



## PREPARATION OF ENTERIC COATED BEADS BY COACERVATION TECHNIQUE-A REVIEW

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### ABSTRACT

NSAID drugs having analgesic and anti-inflammatory effects are being widely administered orally in the treatment of mild to severe pain particularly for rheumatoid arthritis and osteo arthritis patients. Tolerance or addiction to these drugs is not generally a problem with their continuous use in the treatment of pain or in the treatment of acute or chronic inflammatory states. However, these drugs generally have a higher potential for adverse side effects at the upper concentration of their effective dose range therefore, it is important that such non steroidal anti-inflammatory drugs be accurately measured and administered orally. The non steroidal anti-inflammatory drugs like Ibuprofen and Naproxen have been widely prescribed by physicians. These drugs are in general tolerated well by most patients and provide an effective means for control of pain and inflammatory processes, particularly for the rheumatoid arthritis and osteo arthritis patients. However, most frequent adverse effects occurring with administration of Naproxen are gastro intestinal ulceration and bleeding. Enteric coated beads in which the drug is dispersed throughout the polymeric matrix efforts some protection to the gastro intestinal mucosa.

**Keywords:** Enteric Coated Beads, Coacervation Technique, Formulation Development.

### INTRODUCTION

#### ORAL DRUG DELIVERY

Oral drug delivery has been known for decades as the most widely used route of administration among all routes. The reason that the oral route has achieved such popularity may be in part attributed to its ease of administration as well as traditional belief.

Pharmaceutical products designed for oral delivery which are available in the market are mostly immediate-release or conventional which maintains the drug within the therapeutically effective range only even when administered several times a day. This results in a significant fluctuation in the drug level.

#### MICROENCAPSULATION

Microencapsulation is a process by which solids, liquids or even gases may be closed in microscopic particles forming a thin coating as the wall material around the substances. The ultimate development in the 1950s of reproduction paper and ribbons that contained dyes in tiny gelatin capsules released on impact by a typewriter key or the pressure of a pen or pencil was the stimulus for the development of a host of microencapsulated materials,

including drugs [1]. A well designed controlled drug delivery system can overcome some of the problems of conventional therapy and enhance the therapeutic efficacy of a given drug. To obtain maximum therapeutic efficacy, it becomes necessary to deliver the agent to the target tissue in the optimal amount in the right period of time there by causing little toxicity and minimum side effects. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microspheres as carriers for drugs. Microspheres are characteristically free flowing powders consisting of proteins or synthetic polymers which are biodegradable in nature and ideally having particle size less than 200  $\mu\text{m}$ .

Microencapsulation is a process by which very tiny droplets or particles of liquid or solid material are surrounded or coated with a continuous film of polymeric material. Microencapsulation includes Bio encapsulation which is more restricted to the entrapment of a biologically active substance (from DNA to entire cell or group of cells for example) generally to improve its performance &/or enhance its shelf life [2].

Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and of controlling the release characteristics or availability of coated materials.

The drugs, which are sensitive to oxygen, moisture or light, can be stabilized by microencapsulation. Incompatibility among the drugs can be prevented by microencapsulation. Vaporization of many volatile drugs e.g. methyl salicylate and peppermint oil can be prevented by microencapsulation. Many drugs have been microencapsulated to reduce toxicity and GI irritation including ferrous sulphate and KCl. Alteration in site of absorption can also be achieved by microencapsulation [3].

### **Fundamental Considerations**

The realization of the potential that microencapsulation offers involves a basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials, the stability and release characteristics of the coated materials and the microencapsulation methods [4].

### **Release Mechanisms**

Mechanisms of drug release from microspheres are:

#### **1. Degradation controlled monolithic system**

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix.

#### **2. Diffusion controlled monolithic system**

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

#### **3. Diffusion controlled reservoir system**

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

#### **4. Erosion**

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and steryl alcohol etc. [5].

### **Core materials**

The core material, defined as the specific material to be coated, can be liquid or solid in nature. The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved materials. The solid core can be active constituents, stabilizers, diluents, excipients, and release-rate retardants or accelerators. The ability to vary the core

material composition provides definite flexibility and utilization of these characteristics often allows effectual design and development of the desired microcapsule properties [6].

### **Coating materials**

The selection of appropriate coating material decides the physical and chemical properties of the resultant microcapsules/microspheres. The polymer should be capable of forming a film that is cohesive with the core material. It should be chemically compatible, non-reactive with the core material and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability. Generally hydrophilic polymers, hydrophobic polymers (or) a combination of both are used for the microencapsulation process. A number of coating materials have been used successfully; examples of these include gelatin, polyvinyl alcohol, ethyl cellulose, and cellulose acetate phthalate and styrene maleicanhydride. The film thickness can be varied considerably depending on the surface area of the material to be coated and other physical characteristics of the system. The microcapsules may consist of a single particle or clusters of particles. After isolation from the liquid manufacturing vehicle and drying, the material appears as a free flowing powder. The powder is suitable for formulation as compressed tablets, hard gelatin capsules, suspensions, and other dosage forms [7].

### **Coating material properties**

Stabilization of core material, Inert to active ingredients, Controlled release under specific conditions, Film-forming, pliable, Tasteless, Stable, Non-hygroscopic, Suitable viscosity, Economical Soluble in an aqueous media or solvent. The coating can be flexible, brittle, hard, thin etc.

### **Examples of coating materials:**

#### **Water soluble resins**

Gelatin, gum Arabica Starch, Polyvinylpyrrolidone, Carboxymethylcellulose, Hydroxy ethylcellulose, Methylcellulose, Arabinogalactan, Polyvinyl alcohol, Polyacrylic acid.

#### **Water insoluble resins**

Ethyl cellulose, Polyethylene, Polymethacrylate, Polyamide (Nylon), Poly (Ethylene Vinyl acetate), Cellulose nitrate, Silicones, Polylactide-co glycolide.

#### **Waxes and lipids**

Paraffin, Carnauba, Spermaceti, Beeswax, Stearic acid, Stearyl alcohol, Glyceryl stearates.

#### **Enteric resins**

Shellac, Cellulose acetate phthalate, Zein [8].

### **Techniques to manufacture microcapsules**

#### **Preparation of microspheres should satisfy certain criteria**

The ability to incorporate reasonably high concentrations of the drug. Stability of the preparation

after synthesis with a clinically acceptable shelf life. Controlled particle size and dispersability in aqueous vehicles for injection. Release of active reagent with a good control over a wide time scale. Biocompatibility with a controllable biodegradability and Susceptibility to chemical modification.

### Physical methods

#### Air-suspension coating

Microencapsulation by air suspension technique consist of the dispersing of solid, particulate core materials in a supporting air stream and the spray coating on the air suspended particles. Within the coating chamber, particles are suspended on an upward moving air stream. The design of the chamber and its operating parameters effect a recirculating flow of the particles through the coating zone portion of the chamber, where a coating material, usually a polymer solution, is spray applied to the moving particles. During each pass through the coating zone, the core material receives an increment of coating material. The cyclic process is repeated, perhaps several hundred times during processing, depending on the purpose of microencapsulation the coating thickness desired or whether the core material particles are thoroughly encapsulated.

The air suspension process offers a wide variety of coating materials candidates for microencapsulation. The process has the capability of applying coatings in the form of solvent solutions, aqueous solution, emulsions, dispersions or hot melts in equipment ranging in capacities from one pound to 990 pounds. Core materials comprised of micron or submicron particles can be effectively encapsulated by air suspension techniques [9].

#### Coacervation Process

The core material is added to the solution. The core material should not react or dissolve in water (maximum solubility 2%). The core material is dispersed in the solution. The particle size will be defined by dispersion parameter, as stirring speed, stirrer shape, surface tension and viscosity. Size range ca. 2 $\mu$ m - 1200 $\mu$ m. Coacervation starts with a change of the pH value of the dispersion, e.g. by adding H<sub>2</sub>SO<sub>4</sub>, HCl or organic acids. The result is a reduction of the solubility of the dispersed phases (shell material). The shell material (coacervate) starts to precipitate from the solution. The shell material forms a continuous coating around the core droplets. The shell material is cooled down to harden and forms the final capsule. Hardening agents like formaldehyde can be added to the process. The microcapsules are now stable in the suspension and ready to be dried.

The suspension is dried in a spray dryer or in a fluidized bed drier. Spray Drying is a suitable method for heat sensitive Products. The atomized particles assume a spherical shape. The rapid the coating material keeps the core material below 100°C, even if the temperature in the drying chamber is much greater. Microencapsulation

makes the spray drying process easier for sticky products like fruit pulp or juice, with a high content of invert sugar

#### Coacervation-Phase Separation

The general outline of the processes consists of three steps carried out under continuous agitation:

##### 1. Formation of three immiscible chemical phases

A liquid manufacturing vehicle phase, a core material phase, and a coating material phase. To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. The coating material phase, an immiscible polymer in a liquid state, is formed by utilizing one of the methods of the methods of phase separation-coacervation, i.e., by changing the temperature of the polymer solution; or by adding a salt, nonsolvent, or incompatible polymer to the polymer solution; or by inducing a polymer polymer interaction.

##### 2. Deposition of the coating

It consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the material in the manufacturing vehicle. Core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system, brought about by the decrease of the coating material surface area during coalescence of the liquid polymer droplets.

##### 3. Digitization of the coating

It involves rigidizing the coating, usually by thermal, cross-linking, or desolvation techniques, to form a self-sustaining microcapsules. eg. Coacervation Microencapsulation of Talc Particles with Poly (methylmethacrylate) by Pressure-Induced Phase Separation of CO<sub>2</sub>-Expanded Ethanol Solution [10].

#### Centrifugal extrusion

Liquids are encapsulated using a rotating extrusion 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 Rayleigh instability, 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 400 – 2,000  $\mu$ m (16 – 79 mils) in diameter [11].

#### Pan coating

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while the coating material is applied slowly. The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly with respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating, and the process has been extensively employed for the preparation of controlled -release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds, and then coated with protective layers of various polymers.

In practice, the coating is applied as a solution, or as an atomized spray, to the desired solid core material in the coating pans. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in a drying oven [12].

### **Spray drying**

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages is the ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300mPa.s. Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected.

Typically, the particle size of spray congealed products can be accurately controlled when spray drying equipment is used, and has been found to be a function of the feed rate, the atomizing wheel velocity, dispersion of feed material viscosity, and variables [13].

### **Chemical methods**

#### **Solvent Evaporation**

The processes are carried out in a liquid manufacturing vehicle. The microcapsule coating is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the appropriate size microcapsule. The mixture is then heated (if necessary) to evaporate the solvent for the polymer. In the case in which the core material is dispersed in the polymer solution, polymer shrinks around the core. In the case in which core material is dissolved in the coating polymer solution, a matrix - type microcapsule is formed. Once all the solvent for the

polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation. At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The solvent evaporation technique to produce microcapsules is applicable to a wide variety of liquid and solid core materials. The core materials may be either water soluble or water insoluble materials. A variety of film forming polymers can be used as coatings [15].

### **Polymerization**

In this technique the capsule shell will be formed at or on the surface of the droplet or particle by polymerization of the reactive monomers. The substances used are multifunctional monomers. In this process no reactive agents are added to the core material, polymerization occurs exclusively in the continuous phase and on the continuous phase side of the interface formed by the dispersed core material and continuous phase. Initially a low molecular weight pre polymer will be formed, as time goes on the prepolymer grows in size, it deposits on the surface of the dispersed core material there by generating solid capsule shell.

### **Matrix polymer**

In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple method of this type is spray-drying, in which the particle is formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change. Numerous groups are utilizing polymerization techniques to accomplish microencapsulation. Examples are the National Lead Corporation, EurandAmeric [16].

### **Application of microencapsulation**

There are many reasons why drugs and related chemicals have been microencapsulated. The technology has been used widely in the design of controlled release and sustained release dosage forms.

To mask the bitter taste of drugs like: Paracetamol, Nitrofurantoin etc. Many drugs have been microencapsulated to reduce gastric and other G.I. tract irritations. Sustained release Aspirin preparations have been reported to cause significantly less G.I. bleeding than conventional preparations. A liquid can be converted to a pseudo-solid for easy handling and storage.

Hygroscopic properties of core materials may be reduced by microencapsulation. Carbon tetra chlorides and a number of other substances have been microencapsulated to reduce their odor and volatility. Microencapsulation has been employed to provide protection to the core materials against atmospheric effects. Separation of incompatible substance has been achieved by encapsulation [17].

### **NON STEROIDAL ANTI INFLAMMATORY DRUGS**

These are drugs that have analgesic, antipyretic and anti-inflammatory actions in different measures. In

contrast to morphine, they do not depress CNS, do not produce physical dependence, have no abuse liability and are weaker analgesics. They are also called nonnarcotic, nonopioid, or aspirin-like analgesics.

They act primarily on peripheral pain mechanisms, but also in the CNS to raise pain threshold. They are more commonly employed and many are over the counter drugs.

### CLASSIFICATION

NSAIDs can be classified based on their chemical structure or mechanism of action. Older NSAIDs were known long before their mechanism of action was elucidated and were for this reason classified by chemical structure or origin. Newer substances are more often classified by mechanism of action.

#### Salicylates

Aspirin (acetylsalicylic acid), Diflunisal, Salsalate.

#### Propionic acid derivatives

Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen.

#### Acetic acid derivatives

Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone.

#### Enolic acid (Oxicam) derivatives

Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam.

#### Fenamic acid derivatives (Fenamates)

Mefenamic acid, Meclofenamic acid, Flufenamic acid

#### Sulphonanilides

Nimesulide (systemic preparations are banned by several countries for the potential risk of hepatotoxicity)

#### Others

Licofelone acts by inhibiting LOX (lipooxygenase) & COX and hence known as 5-LOX/COX inhibitor

### Mechanism of action [20]

Most NSAIDs act as nonselective inhibitors of the enzyme cyclooxygenase (COX), inhibiting both the cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) isoenzymes. COX catalyzes the formation of prostaglandins and thromboxane from arachidonic acid (itself derived from the cellular phospholipid bilayer by phospholipase A<sub>2</sub>). Prostaglandins act (among other things) as messenger molecules in the process of inflammation. This mechanism of action was elucidated by John Vane (1927–2004), who later received a Nobel Prize for his work (see Mechanism of action of aspirin). Many aspects of the mechanism of action of NSAIDs remain unexplained, for this reason further COX pathways are hypothesized. The COX-3 pathway was believed to fill some of this gap but recent findings make it appear unlikely that it plays any significant role in humans and alternative explanation models are proposed.

### ADVERSE EFFECTS [21]

The widespread use of NSAIDs has meant that the adverse effects of these drugs have become

increasingly prevalent. The two main adverse drug reactions (ADRs) associated with NSAIDs relate to gastrointestinal (GI) effects and renal effects of the agents.

### ENTERIC COATING

This is a process by which drugs are designed to show local action in the intestines without undergoing disintegration and drug release in the stomach. This process depends on pH factors. The dosage form is coated in such a way that it resists dissolution in the acidic gastric fluids but dissolves in the alkaline environment of intestines. Some of the reasons for enteric coating are:

1. It protects acid sensitive drugs from gastric fluid. e.g., enzymes and certain antibiotics.
2. To prevent gastric distress or nausea due to irritation from a drug, e.g., Sodium salicylate.
3. To provide a delayed-release component for repeat-action drugs.
4. To deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form.

### An ideal enteric coating material should have the following properties

- Resistance to gastric fluids.
- Ready susceptibility to intestinal fluids.
- Compatibility with most coating solution component and the drug substrates.
- Non toxicity.
- Low cost.
- Ease of application without specialized equipment without specialized equipment.
- The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.

### Cellulose Acetate Phthalate (CAP)

Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. It is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

### Poly Vinyl Acetate Phthalate (PVAP)

Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrate at pH 5.

### Hydroxyl Propyl Methyl Cellulose Phthalate (HPMCP)

HP55 disintegrates at pH5.5. It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer. Methacrylic acid copolymers:

Two grades are available A and B which differs in the ratio of free carboxyl to ester groups therefore:

Type A has a ratio of 1:1 and disintegrates at pH 6.

Type B has a ratio of 1:2 and disintegrates at pH 7.

Available under the trade names Eudragit L and S correspond to NF types A & B.

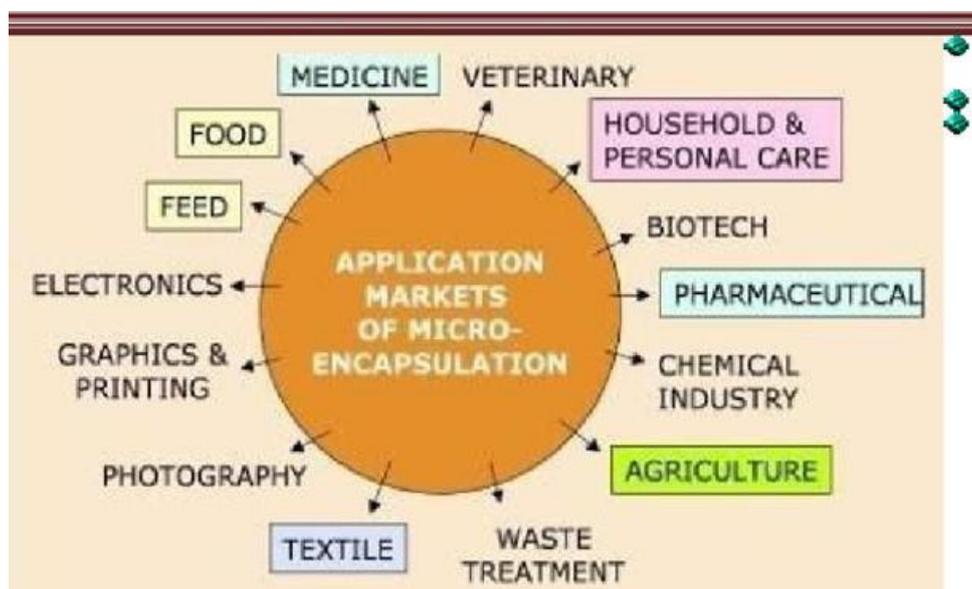
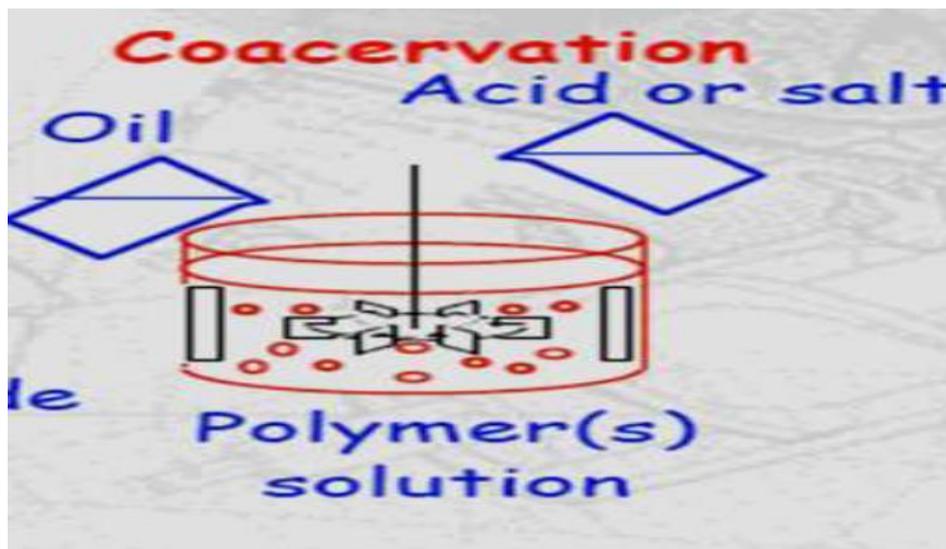
**Table 1 .Examples Of Some Microencapsulated Drugs [18]**

<i>Drug / Core material</i>	<i>Characteristic property</i>	<i>Purpose of encapsulation</i>	<i>Final product form</i>
Actaminophen	Slightly water soluble solid	Taste masking	Tablet
Aspirin	Slightly water soluble solid	Taste masking, sustained release, reduced gastric irritation, separation of incompatibles	Tablet or capsule
Islet of Langerhans	Viable cells	Sustained normalization of diabetic condition	Injectable
Isosorbide dinitrate	Water soluble solid	Sustained release	Capsules
Menthol	Volatile solution	Reduction of volatility, sustained release	Lotion
Progesterone	Slightly water soluble solid	Sustained release	Varied
Potassium chloride	Highly water soluble solid	Reduced gastric irritation	Capsule
Urease	Water soluble enzyme	Permselectivity of enzyme, substrate, and reaction products.	Dispersion
Vitamin A palmitate	Nonvolatile liquid	Stabilization to oxidation	Dry powder

**Table 2. Microencapsulated Processes and their Applicabilities [19]**

#	Method Name	Applicable Material	Particle Size	Production Scale	Process reproducibility and Consistency	Time required for preparation	Cost Factor	Operation Skill required
1	Air Suspension	Solids	35 - 5000	Pilot Scale	Moderate	High	High	High
2	Co - acervation and Phase Separation	Solids & Liquids	2 - 5000	Lab Scale	Good	Less	Less	Less
3	Multiorifice Centrifugal	Solids & Liquids	1 - 5000	Pilot Scale	Moderate	High	High	High
4	Pan Coating	Solids	600 - 5000	Pilot Scale	Moderate	High	High	High
5	Solvent Evaporation	Solids & Liquids	5 - 5000	Lab Scale	Good	Less	Less	Less
6	Spray Drying and Spray Congealing	Solids & Liquids	600	Pilot Scale	Moderate	High	High	High





## CONCLUSION

Non steroidal anti-inflammatory drugs having analgesic and anti-inflammatory properties are widely administered orally in the treatment of mild to severe pain, particularly osteoarthritis and rheumatoid arthritis patients. These drugs generally have high potential for adverse side effects. Enteric coated beads were prepared by coacervation technique using CAP (Cellulose Acetate Phthalate).

Sodium sulphate acts as a coacervating agent by permitting the CAP to come out of the liquid phase and encapsulate the Naproxen drug particle as an enteric coat.

This CAP polymer forms an empty wall over the Naproxen drug rendering it insoluble at pH4 by addition of citric acid. When it has been washed with acidified aqueous solution it removes the Sodium Sulphate.

The preparation of enteric coated beads revealed that stirring speed and curing time greatly affect the size of the beads. Smaller particles can be prepared by adjusting the stirring rate and curing time and also depending upon the height of the syringe and also the size of the needle. It is likely that final size of the beads is a complex function and several variables like needle size, drying conditions, and temperature and reagent concentration.

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