



Scholars Research Library

Der Pharmacia Lettre, 2010, 2(4): 335-354
(<http://scholarsresearchlibrary.com/archive.html>)



An applauded novel drug delivery system for arthritis using NSAIDS by microencapsulation technique -A review

Mradul R. Gupta*, Rahul Kapoor, M. S. Sudheesh, Umesh K. patil

VNS Institute of Pharmacy, Bhopal, (M.P.) India

ABSTRACT

Microencapsulation may be defined as the process of surrounding or enveloping one substance within another substance on a very small scale, yielding capsules ranging from less than one micron to several hundred microns in size. Drug discovery and delivery to retard the degeneration of joint tissues are challenging. Current treatment of different arthritis involves administration of ideal non-steroidal anti-inflammatory drugs (NSAIDs) mainly by oral and parenteral route. Frequent dosing of NSAIDs often leads to patient non compliance. Accounting this problem, drug delivery technologies should be developed which are reduces frequency of dosing along with sustained release of medicament. Among several novel drug delivery systems microencapsulation is one of the novel plot form technology employed to sustain the drug release and reduce or eliminate gastrointestinal irritation, dose intake and ultimately improve the patient compliance in the pharmacotherapy of arthritis, This review reports a comprehensive overview of newly developed microencapsulation technologies as therapeutic targets of arthritis which are may be potentially to reduce adverse side effects induced by NSAIDs.

Key-words:- Microparticulate, Rheumatoid arthritis (RA), COX-1 and COX-2, Sustained release.

INTRODUCTION

The human skeleton and muscle help to make possible the peaceful gyration as well as more safe routine movements of everyday life. Human body naturally produces Glucosamine, which is used to produce proteoglycans, the principal lubricating proteins in our cartilage, tendons, ligaments, synovial fluid and mucous membranes. Imbalance in the regeneration process of these functional elements of the joint leads to friction, pain and inflammation, due to cartilage repair decreases/ceases, cartilage become thinner and bones grind against one another. Arthritis and many other rheumatic diseases are mainly disorders of the supportive or connective tissues of the

bones, tendons, heart valves and joints ranging from minor stiffness to engrave disability and deformity [1]. Although many specific drugs for treatment of major inflammation and/or acute pain like steroidal anti-inflammatory agents or narcotic analgesics are available but ideal NSAIDs should affect only controlled inflammation by modifying inflammatory response to diseases, but not to interfere with normal inflammatory process.

NSAIDs effectively quell the pain and reduce the inflammation that can occur in advanced cases, but they do nothing to halt the disease process [2]. As awareness of the GI side effects associated with NSAIDs increases, safety becomes a primary requisite in treatment. Numerous articles examining the gastric and duodenal damage caused by NSAIDs have been published, however, only recently have the more distal intestinal disturbances induced by these drugs received close attention. There is often a poor correlation between patient reported symptoms of upper GI distress and endoscopically proven gastropathy. This may suggest afflictions of more distal parts of the intestine. The concept of selective and site specific damage to the upper GI tract following NSAIDs has been questioned, particularly by the works of Bjornson, who has demonstrated that patients on chronic NSAID therapy can develop small and large intestinal inflammation which may lead to anemia, hypoalbuminemia, ulceration, 'diaphragm' like strictures, perforation, and hemorrhage[3]. Medical researchers had developed a number of NSAIDs that blocked the body's production of substances playing vital roles in pain and inflammation responses.

A trend in NSAID development has been to improve therapeutic efficacy and reduce the severity of upper GI side effects through altering dosage forms of NSAIDs by modifying release of the formulations to optimize drug delivery. These formulations are designed to increase patient compliance through a prolonged effect and reduce adverse effects through lowered peak plasma concentrations [4]. The successful optimization and development of drug entity, design of dosage form then plays important role. The design of effective drug delivery systems has recently become an integral part of the development of new medicines. Hence, research continuously keeps on searching for ways to deliver drugs over an extended period of time, with a well-controlled release profile. Microencapsulation is a novel technique to develop several novel drug delivery systems either sustained or controlled manner through a various route of administration to avoid dose related adverse effects induced by repeated administration of NSAIDs. The micro particulate drug delivery of NSAIDs was suggested to be the best alternatives for the safe and effective delivery of these drugs. The present article deals with different aspects of the microencapsulation to improve the pharmacotherapy arthritis.

Rheumatoid arthritis;

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disorder that may affect many tissues and organs, but principally attacks the joints producing an inflammatory synovitis that often progresses to destruction of the articular cartilage and ankylosis of the joints. Rheumatoid arthritis can also produce diffuse inflammation in the lungs, pericardium, pleura, and sclera, and also nodular lesions, most common in subcutaneous tissue under the skin. Although the cause of rheumatoid arthritis is unknown, autoimmunity plays a pivotal role in its chronicity and progression. About 1% of the world's population is afflicted by rheumatoid arthritis, women three times more often than men. Onset is most frequent between the ages of 40 and 50, but no age is immune. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility.

Various treatments are available includes physical and occupational therapy. Analgesia (painkillers) and anti-inflammatory drugs, as well as steroids, are used to suppress the symptoms, while disease-modifying antirheumatic drugs (DMARDs) are often required to inhibit or halt the underlying immune process and prevent long-term damage. In recent times, the newer group of biologics has increased treatment options[5,6,7].

Nonsteroidal anti-inflammatory drugs (NSAIDs);

NSAIDs are among the drugs most commonly used in the treatment of inflammation and pain induced by arthritis. Prostaglandins (PGs) are an important group of chemical mediators which are responsible for producing changes, symptoms and signs of inflammation. NSAIDs are heterogeneous group of compounds that are non-selectively by inhibiting both Cyclooxygenase enzymes (COX 1 and COX 2) which are responsible for the biosynthesis of the prostaglandins (PGs) and thromboxanes from its precursor arachidonic acid. COX 1 enzyme is constitutively present in cells. It is a house-keeping enzyme has a physiological function producing prostaglandins which help to keep the stomach and blood vessels clean by making prostacyclin, whereas COX 2 is inducible form and is generated at sites of inflammation. It is reported that NSAIDs provides pain relief by reducing prostaglandin, bradykinins and oxygen radicals. Non selective COX inhibitors produces side effects on long term use and to overcome this problem, selective COX 2 inhibitors were developed. COX 2 inhibitors decreases COX 2 mRNA levels and modulates local and systemic cytokine production in order to reduce inflammation and bone erosion [8, 9].

Mechanism of NSAIDS;

The mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase, which catalyzes arachidonic acid to prostaglandins and leukotrienes. Arachidonic acid is released from membrane phospholipids as a response to inflammatory stimuli. Prostaglandins establish the inflammatory response. Flow digram of mechanisim of NSAIDs has been shown in fig. no. 1.

The cyclooxygenase pathway

NSAIDs work by interfering with the cyclooxygenase pathway. Different mechanisms stimulate the two different types of cyclooxygenase. COX-1 is stimulated continuously by normal body physiology. The COX-1 enzyme is constitutive, meaning that its concentration in the body remains stable. It is present in most tissues and converts arachidonic acid to prostaglandins. These prostaglandins in turn stimulate body functions, such as stomach mucous production and kidney water excretion, as well as platelet formation. The location of the COX-1 enzyme dictates the functions of the prostaglandins it releases. For example, COX-1 in the stomach wall produces prostaglandins that stimulate mucous production. In contrast, the COX-2 enzyme is induced. It is not normally present in cells but its expression can be increased dramatically by the action of macrophages, the scavenger cells of the immune system. COX-2 plays a very important role in inflammation. Cox-2 is involved in producing prostaglandins for an inflammatory response. COX-1 is stimulated continually, and COX-2 is stimulated only as a part of an immune response [10].

Inflammatory role of prostaglandin

Prostaglandins are paracrine secretions (local hormones) - they are released from cells and bring about changes in neighboring cells that carry specific prostaglandin receptors in their

membranes. They are rapidly degraded locally, and generally do not reach the blood stream. The influence, which prostaglandins have, depends upon the type of tissue they are acting upon. Such action may be direct, or as a result of modifying the actions of other signaling molecules. Prostaglandin was released by damaged cells and nearby macrophages and one of their effects is to stimulate pain receptors (nociceptors). At the same time they intensify the effects of other chemical mediators such as histamine and bradykinin. Acting in concert these substances can bring about vasodilatation and an increase in the permeability of capillaries supplying the damaged area, encouraging the migration of phagocytes from the blood through capillary walls into the damaged tissue. As a result of these changes, the blood supply to the area increases, the tissues swell, and pain occurs, signs of inflammation [11].

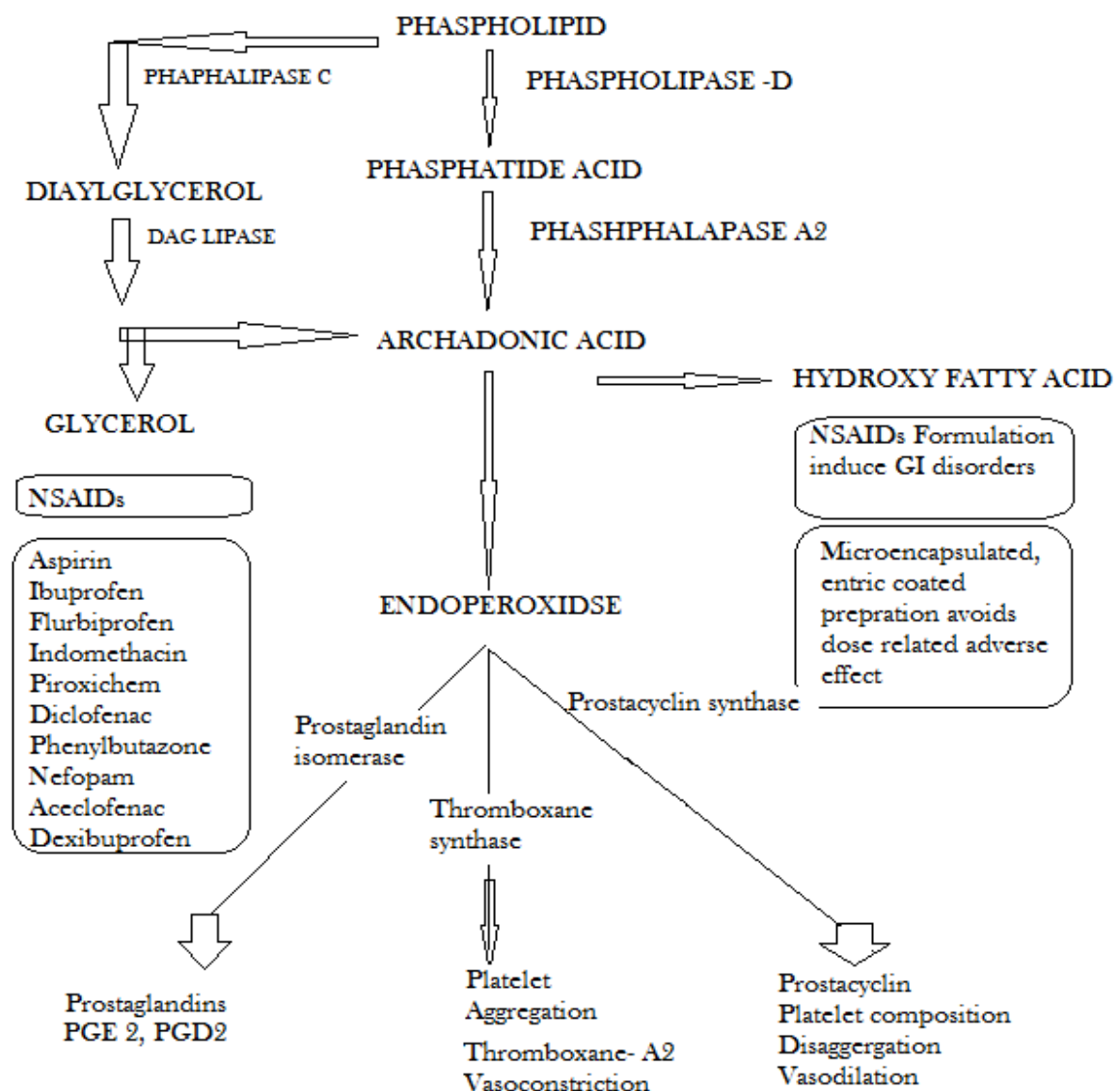


Fig. no. 1 mechanism of NSAIDs

Action of NSAIDs on cyclooxygenase;

The two forms of cyclooxygenase have equal molecular weights and are very similar in structure. However, the attachment site of COX-1 is smaller than the attachment site of COX-2. Therefore, it accepts a narrower range of structures as substrates. The cyclooxygenase active site lies at the end of a long, narrow, hydrophobic tunnel or channel. Three of the alpha helices of the membrane-binding domain lie at the entrance to this tunnel. In various ways, they all act by filling and blocking the tunnel, preventing the migration of arachidonic acid to the active site at the back of the tunnel. They do this by temporarily blocking the attachment site for arachidonic acid on the cyclooxygenase enzyme, thereby preventing it from converting arachidonic acid to prostaglandin. The exception is aspirin, which irreversibly acetylates cyclooxygenase. It takes longer for the effects of aspirin to wear off because new enzymes must be formed by the body to replace the altered enzymes. When COX-1 is acetylated by aspirin, the site for arachidonic acid is blocked. However, when aspirin acetylates COX-2, the active site is still large enough to accept arachidonic acid. [12, 13]

Drug delivery systems;

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience, and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamics profiles with acceptable level of safety to the patient. Since the therapy involves frequent administration of drug, chances of patient noncompliance increase drastically [14, 15]. Parenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments. In spite of advantages of parenteral drug administration in RA, this route is seldomly used due to higher incidences of patient noncompliance and rapid clearance rate of drug which ultimately compels frequent administration of drug. Moreover self medication is not possible; it limits use of this route. [16, 17]

Various clinical reports, post-marketing surveillance studies have revealed that NSAIDs are associated with extensive side effects like gastric-irritation, dyspepsia, peptic ulceration, gastric bleeding, esophagitis, constipation, sodium and water retention, chronic renal failure, intestinal nephritis. CNS effects etc, apart from these side effects GI-disorders are the main side effects caused by repeated administration of NSAIDs especially those are involved in COX-1 inhibitors. [18] The risk of important gastrointestinal damage depends on the dose and frequency of administration. The great therapeutic value of these drugs has made it necessary to develop strategies for avoiding the gastrointestinal risks and allow continuing to associate administration of gastric mucosa protectors and development of formulations by using different novel drug delivery techniques both oral and per-oral route.

Novel drug delivery systems [NDDS]

When the new drug or existing drug is given, altering the formulation and administered through the different route, this process is called as the novel drug delivery systems. NDDS are very important consideration for all pharmaceutical and biotechnology companies. At present the drug

delivery sector of global pharmaceutical market accounts for only percent. If the prediction of the industry experts proves right, the market for new drug delivery systems is likely to reach over US \$54 billion by the year 2007

Over the past few decades, the rise of modern pharmaceutical technology and the amazing growth of the biotechnology industry have revolutionized the approach to drug discovery and development. The close association of people from various fields such as chemistry, biology, medicine and engineering in drug development research has led to the uncovering of the cellular and molecular basis for the action of many drugs. The most common mode of administration of drugs is in the form of pills or injections. These methods of administration meet the requirements of efficacy for several drugs. However, these methods are inadequate for many new drugs such as NSAIDs, which have short half-lives, poor permeability in membranes and are severely toxic when delivered systemically in large doses. To overcome these difficulties, new modes of administration have been the focus of a great deal of research over the past few decades. A Sustained/controlled release drug delivery system should be able to achieve the following benefits:

- (1) Maintenance of optimum therapeutic drug concentration in the blood with minimum fluctuation.
- (2) Predictable and reproducible release rates for extended duration.
- (3) Enhancement of activity duration for short half-life drugs.
- (4) Elimination of side effects, frequent dosing and wastage of drug.
- (5) Optimized therapy and better patient compliance. [19]

Microencapsulation technology now available to develop novel drug delivery systems which not only release drugs in a controlled and predetermined fashion, but which can also target to entire regions of the GI tract and should allow greater control of therapy and potentially minimize dose related adverse effects and improve patient compliance.

Microencapsulation techniques in NSAIDs -

Microencapsulation is a process whereby small discrete solid particles or small liquid droplets are surrounded and enclosed, by an intact shell. The concept of microencapsulation was initially utilized in carbonless copy paper. More recently it has received increasing much attention in pharmaceutical and biomedical applications. The first research leading in the development of microencapsulation procedures for pharmaceuticals was published by Bungenburg de Jong and Kass in 1931 and dealt with the preparation of gelatin spheres by the use of gelatin coacervation process for coating. Drug companies have been quick to realize and exploit the enormous potential of the technology for overcoming formulation and delivery problems in different dosage forms like tablets, capsules, topical, and injectables.

Now a day, the pharmaceutical industries and researchers are involved and taking most challenging to develop newer drug delivery systems by using several coating materials for the microencapsulation of medicines. Thus microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of enrolling environmental protection and of controlling the release characteristics depending on physicochemical properties

of coating materials. Several of these properties can be attained by micropackaging or microparticulate techniques [20].

The terminology used to describe microparticulate formulations can sometimes be inconsistent and confusing to readers unfamiliar with the field. Essentially, the term “microparticle” refers to a particle with a diameter of 1–1000 μm , irrespective of the precise interior or exterior structure. Within the broad category of microparticles, “microspheres” or microbeads specifically refer to spherical microparticles and the subcategory of “microcapsules” applies to microparticles which have a core surrounded by a material which is distinctly different from that of the core. The core may be solid, liquid, or even gas. Despite the specific and logical subcategories, many researchers use the terms interchangeably, often to the confusion of the reader. It is usually assumed that a formulation described as a microparticle is comprised of a fairly homogeneous mixture of polymer and active agent, whereas microcapsules have at least one discrete domain of active agent and sometimes more. Microcapsules can be divided into two broad groups. The first is Aggregate type microcapsules, which have the active ingredient dispersed uniformly throughout a continuous matrix. The matrix may be a solid dry polymer or a gel swollen with solvent. In the case where the gel is swollen with water, the term “hydrogel” is applied. Hydrogel encapsulation systems of this type are generally based on water-soluble polymers, such as alginate, gelatin, pectin, agar, Gellan, or starch. The second is mononuclear microcapsules, which consist of materials that show true “shell-core” morphology. These are similar to an egg in that they have a solid outer shell or flexible membrane surrounding a core that may be a liquid, a solid, or a gel. [21]

Microparticles are generally formulated by encapsulation process whereby an active ingredient is placed into a stabilized form in order to allow it to be conveniently stored or protected from unfavorable conditions until needed. The active ingredient may be dispersed in a protective matrix, or it may be surrounded by a coating, a shell, or a membrane. The release of active ingredient(s) from the protected form may be rapid (such as by crushing or by ingestion), or gradual (such as by dissolution, diffusion, chemically triggered or controlled time-release, or biodegradation). In this manner, it is possible to maximize the effectiveness of the active ingredient by ensuring it is released at the proper time. This “controlled release” can also be made to occur over a programmed time interval (sustained release) or on demand (stimulated release) combination of any biodegradable polymers. [22]

Reasons for Microencapsulation

Microencapsulation of materials is resorted to ensure that the encapsulated material reaches the area of action without getting adversely affected by the environment through which it passes. Amongst the principal reasons for encapsulation are:

1. Separation of incompatible components
2. Conversion of liquids to free flowing solids
3. Increased stability (protection of the encapsulated materials against oxidation or deactivation due to reaction in the environment)
4. Masking of odor, taste and activity of encapsulated materials
5. Controlled release of active compounds (sustained or delayed release)
6. Targeted release of encapsulated materials
7. The ability to incorporate reasonably high concentrations of the drug.

8. Controlled particle size and dispersability in aqueous vehicles for injection.
9. Reduce GI-disorders of acidic drugs (NSAIDs)
10. Susceptibility to chemical modification.
11. Improve the bioavailability of water in-soluble drugs and patient compliance.

Techniques of Microencapsulation-

Although a variety of techniques have been reported for microencapsulation, they can broadly be divided into two main categories. The first category includes those methods in which starting materials are monomers/prepolymers. In these methods chemical reactions are also involved along with microsphere formation. The second category consists of those methods in which starting materials are polymers. Hence, in these methods no chemical reactions are involved and only shape fabrication takes place. Generally the choice of the microencapsulation method depends on the physicochemical characteristics of the drug and polymeric/monomeric material used. Thus appropriate combination of starting materials and synthesis methods can be chosen to produce microencapsulated products with a wide variety of compositional and morphological characteristics.[23]

Drug loading

The active components are loaded over the microspheres principally using two methods, i.e. during the preparation of the microspheres or after the formation of the microspheres by incubating them with the drug. The active component can be loaded by means of the physical entrapment, chemical linkage and surface adsorption. The entrapment largely depends on the method of preparation and nature of the drug or polymer (monomer if used). Maximum loading can be achieved by incorporating the drug during the time of preparation but it may get affected by many other process variables such as method of preparation, presence of additives (e.g. crosslinking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc.

Drug release kinetics

Release of the active constituent is an important consideration in case of microspheres. The release profile from the microspheres depends on the nature of the polymer used in the preparation as well as on the nature of the active drug. The release of drug from both biodegradable as well as non-biodegradable microspheres is influenced by structure or micromorphology of the carrier and the properties of the polymer itself. The drugs could be released through the microspheres by any of the three ways;

(1)***Diffusion:-*** On contact with aqueous fluids in the gastrointestinal tract (GIT), water diffuses into the interior of the particle. Drug dissolution occurs and the drug solutions diffuse across the release coat to the exterior.

(2)***Erosion:-***Some coatings can be designed to erode gradually with time, thereby releasing the drug contained within the particle. The polymer erosion, i.e. loss of polymer is accompanied by accumulation of the monomer in the release medium. The erosion of the polymer begins with the changes in the microstructure of the carrier as water penetrates within it leading to the plasticization of the matrix.

(3)***Osmosis:-*** In allowing water to enter under the right circumstances, an osmotic pressure can be built up within the interior of the particle. The drug is forced out of the particle into the exterior through the coating water diffuse into the core through biodegradable or nonbiodegradable coating, creating sufficient pressure that ruptures the membrane. The burst

effect is mainly controlled by three factors the macromolecule/polymer ratio, particle size of the dispersed macromolecule and the particle size of the microspheres. Drug release from the non-biodegradable type of polymers can be understood by considering the geometry of the carrier. The geometry of the carrier, i.e. whether it is reservoir type where the drug is present as core, or matrix type in which drug is dispersed throughout the carrier, governs overall release profile of the drug or governs overall release profile of the drug or active ingredients. [24]

Polymerization techniques

The polymerization techniques conventionally used for the preparation of the microspheres are mainly as; Normal polymerization, Interfacial polymerization. Both are carried out in liquid phase. They are carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization processes. In bulk, a monomer or a mixture of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the process of polymerization. Suspension polymerization also referred as bead or pearl polymerization. Here it is carried out by heating the monomer or mixture of monomers as droplets dispersion in a continuous aqueous phase. The droplets may also contain an initiator and other additives. [25]

Emulsion polymerization

According to this technique the monomer (alkyl acrylates) is added dropwise to the stirred aqueous polymerization medium containing the material to be encapsulated (core material) and a suitable emulsifier. The polymerization begins and initially produced polymer molecules precipitate in the aqueous medium to form primary nuclei. As the polymerization proceeds, these nuclei grow gradually and simultaneously entrap the core material to form the final microcapsules. Generally lipophilic materials (insoluble or scarcely soluble in water) are more suitable for encapsulation by this technique. Emulsion polymerization differs from suspension polymerization as due to the presence initiator in the aqueous phase, which later on diffuses to the surface of micelles. [26]

Maghsoodi. et. al. were prepared microparticles of naproxen with Eudragit L100 and Aerosil the emulsion solvent diffusion method in order to avoid local gastrointestinal irritation, one of the major side effects of nonsteroidal anti-inflammatory drugs after oral ingestion. The process of preparation involved the use of ethanol as good solvent, dichloromethane as a bridging liquid, water as poor solvent, Aerosil as anti-adhesion agent, and sodium dodecyl sulfate to aid in the dispersion of the drug and excipients into the poor solvent. The incorporation efficiency was enhanced with increasing the ratio of excipients to drug and the initial difference of temperature between the solvent and nonsolvent. Drug release studies of the microparticles confirmed the gastroresistance, and mathematical studies showed that the drug released followed a Hixon and Crowell kinetic. These microparticles represent a simple method for the preparation of drug-loaded enteric microparticles with desired Micromeritic properties and gastro resistance release. [27]

Interfacial polymerization:

As the term "interfacial" implies, this technique involves the polycondensation (condensation polymerization) of two complementary monomers at the interface of a two phase system. For the preparation of microcapsules, this two-phase system is mixed under carefully controlled

conditions to form small droplets of one phase (dispersed phase) in the other one (continuous phase/suspension medium). The material to be encapsulated must be chosen in such a way as to be present (dissolved or dispersed) in the droplets. It is also necessary to use a small amount of a suitable stabilizer to prevent droplet coalescence or particle coagulation during the polycondensation process and capsule formation. Interfacial polycondensation can be utilized to produce both monocoresh type or matrix type microcapsules, depending on the solubility of the polycondensate in the droplet phase. Thus if the polymer is soluble in the droplets, matrix type microcapsules are formed. On the other hand, if the polymer is not soluble, it precipitates around the droplets and leads to the formation of monocoresh type microcapsules. Preparation of microcapsules by interfacial polycondensation is applicable to a large number of polymers including polyamides, polyureas, Polyurethanes, and polyesters. [28, 29]

Miyazaki. et. al. prepare poly n-butylcyanoacrylate (PNBCA) nanocapsules loaded with indomethacin and to evaluate the ability of this carrier system to deliver the drug systemically after its topical application. Poly n-butylcyanoacrylate (PNBCA) nanocapsules of indomethacin were prepared by interfacial polymerization. The in vitro permeation of indomethacin through excised rat skin and an artificial membrane was determined for PNBCA nanocapsules in pH 7.4 phosphate buffer (I), and in PLF-127 gel (II) and were compared against indomethacin incorporated into 25%w/w PLF-127 gel alone (III). The in vivo percutaneous absorption of indomethacin following the application of the PNBCA nanocapsules and a 25%w/w Pluronic F-127 (PLF-127) gel (III) was monitored by the determination of drug plasma levels in rats. The in vitro results indicated a rank order for the three formulations (I, II and III) in both the flux at steady state and the cumulative amounts permeated at 8 hrs. The higher drug plasma levels over 6 hrs of indomethacin PNBCA nanocapsules are in agreement with the determined in vitro permeation results. The presented data show that indomethacin loaded PNBCA nanocapsules can improve the transdermal delivery of indomethacin compared to a conventional gel formulations. [30]

Spray drying and spray congealing:

These methods are based on the drying of the mist of the polymer and drug in the air. Depending upon the removal of the solvent or cooling of the solution, the two processes are named spray drying and spray congealing respectively. The polymer is first dissolved in a suitable volatile organic solvent such as dichloromethane, acetone, etc. The drug in the solid form is then dispersed in the polymer solution under high-speed homogenization. This dispersion is then atomized in a stream of hot air. The atomization leads to the formation of the small droplets or the fine mist from which the solvent evaporates instantaneously leading the formation of the microspheres in a size range 1-100 μm . Microparticles are separated from the hot air by means of the cyclone separator while the traces of solvent are removed by vacuum drying. The water soluble natural polymers, such as starch, gum arabic, chitosan, gellan and sodium alginate are commonly used as the wall-forming materials. One of the major advantages of the process is feasibility of operation under aseptic conditions.[31, 32]

Yapel. et al. prepare ketoprofen-loaded microspheres with a polymeric blend by a spray-drying technique. Solidification is accomplished by rapid evaporation of the solvent in which coating material is solubilized. Organic solutions of two polymers, cellulose acetate butyrate (CAB) and poly (epsilon-caprolactone) (PCL), in different weight ratios, and of ketoprofen were prepared

and sprayed, in different experimental conditions, achieving drugloaded microspheres. The process control variables in this technique were feed material properties, feed rate, method of atomization and drying rate. Spray drying method is rapid, reproducible and easy to scale up. [33]

Single emulsion technique:

The micro particulate carriers of natural polymers of natural polymers i.e. those of proteins and carbohydrates are prepared by single emulsion technique. The natural polymers are dissolved or dispersed in aqueous medium followed by dispersion in non-aqueous medium like oil. Next cross linking of the dispersed globule is carried out. The cross linking can be achieved either by means of heat or by using the chemical cross linkers. The chemical cross linking agents used are glutaraldehyde, formaldehyde, etc. Heat denaturation is not suitable for thermolabile substances. Chemical cross linking suffers the disadvantage of excessive exposure of active ingredient to chemicals if added at the time of preparation and then subjected to centrifugation, washing, separation. [34]

Bayomi et al. was investigated emulsion crosslinking technique using mineral oil or vegetable oil as oil phase and drug polymer solution as aqueous phase is simple and widely used method for the preparation of NSAIDs. Cross-linking can be achieved by chemical agent or heat. Viscosity of the oil phase, concentration of the Cross-linking agent, duration of Cross-linking, etc are the different parameters, which affect the release rate and entrapment efficiency. Gelatin A microspheres of ketorolac tromethamine for intranasal systemic delivery were developed using the emulsification Cross-linking technique. The drug was dispersed in the polymer gelatin and formulated into a w/o emulsion with liquid paraffin, using glutaraldehyde as a Cross-linking agent. [35]

Double emulsion technique:

Double emulsion method of microspheres preparation involves the formation of the multiple emulsions or the double emulsion of type w/o/w and is best suited to water soluble drugs, peptides, proteins and the vaccines. This method can be used with both the natural as well as synthetic polymers. The aqueous protein solution is dispersed in a lipophilic organic continuous phase. This protein solution may contain the active constituents. The continuous phase is generally consisted of the polymer solution that eventually encapsulates of the protein contained in dispersed aqueous phase. The primary emulsion is subjected then to the homogenization or the sonication before addition to the aqueous solution of the poly vinyl alcohol (PVA). This results in the formation of a double emulsion. The emulsion is then subjected to solvent removal either by solvent evaporation or by solvent extraction.[36]

A new oral controlled-release drug delivery system for indomethacin was developed with two polymers using a multiple-emulsification technique. Powdered drug was dispersed in methylcellulose solution, which was emulsified in ethyl cellulose solution in ethyl acetate. The primary emulsion thus formed was re-emulsified in aqueous medium. During this phase, discrete microspheres were formed under optimized conditions. The in vitro drug release followed first-order diffusion-controlled dissolution. More than 85% of the drug was released over 6 hour at pH 6.2 for all dissolution batches. [37]

Emulsion cross-linking technique

Emulsion-crosslinking is the method of choice for the preparation of protein and polysaccharide micro-capsules. Microcapsule formation by this technique involves dispersion of an aqueous solution of the polymer containing core material in an immiscible organic solvent (suspension/dispersion medium) in the form of small droplets. The suspension medium contains a suitable stabilizer to maintain the individuality of the droplet/microcapsules. The droplets are subsequently hardened by covalent crosslinking and are directly converted to the corresponding microcapsules. The crosslinking process is accomplished either thermally (at >500 °C) or by the use of a crosslinking agent formaldehyde, terephthaloyl chloride, etc). Emulsion-crosslinking is a versatile method and can be adopted for microencapsulation of soluble, insoluble, liquid or solid materials, and for the production of both micro and nanocapsules. [38]

Kumbar et al. was investigated encapsulation of diclofenac sodium into crosslinked chitosan microspheres and the effect of crosslinking agent were studied by microspheres of chitosan crosslinked with three different crosslinking agents like glutaraldehyde, sulphuric acid and heat treatment were prepared to encapsulate diclofenac sodium. Chitosan microspheres were produced in a w/o emulsion followed by crosslinking in the water phase by one of the crosslinking methods. Encapsulation of drug was carried out by soaking the already swollen cross linked microspheres in a saturated solution of diclofenac sodium. The in-vitro release studies were performed in 7.4 pH buffer solution. The fastest release of 81% at 500 min was shown when heat cross linked for 3 h. Drug release from the matrices deviated slightly from the Fickian process. [39]

Solvent Evaporation/Solvent Extraction

Microcapsule formation by solvent evaporation/solvent extraction is very similar to suspension crosslinking, but in this case the polymer is usually hydrophobic polyester. The polymer is dissolved in a water immiscible volatile organic solvent like dichloromethane or chloroform, into which the core material is also dissolved or dispersed. The resulting solution is added dropwise to a stirring aqueous solution having a suitable stabilizer like poly (vinyl alcohol) or polyvinylpyrrolidone, etc. to form small polymer droplets containing encapsulated material. With time, the droplets are hardened to produce the corresponding polymer microcapsules. This hardening process is accomplished by the removal of the solvent from the polymer droplets either by solvent evaporation (by heat or reduced pressure), or by solvent extraction (with a third liquid which is a precipitant for the polymer and miscible with both water and solvent). Solvent extraction produces microcapsules with higher porosities than those obtained by solvent evaporation. Solvent evaporation/extraction processes is suitable for the preparation of drug loaded microcapsules based on the biodegradable polyesters such as polylactides, poly (lactide-co- glycolide) and polyhydroxybutyrate.[40]

Giovanni et al. were prepared ketoprofen controlled release microspheres, by emulsion/solvent evaporation, at 15 °C, in order to avoid the formation of semisolid particles. An identical procedure was carried out at 60 °C to speed up the solvent evaporation and the formed semisolid microspheres were directly microencapsulated by complex coacervation and spray-dried in order to recover them as free flowing powder. Microspheres and microcapsules were characterized by In-vitro dissolution studies, and then used for the preparation of tablets. During this step, the compressibility of the prepared powders was measured. Microspheres and microcapsules showed

compaction abilities by far better than those of the corresponding physical mixtures. In fact, it was impossible to obtain tablets by direct compressing drug and polymer physical mixtures, but microspheres and microcapsules were easily transformed into tablets. Finally, *in vitro* dissolution studies were performed and the release control of the tablets was pointed out. Microspheres were able to control ketoprofen release only after their transformation into tablets. Tablets containing eudragit RS were the most effective in slowing down drug release [41].

Coacervation/Phase separation

Coacervation (or phase separation) is widely employed for the preparation of gelatin and gelatin-acacia microcapsules, as well as for a large number of products based on cellulose derivatives and synthetic polymers. Phase separation processes are divided into simple and complex coacervation. Simple coacervation involves the use of a single polymer such as gelatin or ethyl cellulose, in aqueous or organic media, respectively. Complex coacervation involves two oppositely charged polymeric materials such as gelatin and acacia, both of which are soluble in aqueous media. In both the cases, coacervation is brought about by gradual desolvation of the fully solvated polymer molecules. Microencapsulation by coacervation is carried out by preparing an aqueous polymer solution (1-10 %) at 40-50 °C into which the core material (hydrophobic) is also dispersed. A suitable stabilizer may also be added to the mixture to maintain the individuality of the final microcapsules. A suitable desolvating agent (coacervating agent) is gradually introduced to the mixture, which leads to the formation of partially desolvated polymer molecules, and hence their precipitation on the surface of the core particles. The coacervation mixture is cooled to about 5-20 °C, followed by the addition of a crosslinking agent to harden the microcapsule wall formed around the core particles. [42, 43]

Vanessa et al. was prepared chitosan microspheres by using the simple coacervation method and cross linked using epichlorhydrin or glutaraldehyde for the controlled release of diclofenac sodium. The effects of the crosslinking agents on chitosan microspheres over a 12-hour period were assessed with regard to swelling, hydrolysis, porosity, crosslinking, impregnation of diclofenac sodium (DS), and consequently to the release of DS in buffer solutions, simulating the gastrointestinal tract. Release kinetics of diclofenac sodium from these matrices was investigated at pH 1.2, 6.8 and 9.0, simulating the gastrointestinal tract conditions. The results indicated that the release mechanism deviated slightly from Fickian transport. [44]

Fluidized bed coating;

Fluidized bed coating is used for encapsulation of solid core materials including liquids absorbed into porous solids. This technique is used extensively to encapsulate pharmaceuticals. Solid particles to be encapsulated are suspended in a jet of air and then covered by a spray of liquid coating material. The capsules are then moved to an area where their shells are solidified by cooling or solvent vaporization. The process of suspending, spraying and cooling is repeated until the capsule walls are of the desired thickness.[46, 47]

Silva et al. studied the dissolution process of sodium diclofenac granules coated with a polymeric suspension of Eudragit L-30D-55® by fluidized bed. Methacrylic acidmethylmetacrylate copolymer, also known as Eudragit, has been used as a pH sensitive coating material to protect drug substances prior to delivery to the human intestines. The sodium diclofenac granules were prepared by wet granulation technology using microcrystalline

cellulose (MICROCEL), sodium diclofenac, and polyvinylpyrrolidone K30. The granules coating operation was carried out in a fluidized bed with top spraying by a double-fluid nozzle. The dissolution mediums were 0.1N HCl solution and a pH 6.8 phosphate buffer solution, following the pH change dissolution procedure specified in USP for enteric-coated articles: 2 h of exposure to 750 ml of 0.1N HCl followed by testing in 1000 ml of pH 6.8 phosphate buffer, the pH being adjusted with 250 ml of 0.2 M tribasic sodium phosphate solution. The released amount of sodium diclofenac was periodically determined by UV spectrophotometer. The coated product showed gastric resistance properties confirming the feasibility of the fluidized bed for applying enteric coating in granules and pharmaceutical powders [48].

Melt solidification;

Biodegradable microcapsules are also produced by the solidification of molten polymer droplets or by polymer precipitation. A dispersion of the drug in molten polymer is stirred in silicone oil to produce small droplets of the polymer drug mixture. The suspension mixture is then cooled, and the resulting solidified microcapsules are separated from the oil.

Anant et. al. has been developed melt solidification technique to obtain sustained release waxy beads of flurbiprofen. The process involved emulsification and solidification of flurbiprofen-cetyl alcohol melt at significantly low temperature (5°C). The effect of variables, namely, the amount of cetyl alcohol and the speed of agitation, was studied using factorial designs. Drug released from the beads followed zero order kinetics. Burst release was shown to a greater extent in beads containing a lower amount of cetyl alcohol. [49]

Polymer precipitation

In the polymer precipitation process, an aqueous solution of the polymer containing the drug is dropped into a stirred solution, which acts as the precipitating medium. Here, the polymer droplets precipitate immediately and are thus converted into the drug loaded microcapsules.[50]

Sashmal. et. al. was to design and evaluate NSAID loaded Nanoparticles drug delivery system, where Flurbiprofen Nanoparticles with suitable size range are envisaged to concentrate at inflammation sites due to increase fragility of blood vessels at those sites and increased aggregation and prostaglandin synthesis. Materials used were surfactant (pluronic F 68) and polymer (poly lactic co glycolic acid; PLGA). The flurbiprofen loaded nanoparticles were prepared by solvent diffusion nano-precipitation method. Experiment was carried out following 32 factorial designs, where drug-polymer ratio was varied to optimize the formulation. The in-vitro drug release profile from nanoparticles was found to follow Higuchi square root kinetics implying a diffusion dependent release as is expected of an insoluble, nonswellable nature of PLGA. It indicated that nanoparticles formed were matrix in nature, in which flurbiprofen dispersed uniformly. Suitable polynomial models were generated and statistically validated using ANOVA for the different responses, namely drug release (maximization) and particle size (minimization). Optimized formulation were found to have a polymer-drug ratio of 18.89:1 and manufactured at a nonsolvent-solvent ratio of 4:1 to maximized release after 8 hrs and minimized particle size. The study collaborates on the feasibility and suitability of aqueous polymeric drug delivery system, employing statistical design to develop a clinically useful nanoparticles system with targeting potential.[51]

Centrifugal extrusion process

Liquids are encapsulated using a rotating head containing concentric nozzles. In this process, a jet of core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air it breaks, owing to, into droplets of core, each coated with the wall solution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporated from the wall solution. Since most of the droplets are within $\pm 10\%$ of the mean diameter, they land in a narrow ring around the spray nozzle. Hence, if needed, the capsules can be hardened after formation by catching them in a ring-shaped hardening bath. This process is excellent for forming particles in diameter. Since the drops are formed by the breakup of a liquid jet, the process is only suitable for liquid. A high production rate can be achieved of microcapsules can be produced per nozzle per hour per head. [52]

Varshosaz et. al. was to develop piroxicam enteric coated pellets using nonpareil seeds by powder layering technique to minimize its gastrointestinal adverse effects. Inert seeds were prepared by incorporating sugar, Avicel PH 101 and lactose. The obtained cores were then treated by PVP 10 w/v % solution using centrifugal granulator (CF-granulator) and then coated with micronized piroxicam using HPMC solution (8 w/v %) as binder. The piroxicam pellets were finally coated with different polymers (Eudragit L30D-55, Eudragit L100, Eudragit NE30D, Acryleze, or mixture of Eudragits L30D-55 and NE30D) and plasticizers (triethyl citrate and polyethylene glycol 6000). Results showed that Eudragit L30D-55 with 3% weight gain accompanied with TEC produced suitable enteric coated pellets [53].

Vibrational Nozzle process

Core-Shell encapsulation or Micro-granulation (matrix-encapsulation) can be done using a laminar flow through a nozzle and an additional vibration of the nozzle or the liquid. The liquid can consists of any liquids with limited viscosities (0-10,000 mPa·s have been shown to work), e.g. solutions, emulsions, suspensions, melts etc. The solidification can be done according to the used gelation system with an internal gelation (e.g. sol-gel processing, melt) or an external (additional binder system, e.g. in a slurry). The process works very well for generating droplets between applications for smaller and larger droplets depends on the size of orifice and vibration speed of the nozzle.[54,55]

Layer-by-layer adsorption Process;

One important method of microencapsulation is layer-by-layer deposition. In this process polyelectrolyte multilayer's are prepared by sequentially immersing a substrate in positively and negatively charged polyelectrolyte solutions in a cyclic procedure. Core shell particles with tailored size and properties are prepared using colloidal particles as the core material that serves as a template onto which multilayer's are fabricated. Hollow capsules of organic, inorganic or hybrid particles can be obtained by dissolving the core material. This technique is both versatile and simple, with the multiplayer film thickness being controlled precisely by varying the total number of layers deposited.[56]

Arida et al investigated ketoprofen particles were encapsulated with polyions and gelatin to control the release of the drug in aqueous solutions. Charged linear polyions and gelatin were alternatively deposited on 6 μm drug microcrystals through layer-by-layer (LbL) assembly. Sequential layers of poly(dimethyldiallyl ammonium chloride) (PDDA) and poly(styrenesulfonate) (PSS) were followed by adsorption of two to six gelatin/PSS bilayers with

corresponding capsule wall thicknesses ranging from 41 to 111 nm. The release of Ketoprofen from the coated microparticles was measured in aqueous solutions of pH 1.4, 4.1, and 7.4. The release rate has changed at these different pH values. At pH 7.4 the release rate of Ketoprofen from the encapsulated particles was less by 107 times compared to uncoated Ketoprofen. The results provide a method of achieving prolonged drug release and minimized adverse effects of ketoprofen. [57]

Ionotropic gelation technique Ionic-gelation may be defined as a physicochemical process of microdroplet hardening by chelation of polyelectrolyte with polyvalent ions. Such a chelation results in cross-linking the polyelectrolyte molecules while forming a shell in the form of a polymeric gel. The most widely used system is based on gelation of aqueous sodium alginate, gellan and carrageenan solutions by the addition of divalent cations such as calcium chloride, barium chloride; potassium chloride induces the cross-linking of the polymers, and instantaneously formation of discrete solid microparticles. In this method strong spherical shape and narrow particle size with high yield microparticles are formed which are used for the carriers of many NSAIDs drug to minimize the dose related adverse effects and prolong the drug release potential. [58]

Gonzalez-Rodriguez et al. reported alginate/chitosan particulate systems for diclofenac sodium release by ionic gelation (Ca^{2+} and Al^{3+}). 25% w/v of the drug was added to 1.2% w/v aqueous solution of sodium alginate. The solution was stirred till a complete solution was formed. This solution was added dropwise to a solution containing Ca^{2+} or Al^{3+} and chitosan solution in acetic acid. The microspheres formed were left into the original solution for 24 hours for internal gelification. The product is separated by filtration. The release of sodium diclofenac was prevented at acidic pH, while it was complete in a few minutes when pH was raised up to 6.4 and 7.2. The alginate/chitosan ratio and the nature of the jellifying cation controlled the release rate of the drug. [59]

Supercritical fluid technique

Microencapsulation has also been carried out by rapid expansion of supercritical fluid technique. Supercritical fluids are highly compressed gases that possess several advantageous properties of both liquids and gases. Most widely used ones are supercritical CO_2 , alkanes (C_2 to C_4) and nitrous oxide (N_2O). Supercritical CO_2 is widely used for its low critical temperature value in addition to its non-toxic and non-flammable properties. It is also readily available, highly pure and cost effective. It has found applications in encapsulating active ingredients by polymers. Different core materials such as pesticides, pigments, pharmaceutical ingredients, vitamins, flavors and dyes have been encapsulated by using this method. A wide variety of shell materials that either dissolve (paraffin wax, acrylates, polyethylene glycol) or do not dissolve (proteins, polysaccharides) in supercritical CO_2 are used for encapsulating core substances. In this process, supercritical fluid containing the active ingredient and the shell material are maintained at high pressure and then released at atmospheric pressure through a small nozzle. The sudden drop in pressure causes desolvation of the shell material, which is then deposited around the active ingredient (core) and forms a coating layer. [60, 61]

Various formulation have been prepared by different microencapsulation technique are given in table No. 1.

Table No. 1- List of different techniques of microencapsulation used for formulation

NSAIDs drugs	Microencapsulation Techniques	Coating materials
Aspirin Dose-80-100mg, bound-80-90% 30min ,T _{1/2} - 15 min. Protein T _{max} <	Complex coacervation	Acacia, gelatin
	Solvent evaporation	Ethylcellulose
	Oil – in – water emulsion	Ethylcellulose
	Sparry congealing	Hydrogenated soyabean oil
Diclofenc sodium Dose-100-200mg, bound-99%, T _{max} -1-3h, T _{1/2} -1.2-2h Protein	Congealable disperse phase method	Glycerol monostearate, Tween80
	Oil-in-Oil emulsification solvent	Low M.W.polyester
	Emulsification method.	Chitosan, Glutaraldehyde, Aquacoats
	Non-aqueous emulsion method.	Ethylcellulose, HPMCP
Ibuprofen M.Dose-3600mg, bound-99%, T _{max} -1-2 h T _{1/2} - 2.0-2.5 h Protein	Solvent Evaporation	Poly(D,L-lactic acid) Ethylcellulose, Methacrylic polymer, Eudragits, HPMCP, Sodium alginate, Sodium sulphate.
	Co-acervation Phase Separation	EudragitRS100
	Emulsion Solvent- Diffusion Technique	EudragitRL100
	Ionotropic gelation	Sodium alginate, Chitosan, Pectin, Gellan gum
	Spray drying	Cellulose acetate phthalate, Cellulose acetate trimelliate,
	Emulsion-solvent evaporation Ionotropic gelation method	Eudragit RS, RL, S100, HPMCP Sodium aliginate, chitosan, pectin, gellan gum, eudragit.
Flurbiprofen M.Dose-500mg, Plasmabound- 99%, T _{max} -1-2h, T _{1/2} -3 6h	Emulsification solvent evaporation,	EudragitRS-100
	Solvent evaporation	Acrylic & Methacrylic acid esters
	Spray drying	Sodium hyaluronate, PEG-4000
	Ionotropic gelation	Sodium alginate, Calcium chloride, Pectin, Chitosan
Dexibuprofen M.Dose-1000mg, Plasma-bound-98%	Ionotropic gelation	Sodium alginate, Calcium chloride, Chitosan, Pectin Gellan

Tmax-1-2h, T_{1/2}-1.8-3.5h		
Mefenamic acid M.Dose-1500mg Plasma-bound->99% Tmax-2-4h, T_{1/2}-2-3.5h	Spray drying	Cellulose acetate phthalate, Cellulose Acetate
	Emulsion-solvent evaporation	HPMCP, Ethylcellulose

CONCLUSION

Thus arthritis is immensely complex and very likely caused by more than one type of inciting factors. Development of various technologies to tailor various available therapies to the unique circumstances and disease processes of each individual patient will prove very challenging. However, Microencapsulation is a new plat-form for various novel drug delivery systems administered by Oral or parenteral route. The literature revealed that microencapsulation as well accepted technique employed to sustain the drug release and reduce or/ eliminate gastrointestinal irritation, dose intake of NSAIDs and ultimately improve the compliance in the pharmacotherapy of arthritis, inflammation and pain.

REFERENCES

- [1] S.R. Naik and N.R Chatterjee, *Ind. Drugs*, **1993**, 1(30), 1-9.
- [2] Farida Bohra, Neelu Sharma, Rajesh Nema, , *Est, Pharm*, 1997, 4, 39-44.
- [3] I Bjarnason, J Hayllar, A.J Macpherson, A.S Russell, *Gastroenterology* **1993**;104:1832-47.
- [4] J. Sjoegren, L.F Prescott, W.S Nimmo, Rate Control in Drug Therapy, Churchill Livingstone, Edinburgh, **1985**, 38-47.
- [5] Swash. M.-Hutichisons, Clinical methods of NSAIDs, Edinburgh, Glynn (eds), **2007**; 454-467.
- [6] Bridges, *Annual Review Anthropology*, **1992**; 21; 67-91.
- [7] William st. E. Clair, Rheumetoid arthritis, Lippincott Williams and wilkins, USA, **2004**, page no. 31 – 35.
- [8] Alick Cameron, Musgrave, Willium, Oxford dictionary of national biography, Oxford University Press, **2004**, 1655-1721.
- [9] K.D. Tripathi, Essential Medical Pharmacology, Jaypee Publications (p) Ltd New Delhi, **2003**, 5th 167- 184.
- [10] G.H. Hamor, Principles of Medicinal Chemistry Penn: Lea & Febiger, Philadelphia, **1989**, 3rd 15:30.
- [11] A.J Lewis, D.W Furst, Nonsteroidal Anti-Inflammatory Drugs: Mechanisms and Clinical Use, Marcel Dekker New York, NY **1987**, 141-234.
- [12] N.M Davis, A.J McLachlan, R.O Day, K.M Williams. *Clin Pharmacokinet.* **2000**, 38:225-42.
- [13] P. Prithvi Raj, Practical management of pain, Mosby INC, St. Louis. Missouri, third edition, **2000**, page no. 464-469.
- [14] www.niddk.nih.gov/health/digest/summary/nsaids.
- [15] www.arthritis.org/conditions/drug_guide/nsaids/about.

- [16] www.arthritis.about.com/library/week/aa061097.htm.
- [17] Peter Merry, New Hope for NSAIDS, *Est, Pharm*, **1997**,4(1), 33-40.
- [18] F Richy, O Bruyere, O Ethgen, V Rabenda, G Bouvenot, M Audran, et al. *Ann, Rheum, Dis* **2004**; 63:759-66.
- [19] M Lenard, Lichtenberger, Yong Zhou, J Elizabeth, Robert M Dialand, Raphael, *JPPS*, **2006**; 58; 1-8.
- [20] Brahma N Singh, Kwon H Kim, *Pharma. Tech*; **2002**, 886-889.
- [21] M Akers, Parenteral preparations. B.I. Publication Pvt. Ltd, India. **2005**,802-803.
- [22] Yie. W. Chein, *Ind. J.Pharm, Sci*, **1998**, 3, 63-65.
- [23] A.T Florence, P.U Jani, *Drug safety*, **1994**,10(3), 233-266.
- [24] Chowdary and Sri A Ramamurty, *Drugs*, **1992**,25 (10), 389-392.
- [25] Patric B. Deasy “Microencapsulation and related drug process” *Drugs and pharmaceutical Science*, Marcel Dekker Inc Newyork, **1984**, 2nd, 1-22.
- [26] Patent: H Schnoring, M Dahm, G Pampus, Fed. Rep. of Germany, US Patent 4,379,071. (**1983**).
- [27] Patent: Kielbania, A.J.; Emmons, W.D. & Redlich, G.H. Rohm and Haas Company, Philadelphia. US Patent 5,225,278. (**1993**).
- [28] Alexander Kamyshny, Shlomo Megdassi “ Microencapsulation” *Encylo, surface, Colloidal, Sci*, **2004**, 1-15.
- [29] P.F Luckham, Microencapsulation technique of formation and characterisation, *In Controlled Particle, Droplet and Bubble Formation*, edited by Wedlock, D. J. Butterworth Heinemann, Oxford. **1994**.
- [30] F Tiarks, K Landfester, M Antonietti, Preparation of Polymeric Nanocapsules by Miniemulsion Polymerization, *Langmuir*, **2001**, 17, 908-18.
- [31] M Maghsoodi, *AAPS Pharma, Sci, Tech*, **2009**, 10(1),434-439.
- [32] J. M Janssen, K Nijenhuis, *J. Membr. Sci.*, **1992**, 65, 59-68.
- [33] P. W Morgan, Interfacial Polymerization in *Encyclopedia of Polymer Science and Engineering*, John Wiley New York. **1987**, 8, 221-37.
- [34] Miyazaki, S. Takahashi, A. Kubo, *J pharm, pharmaceutical Sci*, **2003**; 6 (2):238-45.
- [35] Patent: Koff US patent 3,080,29, (**1963**).
- [36] A Gharsallaoui, G Roudaut, O Chambin, A Voilley, R Saurel, *Food Res. Int.*, **2007**, 40(9), 1107-121.
- [37] Patent: A. F. Yapel, U.S. Patent 4169804, (**1979**).
- [38] R Arshady, *Polym. Eng. Sci.*, **1989**, 29(24), 1746-1758.
- [39] M.A Bayomi, *Drug Dev Ind Pharm.*, **2004**, 30(4), 329-339.
- [40] C Sankar, B Mishra, *Acta Pharm.* **2003**, 53(2), 101-10.
- [41] I Yamakawa, Y Tsushima, R Machida, R Watanabe, *J.Pharm. Sci.*, **1992**, 81,899-903.
- [42] A Aggarwal, S Kaur, A.K Tiwary, S Gupta, *J Microencapsul.* **2001**. 18(6), 819-823.
- [43] Widder, J. K; Senyei, A. E. & Sears, B. *J. Pharm. Sci.*, **1982**, 71(4), 379-87.
- [44] S.G Kumbar, A.R Kulkarni, M. Aminabhavi, *J Microencapsul*, **2002**. 19(2):173-180.
- [45] R. Arshady, *Polym. Eng. Sci.*, **1990**, 30, 915-24.
- [46] G.F Palmieri, G Bonacucina, P Di Martino, S. Martelli, *J Microencapsul.* **2002**, 19(1):111-119.
- [47] D. J. Burgess, J. F Carless, *Int. J. Pharma.*, **1985**, 27, 61-70.
- [48] H Takenaka, Y Kamashima, S. Y Lin, *J. Pharm. Sci.*, **1980**, 69(5), 513-516.
- [49] Vanessa, L. *plolmeros*, **2005**, 15(1), 6-12.

-
- [50] K Dewettinck, A Huyghebaert, *Trends in Food Sci. and Technol.*, **1999**, 10, 163-68.
- [51] C Fukumori, Y. T Fukuda, Y Hanyu, Y Takeyuchi, Y Oruko, *Chem. Pharm. Bull.*, **1987**, 35(7), 2949-957.
- [52] O.S. Silva, *Drug, Dev, Ind, Pharm*, **2007**, 32(6), 661-667.
- [53] Anant, Paradkar, *AAPS, Pharm, Sci, Tech*, **2003**, 4, 514-522.
- [54] S Banerjee, R Premchandran, M Tata, V. T John, G. L Mcpherson, J Akkara, D Kaplan, *Ind. Eng. Chem. Res.*, **1996**, 35(9), 100-107.
- [55] Swati sashmal, et al, *Pak, J, Pharm Sci*, **2007**, Vol.20 (2), 157-162.
- [56] P Aebischer, *Biomaterials*, **1991**, 12, 50-56.
- [57] Jaleh Varshosaz et, al, *Pharm, Dev, Tech*, **2009**, 14(3) 305-311.
- [58] Caruso, F.; Yang, W.; Trau, D, Renneberg, R. *Langmuir*, **2000**, 16 (23), 8932-936.
- [59] Shimano, *Drug, Dev, Ind, Pharm*, **1995**, 21(3), 331-347.
- [60] F Caruso, W Yang, D Trau, R Renneberg, *Langmuir*, **2000**, 16(23), 8932-936.
- [61] Adi I. Arida, M Moawia, Al-Tabakha, *Eu, J, Pharm, Biopharm*, **2007**, 66(1), 48-54.