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SUSTAINED RELEASE MICROPARTICLES: A REVIEW

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ABSTRACT

Controlled release of drug from micrometrics is of the particular therapeutic importance for oral medication in patients. There are various approaches in delivering a therapeutic substance to the target site in a sustained controlled release fashion. One such approach is using microparticles as carriers for drugs. The idea behind a controlled drug delivery system is to incorporate the drug within a polymeric carrier that controls the release rate of the drug. Various processes, such as diffusion, erosion, and/or swelling can be involved in the control of the overall drug release rate, resulting in a broad spectrum of possible release profiles. Solvent evaporation and extraction based processes are required for the preparation of microparticles. The microparticles show lower percentage compressibility but good flowability, hence a capsule dosage form was thought to be suitable. The microparticle formulation was optimized with respect to size distribution and increased drug loading. The microparticles was physically evaluated with respect to bulk density, angle of repose, and percent compressibility, drug content, swelling study and in-vitro release study. Polyvinyl alcohol is proposed as a polymer to be used for the present controlled release formulation development. The intent of the paper is to highlight the potential of microparticles as a vital dosage form in novel drug delivery.

Key words: Microparticles, Sustain release, Solvent evaporation, Release profile, Therapeutic range, Compressibility

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INTRODUCTION

Oral drug delivery is considered the holy grail of drug delivery because convenience results in high patient compliance. Although oral drug delivery is very desirable, there are many problems encountered in oral delivery that severely restricts conventional oral drug delivery systems. Therefore most of product development activities in oral drug delivery are focused in protecting drug in GIT, improving absorption, prolonging drug absorption and prolonging its residence at the absorption site. Hence, this work aims at development of sustained release dosage form for highly water-soluble drug using polymer controlled drug delivery concept, which includes hydrogel and release modifiers.[1]

Sustained release of drug:

There has been a remarkable increase in the interest in sustained release dosage form, due to prohibitive cost of developing new drug entities, discovery of the new polymers and improvement in efficiency and safety provided by these. SRDDS is a modified dosage form that prolongs the therapeutic activity of the drug. Accordingly, a prodrug or analogue modification of the drug sustains blood level is considered as sustained release system. Several terms have been used to describe the various types of drug delivery systems intended to provide long duration of action.[2]

They are as follows:

Repeat action: A dose of the drug is initially is released immediately after administration, which is usually equivalent to a single dose of conventional drug product. After a certain period a second single dose is released.

Sustained release: This is a specific type of modified release dosage form that allows at least a two-fold reduction in the dosage frequency compared to conventional drug delivery system.

Controlled release: The dosage form in which the drug is released in a planned, predictable and slower than conventional dosage form.[3]

Delayed release dosage form: This is a specific type of modified release dosage form that releases the drug at a particular time. E.g. Enteric coated tablet.

Advantages:

1. Decreased local and systemic side effects.
2. Better drug utilization.
3. Decrease in total dose of the drug.
4. Prevents fluctuation of plasma drug concentration.

5. Better Bio-availability of the drug.
6. Improved efficiency in treatment.
7. Improved patient compliance.
8. Economy.

Disadvantages:

1. Dose dumping.
2. Reduced potential for accurate dose adjustment.
3. Need for additional patient education.
4. Slow absorption may delay the onset of activity, but this is probably unimportant during multiple regimes.

Introduction to Microparticles as Drug Delivery Systems:[1, 2, 4]

Micro-particles are the polymeric entities falling in the range of 1-1000µm. Micro-particles covering two types of the forms as follow Microcapsules are micrometric reservoir systems Microspheres are micrometric matrix systems. Microspheres are matrix systems and essentially spherical in shape, whereas microcapsules may be spherical or non-spherical in shape. Microcapsules are small particles, which contain an active agent or core material surrounded by a coating or shell. Microcapsule size 100 to 150 µm. Microsphere size 1 µm to 1000 µm

Microparticles offer a method to deliver macromolecules by a variety of routes and effectively control the release of such drugs. They may also be used in the delivery of vaccines and molecules such as DNA for use in gene therapy. Microparticles offer effective protection of encapsulated agent against degradation (e.g. enzymatic), the possibility of controlled and local delivery of the drug over periods ranging from few hours to months, and easy administration (compared to alternative forms of controlled release parenteral dosages, such as macro sized implants). Controlled drug delivery systems could be extremely useful in providing the optimal therapy for a given drug molecule[1]. Each drug has a characteristic 'minimum effective concentration', below which no therapeutic effect is observed and a characteristic 'minimum toxic concentration' above which undesired side effects occur (as shown in Figure 1) The range in between is called the 'therapeutic range' or 'therapeutic window'. Depending upon the type of drug and physiological factors, this therapeutic window could be narrow. The optimum effect of many medical treatments is obtained by maintaining the drug concentration in the therapeutic range over a sustained period of time. This is especially true for highly potent drugs, such as anti-cancer drugs. Administration of the entire drug dose at once using conventional

pharmaceutical dosage (e.g. tablets, bolus injection), the whole amount is rapidly released into the stomach, absorbed into the blood stream and distributed throughout the human body. As a result, the rate at which the drug its site of action is often high. Depending on the therapeutic range and administered dose, the risk of toxic side effects can be considerable. As no continuous drug supply is provided and as the human body eliminates the active agent, the concentration decreases again. This results in a fluctuating concentration of the drug levels in the plasma and the therapeutic range is attained during only very short time period.[5,6]

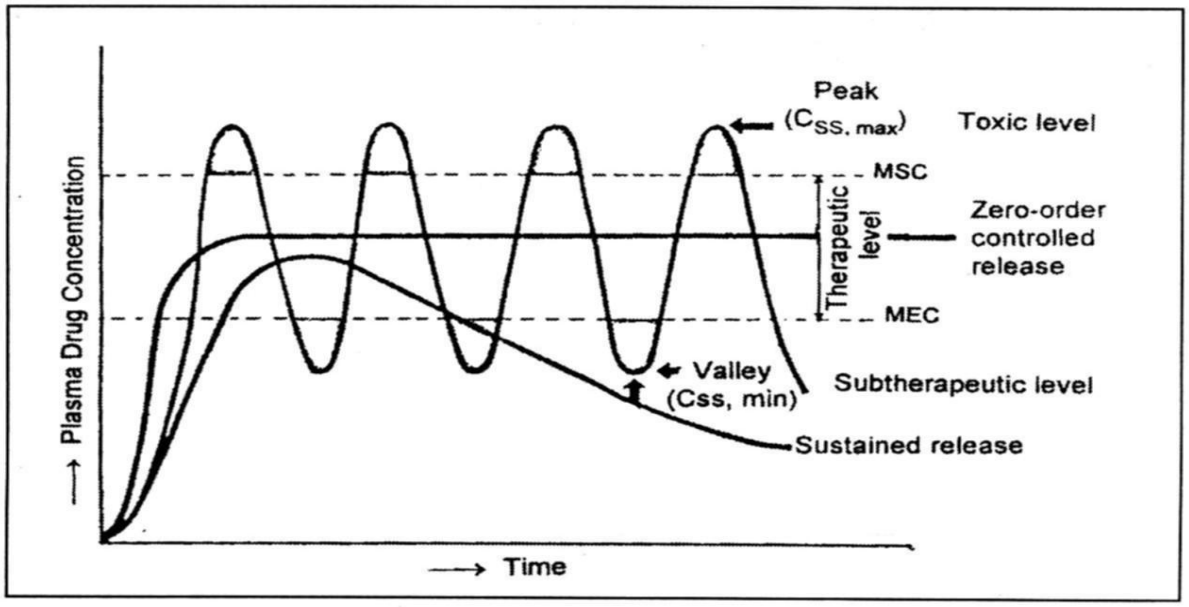

Figure 1: Concentration(c) vs. Time (t) profiles for conventional and controlled release drug delivery

The idea behind a controlled drug delivery system is to incorporate the drug within a polymeric carrier that controls the release rate of the drug. Various processes, such as diffusion, erosion, and/or swelling can be involved in the control of the overall drug release rate, resulting in a broad spectrum of possible release profiles. For example, a continuous drug supply can be provided, compensating for the clearance of the drug from the human body, thus resulting in constant drug concentration at the site of action over a prolonged period.[5, 6]

Techniques for Preparation of Microparticle Drug Delivery: [7]

Within the broad category of microparticles , 'microparticles' specifically refer to spherical microparticles and 'microcapsules' applies to microparticles which have a core surrounded by a material which is distinctly different from that of the core .[4] The core may be solid, liquid or

even gas. A microparticle usually refers to a homogeneous mixture of the polymer and active agent, whereas microcapsules have at least one discrete domain of active agent.(Figure 2)

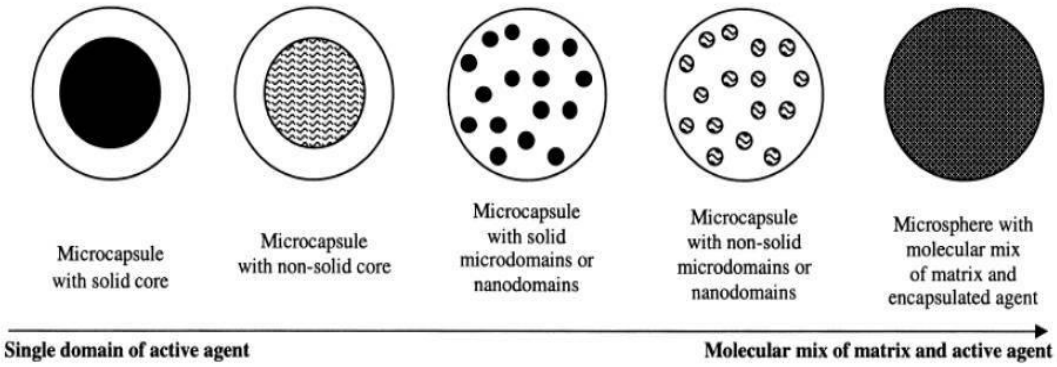

Figure 2: Different categories of microparticles

Solvent evaporation and extraction based processes

Single emulsion process: This process involves oil-in-water (o/w) emulsification[7]. The o/w emulsion system consists of an organic phase comprised of a volatile solvent with dissolved polymer and the drug to be encapsulated, emulsified in an aqueous phase containing a dissolved surfactant.

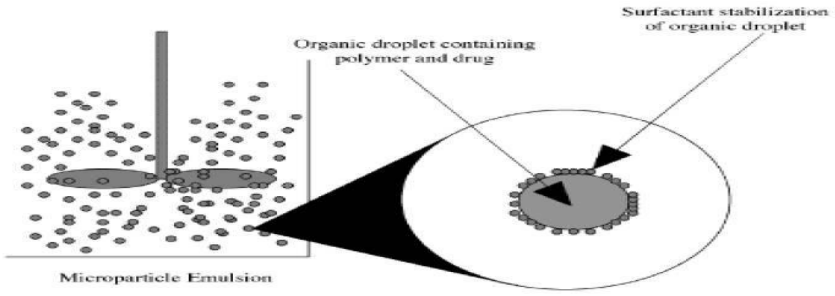

Figure 3: Encapsulation using oil-in-water emulsion technique

A surfactant is included in the aqueous phase to prevent the organic droplets from coalescing once they are formed. The polymer-solvent-drug solution is emulsified (with appropriate stirring and temperature conditions) to yield an o/w emulsion. The emulsion is created by using a propeller or magnetic bar for mixing the organic and aqueous phases (figure 3). Surfactants are used to stabilize the dispersed phase droplets formed during emulsification and inhibit coalescence. Surfactants are in nature and will align themselves at the droplet surface promoting

stability by lowering the free energy at the interface between the two phases. The surfactant also confers resistance to coalescence and microparticle flocculation. PVA is one of the widely used surfactants for producing the PLGA microparticles. Once the emulsion is formed, it is subjected to solvent removal by either evaporation or extraction process to solidify the polymer droplets. In the case of solvent removal by evaporation, the emulsion is maintained at a reduced pressure or at atmospheric pressure and the stirring rate is reduced to enable the volatile solvent to evaporate. The organic solvent leaches out of the droplet into the external aqueous phase before evaporating at the water air interface. In the case of extraction, the emulsion is transferred to a large quantity of water or other quench medium, into which the solvent associated with the oil droplets is diffused out. The rate of solvent removal by extraction depends on the temperature of quench medium, ratio of the emulsion volume to quench medium and the solubility characteristics of the polymer, the solvent and the dispersion medium. A high extraction result will result in formation of particles with a high porosity that could lead to undesirable drug-release profiles. The solvent removal method by extraction is faster (generally <30 minutes) than the evaporation process and hence the microparticles made by this method are often more porous in comparison to those made by solvent evaporation method. One of the disadvantages of the o/w emulsification process is the poor encapsulation efficiency with moderately water-soluble drugs. The drug diffuses out or partitions from the dispersed oil phase into the aqueous continuous phase and microcrystalline fragments of the hydrophilic drugs get deposited on to the microparticle surface and dispersed in the polymer matrix. This results in poor trapping of the hydrophilic drug and initial rapid release of the drug (burst effect). The oil/water emulsification process is thus widely used to encapsulate lipid-soluble drugs. In order to increase the encapsulation efficiency of water soluble drugs, an oil-in-oil emulsion method was developed. In this method, the drug may be dissolved or suspended in the oil phase before being dispersed in another phase. A water-miscible organic solvent like acetonitrile is employed to solubilize the drug in which PLGA or PLA are also soluble. This solution is then dispersed in oil such as light mineral oil in the presence of an oil soluble surfactant like sorbitan, oleate (Span) to yield the o/o emulsion. Microparticles are finally obtained by evaporation or extraction of the organic solvent from the dispersed oil droplets and the oil is washed off by solvents like *n*-hexane. This process is also referred to as water-in-oil (w/o) emulsion method.[8]

Double emulsion process: A double emulsion process is usually employed for drugs not soluble in an organic solvent. A solid-in-oil-in-water emulsion (s/o/w) process could be used to

encapsulate a drug provided its form is of small size. The size of the drug crystal should be at least an order of magnitude smaller than the desired microparticle diameter in order to avoid large bursts associated with dissolution of larger crystals. Smaller crystals will be homogeneously distributed throughout the organic droplets created in emulsion. Hydrophilic drugs (cisplatin, doxorubicin) have been encapsulated using double emulsion process.[9] the problem with encapsulating hydrophilic drugs is the loss of drug to the external aqueous phase during the formation of the microparticle. Along with the loss of drug to the external phase, the remaining drug may migrate to the surface of the droplet before solidifying. To minimize these problems, the organic droplets should be solidified into microparticles as quickly as possible following their formation. This is achieved by using a viscous organic solution of polymer and drug and a large secondary volume of water that attracts the organic solvent into the aqueous phase immediately, thus leaving the microparticle with the encapsulated drug. The viscous dispersed phase minimizes the volume of organic solvent, facilitating its quick removal from the droplet and also makes it more difficult for the solid drug 14 particles/crystal to migrate to its surface, resulting in a more homogeneous distribution of the drug within the particle. Another alternative to encapsulate hydrophilic drugs is to employ the water-in-oil-in water (w/o/w) emulsion process (Figure 4).

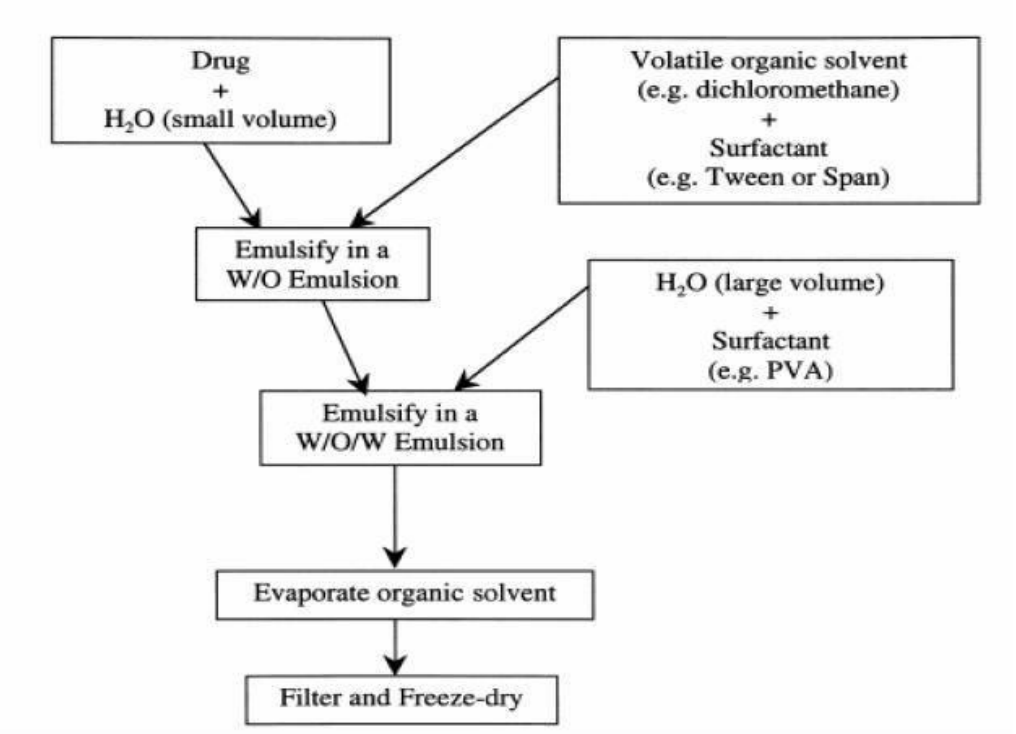

Figure 4: Schematic of w/o/w in-liquid drying process for microparticle preparation

An aqueous solution of the drug is added to an organic phase consisting of the polymer and organic solvent with vigorous stirring to form the first w/o emulsion. This emulsion is then dispersed in another aqueous phase containing more surfactant to form the w/o/w emulsion. A number of hydrophilic drugs like the peptide leuprolide acetate, a luteinizing hormone-releasing, hormone agonist, vaccines, proteins/peptides and conventional molecules have been successfully encapsulated by this method. The problem with this type of emulsion occurs when the inner emulsion is not sufficiently stabilized, resulting in loss of aqueous droplets containing drug to the external aqueous phase. The choice of surfactants that can be used to stabilize the inner emulsion is limited to materials that will dissolve in the organic solvent. Typically, the fatty acid esters of polyoxyethylene or sorbitan are used due to their high solubility in organic solvents and good biocompatibility.[10, 11]

Phase separation: This process consists of decreasing the solubility of the encapsulating polymer by addition of a third component to the polymer solution. This process yields two liquid phases: the polymer containing coacervate phase and the supernatant phase depleted in polymer. The drug which is dispersed/dissolved in the polymer solution is coated by the coacervate. Thus the coacervation process consists of the following three steps: i) phase separation of the coating polymer solution, ii) adsorption of the coacervate around the drug particles, and iii) solidification of the microparticles. The polymer is first dissolved in an organic solution. The water-soluble drugs like proteins are dissolved in water and dispersed in the polymer solution (w/o emulsion). Hydrophobic drugs like steroids are either solubilized or dispersed in the polymer solution. An organic non-solvent is then added to the polymer-drug-solvent system with stirring, which gradually extracts the polymer solvent. As a result, the polymer is subjected to phase separation and it forms soft coacervate droplets that entrap the drug. The system is then transferred to a large quantity of another organic non-solvent to harden the micro droplets and form the final microparticles which are collected by washing, sieving, filtration, or centrifugation, and are finally dried. This process is suitable to encapsulate other water-soluble as well as water-insoluble drugs. However, the coacervation process is mainly used to encapsulate water-soluble drugs like peptides, proteins, and vaccines. The rate at which the first non-solvent is added should be such that the polymer solvent is extracted slowly, allowing sufficient time for the polymer to deposit and coat evenly on the drug particle surface during the coacervation process. The concentration of the polymer used is important as well, since too high a concentration would result in rapid phase separation and non-uniform coating of the drug particles. The coacervate

droplets are extremely sticky and adhere to each other before the complete phase separation or hardening stages of this method. Adjusting the stirring rate, temperature, or the incorporation of an additive is known to rectify this problem. Dichloromethane, acetonitrile, ethyl acetate, and toluene have been used as non-solvents in this process. The non-solvent affects both phase separation and the hardening stages of the coacervation process. The non-solvents should not dissolve the polymer or the drug and should be miscible with the polymer solvent. The second non-solvent should be relatively volatile and should easily remove the first viscous non-solvent by washing. Some of the oils used as the first non-solvent are silicone oil, vegetable oils, light liquid paraffin, low molecular weight liquid polybutadiene, and low molecular weight liquid methacrylic polymers. Examples of the second non-solvent include aliphatic hydrocarbons like hexane, heptanes, and petroleum ether.[12]

Spray drying: Spray-drying is a widely used method in the pharmaceutical industry and has been investigated by several researchers as a method for formulating biodegradable microparticles. It is rapid, convenient, easy to scale-up, involves mild conditions, and is less dependent on the solubility parameters of the drug and the polymer. This method typically uses drug dissolved or suspended in a polymer solution (either organic or aqueous solvent, depending on the polymer used). This solution/suspension is then fed into the spray-drying apparatus, of which the most important component is the nozzle. The polymer/drug solution is mixed rapidly with air and forced through a small diameter orifice. Nebulization of the polymer/drug solution occurs at the nozzle and the resultant droplets are very quickly dried by evaporation (under high-pressure air) before collection. Significant advantages of using this technique include high encapsulation efficiencies and no residual surfactant on the surface of the microparticles. There is no external aqueous phase that can act as a sink for the drug and there is no surfactant present anywhere in the formulation. Parameters that affect the microparticle size and morphology are temperature, pressure (of the air used for drying), nozzle diameter, air/solution volume mixture, and polymer/drug concentrations. Recently Pack *et al* [13] have reported a novel technique based on spray drying to generate PLGA microparticles with uniform size distribution(see Figure 5).The microparticle fabrication protocol is based on passing a solution containing the polymeric material (and the drug to be encapsulated) through a small nozzle to form a smooth cylindrical jet. A piezoelectric transducer, driven by a wave generator at a frequency tuned to match the flow rate and the desired drop size, vibrates the nozzle and breaks down the jet into a train of uniform droplets. An annular, non-solvent carrier-stream over the polymer solution provided

further control over the droplet size and they have fabricated uniform spheres with average diameters from ~ 5 to > 500 μm.[10]

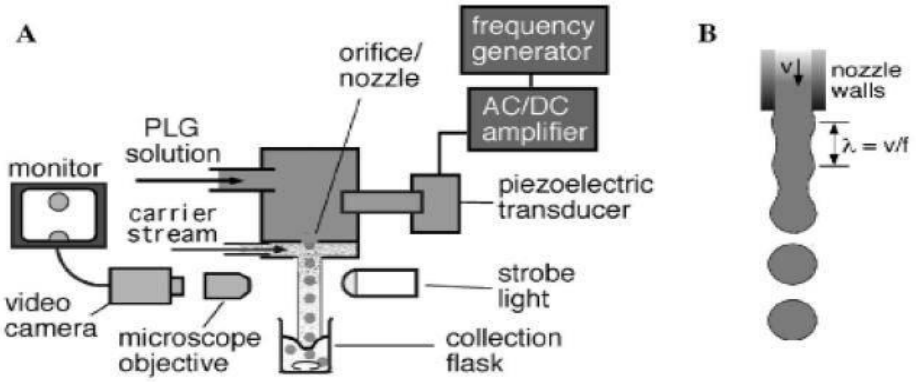

Figure 5: Spray-drying apparatus

Polymerization: A relatively new microparticle method utilizes polymerization techniques to from protective microcapsule coatings in situ. The methods involve the reaction of monomeric units located at the interface existing between a core material substance and a continuous phase in which the core material is dispersed. The continuous or core material supporting phase is usually a liquid or gas, and therefore the polymerization reaction occurs at a liquid-liquid, liquid-gas, solid-liquid, or solid-gas interface.[14]

Solvent extraction: Solvent evaporation method is used for the preparation of microparticles, involves removal of the organic phase by extraction of the organic solvent. The method involves water miscible organic solvents such as isopropanol. Organic phase is removed by extraction with water. This process decreases the hardening time for the microparticles. One variation of the process involves direct addition of the drug or protein to polymer organic solution. The rate of solvent removal by extraction method depends on the temperature of water, ratio of emulsion volume to the water and the solubility profile of the polymer**.**

Chemical and thermal cross-linking: Microparticles made from natural polymers are prepared by a cross-linking process. The polymers include: gelatin, albumin, starch and dextrin. A water-in-oil emulsion is prepared, where the water phase is a solution of the polymer that contains the drug to be incorporated. The oil phase is a suitable vegetable oil or oil-organic solvent mixture containing an oil-soluble emulsifier. Once the desired w/o emulsion is formed, the water-soluble polymer is solidified by some kind of cross-linking process. This may involve thermal treatment

or the addition of a chemical cross-linking agent such as glutaraldehyde to form a stable chemical cross-link as in albumin.

Cross linking using a freeze-thaw technique: When PVA is exposed to a number of freeze–thaw cycles; it takes on the physical characteristics of cross linked PVA. The freezing and thawing procedure produces crystals that act as physical cross links. This is a totally benign method of fabricating these gels, which is a significant advantage over chemically cross linked systems. PVA prepared in this manner does not, however, possess the long-term stability that chemically cross linked gels have.

The properties of PVA hydrogels are largely dependent on the molecular weight, concentration of the solution, time and temperature of freezing, and number of freeze–thaw cycles. As the molecular weight and the number of freeze–thaw cycles increases, the gel structure becomes denser. In his early work, Peppas found that the number of crystallites increased with an increase of the concentration of PVA in the solution. It was also discovered that an increase in the freezing time caused an increase in the crystallinity of the system. Syndiotactic and atactic polymer samples were compared. For every cycle the syndiotactic-rich PVA gels were found to exhibit better gelation and lower flow points than atactic-rich PVA gels due to differences in stereo regularity. Lower PVA concentrations were required to form these gels compared to atactic-rich PVA. These syndiotactic-rich PVA gels were formed even at room temperature, even without undergoing any freeze–haw procedure.

Syndiotactic-rich PVA gels were used to release indomethacin. A number of studies have been conducted to investigate the effect of adding various substances to solutions of PVA (prepared by the freeze–thaw method) on the drug release and the properties of the polymer. Drug release rates from these freeze–thaw gels were decreased by adding sodium alginate or Pluronic® L-62. The strength of the gels was also increased using this technique. The in vitro release of bovine serum albumin from PVA microparticles produced by dispersing PVA in an oil phase and physically cross linking it using a freeze–thaw procedure was investigated. The concentration of the PVA and the particle sizes were found to be important factors in controlling the release rate.

Poly (vinyl alcohol) gel spheres containing drugs (cephalexin and insulin) were prepared by emulsion polymerization and cross linked by a freeze–thaw technique. These spheres were evaluated as oral drug delivery systems and found to prolong the contact time of drugs with the gastrointestinal wall and improve the absorption characteristics by increasing the effective absorption time. PVA freeze–thaw microparticles were investigated for oral administration of

insulin. Absorption enhancers were used to overcome poor membrane permeability. Prolonged residence times in the ileum were observed. PVA gels were loaded with indomethacin and used as rectal suppositories in dogs and rats. Drug levels in plasma remained at steady plateau levels for up to 9 h.

Some drugs are difficult to take orally because of enzymatic degradation as the drug passes through the liver. Since the skin is a fairly impenetrable barrier, only a few drugs inherently possess the properties that allow transdermal drug delivery. In order for a drug to penetrate the skin at significant rates, it must be a low molecular weight material and be soluble in water and oil. PVA freeze–thaw gels were used to deliver ketanserin transdermally for wound healing. These gels were also tested for buccal mucoadhesive delivery of ergotamine tartrate. The mucoadhesive strength of these gels was tested.[15]

Jet milling: An innovative technique for solvent free preparation of microparticles is described. Microparticles were prepared by a melt grinding technique which consists of three consecutive steps of melting in case of placebo microparticles or co-melting of polymer and drug in case of drug loaded microparticles, respectively, and pre-grinding. In a final jet milling step the reduction of the particle size and smoothening of the microparticle surface occurred. Different polymers of PLA and PLGA type were utilized. The influence of the preparation parameters during the process were investigated according to microparticle properties like particle size distribution, surface morphology by executing a $2^{(5-2)}$ factorial design.

A new process to prepare microparticles without the use of organic solvents including a higher portion of drug loading had to be developed in order to circumvent all mentioned Drawbacks of other techniques. The aim of this study was to investigate the suitability of a new melt grinding technique to prepare microspheres. Most impressive advantages are the prevention from toxicity due to the absence of organic solvents during the process and the short preparation time with no drying step necessary. The solvent free melt grinding technique has been shown to be a suitable preparation method for microspheres without a drying step and a very high limit of loading with active agents. The preparation process can be carried out in a reproducible manner. The results demonstrate that microparticle preparation is possible by the following unique melt grinding technique without using organic solvents.[16]

Route of Administration:

Microparticles can be used for the delivery of drugs via different routes. Route of administration is selected depending on the drug properties, diseases state being treated and the condition of

patient. Desirable properties of the microparticles used for the delivery will also change depending on route of administration.[11]

(a) Oral delivery: Oral delivery is the simplest way of drug administration. In oral drug delivery, the microparticles have to pass through frequently changing environments in the GI tract. There is also patient variation in GI content, stomach emptying time and peristaltic activity. Although constrains of the oral route are numbers, on the whole, it less potential danger then the parenteral route. The relatively brief transit time of about 12 hr through the GI tract limits the duration of action that can be expected via the oral route. Recently, it has been reported that microparticles of less than 10 m in size are taken up by the Payer's patches and may increase the retention time in the stomach. Oral administration of polylactide-co–glycodine microparticles containing staphylococcal entertoxin B is effective in including disseminated mucosal IgA antitoxin antibody response.

Also microsphere made from polymers with mucoadhesive properties get attached to the stomach and prolong the residence time in the stomach or intestine and small absorption rate constant can be increased by increasing the retention time in the stomach. Longer et al [17] (1985) studied chlorothiazide release from albumin microparticles by oral administration by mixing it with polycarbophill, a bioadhesive polymer. Improved drug delivery was observed compound to the administered alone.[18]

(b) Parenteral delivery: Most of the microparticles based controlled delivery system are developed with the aim of using the for parenteral administration. Drug released is completely in this case. Microsphere used for parenteral delivery should sterile and should be dispersible in a suitable in a suitable vehicle for injection. Hydrophilic microparticles have the potential advantage of aqueous dispensability as opposed to hydrophobic microparticles for reconstituting them for injection. Surfactants in small concentrations are often necessary for reconstituting hydrophobic particles for injection is aqueous vehicles which are reported to cause adverse tissue reactions and incorporated drug.

EVALUATION OF MICROPARTICLES:

The characterization of the microparticulate carrier is an important phenomenon, which helps to design a suitable carrier for the proteins, drug or antigen delivery. These microparticles have different microstructures. These microstructures determine the release and the stability of the carrier.[19]

Particle size and shape: The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM). Both can be used to determine the shape and outer structure of microparticles. LM provides a control over coating parameters in case of double walled microparticles. The microparticles structures can be visualized before and after coating and the change can be measured microscopically. SEM provides higher resolution in contrast to the LM. SEM allows investigations of the microparticles surfaces and after particles are cross-sectioned, it can also be used for the investigation of double walled systems. Conflocal fluorescence microscopy is used for the structure characterization of multiple walled microparticles. Laser light scattering and multi size coulter counter other than instrumental methods, which can be used for the characterization of size, shape and morphology of the microparticles.

Infrared spectroscopy: FT-IR is used to determine the degradation of the polymeric matrix of the carrier system. The surface of the microparticles is investigated measuring Alternated Total Reflectance (ATR). The IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material. The ATR-FTIR provides information about the surface composition of the microparticles depending upon manufacturing procedures and conditions.[10]

Density determination: Bulk density: The term ―bulk density refers to a measure used to describe a packing of particles or granules. Both loose and tapped bulk densities will be determined.[20]

a. Loose bulk density = mass of powder/volume of packing
b. Tapped bulk density = mass of powder/ tapped volume of packing
c. Weighed amounts of microparticles were taken in a 10-ml measuring cylinder after shaking lightly to break any agglomerates. After observing the initial volume of microparticles the cylinder was allowed to fall under its own weight on a hard surface from the height of 2-5 cm. The tapping was continued at a rate of 120 taps/min until no further change in volume was noted.

Compressibility: This is the value useful in prediction of flowability. The % compressibility of microparticles can be calculated using the following formula:

$$\mathbf{C = pb\text{-}pu/pb \times 100} \text{ ---------- (1)}$$

Where, **pb** = tapped bulk density

pu = loose bulk density

Angle of contact: The angle of contact is measured to determine the wetting property of a micro particulate carrier. It determines the nature of microparticles in terms of hydrophilicity or Hydrophobicity. This thermodynamic property is specific to solid and affected by the presence of the adsorbed component. The angle of contact is measured at the solid/air/water interface. The advancing and receding angle of contact are measured by placing a droplet in a circular cell mounted above objective of inverted microscope. Contact angle is measured at 200C within a minute of deposition of microparticles.

$$\Theta = \tan^{-1} (h/r) \text{ ------ (2)}$$

Where, **h** = height of pile

r = radius of the base of the pile

θ = angle of repose

Determination of drug content: To determine the yield and efficiency of drug loading, microparticles were analyzed for drug content. 100 mg Microparticles were crushed to give fine powder, distilled water was added, and the solution kept for 12 hr. After 12 hr, the solution was sonicated for 30 min. The solution was then filtered through Whatman filter paper No. 1. Two milliliters of clear filtrate was diluted to 100 ml with distilled water. The absorbance of the solution was measured on a Shimadzu UV-1700 at respective absorbance using distilled water as blank. The standard curve of diltiazem HC1 was recorded in distilled water for the exact concentration.[16], [21]

Capture efficiency

The capture efficiency of the microparticles or the percent entrapment can be determined by allowing washed microparticles to lyse. The lysate is then subjected to the determination of active constituents as per monograph requirement. The percent encapsulation efficiency is calculated using following equation

% Entrapment = Actual content/Theoretical content x 100 ----- (3)

Swelling studies: Swelling studies of microparticles having different cross-linking densities were carried out in simulated conditions of gastrointestinal tract. The microparticles (100 mg) were first kept in 0.1N HCl pH 1.2 for 2 hr. Then the fluid was replaced by 50 ml phosphate buffer pH 7.6 and the microparticles were kept for 24 hr at 37°C. The fluid content (%) and equilibrium fluid content (%) of microparticles were calculated**.**

Scanning electron microscopy: Microparticle shape and surface morphology were analyzed by scanning electron microscopy.[16]

Thermal analysis: Thermal analysis was done by differential scanning calorimetry and thermogravimetry.[16]

***In vitro* methods:** There is a need for experimental methods which allow the release characteristics and permeability of a drug through membrane to be determined. For this purpose, a number of *in vitro* and *in vivo* techniques have been reported. *In vitro* drug release studies have been employed as a quality control procedure in pharmaceutical production, in product development etc. Sensitive and reproducible release data derived from Physico chemically and hydro dynamically defined conditions are necessary. The influence of technologically defined conditions and difficulty in simulating in vivo conditions has led to development of a number of *in vitro* release methods for buccal formulations; however no standard *in vitro* method has yet been developed. Different workers have used apparatus of varying designs and under varying conditions, depending on the shape and application of the dosage form developed. Dissolution apparatus[14] Standard USP or BP dissolution apparatus have been used to study *in vitro* release profiles using rotating elements, paddle and basket. Dissolution medium used for the study varied from 900 ml and speed of rotation from 50-100 rpm.

Other methods: Few other methods involving plexi glass sample blocks placed in flasks, agar gel method, Valia-Chein cell USP III dissolution apparatus, etc have also been reported. Although a number of methods have been reported, the ideal method would be one where sink condition is maintained and dissolution time *in vitro* simulates dissolution time *in vivo. In vivo* methods for studying the permeability of intact mucosa comprise of techniques that exploit the biological response of the organism locally or systemically and those that involve direct local measurement of uptake or accumulation of penetrates at the surface. Some of the earliest and simple studies of mucosal permeability utilized the systemic pharmacological effects produced by drugs after application to the oral mucosa. However the most widely used methods include *in vivo* studies using animal models, buccal absorption tests, and perfusion chambers for studying drug permeability.

Animal models: Animal models are used mainly for the screening of the series of compounds, investigating the mechanisms and usefulness of permeation enhancers or evaluating a set of formulations. A number of animal models have been reported in the literature, however, very few *in vivo* (animal). Animal models such as the dog, rats, rabbits, cat; hamster, pigs, and sheep have been reported. In general, the procedure involves anesthetizing the animal followed by administration of the dosage form. In case of rats, the esophagus is ligated to prevent absorption

pathways other than oral mucosa. At different time intervals, the blood is withdrawn and analyzed.

Advantages of Micro Particles as Drug Delivery System[14]

- Protection of unstable, sensitive materials from their environments prior to use.
- Better process ability (improving solubility, dispersibility, flowability).
- Self-life enhancement by preventing degradative reactions.
- Safe and convenient handling of toxic materials.
- Masking of odor or taste.
- Enzyme and microorganism immobilization.
- Controlled and targeted drug delivery.
- Handling liquids as solids.
- To improve bioavailability
- To improve the stability
- Limiting fluctuation within therapeutic range
- Reducing side effects
- Decreasing dosing frequency
- Improving patient compliance.

Application of Microparticles as Drug Delivery Systems[22]

- There are many reasons why drugs and related chemicals have been microparticles. 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 microparticles 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. Eg. Eprazinone.
  - Hygroscopic properties of core materials may be reduced by microparticle eg. Sodium chloride.
  - Microparticles have been employed to provide protection to the core materials against atmospheric effects, e.g. Vit.A. palmitate.

- Separation of incompatible substance has been achieved by encapsulation.

CONCLUSION:

The microparticles offers a variety of opportunities such as protection and masking, better processability, improve bioavailability, decreasing dosing frequency, improve stability, reduced dissolution rate, facilitation of handling, and spatial targeting of the active ingredient. This approach facilitates accurate delivery of small quantities of potent drugs; reduced drug concentrations at sites other than the target organ or tissue; and protection of labile compounds before and after administration and prior to appearance at the site of action.

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