IJPSR (2023), Volume 14, Issue 5 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 04 August 2022; received in revised form, 13 April 2023; accepted 18 April 2023; published 01 May 2023

RECENT ADVANCEMENTS IN THE FORMULATION AND EVALUATION OF MICROPARTICLES AND ITS APPLICATION

Pratiksha Chaudhary, Nitin Kumar, Surya Pratap *, Rajeev, Mohammad Rashid and Sanjar Alam

Department of Pharmaceutics, R. V. Northland Institute, Dadri - 203207, Uttar Pradesh, India.

Keywords:

Microparticles, Polymer, Clarithromycine, Micrometrics, Antibiotic, Microcapsules, USP apparatus IV

Correspondence to Author:
Surya Pratap

Assistant Professor,
Department of Pharmaceutics,
R. V. Northland Institute, Dadri - 203207, Uttar Pradesh, India.

E-mail: suryapratapbsr@gmail.com

ABSTRACT: Introduction: The micro particles and development in the area of micro particles analysis are discussed in this article. **Areas Covered:** Micro particles are a unique drug carrier method that provides an effective therapeutic alternative to single-unit dose forms that are either traditional or rapid release. Micro particles are produced by filling them with firm gelatin or compressing them immediately. When compared to traditional dosage forms, micro particles manufactured using various types of technologies vary their performance and administration of the dosage form. Micro particles have been tested using *in-vitro* release techniques like dialysis membrane sacs, and USP equipment IV. According to comparisons of these techniques, USP apparatus IV is the preferred method right now. Accelerated *in-vitro* release assays were created to reduce the amount of time required for quality control testing. To reduce the necessity for *in-vivo* performance analysis, *in-vitro* and *in-vivo* correlation using real-time and accelerated release data have been produced. Storage stability studies have been carried out to see how different environmental conditions affect microsphere quality over the course of the product's life span (t90). New tests like the *in-vitro* wash off test and floating test have been introduced, as have characterization approaches for various physico-chemical characteristics such drug content, thermal properties and particle size.

INTRODUCTION: A regulated pharmaceutical delivery system can help address a few drawbacks of traditional therapy while simultaneously boosting therapeutic effects. To achieve maximum therapeutic efficacy, the chemical must be transported to the correct location in the appropriate amount and at the correct time, with the least degree of toxic effect possible. A therapeutic substance can be given to the target area in a number of controlled and consistent methods. A few of these ideas are to use micro particles as medication carriers [67].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.14(5).2141-63

This article can be accessed online on www.ijpsr.com

DOI link: https://doi.org/10.13040/IJPSR.0975-8232.14(5).2141-63

Micro particles are free-flowing spherical powders composed of synthetic, biodegradable and non-bio degradable polymers with a particle size should be between 1 to 1000 microns shown in **Fig. 1**. The main purpose of a revolutionary drug delivery system like this is to bypass the limits of traditional dosage forms by boosting increasing bioavailability, patient compliance and more precisely targeting medicines or other active substances [82].

There are two types of micro particles;

- Microcapsules.
- Micrometrics [82].

Microcapsules have a recognizable capsule wall around the encapsulated material, whereas Micro rays have the encapsulated ingredient dispersed within the particulate matrix with the potential for controlled release [18].

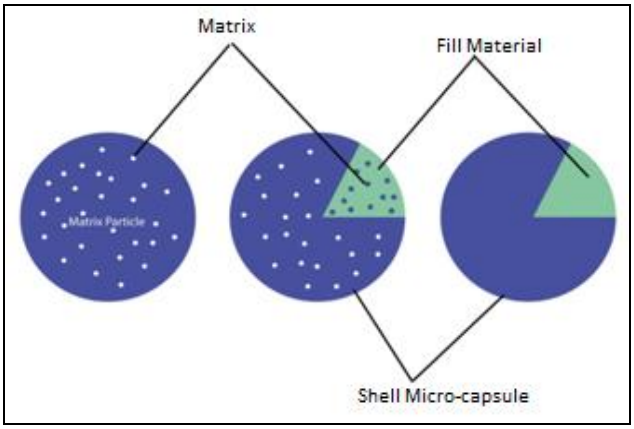


FIG. 1: MICRO PARTICLE

Advantages of Micro Particles:

- Decrease of the size contributes to an increasing surface area and can increase the potency of a material that is difficult to dissolve.
- Providing a steady quantity of medications in the body that can improve patient compliance;
- Dose and risk reduced.
- Drug packaging with polymers prevents the drug avoid enzymatic cleavage while making it suitable for drug method delivery system.
- Less duration of dosing contributes to higher patient compliance.
- Effective usage of medications can enhance the bioavailability, and decrease harmful effects' occurrence or severity.
- Helps protect the GIT from opioids irritants.
- Transform liquid into solid shape and block the unpleasant taste [97].

Disadvantages of Micro Particles:

- The pace of release of the regulated dose procedure varies depending on several parameters such as food and intestinal transfer levels.
- Changes in discharge rate from one dosage to the next.
- Because controlled-release formulations have a larger dosage load, any flaws in the drug substance's release qualities can cause problems such as

1. Potentially dangerous.
2. These dosing types must not be broken or chewed [9].

Materials used in the Micro-Particle Formulation: They are classified as follows in the formulation of microparticle polymers:

- Synthetic polymer
- Natural polymer

Synthetic Polymers are divided into two Parts:

A. Non-biodegradables polymers

Epoxy Polymers, Poly Methyl Methacrylate and Acrolein Glycidyl Methacrylate:

B. Biodegradables polymers

Glycosides, Lactides, and their Co-polymers, Poly Alkyl Cyano Acrylates and Poly Anhydrides:

C. Naturally occurring polymers

Carbohydrates, chemically modified carbohydrates and proteins are just a few of the natural polymers that can be found. Gelatin, Collagen and albumin are some examples of the proteins used. Chemically modified carbohydrates such as polydextran and poly-starch are used, as well as agarose, chitosan and starch [6, 57, 58, 99].

Types of Micro Particles:

- ❖ Bio-adhesive micro particles.
- ❖ Magnetic micro particles.
- ❖ Radioactive micro particles.
- ❖ Floating micro particles.
- ❖ Polymeric micro particles.
- ❖ Biodegradable polymeric micro particles.
- ❖ Synthetic polymeric micro particles [59].

Bio-adhesive Micro Particles: The capacity of a medication to attach to a membrane *via* the

adhesive capabilities of aqueous-soluble polymers is known as adhesion. The adherence of a drug carrier to a mucous membrane, like the nasal mucosa, rectal, ocular or buccal are referred to as bio adhesion. These micro particles shown in **Fig. 2**, spend more time at the application site, resulting in closer contact with the site of absorption and improved pharmacological action [54, 61, 48].

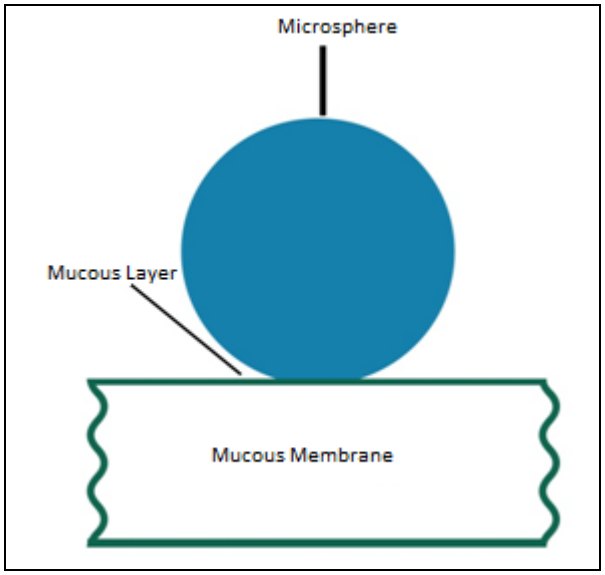


FIG. 2: BIO ADHESIVE MICRO PARTICLE

Magnetic Micro Particles: The medicine is targeted to the illness spot using magnetic micro particles. Magnetic carriers collect magnetic responses from integrated materials and transmit them to the magnetic field. These magnetic Micro particles, shown in **Fig. 3**, are made from chitosan, dextran, and other polymers. The magnetic micro particle allows a large volume of freely spreading pharmaceuticals to be replaced with a smaller amount of magnetically focused meds [26].

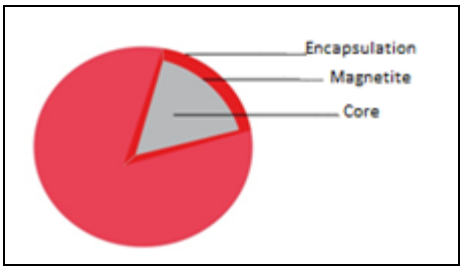


FIG. 3: MAGNETIC MICRO PARTICLE

Radioactive Micro Particles: Radiofrequency immobilization (RFI) is a therapy that uses radio waves to keep the patient immobilized. When micro particles with a diameter of 10-30 nm come into contact with the capillaries, they strike the first capillary bed. They are inserted into the arteries that supply the tumor with oxygen and nutrients. In all of these scenarios, radioactive micro particles shown in **Fig. 4**, provide a large dose of radiation to target regions while inflicting no injury to nearby healthy tissue. The various types of radioactive micro particles are called α-emitters, β-emitters, and γ-emitters [29, 105].

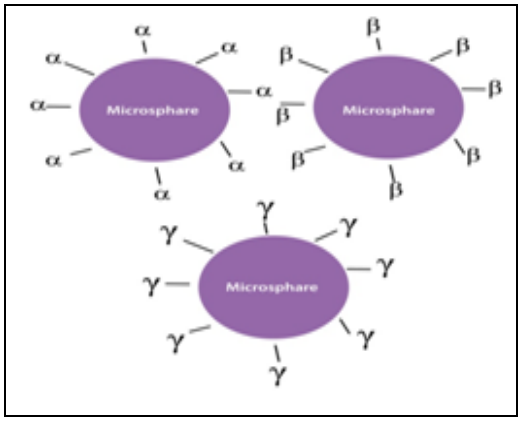


FIG. 4: RADIOACTIVE MICRO PARTICLE

Floating Micro Particles: The micro particle shown in **Fig. 5**, floats in the stomach because its apparent density is less than that of stomach fluid. The drug is slowly released and at the ideal rate when the whole system is in motion with the gastric contents. This improves the residence in the stomach and the variability of the plasmatic concentration.

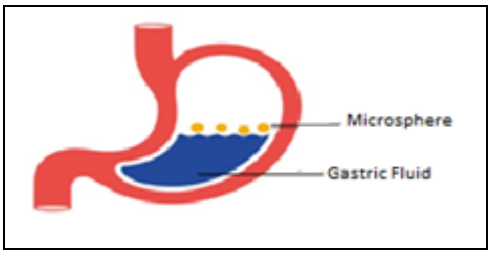


FIG. 5: FLOATING MICROSPHERE

This method has a longer-lasting therapeutic effect and reduces the required doses. With each successive stomach emptying, the sink particles will scatter throughout a vast absorption site, increasing the likelihood of a more or less predictable drug absorption and release profile. Also, because each dose is made up of numerous subunits, there is less chance of dose drift [25, 32, 66].

Polymeric Micro particles: Polymeric Micro particles shown in **Fig. 6**, are classified as follows:

Synthetic Polymers: In medical applications, such as embolic particles, bulking substances, drug carriers, and other applications, synthetic polymeric micro particles have been proved to be secure and biocompatible. The major drawbacks of these micro particles are that they move away from the injection site, raising the risk of embolism and tissue injury [98].

Polymers that Degrade Biodegradable: Natural polymers, such like starch, are biodegradable, biocompatible and bio adhesive. Due to their high degree of swelling in the aqueous media, biodegradable polymers extend the residence duration whenever they come into contact with the mucosa, causing gels to develop.

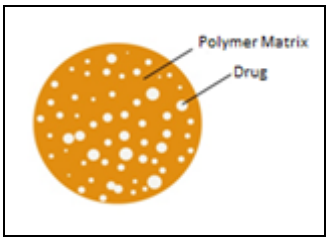


FIG. 6: POLYMERIC MICRO PARTICLE

The rate and quantity of medicine released can be adjusted by gradually changing the polymer concentration and drug release profile. The main issue is that the drug loading capacity of biodegradable Micro particles is challenging in medical applications, making drug release difficult to handle [88].

Method of Preparation:

1. Spray drying
2. Solvent evaporation technology
3. Single emulsion technique
4. Double emulsion technique
5. Phase separation coacervation technology
6. Spray drying and Spray freezing
7. Solvent Extraction
8. Quasi-emulsion solvent diffusion.

Spray Drying: The polymer is softened in a volatile organic solvent like acetone or dichloromethane and then the medication is homogenized in the polymer solution.

The dispersion is subsequently atomized in a stream of hot air, generating small droplets through which the solvent quickly evaporates, resulting in micro particles with sizes ranging from 1 to 100 µm in diameter. A centrifugal separator separates the generated micro particles using hot air, and solvent residues are eliminated by vacuum drying shown in **Fig. 7** [65, 69].

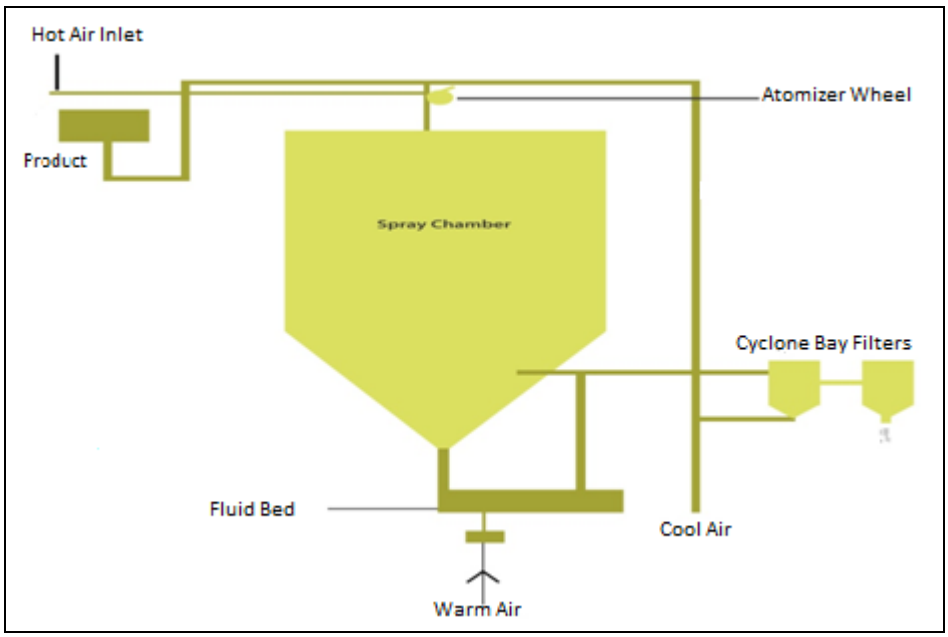


FIG. 7: SPRAY DRYING TECHNIQUE

Solvent Evaporation Technology: It is one of the earliest micro particle production methods. An organic solvent, like methylene chloride, must've been soluble in the medication and the polymer.

Drops can occur when a polymer and drug solution is dispersed in an aqueous medium. The more volatile organic phase can be evaporated with continuous mixing and increased temperatures, leaving the solid polymer-drug particles floating in aqueous solution. The suspension is then washed to remove the remaining particles. This procedure shown in **Fig. 8** [24].

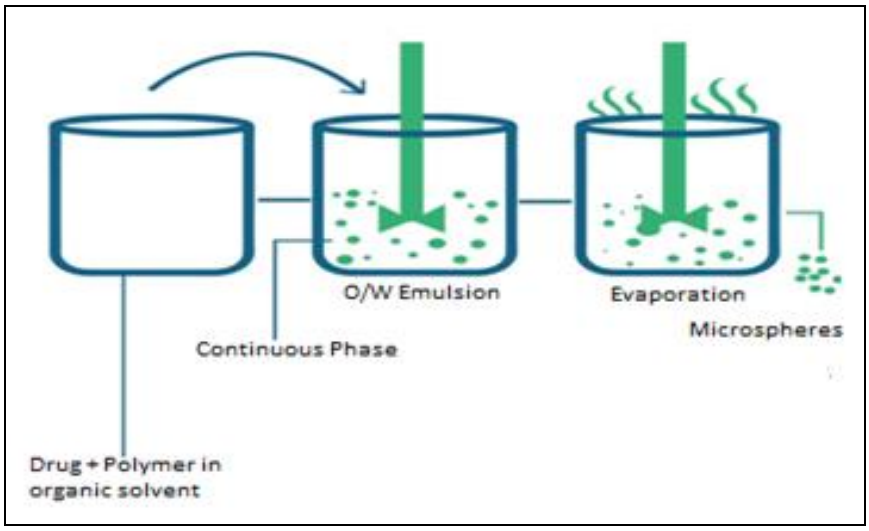
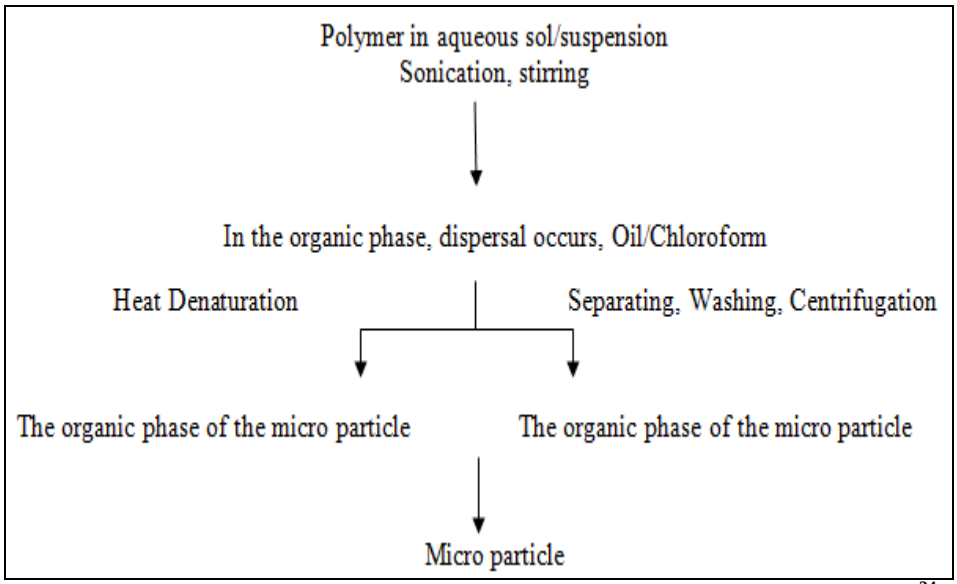


FIG. 8: SOLVENT EVAPORATION TECHNIQUE

Single Emulsion Technique: A number of carbohydrate and protein products are produced using this technology. Natural polymers are soluble in an aqueous media and spread in a non-aqueous medium (oil phase) in this process, with the disseminated particles then cross-linked in one of two ways:

By Heating: Dispersion in hot oil; nevertheless, for heat-labile medicines, this method is useless. Use a chemical cross-linking agent such as glutaraldehyde, formaldehyde or acid chloride. Chemical crosslinking has a disadvantage: excessive exposure [24].



SCHEMATIC REPRESENTATION OF SINGLE EMULSION TECHNIQUE [24]

Double Emulsion Technique: Multiple emulsions or double emulsions of the w/o/w type are created in this micro particle production method, which is appropriate for water-soluble medicines, proteins, vaccines and peptides. This technique, shown in **Fig. 9**, can be used on both manufactured and natural polymers. Throughout the lipophilic organic continuous phase, the aqueous protein solution is dispersed. The active ingredients may be present in this protein solution [78, 79, 80].

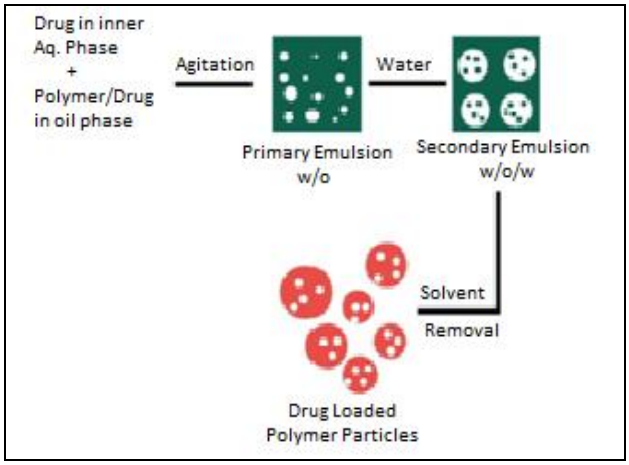
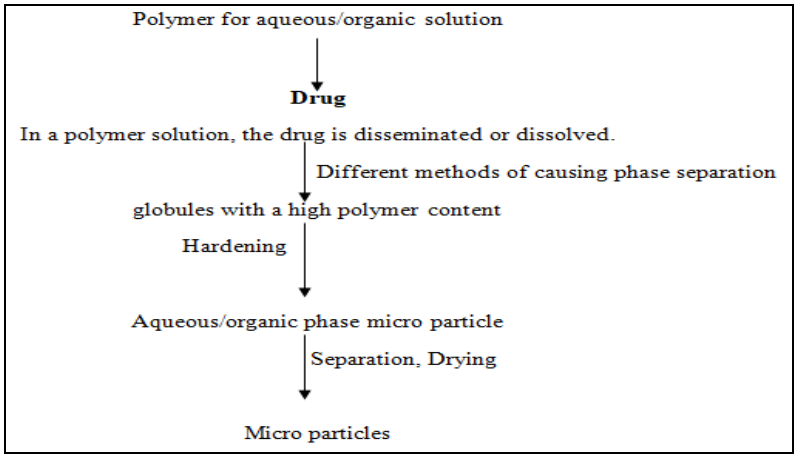


FIG. 9: DOUBLE EMULSION TECHNIQUE

Phase Separation Coacervation Technology: The phase separation method is commonly used to prepare the deposit system.

This approach is used to enclose water-soluble pharmaceuticals, including peptides and proteins and some matrix-type formulations, especially when the medication is hydrophobic, like steroids.

The method depends on reducing the polymer's solubility in the organic phase to influence the formation of coacervates, a polymer-rich phase. When a third component is added to the system, coacervation occurs, creating two phases, one with many polymers and the other not, *i.e.*, supernatant, which is depleted in the polymer. A variety of technologies can be used to phase separate coacervates. Techniques include salt addition, solvent addition, and incompatible polymer addition [7, 54, 55].



SCHEMATIC REPRESENTATION OF PHASE SEPARATION COACERVATION TECHNOLOGY [24]

Spray Drying and Spray Freezing: These techniques, shown in **Fig. 10**, are based on a polymer and drug spray that are air dried. Spray drying and spray freezing are two processes that differ in that the solvent is removed or the solution is cooled [43, 44].

Spray congealing: Spray = Hot melt / Cold air

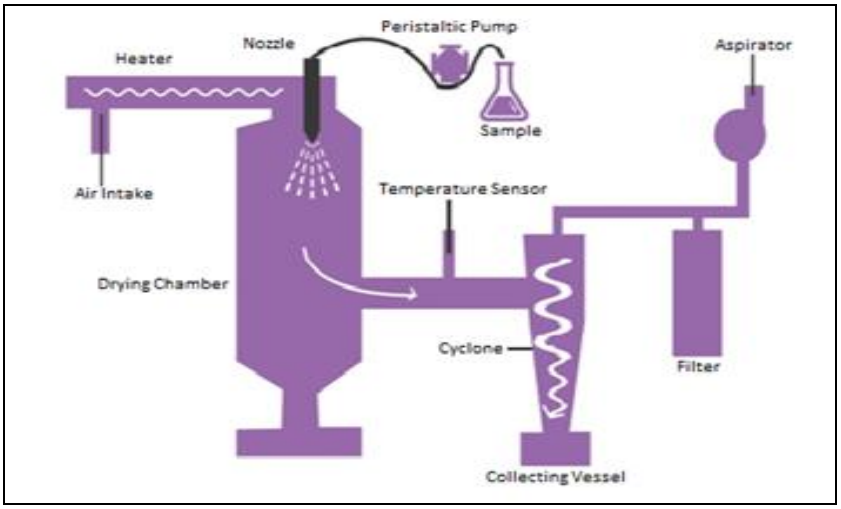
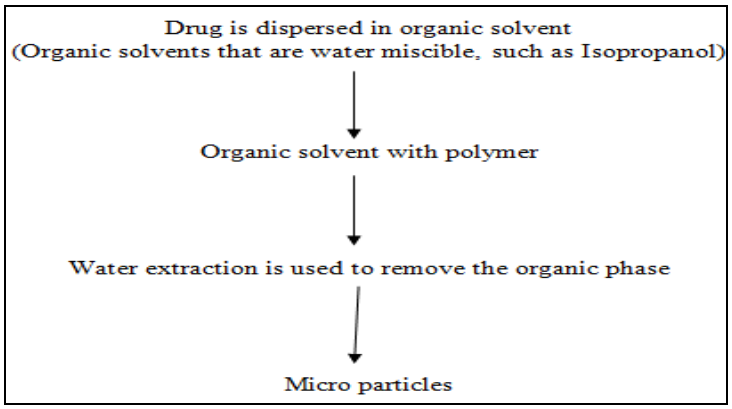


FIG. 10: SPRAY DRYING AND SPRAY FREEZING TECHNIQUE

Extraction of Solvents: The solvent evaporation method involves extracting the non-aqueous solvent and eliminating the organic phase to create micro particles. In this method, isopropanol is employed, which is a water-miscible organic solvent [96]. The extraction process can remove organic phase with the help of water [24].



SCHEMATIC REPRESENTATION OF EXTRACTION OF SOLVENT TECHNIQUE [24]

Quasi-Emulsion Solvent Diffusion: The literature has published a unique quasi-emulsion solvent diffusion approach to generate controlled-release drug-release micro particles with acrylic polymers. Quasi-emulsion solvent diffusion technique shown in **Fig. 11**, which uses polyvinyl alcohol and purified water as the outer phase, can make micro sponges. In the internal phase are drugs, ethanol and polymers. The inner phase is initially produced at 60 degrees centigrade and then the outer phase is introduced at room temperature. The mixture is centrifuged indefinitely for two hours to emulsify it. By sieving the mixture, the micro sponges can be isolated from the rest [30, 109].

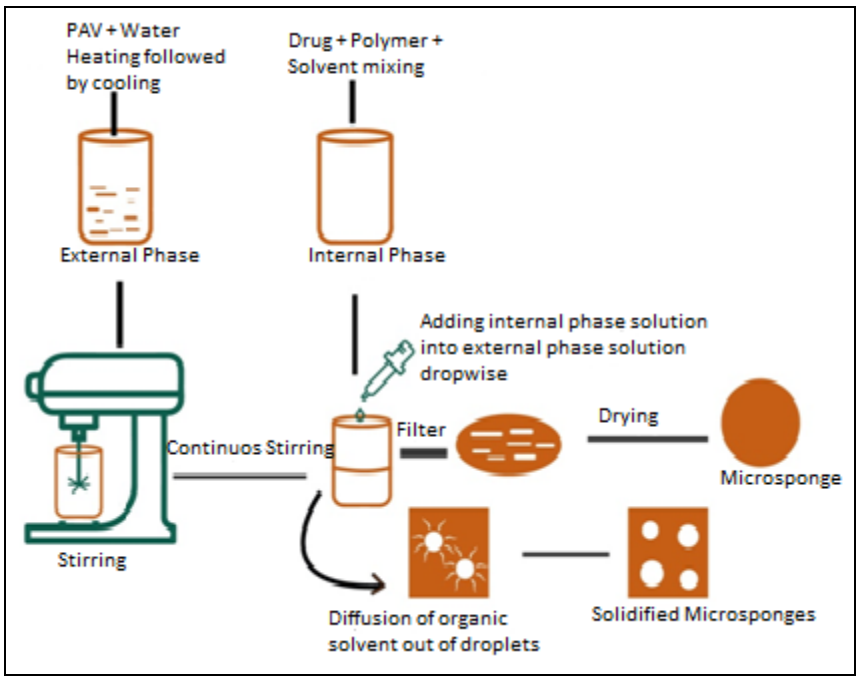


FIG. 11: QUASSI EMULSION SOLVENT DIFFUSION

Evaluation of Micro Particles:

Physicochemical Evaluation:

Particle shape and size: Traditional scanning light microscopy and electron microscopy are the most widely used technologies to observe micro particles. Either method can be used to identify the shape and exterior micro particle's structure. In double-walled micro particles, optical microscopy allows precise control of coating conditions. The architecture of the micro particles can be seen before and after polishing and the modifications can be examined through microscopy.

The resolution of (SEM) scanning electron microscopy is better than that of light microscopy. After the micro particles have been cross-sectioned, (SEM) scanning electron microscopy can be used to examine their surfaces and double-wall systems. The structure of many walled Micro particles is examined using confocal fluorescence microscopy. The micro particles' shape, morphology, and size can be determined using laser light scattering and multi-size grating counter, in addition to experimental approaches [11, 34].

Average particle size is determined by

$$D \text{ mean} = \Sigma n d / \Sigma n$$

Where, n = number of micro particles checked; d = Mean size [24].

Angle of Contact: The wetting property of the micro particle carrier is determined using the contact angle. Micro particles are classified according to their hydrophobicity or hydrophilicity. The adsorbed component controls this thermodynamic characteristic specific to the solid. The contact angle is calculated at the solid/air/water interface. The advancing and receding contact angles are determined by placing the droplet in a circular cell over the objective of an inverted microscope. The contact angle is measured at 2000 °C in one minute from when the micro particles are deposited [74].

Percentage Yield: The amount of medication and polymer used in each batch is divided by the number of micro particles recovered from that batch, then by 100 [24].

Isoelectric Point: The isoelectric point was calculated by micro electrophoresis, which was used to assess the electrophoretic mobility of the micro particles. The time it takes for particles to travel a distance of 1 mm at different PH values ranging from 3 to 10 is used to calculate average velocity. This data can be used to calculate a particle's electrical motion. The surface charge, ionizable behavior, and ion absorption features of micro particles can all affect their electrophoretic mobility [93].

Swelling Index: It is calculated by finding out how many micro particles swell in a specific solvent. The degree of equilibrium swelling of the micro particles can be calculated by soaking 5 mg of dry micro particles in 5 ml of buffer solution one night into a measuring cylinder. It is determined using the formula provided [24].

Swelling index = mass of swollen micro particles minus mass of dry micro particles divided by mass of dry micro particles multiplied by 100.

Determining Density: A multi-volume pycnometer can be used to determine the density of the micro particles. A correctly weighted sample is put in a cup in the multi-volume pycnometer. The chamber is filled with helium and allowed to expand under continuous pressure. As a result of the expansion, the pressure inside the chamber lowers. The two consecutive pressure drop figures were obtained at different starting pressures. The density and volume of the micro particle carrier are determined using two pressure readings [12].

Fourier Transform Infrared Spectroscopy: The decadence of the carrier system's polymeric matrix is measured using Fourier transform IR spectroscopy. The surface of the micro particles is examined using ATR (alternate total reflectance). The infrared light that passed through the alternating total reflectance cell was reflected multiple times through to the sample, resulting in IR spectra dominated by surface materials. Alternating total reflectance FTIR spectroscopy can reveal the surface components of micro particles depending on manufacturing techniques and conditions [24].

Chemical Analysis using Electron Spectrometry: ESCA [electron spectroscopy for chemical analysis] can be used to determine the surface chemistry of micro particles. In chemical analysis, electron spectroscopy can be used to identify the atomic structure of a surface. The surface degradation of biodegradable micro particles can be determined using spectra generated by electron spectrometry for chemical analysis [42].

Entrapment Efficiency: A certain number of micro particles is weighed and crushed. After that, it was dissolved in a buffer solution and filtered using a stirrer. A UV spectrophotometer is used to evaluate the filtrate at a given wavelength using a calibration curve [24]. The percentage of the experimental drug concentration to the theoretical

drug concentration multiplied by 100 is the drug entrapment efficacy.

***In-vitro* Methods:** This method can be used to determine the drug release profile and penetration of medication through a barrier. The *in-vitro* approach is used as a product testing technique in pharmaceutical manufacture and product development. It's critical to have consistent and repeatable release data derived from chemically, physically, and hydro-dynamically established conditions [24].

Beaker Method: In this operation, the dosage form is attached to the bottom of the medium beaker and is continuously agitated with an overhead stirrer. In literature research, the average volume employed ranges from 50 to 500 ml, with a mixing rate of 60 to 300 rpm [24].

Interface Diffusion Method: Dearden and Tomlinson came up with this approach. There are four different parts in all. Compartment A, first filled with a pharmaceutical concentration in buffer, represents the oral cavity. The buccal membrane is represented by compartment B, which has 1 octanol, while body fluids are represented by compartment C, which has 0.2 M HCl. Protein binding is represented by Compartment D, which also has 1-octanol. Before using, the watery phase and 1-octanol must be saturated. A syringe retrieves samples from compartment A and returns them to compartment A [24].

Modified Keshary Chien Cell Method: Advanced laboratory technology is required. At 37 degrees Celsius, it comprises a Keshary Chien cell using distilled water (50 ml) as the dissolving medium. The TMDDS (Trans Membrane Drug Delivery System) is housed in a glass tube with a 10# sieve at the bottom that spreads with the help of the medium 30 times per minute [24].

Dissolution Apparatus Method: Paddle and basket spinning elements have been employed to evaluate *in-vitro* release properties using typical BP dissolving or USP apparatus. The study's dissolving media ranges from 100 to 500 ml, with rotation speeds of 50 to 100 rpm [24].

***In-vivo* Method:** The transparency of intact mucous is determined using techniques that offer the biological response of the organism locally or systemically, as well as those that involve direct local examination of chemical uptake or aggregation on its surface. Animal models and buccal absorption investigations are the most commonly used *in-vivo* research methods [24].

Animal Models: It's mostly used to screen many compounds, determine how they act, and evaluate many formulations. Dogs, rats, pigs, and sheep are just a few animal models available. The technique includes anesthetizing the animal, administering the dose, drawing blood at various intervals, and analyzing the results [24].

Buccal Absorption Test: For pharmaceutical combinations of one or several components, it is the most appropriate and reliable approach to determine the degree of loss of the drug from the human oral cavity. Adult subjects swish a 25 ml sample of the test solution for 15 minutes prior to expulsion to measure drug absorption kinetics while the medication is still in the mouth cavity.

To determine the importance of the medicine on a scale of importance structure, contact time, drug concentration at first use, and solution pH. The amount of drug remaining in the expelled volume is calculated to determine how much drug was absorbed [24].

Correlations between *In-vitro* and *In-vivo*: The association between *in-vitro* dissolving rates and the rate and degree of availability as assessed by blood concentrations of the medication or metabolite and urinary excretion is referred to as *'in-vitro-in-vivo* correlations. Such links make it possible to create product criteria related to bioavailability [13, 71].

***In-vitro* Drug Dissolved percentage vs Peak Plasma:**

Concentration: One method to measure the association *in-vivo* and *in-vitro* is to calculate the percentage of drug released from various types of dosage forms, as well as the maximum plasma concentrations obtained by them, and compare them. Poorly made dosage forms are expected to release less drug than well-made dosage forms, resulting in a decreased amount of drug available for absorption [13, 71].

Percentage of Dissolved Drug vs Percentage of Absorbed Drug: If the dissolution rate is the limiting phase in drug absorption and the drug is absorbed after dissolution, a liner connection can be generated by comparing the percentage of drug absorbed with the percentage of drug dissolved. If the rate of absorption is the rate-limiting step in medication bioavailability, a change in dissolution rate may not be reflected in a change in the rate and extent of drug absorption from the dosage form [14, 71].

Absorption Rate vs. Dissolution Rate: Generally, calculating the absorption rate is more difficult than calculating the absorption time. Absorption time can be used to correlate absorption and dissolution data because a drug's absorption rate and time are inversely connected. The absorption time of the dosage form can be used to differentiate between rapid and delayed absorption of the drug in the study of drug correlation *in-vitro* and *in-vivo*. The shorter it takes to absorb a specific amount of medicine, the faster it is absorbed. It has to do with how long it takes the same amount of medicine to be absorbed from the dose form [14, 71].

Percentage of Drug Dissolved Versus Drug Concentration in Serum: For medications whose absorption from the gastrointestinal tract is limited by the dissolution rate, a linear relationship can be constructed between the percentage of drug dissolved at particular periods and the serum drug concentrations at those times [14, 71].

Percentage of Dissolved Drug vs. Percentage of Excreted Dose in the Urine: The percentage of a drug absorbed is proportional to the fraction of a drug dissolved. The weight of the drug in the body and the weight of the drug excreted in the urine have a link. As a result, a liner relationship between the amount of dissolved drug and the amount of released dose in the urine can be established [14, 71].

Recent Advances in Testing of Micro-Particle:

Advances in Characterization of Physico-chemical Properties of Micro Particles:

Advancement in Particle size Morphological Characterization: Laser light scattering/confocal fluorescence microscopy, light microscopy [LM], scanning electron microscopy [SEM] and multi-size grating counter are among the many methods used to assess particle size and the morphology of the micro particles. The most extensively utilized procedures for obtaining detailed information on the surface morphology of micro particles are optical LM and SEM. By seeing micro particles before and after the coating process, LM can be used to evaluate the micro particle coating parameter. Both disadvantages of LM are low resolution and the need for a high sample size to acquire trustworthy results.

SEM provides elemental information when paired with energy-dispersive or wavelength-dispersive X-ray spectroscopy. SEM is primarily used to investigate the form and surface of micro particles and their cross sections to reveal their internal structure. The images obtained by SEM have a higher resolution and are three-dimensional than those obtained by LM. Because electrons are used to build topographic and 3-D pictures, SEM has a higher resolution. The SEM's greatest resolution (distance between two items that can be separated and observed as different objects) is 10–20 nm, but the LM's is 200–300 nm. If the material is not covered with a conductive substance, it will tend to charge in the electron beam, resulting in inaccurate scans and image abnormalities. As a result, SEM imaging sample must be covered with a very fine layer of an electrically conductive material like gold.

Micro particle sizes are often determined using light scattering methods. Simple sample preparation, no substantial experience required, quick measurement, and detailed results are all advantages of this procedure. However, massive particle interference, thick particle deposition, and multiple light scattering can all undermine the precision of the results. Because of the limits of individual procedures, it is sometimes necessary to employ a combination of techniques to determine particle size [36, 77].

Advancement in Entrapment Efficiency Characterization: Entrapment efficiency refers to the capture efficiency of the drug, or the ratio of drug entrapment in the micro particles. A known amount of micro particles is dissolved in a solvent (such as methanol and ethanol *etc*.) and free drug is released to determine drug content.

A suitable solvent is utilized to dissolve or lyse the micro particles, depending on the solubility of the matrix and the active component. After that, the drug content is evaluated using an analytical technique such as high-performance liquid chromatography or according to the pharmacopoeial monograph. The following formula is used to compute the entrapment efficiency.

Actual content / Theoretical content x 100 Equals percent entrapment[33, 35, 36, 63]

Advancement in Polymer Molecular Weight Characterization: The molecular weight of polymers influences the first release pattern and duration of a microparticle matrix. It is vital to remember that high shear processing (such as homogenization and ultrasonic mixing) as well as hydrolytic breakdown caused by a humid environment might influence polymer molecular weight [55].

Certain medications can potentially expedite polymer decomposition, resulting in quicker release. As a result, keeping an eye on the molecular weight is crucial. Size exclusion chromatography is commonly used to determine polymers' molecular weight (gel permeation chromatography) [64]. To ensure acceptable product performance (i.e., *in-vitro* release) throughout the shelf life, a standard for an appropriate polymer molecular weight range should be established. The most commonly used polymer for micro particles, PLGA, is susceptible to deterioration from ionizing radiation, dampness, and high temperatures [36, 41, 55].

Advancement in Floating Test Characterization: This test is done to see if micro particles have the ability to float and, as a result, prolong GI retention. As defined by United States Pharmacopeia (USP) Device II, micro particles are dispersed throughout the surface of the release medium and permit to float or settle for a specified period of time under continuous stirring. At the last of the test time, the settled and floating micro particles are recovered one by one. Drying and weighing of the micro-particles and the buoyancy of the micro- particles is then estimated using the following equation.

$$100 \times (Qf/(Qf + Qs)) = \text{buoyancy (percent)}$$

Qs and Qf are settled micro particle and the weight of the floating micro particles, respectively. The micro particles must float long enough for the drug to be completely released [30].

Advancement in Micro Particles:

Characterization in *In-vivo* Buoyancy Study: The *in-vivo* transit behavior of buoyant and non-buoyant micro particle was assessed using scintigraphy in a rabbit model to establish that they provide appropriate stomach retention [52, 82, 83, 84].

Advance in the Characterization of Micro Particles in the *In-vitro* Wash Assay: The mucoadhesive characteristics of the micro particles are evaluated using an *in-vitro* washout test. A piece of intestinal mucosa/mucous membrane is placed on a glass slide, a number of micro particles are spread on the tissue sample, and the slide is hung in a tablet disintegration machine. The disintegration machine is operated at low speed in an up and down motion using a suitable release medium (such as 0.1N HCl, pH 1.2 and phosphate buffer, pH 7.4). At various time periods, the number of micro particles still attached to the mucous membrane is counted [54, 82, 83, 84].

Advancement in Swelling Index Characterization: The swelling index is commonly used for mucoadhesive micro particles. Before water ingress is established, the micro particles are suspended in a particular solvent and allowed to expand fully. After complete equilibrium, excess water sticking to the micro particles is removed using a soft tissue before weighing the swollen micro particles. After that, the micro particles are allowed to dry completely until no weight change is visible. The percentage of water uptake can then be calculated using the formula below.

Weight of swollen micro particles - weight of dry micro particles / Weight of dry micro particles x 100 = percentage of water absorption [36]

Advancement in Drug–polymer Interaction Characterization: Interactions between the micro particle polymer and the encapsulated medication may result in poor delivery and possibly loss of therapeutic protein function. Fourier transform infrared [FT-IR] spectroscopy is frequently employed to discover any interactions between the medication and the polymer by comparing the

drug's IR spectra to the reference standard's spectra. Changes in frequency and peaks indicate the interaction between the drug and polymer. To measure polymer degradation, attenuated total reflectance FR-IR is employed to provide information on the surface composition of micro particles [54].

Advancement in Chemical Analysis Characterization: Electron spectroscopy is utilized to analyze any surface degradation to assess the atomic composition of micro particle surfaces. A brief description of this procedure is offered here because it is not commonly published. The photoelectric effect is used to emit electrons from the nucleus of the samples by means of an incident monochromatic X-ray beam. The top 10 nm of the micro particle surface's kinetic energy and the number of electrons released are measured. The kinetic energies of these released electrons are equal to the X-ray energy minus the electrons' binding energy and the work function of the device. Binding energies specific to the particular elements may be determined from the released electrons' kinetic energies, and the binding energies' intensity can be utilized to quantify the particular element. This approach, on the other hand, has difficulty detecting hydrogen and helium. The detection limit is in the tens of thousands of parts per million range [36].

Advancement in Protein Integrity Determination Characterization: During processing and *in-vitro* release testing, encapsulated proteins are exposed to stress, leading to stability concerns (such as alteration of structural integrity, aggregation, denaturation, and loss of activity). Processing and/or release testing at a pH corresponding to the protein's isoelectric point (pI) will cause considerable precipitation due to the molecule's low solubility. The determination of pI is done using a variety of electrophoretic techniques, including isoelectric focusing, gel electrophoresis, capillary electrophoresis, and pressure-mediated capillary electrophoresis. The pI value is used to ensure the structural integrity and stability of the encapsulated proteins. Polarization interferometry, nuclear magnetic resonance spectroscopy, X-ray crystallography can be used to identify protein structure and ensure its integrity [28, 72, 86, 101].

Advancement in Density/Porosity Determination Characterization: The density of the powder is used to determine flow and porosity. The multivolume pycnometer is the most extensively used equipment for determining microparticle density. Another approach for determining the porosity of micro particles is porosimetry, specifically mercury porosimetry [6].

Advancement in Contact angle Characterization: Based on their wetting qualities, the contact angle is used to describe the hydrophilicity/ hydrophobicity of micro particles [6].

Advancement in Flow Properties Characterization: Because micro particles are powder dosage forms, determining flow parameters and avoiding segregation/dosage non-uniformity is crucial. Understanding the flow characteristics while packing and administering the completed drug is also important.

Measurement of flow characteristics is part of comparison testing and quality control. Tested flow parameters for micro particle products are tapped density, compressibility index, angle of response and true density. For example, the angle of repose of magnetic Micro particles has been investigated.

Flow properties are influenced by particle size and distribution, particle shape, chemical composition, moisture content, humidity, and temperature [17, 45].

Advances in *In-vitro* Drug Release Testing: USP standard dissolution apparatus such as Apparatus IV [flow-Through cell] and Apparatus II [rotating paddle] (flow-through cell) were used for the *in-vitro* micro particle release test [5, 90].

Non-compendial techniques have also been used, such as simple and sort, dialysis bag and reverse dialysis bag. However, there are currently no standard *in-vitro* release test procedures for micro particles. Various criteria (such as drug and polymer characteristics, micro particle properties, apparatus geometry and hydrodynamics, receiving media, and sink conditions) must be evaluated to develop the best *in-vitro* release test procedures with a strong discriminatory capacity. The USP IV apparatus is currently the\ method of choice for micro particles.

Other processes may be used, although regulatory authorities will normally require an explanation if the USP IV set is not used. *In-vitro* release testing quality control procedures should be selective, reproducible and sensitive [14, 19, 51, 102, 108].

USP Apparatus II (Paddle Type): Micro particle release *in-vitro* was studied using the USP apparatus II with and without dialysis sacs. When apparatus II is used without dialysis sacs, micro particles float on the surface of the release fluid, impeding medication release in some situations. When apparatus II was utilized alone rather than in conjunction with the dialysis sacs, the overall cumulative percentage release was found to be lower. Furthermore, USP Apparatus II mandates that the media be sampled and the micro particles be removed from the media for analysis, posing the risk of sample loss and mistake. In comparison to USP apparatus IV, the USP apparatus II takes longer and requires more people [106].

Sample and Separate Methods: Micro particle release investigations for research objectives frequently employ non-compendial sample and separate procedures. Micro particles are suspended in the release medium at a specific temperature (usually 37°C) and agitated continuously. Release samples are collected and centrifuged to separate the medium from the settled micro particles (if any). After each sample collection, an equivalent amount of fresh medium is supplied to the release medium container to keep the overall volume constant throughout the test. After certain periods of time, a complete replacement of the medium may be required to prevent drug degradation and/or maintain sink conditions. In sample and separate procedures, characteristics such as sample vial/vessel size, agitation speed, and sampling methods can be changed. Because of many limitations such as product aggregation and sample loss during the separation processes, sample and separate is not reliable, which might result in erroneous release profiles. Other drawbacks include centrifugal force disrupting the formulation and the use of vials/tubes/bottles of varying size, making inter-laboratory comparisons problematic [15, 57, 106].

Dialysis Sac Technique: The dialysis bag technique uses correct dialysis membranes with appropriate molecular weight cutoffs for the specific drug, passing the drug to flow with the help of the membrane into the release fluid, avoiding any interaction between the drug and the membrane [27]. The bag/dialysis bag is closed at both ends after introducing the micro particles (suspended in the release medium). The sack/dialysis bag is suspended in the appropriate release medium in the test container under constant agitation (accomplished using a shaker bath or paddle apparatus). To aid in drug dispersion, the volume of delivery medium in the bag is kept 5-10 times less than that in the test container.

Test criteria to be evaluated include the rate of agitation, the volume of donor and acceptor cells, and the molecular weight of the dialysis membrane. The dialysis method has several advantages, including the ease with which samples can be extracted and the separation of micro particles. The dialysis bag method was successfully used with a peptide-loaded biodegradable micro particle system to obtain good correlation between *in-vivo*. *In-vitro* data, and *in-vitro* data was used to determine micro particle performance *in-vivo* [52]. The dialysis method has several disadvantages, including:

1. Obtaining enough agitation to obviate micro particle aggregation within the dialysis bags is problematic.
2. Insufficient agitation may cause a delay in reaching the equilibrium concentration of the drug.
3. Its use is restricted to drugs that do not bind to dialysis membranes.
4. Within the dialysis bag, there was a violation of the sink conditions.

Sink conditions can be breached due to the little volume of release media inside the dialysis sacs and the dialysis sac membranes' small surface area. To address the issue of sink conditions being breached, the reverse dialysis process was developed. The released drug diffuses slowly into the dialysis sacs thanks to micro particles in this treatment's external release medium phase [19].

USP Apparatus IV Method: The USP Pharmacologic IV Apparatus is now the preferred method for *in-vitro* micro particle release testing. It

can be done in both open and closed configurations, with different flow rates and temperatures, and with different types of flow-through cells [15]. Using a modified flow-through cell technique, micro particle drug release was investigated. The microparticles and glass beads are mixed in a modified flow-through method. The glass beads are employed to:

- Avoid micro particle aggregation and, as a result, a change in the cumulative percentage release due to changing surface area.
- Reduce dead volume within the cells.
- Improve laminar flow. To avoid backpressure, a proper ratio of glass beads to micro particles and appropriate filter types (used to filter the medium exiting the flow-through cells) must be utilized [36].

The USP IV set simulates the injection site, and the constantly circulating medium around the micro particles mimics the dynamic environment *in-vivo*, due to the limited volume of medium in flow-through cells (similar to subcutaneous tissues). Furthermore, compared to classical *in-vitro* release protocols such as sample, strip and USP, Apparatus II: No aggregation; data has the most cumulative release and the least volatility; sink conditions are easy to maintain. Multiple media types (with varying pH and ionic strength) can be used; the flow rate can be controlled to control drug diffusion from the microparticles, and the medium can be easily changed with another medium type throughout the test if necessary. The USP IV device has several advantages over other methods when used with fiber optic UV probes.

The probes are withdrawn from the flow through cells and placed in medium reservoirs, reducing inaccuracy caused by suspended micro particles and air bubbles (due to agitation) interfering with the fiber-optic probes. Introducing fiber optic probes enables continuous monitoring of the first burst release of medication by the micro particles (where the release rate can be rapid) [104,111].

The USP apparatus IV may effectively analyze both protein-loaded and small-molecule-loaded micro particles. The USP IV set was compared with a different sample and technique for the *in-vitro* release test of protein-containing micro particles (bovine serum albumin). While protein adsorption on the hydrophobic surfaces of USP apparatus IV can cause an unexpected decrease in overall cumulative percent protein release, this can be avoided by using a suitable surfactant such as sodium dodecyl sulphate (SDS) [104, 111].

The USP apparatus IV comprises several important pieces, such as O-rings, filters, and valves, all of which must be in good working order for the apparatus to function properly. O-rings and filters may fail if apparatus IV is run for an extended period of time (weeks to months). Furthermore, tiny particle fragments and polymer and polymer degradation products can clog filters, causing backpressure issues. Modifications to the procedure, such as a change in the solvent and changes to the necessary portions, may be able to remedy these issues.

The modified USP apparatus IV method is regarded as an excellent compendia dissolution method for micro particles due to its advantages [104, 111].

***In-vivo* Testing Methods:** Using various animal models, *in-vivo* drug release testing is carried out to examine tissue distribution and pharmacokinetics of medicines released from micro particles. *In-vivo* investigations are also carried out to assess drug and product stability. The following factors should be considered while designing *in-vivo* release tests:

- ✓ Choosing an appropriate animal model that takes into account the animal's lifespan, especially when testing formulations with a long duration of action.
- ✓ Antibodies could be produced while employing human-derived protein therapies due to immunogenicity, which could influence medication pharmacokinetics and pharmacodynamics of proteins [30, 39].

An appropriate animal model can be chosen following literature research and a comparison of the injection site in animals and humans to evaluate any inter-species variances. For micro particle performance testing, animal models such as rats and rabbits have been routinely used [11].

Blood or urine samples are collected over a period of time after micro particles are delivered. Different extraction processes (such as liquid-liquid and protein precipitation) extract drugs from the biological matrix. To assess the extracted chemicals, researchers use a variety of techniques, including liquid chromatography-mass spectrometry, ultra-performance liquid chromatography-tandem mass spectrometry and liquid chromatography-tandem mass spectroscopy. *In-vivo* drug release from micro particles is influenced by two types of variables: factors that are dependent on the delivery system and factors that are not dependent on the delivery system (such as increased drug release as result of enzymatic deterioration of the polymers and phagocytosis; such as reduced drug release as a result of protein adsorption) characteristics and considerations unrelated to a delivery system (such as food, fluid viscosity, and connective tissue that limit drug diffusion, drug absorption into fatty tissues that affect drug partitioning, as well as fluid volume and muscle movement at the injection site that affect the volume available for drug dissolution and systemic absorption). In addition, fasting and fed conditions alter drug release and bioavailability after oral administration of micro particles. Micro particles spend more time in the stomach when they feed, delaying the amount of drug accessible at the site of action [89].

Recent Advancement of Chitosan Polymer:

Effects on Cholesterol Levels: Chitosan and cellulose were chosen as examples of fibers with high, intermediate and low bile acid binding capabilities. Liquid cholesterol levels nearly doubled to 4.3mm in a control group of mice fed a high fat/high cholesterol diet for three weeks, but the inclusion of either of these fibers in 7.5 percent of the diet prevented this increase. Furthermore, when these fibers were provided, the HFHC diet lowered the quantity of cholesterol deposited in liver storage. Although all three fiber types were hypocholesterolemia, cholestyramine induced the greatest cholesterol loss in liver tissue. Reduced cholesterol intake (food) decreases cholesterol absorption efficiency and increased fecal excretion of bile acids and cholesterol where the processes behind cholestyramine's strong bile acid binding ability are responsible for the latter effects. On the other hand, cellulose or chitosan lowered cholesterol absorption or fecal sterol production [23, 110].

Increase Stability of Drug: Combining a drug with chitosan, generating a suspension and then kneading it for 45 minutes until dough develops the stability of the medicine. This dough mass is screened 16 times to produce granules that are entirely stable in all situations [110].

Patients with Orthopedic Problems: Chitosan is a biopolymer with healing and antimicrobial properties, making it an excellent material for bioactive coatings for orthopedic. It has been proven to promote wound healing, bone regeneration and tissue growth [49].

Cosmetic Industry: The unique quaternary chitosan derivatives in the formula distinguishes cosmetic formulations for hair or skin treatment. Chitosan derivatives have a high molecular weight and have been demonstrated to strengthen and condition hair compared to keratin [49, 103].

As a Dental Drug: Chitosan has been demonstrated to hasten wound recovery and protect against the formation of excessive scars, resulting in a more attractive skin surface. Chitosan is also used as a dressing for oral mucosal lesions and as a buffer following intensive maxillary sinusitis therapy.

It is also being investigated as an absorbent membrane for periodontal surgery. Chitosan has a broad range of biological activities. It is advertised as a health food that can help treat a broad range of ailments, including diabetes, hepatitis, arthritis, cancer and more [103].

Chitosan as Permeation Enhancer: Chitosan has been proven to unclose inflexible junctions in cell membranes due to its cationic characteristics. This feature has prompted interest in using chitosan as a penetration enhancer for hydrophilic medicines like peptides with poor oral bioavailability.

Because interactions between the positive charges and the cell membrane produce absorption amplification, the phenomena is concentration and pH dependent. Increased permeability would be obtained by raising the polymer's charge density [103, 110].

As a Mucoadhesive Excipient, Chitosan: By increasing the duration, a medicine spends in the intestinal tract, bio adhesiveness is commonly utilized to boost oral bioavailability. When chitosan is compared to other commonly used polymeric excipients including cellulose, Xanthan gum, and starch, the cationic polymer outperforms the natural polymers in terms of bio adhesion [110].

TABLE 1: LIST OF MARKETED MICROSPHERES DRUG PRODUCTS

S. no.	Drug	Commercial name	Company name	Therapeutic use	Method of preparation	Reference
1.	Naltrexone	vivitrol	alekem	Opioidantagonist *via* IM route	Double emulsion (oil in water)	Akala, *et al*., 2011.[3] Bala M, *et al*., 2020.[10]
2.	Octreotide	Sandostatin LAR	Novartis	Treat acromegaly *via* Im route	Phase separation	Rhee Y S, *et al*., 2011.[85]
3.	Risperidone	RISPERDAL CONSTA	Janssen®/ Alkermes, Inc	Treat schizophrenia *via* IM route	Double emulsion (oil in water)	Souza SD. *et al*., 2014.[94]
4.	Leuprolide	Lupron Depot®	Abbott Healthcare	Prostate cancer/ Endometriosis *via* i.m.	Methods are double emulsion-solvent evaporation and self-healing microencapsulation	Hirota K, *et al*., 2016.[31]
5.	Triptorelin	Trelstar™ depot	Pfizer	Prostate cancer via i.m.	Phase separation	Shi Y, *et al*., 2005.[91]
6.	Somatropin	Nutropin® Depota	Genentech/Alk Ermes	Growth Deficiencies *via* s.c.	Cryogenic spray drying or double-emulsion solvent evaporation techniques	Jostel A, *et al*., 2006.[40]
7.	Bromocriptine	Parlodel LAR™	Novartis	Parkinsonism *via* s.c. or i.m.	Spray drying	Clarke N, *et al*., 1998.[22]
8.	Buserelin	Micro particles Suprecur® MP (inj.)	Sanofi		Vibration method	Usamia M, *et al*., 2007.[100]
9.	Lanreotide	Somatuline® LA	Ipsen-Beafour	Acromegaly *via* I.M route	Self-assemblymethod/ phase separation method	Wolin EM, *et al*., 2016.[107]
10.	Minocycline	Micro particles Minocin MR MinozOD 100	Pfizer Ranbaxy laboratories Ltd.	Periodontal disease *via* oral route	Ionic gelation method	Calasans-Maia MD, *et al*., 2019.[16]
11.	Metformin HCl	Micro particles	Generic formulation	Anti-diabeticvia oral route	emulsion-solvent evaporation method	Choudhary PK, *et al*., 2008.[20]
12.	Amoxicillin trihydrate	Micro particles	Generic formulation	Antibiotic *via* oral route	solvent evaporation method	Singh SK, *et al*., 2010.[92]
13.	Ibuprofen	Beads	Generic formulation	Analgesic via oral route	Ionotropic gelation method	Khazaeli P, *et al*., 2008.[50]
14.	Pioglitazone HCl	Mucoadhesive micro particles Floating micro particles	Generic formulation	Anti-diabetic *via* oral route	ionotropic external gelation method.	Sriram N, *et al*., 2016.[95]
15.	Trimetazidine Hcl	Micro particles	Generic formulation	Anti-anginal *via* oral route	Ionic cross-linking technique	Pavan veena C, *et al*., 2010.[75]
16.	Furosemide	Micro particles	Generic formulation	Diuretic *via* oral route	ionic cross-linking technique, W/O emulsion system, Spherical crystallization technique.	Dsa M K, *et al*., 2008.[23] Akbuja J, *et al*., 1994.[4]
17.	Insulin	Micro particles	Generic formulation	Anti-diabetic *via* s.c route.	Emulsification method and drug	Kumar T, *et al*., 2005.[56]

					loaded by diffusion filling method	
18.	Aceclofenac	Micro particles	Generic formulation	Analgesic *via* oral and parenteral route.	Solvent evaporation technique.	RadhikA P R, *et al*., 2008.[81]
19.	Acyclovir	Mucoadhesive Micro particles Micro particles for ophthalmic administration	Generic formulation	Antiviral via oral and ocular route	emulsification phase separation technique multiple emulsion technique	Md S, *et al*., 2011.[60] Genta, *et al*., 1997.[27]
20.	Ranitidine Hcl	Micro particles Aciloc injection Aciloc Tablets	Generic formulation Cadila Pharmaceuticals Ltd.	Antacid *via* oral ,i.v and i.m route	cross-linking emulsification method, Spray drying method.	Sahu V K, *et al*., 2017.[87]
21.	Glipizide	Micro particles Bimode SR DimicronMR Minidiab OD	Emcure Pharmaceuticals Ltd.Serdia Pharmaceuticals Pvt.Pfizer	Oral Hypoglycemic *via* oral route	simple emulsification phase separation technique	Patel J K, *et al*., 2005.[73]
22.	Captopril	Micro particles Bio adhesivesystem, semi solid matrix system, Coatedtablet, Beadlets, Hydrophobic tablets.	Generic formulation	ACE Inhibitor *via* oral route	Ionic gelation method, Solvent evaporation technique.	Sahu S, *et al*., 2012.[87] Khamanga SM, *et al*., 2012.[48] Nur A O *et al*., 1999.[68]
23.	Ketoprofen	Micro particles Oruvail SR Ketofan SR	Generic formulation Sanofi Amriya Pharma	Analgesic *via* i.m, i.v and orally	Solvent evaporation method, Spray drying method	Abdallah MH, *et al*., 2012.[2] Palmieri GF, *et al*., 2002.[70]
24.	Salbutamol sulphate	Micro particles Asthalin SA-8	Generic formulation Cipla Ltd.	Bronchodilator via i.v and oral route	Solvent evaporation method, coacervation phase separation method	Prasanth VV, et al.,2011.[78] Jayan SC, *et al*., 2009.[37]
25.	Torsemide	Micro particles	Generic formulation	Diuretic *via* oral and i.v route	ion gelation method	Mishra B, *et al*., 2010.[62]
26.	Montelukast sodium	Micro particles Mucoadhesive tablets	Generic formulation	Antiallergic *via* oral route	Spray drying method Direct compression method	Panchal R, et al.,2012.[71] Bithi F A, *et al*., 2017.[12]
27.	Famotidine	Micro particles	Generic formulation	Antiulcer *via* i.m, i.v and oral route	w/o emulsification solvent evaporation method	Arya RKK, *et al*., 2010.[8]
28.	Metronidazole	Micro particles Flagyl	Generic formulation Nicholas Piramal India Ltd.	Antiamoebic*via* oral and i.v route	ionic gelation method	Cirri M, *et al*., 2021.[21]

Micro particle Applications:

Delivery of Vaccines with Micro Particles: A vaccination must defend against the bacteria or it's harmful product. These features should be included in an ideal vaccine: safety, ease to use, efficacy, and affordability. It's challenging to strike a balance between safety and minimizing unpleasant reactions. The degree to which the antibody response is formed and the query of safety are intimately tied to the application strategy. Traditional vaccines have flawed that biodegradable vaccine delivery systems for parenteral immunizations can remedy [42].

Gene Delivery using Micro Particles: Viral vectors, non-ionic liposomes, polycationic complexes and microcapsules are used to deliver genetic drugs. Virus vectors are ideal for genotype delivery because they are very efficient and can target a broad range of cells. However, when administered *in-vivo*, they cause immunological reactions and have deleterious consequences. Non-viral delivery techniques for gene therapy have been studied to overcome the limitations of viral vectors. Non-viral delivery approaches provide a number of merits, including ease of preparation, cell/tissue targeting, decreased immune response, unrestricted plasmid size, and repeatable large-scale output. The polymer will be used in gene delivery applications as a DNA carrier [1, 38, 46, 47].

Using Microparticle Carriers to Target: Pharmaceutical site-specific distribution, also known as targeted medication delivery, is a well-known concept getting much traction. A drug's therapeutic efficacy is determined by its capability to reach and engage target receptors. Drug activity mediated by the utilization of a transporter system is linked to the ability to efficiently, consistently, and specifically exit group [65].

Monoclonal Antibodies Facilitated Micro Particles Targeting: Monoclonal antibodies that attack micro particles are known as immune micro particles. This approach is used to target specific websites precisely. Monoclonal antibodies are molecules with an extremely limited range of applicability. Micro particles containing bioactive substances can be targeted to specific sites using monoclonal antibodies (Mabs) with high specificity. Mabs can directly bind to micro particles thanks to covalent coupling. The antibodies can bind to amino, free aldehyde or hydroxyl groups on the shell of the micro particles. Attaching maps to micro particles can be done in a number of ways;

- Adsorption, both nonspecific and selective.
- Direct coupling.
- Reagent coupling [65].

Chemotherapy with Micro Particles: Micro particles as carriers of anticancer medicines are one of the most promising applications. Microparticles were required due to increased leaky vasculature and endocytic activity. Covering the soluble polyoxymethylene micro particles creates invisible, microparticles. Non-stealth Microparticles that accumulate in the RES [Reticulo Endothelial System] could also be used to treat cancer [53, 105].

Imaging: Micro particles have been thoroughly researched and used in a variety of applications. Radioactively labeled micro particles can be used to imaging tissues, organs, cell lines and various cells.

When imaging specific regions, the particle size range of micro particles becomes a serious concern. Particles inserted into a vein other than the portal vein become stuck in the lungs' capillary bed. Using tagged human serum albumin micro particles, this phenomenon is employed to get scintigraphy images of lung tumor masses [24].

Micro Particles with Porous Surfaces that can be Applied to the Skin: Micro sponges are Micro porous particles with several interconnected voids that range in size from 5 to 300 microns. These porous Microparticles with active compounds can be used in creams, lotions, and powders and can trap different types of active components such as fragrances, essential oil sand emollients. Micro sponges are non-foldable structures with a porous surface that slowly release active chemicals [24].

Nasal Medication Administration: Intranasal (IN) administration provides a number of practical and theoretical merits for the systemic and local delivery of a variety of therapeutic substances. Intranasal delivery is painless, doesn't require needles, and doesn't necessitate sterile preparation. It's also self-contained. Many microvilli, a penetrable endothelium membrane, and a highly vascularized epithelium in the nasal mucosa contribute to the beginning of therapeutic impact.It covers a wide range of drug administration methods, equipment, formulations, and nose and nasal cavity procedures. Depending on the therapeutic goal, intranasal drugs can be used for local or systemic treatment. It is critical to couple the bio adhesive properties to the micro particles due to the additional benefits of efficient drug absorption and increased bioavailability, much closer contact with the mucosal layer and a reduction in the frequency of drug administration

due to reduced mucociliary clearance of adhering drug delivery systems to the nasal mucosa by administering medication through the nose [24].

Controlled Gastro Protective Delivery System: Buoyant systems are low-density systems that float on gastric contents and remain in the stomach for longer periods of time than usual dosage forms. The ability to adjust the emptying time of dosage forms is a great advantage for dosage forms since stomach emptying is such a fickle process. On the other hand, building controlled release systems to improve absorption and bioavailability presents several obstacles.

The medicine is administered slowly and at the correct rate since the system floats above the gastric contents, resulting in less variation in plasma drug concentration and longer gastronomy retention time. Polymers such as polyvinyl acetate, Eudragit, Methocil, agar, polycarbonates, cellulose acetate, chitosan and other polymers are utilized in gastroprotective controlled release systems [24].

Implantable Gadgets: In the medical field, microencapsulation has been used to encapsulate live cells. Encapsulating artificial cells and macromolecules including hormones, peptides and proteins improves biocompatibility, preventing undesired immunological reactions that could result in rejection or inactivation. The micro particles are used to keep the components separate until they are required to function. Micro particles are employed in the biotechnology industry to help separate organisms and their recombinant products [24].

Oral Medication Administration: Rabbits were used to investigate the possibility of a polymer matrix carrying diazepam as an oral medication delivery mechanism. He discovered that a film constructed from a 1:0.5 ratio of medication and polymer could have been a viable alternative to typical tablet formulations. Polymers' capacity to form films could lead to the creation of film dosage forms as a replacement for medicinal pills. When paired with the amine group's two major processes, the pH sensitivity of the polymer begins to distinguish it as a one-of-a-kind polymer for oral drug administration applications [24].

Ocular Delivery Micro Particles: Glaucoma is treated with the majority of drug-loaded ocular delivery devices, especially cholinergic agonists such as pilocarpine. Micro particles with biodegradable properties from a very short period [1 to 3 minutes] can extend the low elimination half-life of aqueous eye drops to a larger length [15-20 minutes]. For instance, poly alkyl cyanoacrylate [74, 76].

Applications for Pharmaceuticals: Microencapsulated pharmaceuticals in the market include progesterone, theophylline, aspirin and derivatives, antihypertensives, pancrelipase, and potassium chloride. Microencapsulated Potassium Chloride is used to protect against intestinal problems that may be caused by potassium chloride. The microcapsules' dispersibility and the ions' regulated release reduce the risk of excessive localized salt concentrations, which can lead to perforation, ulceration and bleeding. Injectable and inhalation treatments containing micro particles have also been proposed.

The amount of research done in this subject or the benefits that can be realized with this technology are not reflected in the number of commercially accessible items. Cost factors have influenced the quantity of medicinal microencapsulated goods. Most encapsulation procedures are costly and require a substantial money investment in appliance. spray or drum coating and spray drying are exceptions, as the requisite appliance may already be on hand within the company. Most microencapsulation techniques are patent protected, which adds to the cost [1].

CONCLUSION: The study summarizes key physicochemical aspects of microspheres, such as drug content, particle size and thermal characteristics, as well as advances in characterization approaches. Micro particles *in-vitro* release testing is a significant physicochemical attribute. Micro particles are tested using a variety of compendial and non-compendial *in-vitro* release-testing procedures, including USP equipment IV, dialysis membrane sacs. Based on a comparison of the respective benefits and drawbacks of various methods, modified USP apparatus IV appears to be the method of choice. Quality control measures such as high temperature have been used to design accelerated *in-vitro* release tests. These accelerated

release-testing techniques must be highly correlated with *in-vitro* real-time release-testing procedures. To reduce the necessity for *in-vivo* performance evaluation, IVIVCS based on real-time and accelerated release data can be produced.

Storage stability studies are required to investigate the impact of a wide range of environmental conditions on microsphere quality over the product's life span. Various novel assays have been created, including the *in-vitro* wash-off test and the floating test and improvements in physicochemical feature characterization approaches. The micro particles drug delivery system is the most preferred medication administration system due to its benefits of controlled and sustained release action, better stability, lower frequency of administration, dissolving rate and bioavailability. The micro particles are spherical microspheres that deliver the medicine to the target location with pinpoint accuracy if customized and maintain the optimum concentration at the place of interest without side effects. The medicine is contained within a unique polymeric membrane in the center of the micro particles. Micro particles will play a very important and central role in novel drug delivery in the upcoming years, particularly in diseased cell sorting, diagnostic tests, targeted, secure, specific & effective *in-vitro* delivery & supplements as smaller versions of damaged tissue & organs in the body, by combining different other techniques.

ACKNOWLEDGEMENTS: Authors are highly thankful to the Principal and Management of R.V. Northland Institute for providing library as well as computer lab facilities.

CONFLICTS OF INTEREST: There is no conflict of interest among the authors, and the project work is not funded from any sources.

REFERENCES:

1. Abbaraju KS and Begum N: Biomedical applications of microspheres. J Modern Drug Discov Drug Deliv Res 2015; 4(2): 1-5.
2. Abdallah MH and Sammour OA: "Development and characterization of controlled release ketoprofen micro particles." Journal of Applied Pharmaceutical Science 2012; 2(3): 60-67.
3. Akala EO and Wiriyacoonkasem P: "Studies on *in-vitro* availability, degradation, and thermal properties of naltrexone-loaded biodegradable micro particles." Drug Development and Industrial Pharmacy 2011; 37(6): 673-684. https://doi.org/10.3109/03639045.2010.535540
4. Akbuja J and Durmaz G: "Preparation and evaluation of cross-linked chitosan micro particles containing furosemide." International Journal of Pharmaceutics 1994; 111(3): 217-222. https://doi.org/10.1016/0378-5173(94)90344-1
5. Aklonis JJ and MacKnight WJ: Transitions and relaxations in amorphous polymers. In: Aklonis JJ, MacKnight WJ, editors. Introduction to polymer vis- coelasticity. 2nd ed. New York: Wiley-Interscience 1983.
6. Alagusundaram M, Madhu Sudana Chetty C and Umashankari K: Microspheres as a novel drug delivery system – a review. Int J Chem Tech Res 2009; 1: 526–534.
7. Alagusundaram M: Microspheres as a Novel Drug Delivery Sysytem - A Review, International Journal of Chem Tech Research 2009; 1(3): 526-534.
8. Arya RKK and Singh R: "Mucoadhesive micro particles of famotidine: preparation characterization and *in-vitro* evaluation." International Journal of Engineering Science and Technology 2010; 2(6): 1575-1580.
9. B. Sree Giri Prasad: Microspheres as Drug Delivery System – A Review. J Glob Trends Pharm Sci 2014; 5(3): 1961–1972.
10. Bala M and A. Moudgil: "An Update on Biodegradable Micro particles Loaded with Naltrexone." Int J Pharma Res Health Sci 2020; 8(2): 3143-46.
11. Barkai A, Pathak V and Benita S: Polyacrylate (Eudrugit retard) microspheres for oral controlled release of nifedipine. I. Formulation design and process optimization. Drug Dev Ind Pharm 1990; 16: 2057-2075.
12. Bithi FA and Saha T: Preparation and *in-vitro* evaluation of mucoadhesive tablets of montelukast sodium." Bangladesh Pharmaceutical Journal 2017; 20(2): 123-131.
13. Bodmeier R and Chen H: Preparation and characterization of microspheres containing the anti-inflammatory agents, Indomethacin, ibuprofen and kitoprofen. J. Controlled Release 1989; 10: 167175. https://doi.org/10.1016/0168-3659(89)90059-X
14. Brahmankar DM and Jaiswal Sunil B: Biopharmaceutics and Pharmackinetics- A Treatise. Vallabh Prakashan, Delhi 2005; 315-336.
15. Burgess DJ, Crommelin DJA and Hussain AJ: EUFEPS workshop report, assuring quality and performance of sustained and controlled release parenterals. Eur J Pharm Sci 2004; 21: 679–690.
16. Calasans-Maia MND and Junior CABB: "Micro particles of alginate encapsulated minocycline-loaded nanocrystalline carbonated hydroxyapatite: Therapeutic potential and effects on bone regeneration." International Journal of Nanomedicine 2019; 14: 4559. 10.2147/IJN.S201631
17. Chandna A, Batra D and Kakar S: A review on target drug delivery: magnetic microspheres. J Acute Dis 2013; 2: 189–195. doi:10.1016/S2221-6189(13)60125-0.
18. Chaudhari A, Jadhav RK and Kadam JV: An overview: Microspheres as a nasal drug delivery system. Int J Pharm Sci Rev Res 2010; 5(1).
19. Chidambaram N and Burgess DJ: A novel *in-vitro* release method for submicron sized dispersed systems. AAPS Pharm Sci Tech 1999; 1: 11.
20. Choudhury PK and Kar M: "Controlled release metformin hydrochloride micro particles of ethyl cellulose prepared by different methods and study on the polymer affected parameters." Journal of Microencapsulation 2009; 26(1): 46-53.
21. Cirri M and Maestrelli F: "Development and microbiological evaluation of chitosan and chitosan-alginate micro particles for vaginal administration of

metronidazole." International Journal of Pharmaceutics; 2021; 598: 1-11.
22. Clarke N and O'Connor K: Influence of Formulation Variables on the Morphology of Biodegradable Micropartieles Prepared by Spray Drying." Drug Development and Industrial Pharmacy 1998; 24(2): 169-174. https://doi.org/10.3109/03639049809085602
23. Das MK and Senapati PC: Evaluation of furosemide-loaded alginate microspheres prepared by ionotropic external gelation technique. Acta Pol Pharm 2007; 64(3): 253-62.
24. Das, Manoj Kumar, Abdul Baquee Ahmed and Dipankar Saha: "Microsphere a drug delivery system: A review." Int J Curr Pharma Res 2019; 11(4): 34-41.
25. Desai S and Bolton S: A floating controlled release drug delivery system: *in-vitro-in-vivo* evaluation. Pharma. Res., 1993; 10: 1321-1325. https://doi.org/10.1023/A:1018921830385
26. Dutta P, Sruti J, Patra CN and Rao M: Floating microspheres: Recent trends in the development of gastro rententive floating drug delivery system. Int J Pharm Sci Nanotech 2011; 4(1): 1296-06. https://doi.org/10.37285/ijpsn.2011.4.1.2
27. Genta I and Conti: B. Bioadhesive Micro particles for ophthalmic administration of acyclovir." Journal of Pharmacy and Pharmacology 1997; "49(8): 737-742.https://doi.org/10.1111/j.2042-7158.1997.tb06103.x
28. Glukhovskiy PV and Vigh G: A simple method for the determination of isoelectric points of ampholytes with closely spaced pKa values using pressure-mediated capillary electrophoresis. Electrophoresis 1998; 19: 3166–3170. doi:10.1002/elps.1150191819.
29. Hafeli V: Radioactive microsphere for medical application. Adv Chem Phys 2002; 7: 213-248.
30. Hickey T, Kreutzer D and Burgess DJ: *In-vivo* evaluation of a dexamethasone/PLGA microsphere system designed to suppress the inflammatory tissue response to implantable medical devices. J Biomed Mater Res 2002; 61: 180– 187. doi:10.1002/jbm.10016.
31. Hirota K and Doty AC: "Characterizing release mechanisms of leuprolide acetate-loaded PLGA micro particles for IVIVC development I: *in-vitro* evaluation." Journal of Controlled Release 2016; 244: 302-313.
32. Iannaccelli V, Coppi G, Bernabei MT and Cameroni R: Air compartment multiple unit system for prolonged gastric residence: part1. Formulation study. International Journal of Pharmacy 1998; 174: 47-54.
33. Jain NK: Controlled and Novel drug delivery: 04 Edition: 21: 236-237.
34. Jain SK, Agrawal GP and Jain NK: A novel calcium silicate based microspheres of repaglinide: *in-vivo* investigations. J Control Release 2006; 113: 111–116. doi:10.1016/j. jconrel.2006.04.005.
35. Jain SK, Agrawal GP and Jain NK: Evaluation of porous carrier- based floating orlistat microspheres for gastric delivery. AAPS Pharm Sci Tech. 2006; 7: E54–E62. doi:10.1208/ pt070490.
36. Janki V. Andhariya & Diane J. Burgess: "Recent advances in testing of micro particle drug delivery systems". Expert Opinion on Drug Delivery 2016; 13(4): 1-16. https://doi.org/10.1517/17425247.2016.1134484
37. Jayan SC and Sandeep A: "Design and in-vitro evaluation of gelatin micro particles of salbutamol sulphate. Hygeia1 2009; (1): 17-20.
38. Jayaprakash S, Halith SM, Mohamed Firthouse PU and Kulaturanpillai K: Preparation and evaluation of biodegradable microspheres of methotrexate. Asian J Pharm 2009; 3: 26-46.
39. Joseph N, Lakshmi S and Jayakrishnan A: A floating- type oral dosage form for piroxicam based on hollow polycarbonate microspheres: *in-vitro* and *in-vivo* evaluation in rabbits. J Control Release 2002; 79: 71–79.
40. Jostel A and Shalet SM: Prospects for the development of long-acting formulations of human somatropin." Treatments in Endocrinology 2006; 5(3): 139-145.https://doi.org/10.2165/00024677-200605030-00002
41. Kadajji GV, Betageri GV and Venkatesan N: Approaches for dissolution testing of novel drug delivery systems. Am Pharm Rev 2011; 14(6): 38–44.
42. Kawashia Y, Niwa T, Takeuchi H, Hino T, Itoh Y and Furuyamas: Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. J Pharma Sci 1991; 81: 472–478. https://doi.org/10.1002/jps.2600800515
43. Kawashima Y, Niwa T and Takeuchi H: Preparation of multiple unit hollow microspheres (microballoons) with acrylic resin containing tranilast and their drug release characteristics (*in-vitro*) and floating behavior (*in-vivo*). J Control Release 1991; 16: 279–289. doi:10.1016/0168 3659(91)90004-W.
44. Kawashima Y, Niwa T, Takeuchi H, T. Hino and Y. Ito: Preparation of multiple unit hollow microspheres (microbal loons) with acrylic resin containing tranilast and their drug release characteristics (*in-vitro*) and floating behavior (*in-vivo*). J. Control. Release 1991; 16: 279-290.
45. Kawatra M, Jain U and Ramana J: Recent advances in floating microspheres as gastro-retentive drug delivery system: a review. Int J Recent Adv Pharm Res 2012; 2: 5–23.
46. Kazi M and Zakir Hossain: Development of microspheres for biomedical applications: a review, Prog Biomater, 2014; 1-19. https://doi.org/10.1007/s40204-014-0033-8
47. Kedzierewicz F, Thouvenot P and Lemut J: Evaluation of peroral silicone dosage forms in humans by gammascintigraphy. J Control Release 1999; 58: 195–205.
48. Khamanga SM and Walker RB: "*In-vitro* dissolution kinetics of captopril from micro particles manufactured by solvent evaporation." Dissolution Technologies 2021; 19(1): 42-52.
49. Khandai M, Chakraborty S, Sharma A, Pattnaik S, Patra ChN and Dinda SC: Preparation and evaluation of algino-sericin mucoadhesive microspheres: An approach for sustained drug delivery. J Adv Pharm Res 2010; 1: 48-60.
50. Khazaeli P and Pardakhti A: "Formulation of ibuprofen beads by ionotropic gelation." Iranian Journal of Pharmaceutical Research 2008; 7(3): 163-170.
51. Kokkona M, Kallinteri P and Fatouros D: Stability of SUV lipo- somes in the presence of cholate salts and pancreatic lipases: effect of lipid composition. Eur J Pharm Sci 2000; 9: 245–252. https://doi.org/10.1016/S0928-0987(99)00064-0
52. Kostanski JW and DeLuca P: A novel *in-vitro* release technique for peptide-containing biodegradable microspheres. AAPS PharmSciTech 2000; (1): 30–40.
53. Kreuter J, Nefzger M, Liehl E, Czok R and Voges R: Microspheres – A Novel Approach in Drug Delivery System. J Pharm Sci 1983; 72: 1146.
54. Kumar A, Mahajan S and Bhandari N: Microspheres: a review. World J Pharm Pharm Sci 2017; 6: 724-40.
55. Kumar R and Palmieri MJ: Points to consider when establishing drug product specifications for parenteral

microspheres. Aaps J 2010; 12: 27–32. DOI: 10.1208/s12248-009-9156-6.
56. Kumar TM and Paul W: "Bioadhesive, pH responsive micromatrix for oral delivery of insulin." Trends Biomater. Artif. Organs 2005; 18(2): 198-202.
57. Lehr CM, Bouwstra JA and Tukker JJ: Intestinal transit of bioadhesive microspheres in an in situ loop in the rat - a comparative study with copolymers and blends based on poly (acrylic acid). J Control Release 1990; 13: 51–62. doi:10.1016/0168-3659(90)90074-4.
58. Okubo M: Production of submicron-size monodisperse polymer particles having aldehyde groups by seeded aldol condensation polymerization, Colloid and Polymer Science 1993; 271: 109–113. https://doi.org/10.1007/BF00651812
59. Mahale, Manisha M and Saudagar RB: "Microsphere: a review." Journal of drug delivery and therapeutics 2019; 9: 3: 854-856.
60. Md S and A. Ahuja: "Gastroretentive drug delivery system of acyclovir-loaded alginate mucoadhesive micro particles: formulation and evaluation." Drug Delivery 2011; 18(4): 255-264.
61. Meghna KS, Krishna MP, Giridas S, Sreelakshmi C and Vijayakumar B: Microsphere a drug delivery system–a review. Int J Novel Trends Pharm Sci 2017; 7: 109-18.
62. Mishra B and Sahoo S: "Formulation and Evaluation of Torsemide intragastric buoyant sustained release micro particles." Journal of Pharmacy Research 2010; 3(2): 742-746.
63. Mukund J, Bhujbal R and Ranpise N: Floating microspheres: a review. Braz J Pharm Sci 2012; 48: 17–30.
64. Murty SB, Goodman J and Thanoo BC: Identification of chemically modified peptide from poly (D, L-lactide-coglycolide) microspheres under *in-vitro* release conditions. AAPS Pharm Sci Tech 2003; 4: 392–405. doi:10.1208/ pt040450.
65. Nair R and Reddy B: Application of chitosan microspheres as drug carriers: a review. J Pharm Sci Res 2009; 1: 1-12.
66. Najmuddin M, Ahmed A, Shelar S, Patel V and Khan T: Floating microspheres of ketoprofen: formulation and evaluation. International Int. J Pharm Pharm Sci 2010; 2(2): 83-87.
67. Nikam, Vikrant K, Gudsoorkar VR, Hiremath SN, Dolas RT and Kashid VA: "Microspheres-A Novel drug delivery system: An overview." Int J Pharm Chem 2012; 1: 1.
68. Nur AO and Zhang JS: "Recent progress in sustained/controlled oral delivery of captopril: an overview." International Journal of Pharmaceutics 2000; 194(2): 139-146. https://doi.org/10.1016/S0378-5173(99)00362-2
69. Orienti I, Aiedeh K, Gianasi E, Bertasi V and Zecchi V: Indomethacin loaded chitosan microspheres correlation between the erosionprocess and release kinetics. J Microencapsul 1996; 13: 463-72.
70. Palmieri GF and Bonacucina G: Gastro-resistant micro particles containing ketoprofen." Journal of Microencapsulation 2002; 19(1): 111-119. https://doi.org/10.1080/02652040110065477
71. Panchal R, Patel H, Patel V, Joshi P and Parikh AFormulation and evalution of montelukast sodium - chitosan based spray dried microspheres for pulmonary drug delivery. J Pharm Bioallied Sci Mar 2012; 4(1): 110-1. doi: 10.4103/0975-7406.94160. PMID: 23066182; PMCID: PMC3467819.
72. Park TG: Degradation of poly (D, L-lactic acid) microspheres: effect of molecular weight. J Control Release 1994; 30: 161–173. doi:10.1016/0168-3659(94)90263-1.
73. Patel JK and Patel RP: "Formulation and evaluation of mucoadhesive glipizide micro particles." Aaps Pharmscitech 2005; 6(1): 49-55.
74. Patil NV, Wadd NV, Thorat SS and Upadhye SS: "Microspheres: A novel drug delivery system." Am J Pharm Tech Res 2020; 10(02): 286-301.
75. Pavanveena C and Kavitha K: "Formulation and evaluation of trimetazidine hydrochloride loaded chitosan Micro particles 2010; 2: 11-14.
76. Pradeesh TS, Sunny MC, Varma HK and Ramesh P: Preparation of microstructured hydroxyapatite microspheres using oil in water emulsions. Bull Materials Sci 2005; 28: 383-90.
77. Prajapati SK, Tripathi P and Ubaidulla U: Design and development of gliclazide mucoadhesive microcapsules: in-*vitro* and *in-vivo* evaluation. AAPS Pharm Sci Tech 2008; 9: 224–230. doi:10.1208/s12249-008-9041-0.
78. Prasanth VV, Moy AC, Mathew ST and Mathapan R: Microspheres An overview. Int J Res Pharm Biomed Sci; 2011; 2: 332 8.
79. Prasanth VV, Moy AC, Mathew ST and Mathapan R: Microspheres An overview. Int J Res Pharm Biomed Sci 2011; 2: 332 8.
80. Prasanth VV and Chakraborty A: "Formulation and evaluation of Salbutamol sulphate micro particles by solvent evaporation method." Journal of Applied Pharmaceutical Science 2011; 1(5): 133-137.
81. Radhika PR, Luqman M: "Preparation and evaluation of delayed release aceclofenac micro particles." Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm 2008; 2(4): 252-254.
82. Rastogi V, Shukla SS, Singh R, Niharika Lal and Yadav P: Micro particles:A Promising Drug Carrier." J. drug deliv. Ther 2016; 6(3): 18-26. DOI https://doi.org/10.22270/jddt.v6i3.1196
83. Rathinaraj BS, Rajveer C and Sudharshini S: Preparation and evaluation of mucoadhesive microcapsules of Nimodipne. Int J Res Pharmaceutics 2010; 1:219–224.
84. Reddy VM, Patil P and Biradar KV: Development and evaluation of mucoadhesive microspheres of Nimodipine. Int Res J Pharm 2011; 2: 91–98.
85. Rhee YS and Sohn M: "Sustained-release delivery of octreotide from biodegradable polymeric micro particles." Aaps Pharmscitech 2011; 12(4): 1293-1301. https://doi.org/10.1208/s12249-011-9693-z
86. Righetti PG, Gelfi C and Perego M: Capillary zone electrophoresis of oligonucleotides and peptides in isoelectric buffers: theory and methodology. Electrophoresis 1997; 18: 2145–2153. doi:10.1002/elps.1150181205.
87. Sahu S and Chourasia A: "Formulation and evaluation of captropril micro particles by ionic gelation technique. Int J Pharm Sci 2012; 3:1377-1379.
88. Saralidze K, Leo H., Koole, Menno L and Knetsch W: Polymeric Microspheres for Medical Applications, Materials 2010: 3: 3357- 64.
89. Sato Y, Kawashima Y and Takeuchi H: Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. J Control Release 2004; 98: 75–85. doi:10.1016/j.jconrel.2004.04.021.
90. Shen J and Burgess DJ: Accelerated *in-vitro* release testing methods for extended release parenteral dosage forms. J Pharm Pharmacol 2012; 64: 986–996. doi:10.1111/j.2042-7158.2012.01482.x.

91. Shi Y and L. Li": Current advances in sustained-release systems for parenteral drug delivery." Expert Opinion on Drug Delivery 2005; 2(6): 1039-1058. https://doi.org/10.1517/17425247.2.6.1039
92. Singh S, Chidrawar VR: "Pharmaceutical characterization of amoxicillin trihydrate as mucoadhesive micro particles in management of H. pylori." International Journal of Pharm Tech Research 1010; 2(1): 348-358.
93. Sinha VR, Agrawal MK and Kumria R: Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. Curr Drug Delivery: 2005; 2: 1-8.
94. Souza S and Faraj JA: "Development of risperidone PLGA micro particles." Journal of Drug Delivery 2014; 1-11.
95. Sriram N and Katakam P: "Formulation and evaluation of mucoadhesive micro particles of pioglitazone hydrochloride prepared by ionotropic external gelation technique." Journal of Encapsulation and Adsorption Sciences 2016; 6(1): 22-34. 10.4236/jeas.2016.61003.
96. Suvarna V: microspheres: a brief review. Asian J Biomed Pharm Sci 2015; 5(47): 13-19.
97. Tarun Virmani: (Pharmaceutical Application of Microspheres: An Approach for the Treatment of Various Diseases Int. J Pharm Sci Rev Res 2017; 7: 3252-3260.
98. Trivedi P, Verma AML and Garud N: Preparation and Characterization of Acclofenac Microspheres. Asian J Pharm 2008; 2(2): 110-15.
99. Tsuyoshi Kojima: Preparation and Evaluation *in-vitro* of Polycarbonate Microspheres Containing Local Anesthetics, Chemical and Pharmaceutical Bulletin 1984; 2(7): 2795-2802.
100. Usami M and Misawa K: Buserelin acetate micro particle dispersion effects drug release and plasma E1 levels." International Journal of Pharmaceutics 2007; 339(1-2): 130-138. https://doi.org/10.1016/j.ijpharm.2007.02.025
101. Varcheh NN, Luginbuehl V and Aboofazeli R: Preparing poly (lactic-co-glycolic acid) (PLGA) microspheres containing lysozyme-zinc precipitate using a modified double emulsion method. Iran J Pharm Res 2011; 10: 203. PMID 24250344
102. Vemuri S, Yu C and Pushpala S: Drug release rate method for a liposome preparation. Drug Dev Ind Pharm 1991; 17: 183–192. doi:10.3109/03639049109043818.
103. Virmani T and Gupta J: Pharmaceutical application of microspheres: An approach for the treatment of various diseases. Int J Pharm Sci Res 2017; 8(8): 3252-60.
104. Voisine J, Zolnik B and Burgess DJ: In situ fiber optic method for long-term *in-vitro* release testing of microspheres. Int J Pharm 2008; 356: 206–211.
105. Vyas SP and Khar RK: Targeted and Controlled Drug Delivery, Novel Carrier Systems, first reprint 2004; 418, 419, 420, 423, 424, 444-454.
106. Wei Y and Zhao L: *In-vitro* and *in-vivo* evaluation of ranitidine hydrochloride loaded hollow microspheres in rabbits. Arch Pharm Res 2008; 31: 1369–1377. doi:10.1007/ s12272-001-2119-9.
107. Wolin EM and Manon A: "Lanreotide depot: an antineoplastic treatment of carcinoid or neuroendocrine tumors." Journal of Gastrointestinal Cancer 2016; 47(4): 366-374. https://doi.org/10.1007/s12029-016-9866-9
108. Xiao C, Qi X and Maitani Y: Sustained release of cisplatin from mul- tivesicular liposomes: potentiation of antitumor efficacy against S180 murine carcinoma. J Pharm Sci 2004; 93:1718–1724. DOI:10.1002/jps.20086.
109. Yadav R, Bhowmick M, Rathi V and Rathi J: Design and characterization of floating microspheres for rheumatoid arthritis, J of Drug Delivery and Therap 2019; 9(2): 76-81
110. Yong Z, Lili C, Feng L, Nianqiu S and Chunlei L: Design, fabrication and biomedical applications of zein-based nano/micro-carrier systems. Int J Pharm 2016; 512: 191-10.
111. Zolnik BS, Raton JL and Burgess DJ: Application of USP apparatus 4 and in situ fiber optic analysis to microsphere release testing. Dissolut Technol 2005; 12: 11–14. doi:10.14227/DT210314P1.

How to cite this article:
Chaudhary P, Kumar N, Pratap S, Rajeev, Rashid M and Alam S: Recent advancement in the formulation and evaluation of micro particle and its application. Int J Pharm Sci & Res 2023; 14(5): 2141-63. doi: 10.13040/IJPSR.0975-8232.14(5).2141-63.