Open Access Contents
Int. J. Res. Pharm & Allied Sci
| January - March 2023 | Vol. 1 | Issue 1 |

Full Length Original Research Paper

Recent Advancement in the Formulation and Evaluation of Micro particle and Its Application

www.ijrpas.co

Pratiksha Chaudhary,

Nitin Kumar,

Surya Pratap*,

Rajeev,

Mohammad Rashid,

Sanjar Alam

* Asst. Professor, Department of Pharmaceutics, R. V. Northland Institute, G. B. Nagar, U.P., INDIA

Corresponding Authors:

Surya Pratap
Email: suryapratapbsr@gmail.com

Abstract:
The micro particles and development in the area of micro particles analysis are discussed in this article. 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. Produce the micro particles 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, Sample and separate 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-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.

Keywords:. *Microparticles, Polymer, Clarithromycine, Micrometrics, Antibiotic, Orthopedic, Microcapsules, USP apparatus IV.*

Introduction

A regulated pharmaceutical delivery system can help address a few of the 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 as possible. A therapeutic substance can be given to the target area in a number of controlled and consistent methods. A few of these ideas is to use micro particles as medication carriers (Nikam et al., 2012).

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 (Rastogi et al., 2016).

There are two types of micro particles;

- Microcapsules.
- Micrometrics (Rastogi et al., 2016).

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 (Chaudhary et al., 2010).

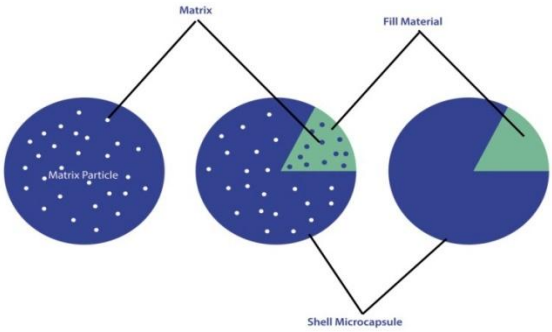

Figure 1 Micro particle

Advantages of Micro particles

- Decrease of the size contributes to an increasing the area of the surface 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 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 (Virmani et al., 2017).

Disadvantages of Micro particles

- The pace of release of the regulated dose procedure, which varies depending on a number of 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 (B sree et al., 2017)

Materials used in the micro particle formulation:

They are classified as follows in the formulation of micro particle polymers:

- synthetic polymer
- Natural polymer

A. Synthetic polymersaredivided 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.

B. 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 polystarch are used, as well as carbohydrates such as agarose, chitosan and starch. (Alagusundaram et al., 2009; Lehr et al., 1990; M et al., 1990; Mahale et al., 2019).

Types of Micro particles

- Bio-adhesive micro particles
- Magnetic micro particles
- Radioactive micro particles
- Floating micro particles
- Polymeric Micro particles.
  1) Biodegradable polymeric micro particles.
  2) Synthetic polymeric micro particles (Mahale et al., 2019).

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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 which are shown in fig-2, spend more time at the application site, resulting in closer contact with the site of absorption and improved pharmacological action (Kumar et al., 2017; Meghna et al., 2017; Khamanga et al., 2021).

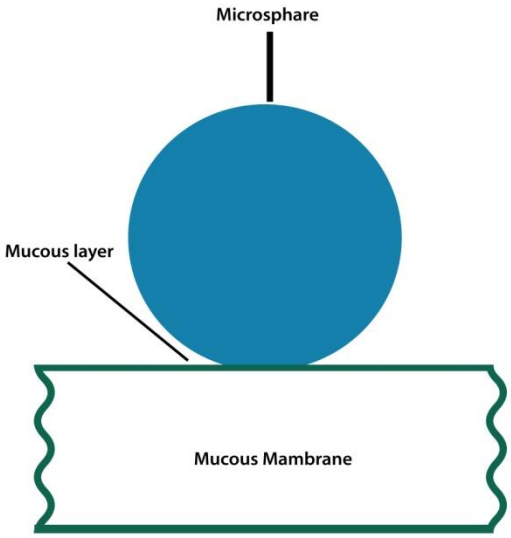

Figure 2 Bio adhesive micro particle

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 has the advantage of allowing a large volume of freely spreading pharmaceuticals to be replaced with a smaller amount of magnetically focused meds (Dutta et al., 2011).

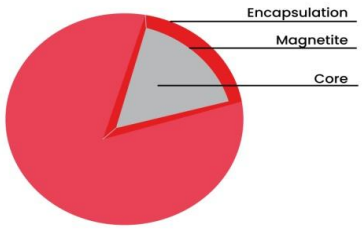

Figure 3 Magnetic micro particle

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 the healthy tissue. The various types of radioactive micro particles are called α-emitters, β-emitters, and γ-emitters (Hafeli, 2002; Vyas and Khar, 2004).

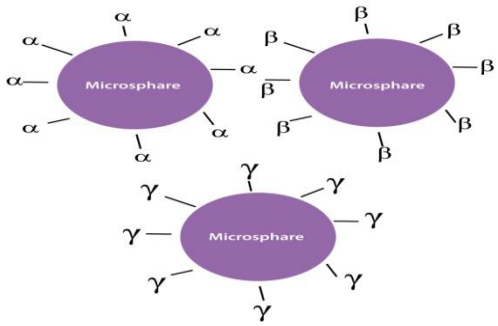

Figure 4 Radioactive micro particle

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, which improves the residence in the stomach and the variability of the plasmatic

concentration. This method has a longer-lasting therapeutic effect and reduces the number of doses required. 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 (Desai and Bolton, 1993; Iannaccelli et al., 1998; Najmuddin et al., 2010).

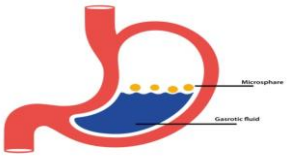

Figure 5 Floating microsphere

Polymeric Micro particles

Polymeric micro particles shown in fig-6 are classified as follows:

Syntheticpolymers

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 (Trivedi et al., 2008).

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. 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 in medical applications, the drug loading capacity of biodegradable micro particles is challenging, making drug release difficult to handle (Saralidze et al., 2010).

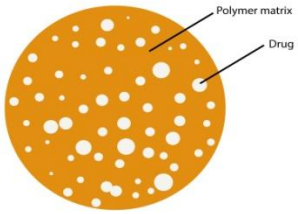

Figure 6 Polymeric micro particle

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 (Nair and Reddy, 2009; Orienti et al., 1996).

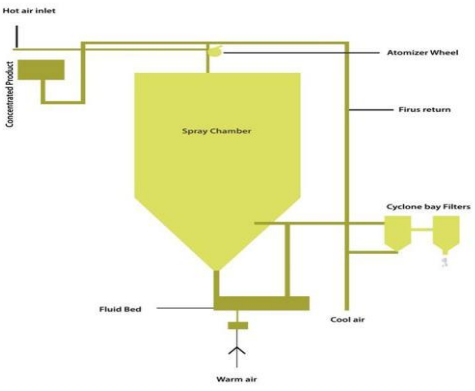

Figure 7 Spray drying technique

Solvent evaporation technology

It is one of the earliest methods of producing micro particles. An organic solvent, such like methylene chloride, must've been soluble in both 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 (Das et al., 2019).

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 chemicalcross-linking agent such as glutaraldehyde, formaldehyde or acid chloride, for example. Chemical crosslinking has a disadvantage: excessive exposure (Das et al., 2019).

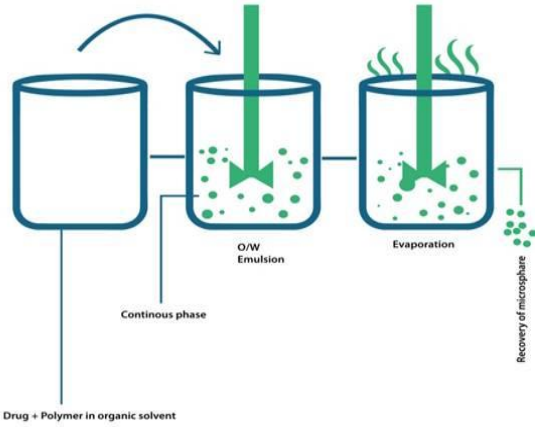

Figure 8 Solvent evaportaion technique

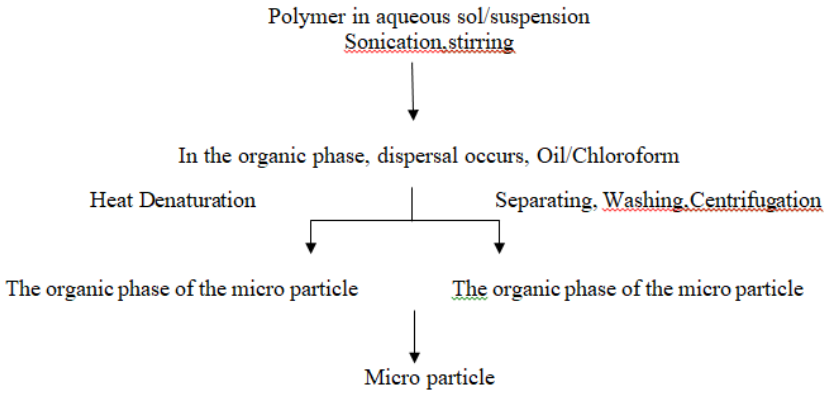

Figure 9 Schematic representation of Single emulsion technique

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. (Prasanth et al., 2011; Prasanth et al., 2011)

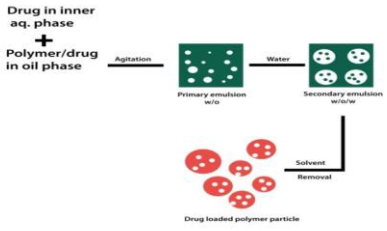

Figure 10 Double emulsion technique

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

Phase separation coacervation technology

Phase separation method is commonly used to prepare the deposit kind of a system.This approach is used to enclose water-soluble pharmaceuticals including peptides and proteins, as well as some matrix-type formulations, especially when the medication is hydrophobic like steroids. The method is depended on reducing the solubility of the polymer 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, resulting in the creation of two phases, one with a lot of polymers and the other is not, i.e., supernatant, which is depleted in polymer. A variety of technologies can be used to phase separate coacervates. Techniques include salt addition, solvent addition, and incompatible polymer addition (Alagusundaram et al., 2011; Kumar et al., 2017; Kumar and Palmieri , 2010).

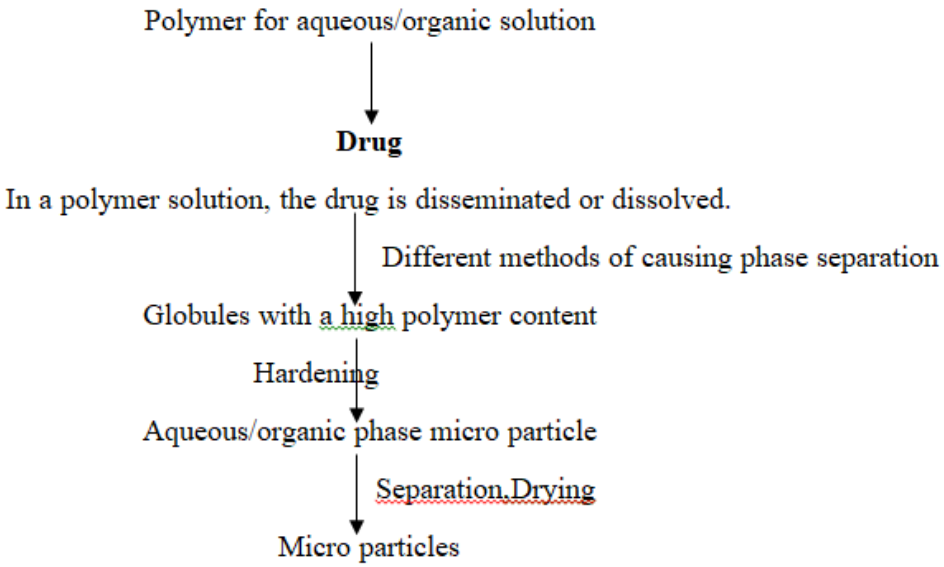

Figure 11 Schematic representation of Phase separation coacervation technology (Das et al., 2019)

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 (Kawashima et al., 1991).

spray congealing: Spray = Hot melt/Cold air

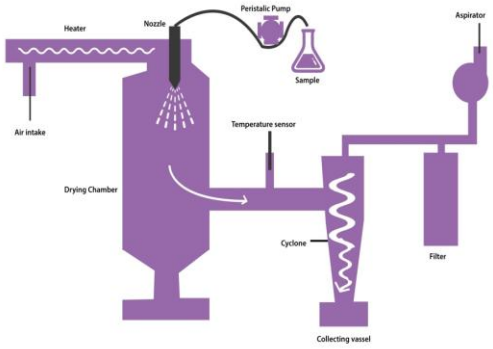

Figure 12 Spray drying and Spray freezing technique

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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 (Suvarna, 2015). Organic phase can be remove by the extraction process with the help of water (Das et al., 2019).

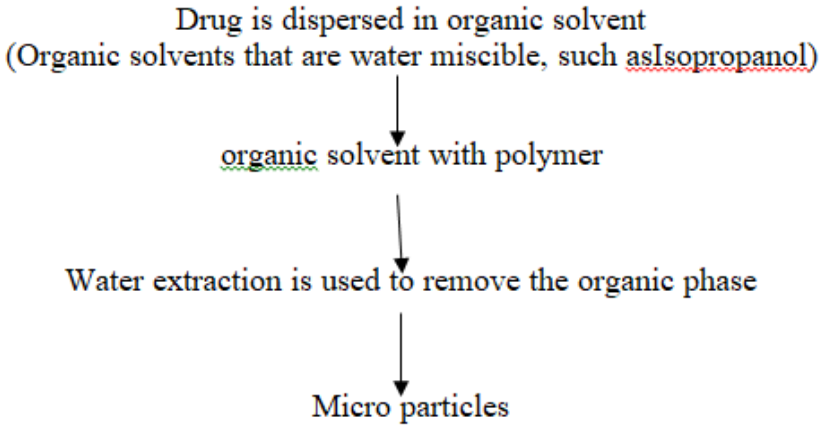

Figure 13 Schematic representation of Extraction of solvent technique (Das et al., 2019)

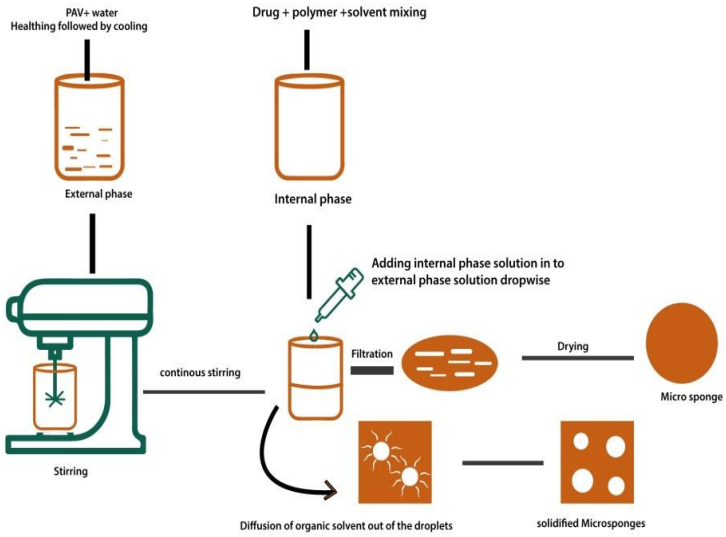

Figure 14 Quassi emulsion solvent diffusion

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 be used to 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 (Hickey et al., 2002; Yadav et al., 2019).

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, as well as double-wall systems. Using confocal fluorescence microscopy, the structure of many walled micro particles is examined. The shape, morphology, and size of the micro particles can be determined using laser light scattering and multi-size grating counter, in addition to experimental approaches (Barkai et al., 1090; Jain et al., 2006).

average particle size is determined by

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

Where, n = number of micro particles checked;

d = Mean size (Das et al., 2019).

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 existence of the

adsorbed component controls this thermodynamic characteristic, which is 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 (Patil et al., 2020).

Percentage yield

The entire amount of medication and polymer used in each batch is divided by the number of micro particles recovered from that batch, then divided by 100 (Das et al., 2019).

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 (Sinha et al.,2005).

Swelling index

It is calculated by finding out how many micro particles swell in a specific solvent. By soaking 5 mg of dry micro particles in 5 ml of buffer solution one night in to a measuring cylinder, the degree of equilibrium swelling of the micro particles can be calculated. It is determined using the formula provided (Das et al., 2019).

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. In the multi-volume pycnometer, a correctly weighted sample is put in a cup. 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 (Bithi et al., 2017).

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 that were dominated by surface materials. Alternating

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

total reflectance FTIR spectroscopy can reveal the surface components of micro particles depending on manufacturing techniques and conditions (Das et al., 2019).

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 (Kawashia et al., 1991).

Entrapment efficiency

A certain number of micro particles is weighed and crushed. After that, it was dissolved in buffer solution and filtered using a stirrer. A UV spectrophotometer is used to evaluate the filtrate at a given wavelength using a calibration curve (Das et al., 2019).

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 a medication through a barrier. The in vitro approach is used as a product testing technique in both pharmaceutical manufacture and product development. It's critical to have consistent and repeatable release data derived from chemically, physically and hydro dynamically established conditions (Das et al., 2019).

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 (Das et al., 2019).

Interface diffusion method

Dearden and Tomlinson came up with this approach. There are four different parts in all. Compartment A, which is 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 is used to retrieve samples from compartment A and return them to compartment A· (Das et al., 2019).

Modified Keshary Chien cell method

The use of advanced laboratory technology is required.At 37 degrees Celsius, it comprises of 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 (Das et al., 2019).

Dissolution apparatus method:

Using typical BP dissolving or USP apparatus, paddle and basket spinning elements have been employed to evaluate in vitro release properties. The study's dissolving media ranges from 100 to 500 ml, with rotation speeds of 50 to 100 rpm (Das et al., 2019).

***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 two of the most commonly used in vivo research methods (Das et al., 2019).

Animal models

It's mostly used to screen a large number of compounds, determine how they act, and evaluate a large number of formulations. Dogs, rats, pigs, and sheep are just a few of the animal models available. The technique includes anaesthetizing the animal, administering the dose, drawing blood at various intervals, and analyzing the results (Das et al., 2019).

Buccal absorption test

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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 find out how important the medicine is 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 (Das et al., 2019).

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 (Bodmeier and Chen, 1989; Panchal et al., 2012)

In Vitro Drug Dissolved percentage vs Peak Plasma Concentration

One the 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 (Bodmeier and Chen, 1989; Panchal et al., 2012).

Percentage of dissolved drug vs percentage of absorbed drug

If the rate of dissolution is the limiting phase in drug absorption and the drug is totally 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 (Brahmankar and Jaiswal, 2005; Panchal et al., 2012).

Absorption rate vs Dissolution rate

Generally, it is difficult to calculate the rate of absorption than it is to calculate the absorption time.Absorption time can be used to correlate absorption and dissolution data because the absorption rate and time of a drug 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 the time 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 (Brahmankar and Jaiswal, 2005; Panchal et al., 2012).

Percentage of drug dissolved versus drug concentration in serum

For medications whose absorption from the gastrointestinal tract is limited by the rate of dissolution, a linear relationship can be constructed between the percentage of drug dissolved at particular periods and the serum drug concentrations at those times (Brahmankar and Jaiswal, 2005; Panchal et al., 2012)

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 drug in the body and the weight of 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 (Brahmankar and Jaiswal, 2005; Panchal et al., 2012) .

Recent advances in testing of micro particle:

Advances in characterization of physicochemical 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

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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. Low resolution and the need for a high sample size to acquire trustworthy results are both disadvantages of LM.

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, as well as their cross sections, in order 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 greatest resolution (distance between two items that can be separated and observed as different objects) of the SEM 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 (Janki et al., 2016; Prajapati et al., 2008).

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 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 (Jain et al., 2006; Janki et al., 2016; Mukiund et al., 2012).

Advancement in Polymer molecular weight characterization

The first release pattern and duration of a micro particle matrix is influenced by the molecular weight of polymers.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 (Kumar and Palmieri , 2010). Certain medications have the potential to 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 find out the molecular weight of polymers (gel permeation chromatography). 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 (Janki et al., 2016; Kadajji et al., 2011; Kumar and Palmieri, 2010).

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 floatingmicro particles are recovered one by one. Drying and Weighing of the Micro

particle Fractions The buoyancy of the micro particles is then estimated using the following equation.

100 x (Qf/(Qf + Qs)) = buoyancy (percent)

Qs and Qf are settled micro particle and the weight of the floating micro particles, respectively. Themicro particles must float long enough for the drug to be completely released (Hickey et al., 2002).

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 (Kostanski et al., 2002; Rastogi et al., 2016; Rathinaraj et al., 2010; Reddy et al., 2011).

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 (Kumar et al., 2017; Rastogi et al., 2016; Rathinaraj et al., 2010; Reddy et al., 2011).

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 fully expand. 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 (Janki et al., 2016).

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. By comparing the drug's IR spectra to the reference standard's spectra, Fourier transform infrared [FT-IR] spectroscopy is frequently employed to discover any interactions between the medication and the polymer.The interaction between drug and polymer is indicated by changes in frequency and peaks. To measure polymer degradation, attenuated total reflectance FR-IR is employed to provide information on the surface composition of micro particles (Kumar et al., 2017).

Advancement in Chemical analysis characterization

To analyze any surface degradation, electron spectroscopy is utilized 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 numbers 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 kinetic energies of the released electrons, and the intensity of the binding energies 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 (Janki et al., 2016).

Advancement in Protein integrity determination characterization

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

During processing and in vitro release testing, encapsulated proteins are exposed to stress, which can lead to stability concerns (such as alteration of structural integrity, aggregation, denaturation, and loss of activity). Processing and/or release testing at a PH that corresponds to the protein's isoelectric point (pI) will cause considerable precipitation due to the molecule's low solubility at this PH. 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 (Glukhovskiy and Vigh, 1998; Park et al., 1994; Righetti et al., 1997; Varcheh et al., 2011).

Advancement in Density/porosity determination characterization

The density of the powder is used to determine flow and porosity. The most extensively used equipment for determining micro particle density is the multivolume pycnometer. Another approach for determining the porosity of micro particles is porosimetry, specifically mercury porosimetry (Alagusundaram et al., 2009).

Advancement in Contact angle characterization

Based on their wetting qualities, contact angle is used to describe the hydrophilicity/ hydrophobicity of micro particles (Alagusundaram et al., 2009).

Advancement in Flow properties characterization

Because micro particles are powder dosage forms, determining flow parameters and avoiding segregation/dosage non uniformity is crucial. It's also important to understand the flow characteristics while packing and administering the completed drug. 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 (Chandna et al., 2013; Kawatra et al., 2012).

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 (Shen and Burgess, 2012; Aklonis and MacKnight, 1983). Noncompendial 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 andsensitive. (Brahmankar and Jaiswal, 2005; Xiao et al., 2004).

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

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

apparatus IV, the USP apparatus II takes longer and requires more people(Wei and Zhao 2008).

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 a reliable procedure, 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 (Wei and Zhao, 2008; Lehr et al., 1990).

Dialysis sac technique

The dialysis bag technique uses correct dialysis membranes with appropriate molecular weight cutoffs for the specific drug, passing the drug to simply flow with the help of the membrane into the release fluid, avoiding any type of interaction between the drug and the membrane. (Genta I et al., 1997) 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 a number of 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 and in vitro data, and in vitro data was used to determine micro particle performance in vivo.(Kostanski J and Deluca P., 2000) 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 the external release medium phase of this treatment (Chidambaram and Burgess, 1999).

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 (Burgess et al., 2004).Using a modified flow-through cell technique, micro particle drug release was investigated. In a modified flow-through method, the micro particles and glass beads are mixed.The glass beads are employed to:

(1) avoid micro particle aggregation and, as a result, a change in the percentage cumulative release due to changing surface area.

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

(2) Reduce dead volume within the cells.
(3) 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 (Janki et al., 2016).

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 types of media (with varying pH and ionic strength) can be used; the flow rate can be controlled to control drug diffusion from the micro particles; 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 in conjunction 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. The introduction of fiber optic probes enables for continuous monitoring of the first burst release of medication by the micro particles (where the release rate can be rapid) (Voisine et al., 2008; Zolnik et al., 2005).

The USP apparatus IV may be used to analyze both protein-loaded and small-molecule-loaded micro particles effectively.A comparison of the USP IV set with a different sample and technique was performed 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) (Voisine et al., 2008; Zolnik et al., 2005).

The USP apparatus IV is made up of a number of 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, as well as 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 an excellent compendia dissolution method for micro particles due to its several advantages (Voisine et al., 2008; Zolnik et al., 2005).

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:

(1) Choosing an appropriate animal model that takes into account the animal's lifespan, especially when testing formulations with a long duration of action.

(2) Antibodies could be produced while employing human-derived protein therapies due to immunogenicity, which could influence medication pharmacokinetics and pharmacodynamics of proteins (Hickey et al., 2002; Joseph et al., 2002).

Following literature research and a comparison of the injection site in animals and humans to evaluate any inter-species variances, an appropriate animal model can be chosen. For micro particle performance testing, animal models such as rats and rabbits have been routinely used (Barkai et al., 1990).

Blood or urine samples are collected over a period of time after micro particles are delivered. Different extraction processes (such liquid-liquid and protein precipitation) are

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

employed to 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 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 (Sato et al., 2004).

Recent Advancement of Chitosan polymer:

Effects on cholesterol levels:

As examples of fibers with high, intermediate and low bile acid binding capabilities, chitosan and cellulose were chosen. 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 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 loss of cholesterol in liver tissue. Reduce cholesterol intake (food) decreased 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(Das and Senapati, 2007; Yong et al., 2016).

Increase Stability of Drug

Combining a drug with chitosan, generating a suspension and then kneading it for 45 minutes until a dough develops the stability of the medicine. This dough mass is screened 16 times to produce granules that are entirely stable in all situations (Yong et al., 2016).

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 (Khandai et al., 2010).

Cosmetic Industry

The presence of 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 when compared to hair keratin (Khandai et al., 2010; Virmani and Gupta, 2017).

As dental drug

Chitosan has been demonstrated to hasten wound recovery and protect 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 and is advertised as a health food that can help treat a broad range of ailments, including diabetes, hepatitis, arthritis, cancer and more (Virmani and Gupta, 2017)

Chitosan as Permeation Enhancer

Chitosan has been proven to unclosed 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 that have poor oral bioavailability. Because interactions between the positive

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

charges on 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 (Virmani and Gupta, 2017; Yong et al., 2016).

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 (Yong et al., 2016).

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. Bala M, et al., 2020.
2.	Octreotide	Sandostatin LAR	Novartis	Treat acromegaly via Im route	Phase separation	Rhee Y S, etal., 2011.
3.	Risperidone	RISPERDAL CONSTA	Janssen®/ Alkermes, Inc	Treat schizophrenia via IM route	Double emulsion (oil in water)	Souza S D. etal., 2014.
4.	Leuprolide	Lupron Depot®	Abbott Healthcare	Prostate cancer/ Endometriosis via i.m.	Methods are double emulsion-solvent evaporation and self-healing microencapsulation	Hirota K, etal., 2016.
5.	Triptorelin	Trelstar™ depot	Pfizer	Prostate cancer via i.m.	Phase separation	Shi Y, etal., 2005.
6.	Somatropin	Nutropin® Depota	Genentech/Alk Ermes	Growth Deficiencies via s.c.	Cryogenic spray drying or double-emulsion solvent evaporation techniques	Jostel A, etal., 2006.
7.	Bromocriptine	Parlodel LAR™	Novartis	Parkinsonism via s.c. or i.m.	Spray drying	Clarke N, etal., 1998.
8.	Buserelin	Micro particles Suprecur® MP (inj.)	Sanofi		Vibration method	Usamia M, etal., 2007.
9.	Lanreotide	Somatuline® LA	Ipsen-Beafour	Acromegaly via I.M route	Self-assemblymethod /phase separation method	Wolin E M, etal., 2016.
10.	Minocycline	Micro particles		Periodontal disease via oral route	Ionic gelation method	Calasans-Maia M D, etal2019.

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

		Minocin MR MinozOD 100	Pfizer Ranbaxy laboratories Ltd.			
11.	Metformin Hcl	Micro particles	Generic formulation	Anti-diabeticvia oral route	emulsion-solvent evaporation method	Choudhary P K, etal., 2008.
12.	Amoxicillin trihydrate	Micro particles	Generic formulation	Antibiotic Via oral route	solvent evaporation method	Singh S K, etal., 2010.
13.	Ibuprofen	Beads	Generic formulation	Analgesic Via oral route	Ionotropic gelation method	Khazaeli P, etal., 2008.
14.	Pioglitazone Hcl	Mucoadhesive micro particles Floating micro particles	Generic formulation	Anti-diabetic Via oral route	ionotropic external gelation method.	Sriram N, etal., 2016.
15.	Trimetazidine Hcl	Micro particles	Generic formulation	Anti-anginal Via oral route	Ionic cross-linking technique	Pavan veenaC, etal., 2010.
16.	Furosemide	Micro particles	Generic formulation	Diuretic Via oral route	ionic cross-linking technique, W/O emulsion system, Spherical crystallization technique.	Dsa M K, etal., 2008. Akbuja J, etal., 1994.
17.	Insulin	Micro particles	Generic formulation	Anti-diabetic via s.c route.	Emulsification method and drug loaded by diffusion filling method	Kumar T, etal., 2005.
18.	Aceclofenac	Micro particles	Generic formulation	Analgesic via oral and parenteral route.	Solvent evaporation technique.	RadhikA P R, etal., 2008.
19.	Acyclovir	Mucoadhesive Micro particles	Generic formulation	Antiviral via oral and ocular route	emulsification phase separation	Md S, etal., 2011.

Covered in & Embase, Elsevier **Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78**

		Micro particles for ophthalmic administration			technique multiple emulsion technique.	Genta, etal., 1997.
20.	RanitidineHcl	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.
21.	Glipizide	Micro particles Bimode SR Di micronMR Minidiab OD	 Emcure Pharmaceuticals Ltd. Serdia Pharmaceuticals Pvt. Pfizer	Oral Hypoglycemic via oral route	simple emulsification phase separation technique	Patel J K, etal., 2005.
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, etal., 2012.[87] Khamanga S M, etal., 2012.[48] Nur A O, etal., 1999.[68]
23.	Ketoprofen	Micro particles	Generic formulation Sanofi Amriya Pharma	Analgesic via i.m, i.v and orally	Solvent evaporation method, Spray drying method	Abdallah M H, etal., 2012.[2] Palmieri G F, et al., 2002.[70]

Covered in & Embase, Elsevier **Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78**

		Oruvail SR Ketofan SR				
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 V V, et al.,2011.[78] Jayan S C, 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 R K K, et al., 2010.[8]
28.	Metronidazole	Micro particles Flagyl	Generic formulation Nicholas Piramal India Ltd.	AntiamoebicVia 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, as well as the query of safety, are both intimately tied to the application strategy. Traditional vaccines have flawed that biodegradable vaccine delivery systems for parenteral immunizations can remedy (Kawashia et al., 1991).

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

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

carrier (Abbaraju and Begum .,2015; Jayaprakash et al., 2009)

Using micro particle carriers to target

Pharmaceutical site-specific distribution, also known as targeted medication delivery, is a well-known concept that is getting a lot of 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 the group (Murty et al., 2003).

Monoclonal antibodies facilitated micro particles targeting

Monoclonal antibodies that attack micro particles are known as immune micro particles. This approach is used to precisely target specific websites. 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 (Nair R, Reddy B., 2009)

Chemotherapy with micro particles

Micro particles as carriers of anticancer medicines are one of the most promising applications. Micro particles were required due to increased leaky vasculature and endocytic activity. Covering the soluble polyoxymethylene microparticles creates invisible micro particles. Non-stealth micro particles that accumulate in the RES [Reticulo Endothelial System] could also be used to treat cancer (Kreuter et al., 1983; Vyas and Khar, 2004).

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 tumor masses in the lungs (Das et al., 2019).

Micro particles with porous surfaces that can be applied to the skin

Micro sponges are porous micro particles with several interconnected voids that range in size from 5 to 300 microns. These porous micro particles 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 (Das et al., 2019).

Nasal medication administration

Intranasal (IN) administration provides a number of practical and theoretical merits for 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. A great number of microvilli, a penetrable endothelium membrane, and a highly vascularized epithelium in the nasal mucosa contribute to fast beginning of therapeutic impact. It covers a wide range of drug administration methods, equipment, formulations, and procedures for the nose and nasal cavity. Intranasal drugs can be used for local or systemic treatment, depending on the therapeutic goal. 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 (Das et al., 2019).

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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. Building controlled release systems to improve absorption and bioavailability, on the other hand, presents a number of 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 (Das et al., 2019).

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 (Das et al., 2019).

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 (Das et al., 2019).

Ocular delivery micro particles

Glaucoma is treated with the majority of drug-loaded ocular delivery devices, especially cholinergic agonists such as pilocarpine. Micro particles having biodegradable properties from a very short period [1 to 3 minutes] can be used to extend the low elimination half-life of aqueous eye drops to a larger length [15-20 minutes]. For instance, polyalkylcyanoacrylate (Patil et al., 2020; Pradeesh et al., 2005).

Applications for pharmaceuticals

Microencapsulated pharmaceuticals presently in the market include progesterone, theophylline, aspirin and derivatives, antihypertensives, pancrelipase, potassium chloride. Microencapsulated Potassium Chloride is used to protect 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. The majority of encapsulation procedures are costly and necessitate 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. The fact that most microencapsulation techniques are patent protected adds to the cost. (Abbaraju and Begum, 2015)

Conclusion

The study summarizes key physicochemical aspects of microspheres, such as drug content,

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78

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 and sample and separate. Based on a comparison of the respective benefits and drawbacks of various methods, modified USP apparatus IV appears to be the method of choice at the moment. 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. To investigate the impact of wide range of environmental conditions on microsphere quality over the product's life span, storage stability studies are required. Various novel assays have been created, including the In vitro wash off test and the floating test, as well as 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 are used to deliver the medicine to the target location with pinpoint accuracy if customized, and to 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 test, targeted, secure, specific & effective in vitro delivery & supplements as smaller versions of damaged tissue & organs in the body, by combining different other techniques.

Acknowledgement: Authors are thankful to the management of RV Northland Institute of Pharmacy for providing appropriate resources for writing this review paper.

Conflict of Interest: There is no conflict of interest.

References

1. Abbaraju K S and Begum N, (2015) Biomedical applications of microspheres, J. modern drug discov. drug deliv. res., 4 (2), Page 1-5.
2. Abdallah, M. H., O. A. Sammour, et al. (2012) "Development and characterization of controlled release ketoprofen micro particles." Journal of Applied Pharmaceutical Science ;2(3): 60-67.
3. Akala, E. O., P. Wiriyacoonkasem, et al. "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 G. Durmaz (1994) "Preparation and evaluation of cross-linked chitosan micro particles containing furosemide." International journal of pharmaceutics;111(3): 217-222. https://doi.org/10.1016/0378-5173(94)90344-1
5. Aklonis JJ, MacKnight WJ. (1983) Transitions and relaxations in amorphous polymers. In: Aklonis JJ, MacKnight WJ, editors. Introduction to polymer vis- coelasticity. 2nd ed. New York: Wiley-Interscience.
6. Alagusundaram M, Madhu Sudana Chetty C, Umashankari K, et al. (2009) Microspheres

as a novel drug delivery system – a review. Int J ChemTechRes;1:526–534.
7. Alagusundaram.M, et. al., (2009) Microspheres as a Novel Drug Delivery Sysytem - A Review, International Journal of Chem Tech Research, 1 (3), Page 526-534.
8. Arya, R. K. K., R. Singh, et al. (2010) "Mucoadhesive micro particles of famotidine: preparation characterization and in vitro evaluation." International Journal of Engineering science and technology;2(6):1575-1580.
9. B. Sree Giri Prasad, et. al., (2014) Microspheres as Drug Delivery System – A Review, J. Glob. Trends Pharm. Sci., 5(3), Page 1961–1972.
10. Bala, M., A. Moudgil, et al. "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, 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, F. A., T. Saha, et al. (2017)"Preparation and in vitro evaluation of mucoadhesive tablets of montelukast sodium." Bangladesh Pharmaceutical Journal ;20(2): 123-131.
13. Bodmeier R, Chen H. (1989) Preparation and characterization of microspheres containing the anti-inflammatory agents, Indomethacin, ibuprofen and kitoprofen. J. Controlled Release;10: 167175. https://doi.org/10.1016/0168-3659(89)90059-X
14. Brahmankar D.M., Jaiswal Sunil B.(2005) Biopharmaceutics and Pharmackinetics- A Treatise. Vallabh Prakashan, Delhi, pg.no. 315-336.
15. Burgess DJ, Crommelin DJA, Hussain AJ, et al. (2004) EUFEPS workshop report, assuring quality and performance of sustained and controlled release parenterals. Eur J Pharm Sci.21:679–690.
16. Calasans-Maia, M. n. D., C. A. B. B. Junior, et al. "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, Kakar S, et al. (2013) A review on target drug delivery: magnetic microspheres. J Acute Dis. 2:189–195. doi:10.1016/S2221-6189(13)60125-0.
18. Chaudhari A, Jadhav RK, Kadam JV. (2010) An overview: Microspheres as a nasal drug delivery system. Int. J. Pharm. Sci. Rev. Res.,5(1).
19. Chidambaram N, Burgess DJ. (1999) A novel in vitro release method for submicron sized dispersed systems. AAPS PharmSciTech. 1:E11.
20. Choudhury, P. K. and M. Kar (2009) "Controlled release metformin hydrochloride micro particles of ethyl cellulose prepared by different methods and study on the polymer affected parameters." Journal of Microencapsulation ;26(1): 46-53.
21. Cirri, M., F. Maestrelli, et al. (2021) "Development and microbiological evaluation of chitosan and chitosan-alginate micro particles for vaginal administration of metronidazole." International journal of pharmaceutics;598:1-11.
22. Clarke, N., K. O'Connor, et al."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. (2007) Evaluation of furosemide-loaded alginate microspheres prepared by ionotropic external gelation technique. Acta Pol Pharm; 64(3): 253-62.
24. Das, Manoj Kumar, Abdul Baquee Ahmed, and Dipankar Saha. (2019) "Microsphere a drug delivery system: A review." Int J Curr Pharma Res 11, no. 4 : 34-41.

25. Desai S., Bolton S. (1993) A floating controlled release drug delivery system: in-vitro – in-vivo evaluation. Pharma. Res.,10:1321-1325. https://doi.org/10.1023/A:1018921830385
26. Dutta P, Sruti J, Patra CN and Rao M. (2011) Floating microspheres: Recent trends in the development of gastro rententive floating drug delivery system. Int J Pharm Sci Nanotech; 4(1): 1296-06. https://doi.org/10.37285/ijpsn.2011.4.1.2
27. Genta, I., B. Conti, et al. (1997) "Bioadhesive micro particles for ophthalmic administration of acyclovir." Journal of pharmacy and pharmacology;49(8): 737-742.https://doi.org/10.1111/j.2042-7158.1997.tb06103.x
28. Glukhovskiy PV, Vigh G. (1998) A simple method for the determination of isoelectric points of ampholytes with closely spaced pKa values using pressure-mediated capillary electrophoresis. Electrophoresis.19:3166–3170. doi:10.1002/elps.1150191819.
29. Hafeli V. (2002) Radioactive microsphere for medical application.Adv. Chem. Phys. , 2002,7:213-248.
30. Hickey T, Kreutzer D, Burgess DJ, et al. (2002) In vivo evaluation of a dexamethasone/PLGA microsphere system designed to suppress the inflammatory tissue response to implantable medical devices. J Biomed Mater Res. ;61:180– 187. doi:10.1002/jbm.10016.
31. Hirota, K., A. C. Doty, et al. "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 M.T., Cameroni R. (1998) Air compartment multiple unit system for prolonged gastric residence:part1. Formulation study. International Journal of Pharmacy,174:47-54.
33. Jain N.K., Controlled and Novel drug delivery: 04 Edition: 236-237,21.
34. Jain SK, Agrawal GP, Jain NK. (2006) A novel calcium silicate based microspheres of repaglinide: in vivo investigations. J Control Release.113:111–116. doi:10.1016/j. jconrel.2006.04.005.
35. Jain SK, Agrawal GP, Jain NK. (2006) Evaluation of porous carrier- based floating orlistat microspheres for gastric delivery. AAPS PharmSciTech.7:E54–E62. doi:10.1208/ pt070490.
36. Janki V. Andhariya& Diane J. Burgess, (2016) "Recent advances in testing of micro particle drug delivery systems",Expert opinion on drug delivery .13(4):1-16. https://doi.org/10.1517/17425247.2016.1134484
37. Jayan, S. C., A. Sandeep, et al. (2009) "Design and in-vitro evaluation of gelatin micro particles of salbutamol sulphate.'';Hygeia1(1): 17-20.
38. Jayaprakash S, Halith SM, Mohamed Firthouse PU, Kulaturanpillai K. (2009) Preparation and evaluation of biodegradable microspheres of methotrexate. Asian J Pharm ;3:26-46.
39. Joseph N, Lakshmi S, Jayakrishnan A. (2002) A floating- type oral dosage form for piroxicam based on hollow polycarbonate microspheres: in vitro and in vivo evaluation in rabbits. J Control Release. 79:71–79.
40. Jostel, A. and S. M. Shalet "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, Venkatesan N. (2011) Approaches for dissolution testing of novel drug delivery systems. Am Pharm Rev.14(6):38–44.
42. Kawashia Y, Niwa T, Takeuchi H, Hino T, Itoh Y, Furuyamas. (1991) Characterization of polymorphs of tranilast anhydrate and tranilast monohydrate when crystallized by two solvent change spherical crystallization techniques. J Pharma Sci:81:472–478. https://doi.org/10.1002/jps.2600800515
43. Kawashima Y, Niwa T, Takeuchi H, et al. (1991) 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.16:279–289. doi:10.1016/0168 3659(91)90004-W.
44. Kawashima Y, Niwa T, Takeuchi H, T. Hino, Y. Ito. (1991) 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, 16, 279-290.
45. Kawatra M, Jain U, Ramana J. (2012) Recent advances in floating microspheres as gastro-retentive drug delivery system: a review. Int J Recent Adv Pharm Res.2:5–23.
46. Kazi M. Zakir Hossain, et. al., (2014) Development of microspheres for biomedical applications: a review, Prog Biomater, Page 1-19. https://doi.org/10.1007/s40204-014-0033-8
47. Kedzierewicz F, Thouvenot P, Lemut J, et al. (1999) Evaluation of peroral silicone dosage forms in humans by gammascintigraphy. J Control Release.58:195–205.
48. Khamanga, S. M. and R. B. Walker (2021) "In vitro dissolution kinetics of captopril from micro particles manufactured by solvent evaporation." Dissolution technologies ;19(1): 42-52.
49. Khandai M, Chakraborty S, Sharma A, Pattnaik S, Patra ChN, Dinda SC et, al. (2010) Preparation and evaluation of algino-sericin mucoadhesive microspheres: An approach for sustained drug delivery. J Adv Pharm Res. 1: 48-60.
50. Khazaeli, P., A. Pardakhti, et al. (2008) "Formulation of ibuprofen beads by ionotropic gelation." Iranian Journal of Pharmaceutical Research;7 (3): 163-170.
51. Kokkona M, Kallinteri P, Fatouros D, et al. (2000) Stability of SUV lipo- somes in the presence of cholate salts and pancreatic lipases: effect of lipid composition. Eur J Pharm Sci.9:245–252. https://doi.org/10.1016/S0928-0987(99)00064-0
52. Kostanski JW, DeLuca P. (2000) A novelin vitro release technique for peptide-containing biodegradable microspheres. AAPS PharmSciTech.1(1):30–40.
53. Kreuter J, Nefzger M, Liehl E, Czok R, Voges R. (1983) Microspheres – A Novel Approach in Drug Delivery System. J Pharm sci:72:1146.
54. Kumar A, Mahajan S, Bhandari N. (2017) Microspheres: a review. World J Pharm PharmSci ;6:724-40.
55. Kumar R, Palmieri MJ Jr. (2010) Points to consider when establishing drug product specifications for parenteral microspheres. AapsJ.;12:27–32. DOI:10.1208/s12248-009-9156-6.
56. Kumar, T. M., W. Paul, et al.(2005) "Bioadhesive, pH responsive micromatrix for oral delivery of insulin." Trends Biomater. Artif. Organs;18(2): 198-202.
57. Lehr C-M, Bouwstra JA, Tukker JJ, et al. (1990) 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. ;13:51–62. doi:10.1016/0168-3659(90)90074-4.
58. M. Okubo, et. al., (1993) Production of submicron-size monodisperse polymer particles having aldehyde groups by seeded aldol condensation polymerization, Colloid and Polymer Science, 271, Pages109–113. https://doi.org/10.1007/BF00651812
59. Mahale, Manisha M., and R. B. Saudagar. (2019)"Microsphere: a review." *Journal of drug delivery and therapeutics* 9, no. 3-s : 854-856.
60. Md, S., A. Ahuja, et al. (2011) "Gastroretentive drug delivery system of acyclovir-loaded alginate mucoadhesive micro particles: formulation and evaluation." Drug Delivery ;18(4): 255-264.
61. Meghna KS, Krishna MP, Giridas S, Sreelakshmi C, Vijayakumar B. (2017) Microsphere a drug delivery system–a review. Int J Novel Trends Pharm Sci ;7:109-18.
62. Mishra, B., S. Sahoo, et al. (2010) "Formulation and Evaluation of Torsemide intragastric buoyant sustained release

micro particles." Journal of pharmacy research ;3(2): 742-746.
63. Mukund J, Bhujbal R, Ranpise N. (2012) Floating microspheres: a review. Braz J Pharm Sci. ;48:17–30.
64. Murty SB, Goodman J, Thanoo BC, et al. (2003) Identification of chemically modified peptide from poly (D, L-lactide-coglycolide) microspheres under in vitro release conditions. AAPS PharmSciTech.4:392–405. doi:10.1208/ pt040450.
65. Nair R, Reddy B. (2009) Application of chitosan microspheres as drug carriers: a review. J Pharm Sci Res ;1:1-12.
66. Najmuddin M., Ahmed A., Shelar S., Patel V., Khan T. (2010)Floating microspheres of ketoprofen: formulation and evaluation. InternationalInt. J. Pharm. Pharm. Sci. ,2(2),83-87.
67. Nikam, Vikrant K., V. R. Gudsoorkar, S. N. Hiremath, R. T. Dolas, and V. A. Kashid. (2012) "Microspheres-A Novel drug delivery system: An overview." Int. j. pharm. chem. 1, no. 1 .
68. Nur, A. O. and J. S. Zhang. (2000) "Recent progress in sustained/controlled oral delivery of captopril: an overview." International journal of pharmaceutics ;194(2): 139-146. https://doi.org/10.1016/S0378-5173(99)00362-2
69. Orienti I, Aiedeh K, Gianasi E, Bertasi V, Zecchi V. (1996) Indomethacin loaded chitosan microspheres correlation between the erosionprocess and release kinetics. J Microencapsul ;13:463-72.
70. Palmieri, G. F., G. Bonacucina, et al. (2002)"Gastro-resistant micro particles containing ketoprofen." Journal of Microencapsulation;19(1): 111-119. https://doi.org/10.1080/02652040110065477
71. Panchal R, Patel H, Patel V, Joshi P, Parikh A. (2012) Formulation and evalution of montelukast sodium - chitosan based spray dried microspheres for pulmonary drug delivery. J Pharm Bioallied Sci. Mar;4(Suppl 1):S110-1. doi: 10.4103/0975-7406.94160. PMID: 23066182; PMCID: PMC3467819.
72. Park TG. (1994) Degradation of poly (D, L-lactic acid) microspheres: effect of molecular weight. J Control Release.30:161–173. doi:10.1016/0168-3659(94)90263-1.
73. Patel, J. K., R. P. Patel, et al. (2005) "Formulation and evaluation of mucoadhesive glipizide micro particles." AapsPharmscitech ;6(1): E49-E55.
74. Patil, N. V., N. V. Wadd, S. S. Thorat, and S. S. Upadhye. (2020) "Microspheres: A novel drug delivery system." *Am. J. PharmTech Res* 10, no. 02 : 286-301.
75. Pavanveena, C., K. Kavitha, et al.(2010) "Formulation and evaluation of trimetazidine hydrochloride loaded chitosan micro particles.";2; 11-14.
76. Pradeesh TS, Sunny MC, Varma HK, Ramesh P. (2005) Preparation of microstructured hydroxyapatite microspheres using oil in water emulsions. Bull Materials Sci ;28:383-90.
77. Prajapati SK, Tripathi P, Ubaidulla U, et al. (2008) Design and development of gliclazide mucoadhesive microcapsules: in vitro and in vivo evaluation. AAPS PharmSciTech. ;9:224–230. doi:10.1208/s12249-008-9041-0.
78. Prasanth V.V., Moy A. C., Mathew S. T., Mathapan R. (2011) Microspheres An overview, Int. J. Res. Pharm. Biomed. Sci; 2:332 8.
79. Prasanth V.V., Moy A. C., Mathew S. T., Mathapan R. (2011) Microspheres An overview, Int. J. Res. Pharm. Biomed. Sci; 2:332 8.
80. Prasanth, V. V., A. Chakraborty, et al. (2011) "Formulation and evaluation of Salbutamol sulphate micro particles by solvent evaporation method." Journal of Applied Pharmaceutical Science;1(5): 133-137.
81. Radhika, P. R., M. Luqman, et al.(2008) "Preparation and evaluation of delayed release aceclofenac micro particles." Asian Journal of Pharmaceutics (AJP): Free full text articles from Asian J Pharm ;2(4):252-254.

82. Rastogi V, Shukla S S, Singh R, Niharika Lal, Yadav P. (2016)"Micro particles:A Promising Drug Carrier." J. drug deliv. Ther. 6(3), 18-26.DOI https://doi.org/10.22270/jddt.v6i3.1196
83. Rathinaraj BS, Rajveer C, Sudharshini S, et al. (2010) Preparation and evaluation of mucoadhesive microcapsules of Nimodipne. Int J Res Pharmaceutics.1:219–224.
84. Reddy VM, Patil P, Biradar KV, et al. (2011) Development and evaluation of mucoadhesive microspheres of Nimodipine. Int Res J Pharm. 2:91–98.
85. Rhee, Y.-S., M. Sohn, et al. "Sustained-release delivery of octreotide from biodegradable polymeric micro particles." AapsPharmscitech 2011;12(4): 1293-1301. https://doi.org/10.1208/s12249-011-9693-z
86. Righetti PG, Gelfi C, Perego M, et al. (1997) Capillary zone electrophoresis of oligonucleotides and peptides in isoelectric buffers: theory and methodology. Electrophoresis. 18:2145–2153. doi:10.1002/elps.1150181205.
87. Sahu, S., A. Chourasia, et al.(2012) "Formulation and evaluation of captropril micro particles by ionic gelation technique.",Int. J. Pharm. Sci3: 1377-1379.
88. Saralidze K, Leo H., Koole, Menno L, Knetsch W. (2010) Polymeric Microspheres for Medical Applications, Materials:3:3357- 64.
89. Sato Y, Kawashima Y, Takeuchi H, et al. (2004) Pharmacoscintigraphic evaluation of riboflavin-containing microballoons for a floating controlled drug delivery system in healthy humans. J Control Release.98:75–85. doi:10.1016/j.jconrel.2004.04.021.
90. Shen J, Burgess DJ. (2012) Accelerated invitro release testing methods for extended release parenteral dosage forms. J Pharm Pharmacol. ;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. K., V. R. Chidrawar, et al. (1010) "Pharmaceutical characterization of amoxicillin trihydrate as mucoadhesive micro particles in management of H. pylori." International Journal of PharmTech Research ;2(1): 348-358.
93. Sinha, v. R.; Agrawal, M. K.; Kumria, R. (2005) Influence of formulation and excipient variables on the pellet properties prepared by extrusion spheronization. Curr. Drug Delivery: 2:1-8.
94. Souza, S., J. A. Faraj, et al. "Development of risperidone PLGA micro particles." Journal of Drug Delivery2014;1-11.
95. Sriram, N. and P. Katakam (2016) "Formulation and evaluation of mucoadhesive micro particles of pioglitazone hydrochloride prepared by ionotropic external gelation technique." Journal of Encapsulation and Adsorption Sciences;6(1): 22-34. 10.4236/jeas.2016.61003.
96. Suvarna V, microspheres: a brief review, (2015)Asian j. biomed. pharm. sci., 5(47):13-19.
97. Tarun Virmani, et. al., (2017) Pharmaceutical Application of Microspheres: An Approach for The Treatment of Various DiseasesInt. J. Pharm. Sci. Rev. Res., 7 Page 3252-3260.
98. Trivedi P, Verma AML, Garud N. (2008) Preparation and Characterization of Acclofenac Microspheres, Asian J. Pharm.:2(2):110-15.
99. Tsuyoshi Kojima, et. al., (1984) Preparation and Evaluation in Vitro of Polycarbonate Microspheres Containing Local Anesthetics, Chemical and Pharmaceutical Bulletin, 32(7) Pages 2795-2802.
100. Usami, M., K. Misawa, et al."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, Aboofazeli R, et al. (2011) Preparing poly (lactic-co-glycolic acid) (PLGA) microspheres containing lysozyme-zinc precipitate using a

modified double emulsion method. Iran J Pharm Res.10:203. PMID 24250344
102. Vemuri S, Yu C, Pushpala S, et al. (1991) Drug release rate method for a liposome preparation. Drug Dev Ind Pharm. 17:183–192. doi:10.3109/03639049109043818.
103. Virmani T and Gupta J. (2017) Pharmaceutical application of microspheres: An approach for the treatment of various diseases. Int J Pharm Sci Res; 8(8): 3252-60.
104. Voisine J, Zolnik B, Burgess DJ. (2008) In situ fiber optic method for long-term in vitro release testing of microspheres. Int J Pharm.356:206–211. doi: 10.1016/j.ijpharm. 2008.01.017.
105. Vyas S.P., Khar R.K. (2004) Targeted and Controlled Drug Delivery, Novel Carrier Systems, first reprint, pg.no. 418, 419, 420, 423, 424, 444-454.
106. Wei Y, Zhao L. (2008) In vitro and in vivo evaluation of ranitidine hydrochloride loaded hollow microspheres in rabbits. Arch Pharm Res.31:1369–1377. doi:10.1007/ s12272-001-2119-9.
107. Wolin, E. M., A. Manon, et al. "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, Maitani Y, et al. (2004) Sustained release of cisplatin from multivesicular liposomes: potentiation of antitumor efficacy against S180 murine carcinoma. J Pharm Sci. 93:1718–1724. DOI:10.1002/jps.20086.
109. Yadav R, Bhowmick M, Rathi V, Rathi J,(2019) Design and characterization of floating microspheres for rheumatoid arthritis, Journal of Drug Delivery and Therapeutics ; 9(2-s):76-81
110. Yong Z, Lili C, Feng L, Nianqiu S, Chunlei L, et al. (2016) Design, fabrication and biomedical applications of zein-based nano/micro-carrier systems. Int J Pharm. 512: 191-10.
111. Zolnik BS, Raton J-L, Burgess DJ. (2005) Application of USP apparatus 4 and in situ fiber optic analysis to microsphere release testing. Dissolut Technol.12:11–14. doi:10.14227/DT210314P1.

Covered in & Embase, Elsevier Int. J. Res. Pharm & Allied Sci 2022, January-March 2023, 1 (1): 48-78