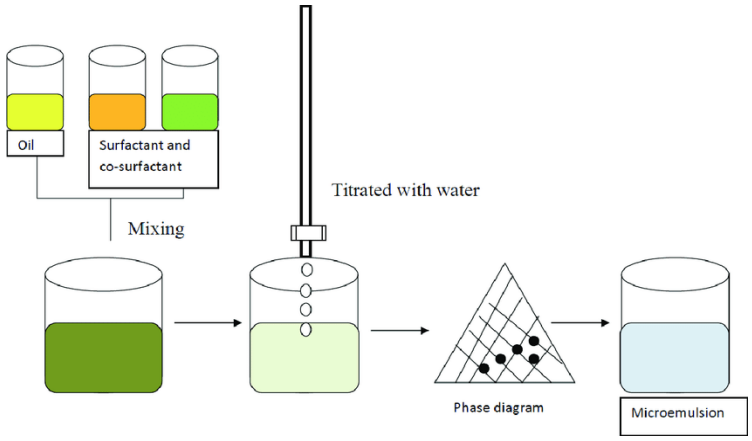

Figure 15: Phase titration [40]

2. Phase Inversion Method

Microemulsion phase inversion happens with the addition of excess dispersed phase, leading to quick physical alteration, such as particle size, which impacts drug release. In the case of nonionic surfactants, changes in temperature result in phase inversion, shifting from oil-in-water to water-in-oil microemulsion. This temperature-based process is referred to as the Phase Inversion Temperature (PIT) process. Alternatively, salt concentration or pH value can also result in phase inversion. Moreover, the spontaneous curvature of the surfactant can be modified by varying the water volume fraction, reversing the microemulsion from water-in-oil to oil-in-water.

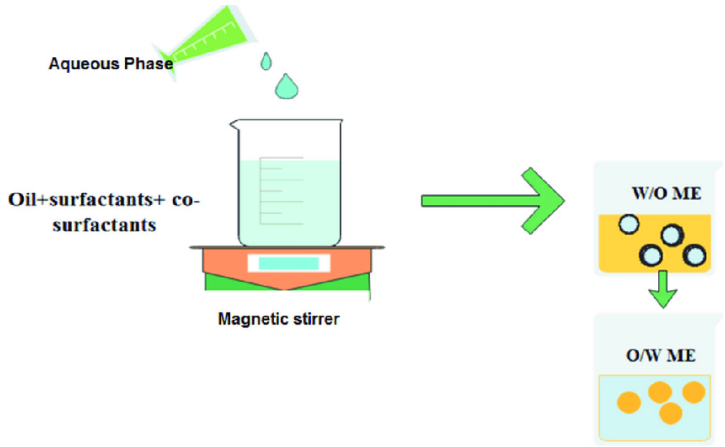

Figure 16: Phase inversion [41]

4.6 Evaluation factors of microemulsions [38]

Several major factors are evaluated for assessing microemulsions as mentioned below:

1. Stability and Consistency

Microemulsions are visually examined for homogeneity, optical clarity, and fluidity to ensure that they are stable in the long run.

2. Microstructure

Analysis under a cross-polarizing microscope verifies the absence of birefringence, hence the liquid crystalline system is eliminated.

3. Optical Properties

Transmittance of the microemulsions is spectrophotometrically measured to obtain the percent transmittance

4. Electrical Properties

Conductivity is determined through a conductometer to study the behavior of the microemulsion.

5. Rheological Properties

Measurements of viscosity are carried out in a Brookfield viscometer to study the flow behavior of the microemulsion.

6. Particle Size and Charge

Globule size and zeta potential are measured by dynamic light scattering for the knowledge of the dispersion property of the microemulsion.

7. Long-term Stability

The optimized microemulsion is kept under different conditions of temperature and monitored occasionally by phase separation.

Marketed formulations of Micro-formulation

Over-the-counter cosmetics, sunscreens, and prescription drugs. This type of drug delivery technology could result in a better comprehension of the healing of several diseases. Therefore, the micro-sponge-based drug delivery technology will probably emerge as a useful drug delivery matrix material for numerous therapeutic purposes in the future [42].

Table 1: Marketed formulations of Micro-formulations

Sr. No	Drug	Product name	Company	Therapeutic area	Types of micro-formulations
1.	Riseridine [43]	Resperdalconsta	Janseen	Antipsychotic	Microspheres
2.	Minocycline [43]	Arestin	Orapharma	Dentistry/periodontology	Microspheres
3.	Bromocriptine [43]	Cycloset/parlodel	Novartis	Neurology/endocrinology	Microspheres

4.	Cyclosporine-a [44]	Restasis	Allergan	Immunomodulation	Microemulsion
5.	Diazepam[44]	Diazemuls	Braun Melsungen	Sedation	Microemulsion
6.	Etomidate [44]	Etiomidat	Dumex	Anesthesia	Microemulsion
7.	Teriparatide [45]	Forsteo	Corium International in the U.S.A.	Osteoporosis	Microneedle
8.	Basal-bolus insulin[45]	V-go	Valeritusinc (U.S.A)	Type-2 diabetes	Microneedle
9.	Insulin [45]	Jewelpump.	Debiotech (Switzerland)	Type-1 and type-2 diabetes	Microneedle
10.	Acyclovir [46]	Zovirax	Glaxosmithkline	Antiviral	Microsponges
11.	Celecoxib [46]	Celebrex	Pfizer	Osteoarthritis	Microsponges
12.	Ketoprofen [46]	Orudis	Abbvie	NSAID	Microsponges

Future prospects of micro-formulations as a drug delivery system

Microsponges are new porous carriers made up of polydisperse cavities within a network of stable walls that can entrap an assortment of therapeutic and cosmetic agents. Their distinctive structure facilitates the controlled and prolonged release, minimizing side effects and enhancing compliance by the patient. Microsponges have found utility in dermal formulations such as sunscreens, anti-acne, and anti-dandruff medications, and are being more investigated for the delivery of thermostable substances, including vaccines, peptides, and nucleic acid-based medicines. Aside from pharmaceuticals, micro-sponges are being developed for use in tissue engineering, regenerative medicine, stem cell proliferation, and novel routes of administration, clearly demonstrating their extensive reach in healthcare, biotechnology, and cosmetic products [16].

Microemulsion technology will see dramatic improvement in the future as research widens its scope and streamlines formulation processes. In pharmaceuticals, the marriage of microemulsions with nanotechnology can potentially enable drugs to be targeted specifically at a given tissue with improved therapeutic efficacy and diminished systemic side effects. Another area that shows great promise is the incorporation of responsive materials that react to external stimuli like temperature, pH, or biochemical signals. Such "smart" systems could deliver controlled release and site-specific activity in both medical and cosmetic applications. Generally, innovation in this area will likely yield flexible delivery systems with enhanced safety, efficacy, and patient compliance [42].

Future advancements in microsphere technology are expected to be influenced by developments innanotechnology, gene therapy, and immunotherapy. Merging distinct disciplines would allow microspheres to be used as targeted carriers for individualized and locational drug delivery. These systems

promise to maximize therapeutic impacts, decrease off-targeting, and promote compliance in patients. They are particularly promising for the treatment of cancers, autoimmune diseases, and genetic diseases that remain difficult to treat with conventional treatments. With increasing research in biotechnology and material sciences, microsphere-based carriers are expected to develop into flexible and multifunctional platforms for future clinical applications [47].

Emerging trends in microneedling point towards several new directions. Nano-needling with the use of ultra-fine needles provides more precise and less invasive treatments, but does not have long-term safety information. Combination with regenerative medicine, specifically stem cells and growth factors, promises enhanced healing, albeit with limited clinical verification. Microneedling as a vehicle for gene therapy delivery could offer specific solutions to genetic and dermatologic disorders, but poses ethical and safety concerns. Utilization in systemic disease through transdermal delivery might provide minimally invasive alternatives, though evidence is scarce. Integration of microneedling with newer modalities and an increase in clinical trials might further enhance therapeutic benefit [48].

Conclusion

Ultimately, micro-formulations offer exceptional opportunities and serve as powerful tools in the field of drug delivery systems dedicated to controlled release and targeted therapy. As this field continues to grow, micro-formulations will likely play an important role in overcoming therapeutic challenges related to targeted delivery systems and significantly improve healthcare outcomes. Micro-formulations are versatile, customizable, and hold great potential for extensibility, due to which, they are a promising means for applications in personalized, regenerative medicines and beyond. With time, new materials, advanced techniques, and varied applications will surely emerge, which can enhance the safety and efficacy of micro-formulations.

Acknowledgement

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