IJRAR.ORG E-ISSN: 2348-1269, P-ISSN: 2349-5138

INTERNATIONAL JOURNAL OF RESEARCH AND ANALYTICAL REVIEWS (IJRAR) | IJRAR.ORG

An International Open Access, Peer-reviewed, Refereed Journal

An Insight into Enteric Coated Microspheres: What? Why? & How?

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ABSTRACT

The enteric coated microspheres are one of the novel drug delivery systems that can be used as therapeutic alternative to traditional or immediate release unit dosage form. Enteric coated microspheres inhibit drug breakdown in the stomach`s acidic environment while also enhance drug solubility, which improves drug bioavailability. This approach also helps to prevent side effect like gastrointestinal burning and inflammation. These enteric coated microspheres were either prepared and packed in hard gelatine or directly compressed. When compared to standard dosage form, microspheres that are manufactured utilising various process affect their effectiveness and administration. The quality of microspheres will be assessed using several ways. In the future, enteric coated microspheres will play a key role in innovative drug delivery.

Keywords: Microspheres, Enteric coatings, Advance drug delivery, Gastric discomfort, Polymers, Applications, Methods of preparations.

INTRODUCTION

Microspheres, as the name indicates, are spherical particles of micrometer dimensions ranging 1-1000µm, including dispersed drugs in certain solution or microcrystalline shape. Often microspheres and microcapsules are taken as members of similar formulation family due to close similarity in shape and size. An enteric coating is a polymer barrier that prevents oral medication from dissolving or disintegrating in the stomach [1].

This protects the drug from acidic gastric environment, shields the stomach from the drug`s harmful effects, or allows the drug to be released after the stomach, typically in the intestine. Several medications are sensitive to gastric pH and must be protected against gastric breakdown. Enteric coating is another successful approach for medication targeting such as gastric resistant drug [2].

The phrase enteric coating is not totally accurate from a pharmacological standpoint, as gastric resistance can also be achieved by adding an enteric polymeric structure to the dosage form matrix. Enteric coating is a strategy to improve the solubility of drug that belongs to BCS class 2nd, (poor solubility and good permeability), and are absorbed from the stomach as well as small intestine and also reduces side effect of the drug i.e. gastric irritation [3].

Some Enteric Coating polymers are [4] -:

- Polyvinyl Acetate Phthalate (PVAP). [5]
- Shellac.
- Cellulose Acetate Trimellitate (CAT).
- Sodium Alginate [6].
- Cellulose Acetate Phthalate (CAP).
- Hydroxy Propyl Methyl Cellulose (HPMC).
- Cellulose Acetate Succinate.
- Eudragit. [7]

ADVANTAGES OF ENTERIC COATING MICROSPHERES [8-9-10]

1. Prevents the drug from being harmed by highly acidic environment of stomach.
2. Drug concentration is reduced at a location other than the tissue or target organ.
3. Reduce the dose and the toxicity.
4. Provide drugs with a consistent and long-lasting therapeutic effect.

PREPARATION TECHNIQUES

- SOLVENT EVAPORATION [11-12]
- COACERVATION [13]
- FREEZE DRYING [14].
- SPRAY DRYING [15]
- PRECIPITATION [16]
- SINGLE EMULSION [17-18]
- DOUBLE EMULSION [17,19]
- IONOTROPIC GELATION [20]

"SOLVENT EVAPORATION" – This process is carried out in vehicle phase of liquid manufacturing. The microcapsule coating is dispersed in the volatile solvent which immiscible with the vehicle phase of liquid manufacturing. A core material which is microencapsulated is dissolved in the coating polymer solution. Agitation with the core material mixture is dissolved in the liquid manufacturing vehicle phase to obtain appropriate size microcapsule. Then the mixture is heated if necessary to evaporate and the solvent for the polymer of the core material is dissolved in the polymer solution, around the core, polymer shrinks. If core material is dissolved in the coating polymer solution, matrix type microcapsules are formed. The core materials are either water soluble or soluble materials.[12]

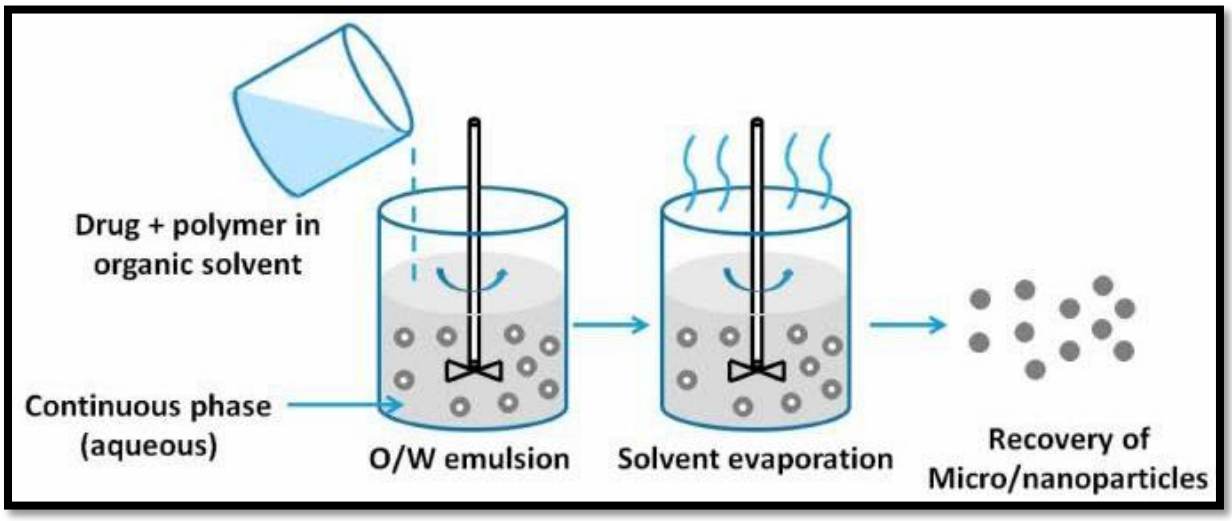

Figure 01 -: SOLVENT EVAPORATION TECHNIQUE

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"COACERVATION" - This process is based on the principle of decreasing the solubility of polymer in organic phase which affects the formation of polymer rich phase called the coacervates. In this method, drug particles are dispersed in a solution of polymer and an incompatible polymer is added to system which makes first polymer for the phase separation.[13]

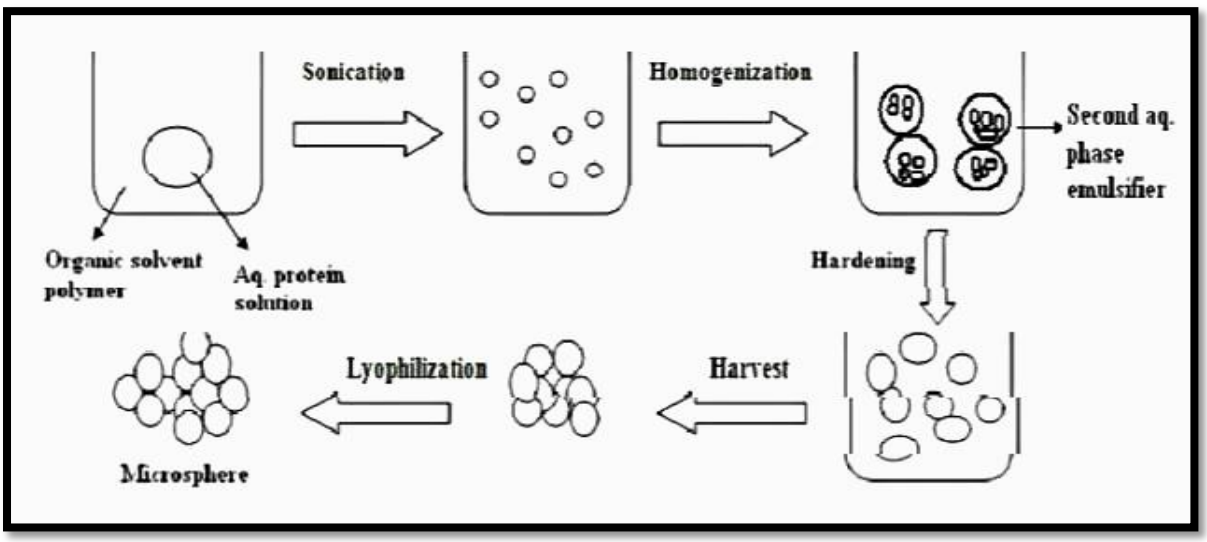

FIGURE 02 -: COACERVATION TECHNIQUE

"FREEZE DRYING" - This technique is used to make microspheres, in which protein plays a role of API. Freezing, sublimation, primary drying and secondary drying are all techniques used in this process. At freezing, the component`s eutectic point is calculated. Cryoprotectants will stabilises API molecules by eliminating water and generating a glass matrix with reduced intermolecular interactions by building hydrogen bonds between molecules during this occurrence. This cycle is beneficial to heat tolerant compounds. Freezing drying causes solidification, which allows particle to be reconstituted in aqueous fluids [14].

"SPRAY DRYING" - In spray drying technique, polymer is first dissolved in volatile organic solvent such as dichloromethane, acetone, etc. The drug in solid form is then dispersed in to polymeric solution with the high-speed homogenization. This dispersion is then atomized in hot air stream. The atomization leads to the form of small droplets from which the solvent evaporates instantly leads the formation of the microspheres in the size range 1-100 micro meter. Microparticles are separated from hot air by the cyclone separator while the

trace of solvent is removed by vacuum drying. The major disadvantage of this process is feasibility of operation under aseptic conditions. [15]

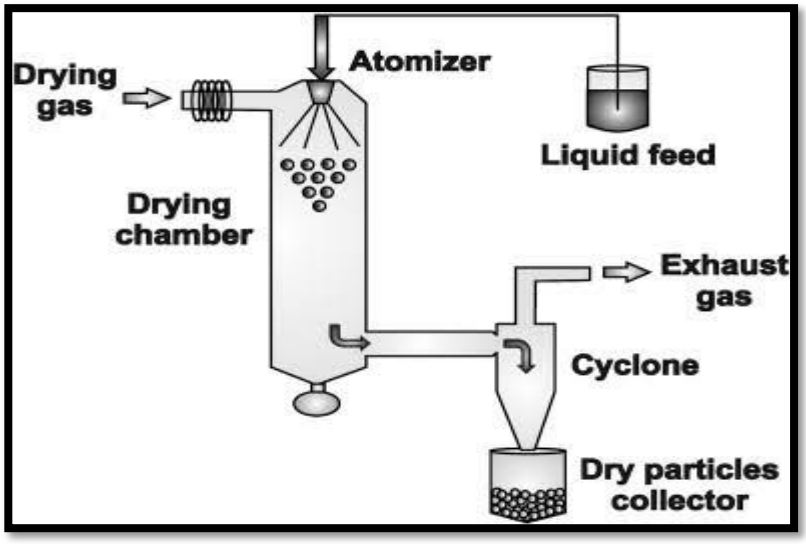

FIGURE 03 -: SPRAY DRYING TECHNIQUE

"PRECIPITATION" - It is a type of evaporation that has been altered. Polar droplets are dispersed across a non-polar medium in the emulsion. A co-solvent can be used to remove solvent from droplets. As polymer concentrations rises, precipitation occurs, resulting in a micro-spheric suspension [16].

"SINGLE EMULSION" – The micro particulate carriers of the natural polymer i.e. proteins and carbohydrates are prepared by the single emulsion technique. Natural polymers are dissolved in aqueous medium which is followed by the dispersion in non-aqueous medium like oil. In next step, the cross linking of dispersed globules is carried out. The cross linking can be achieved by the heat or by using the chemical cross linkers. The chemical cross-linking agents used are glutaraldehyde, formaldehyde, acid chloride [17]. Heat denaturation is not suitable for the thermolabile substance. Chemical cross linking having the disadvantages of excessive exposure of active ingredient to chemical if added at time of preparation and then subjected to centrifugation, washing, separation, nature of the surfactants used to stabilize the emulsion phases can greatly influence by the size, size distribution, surface morphology and loading drug release, and bio performance of the final multiarticulate products. [18].

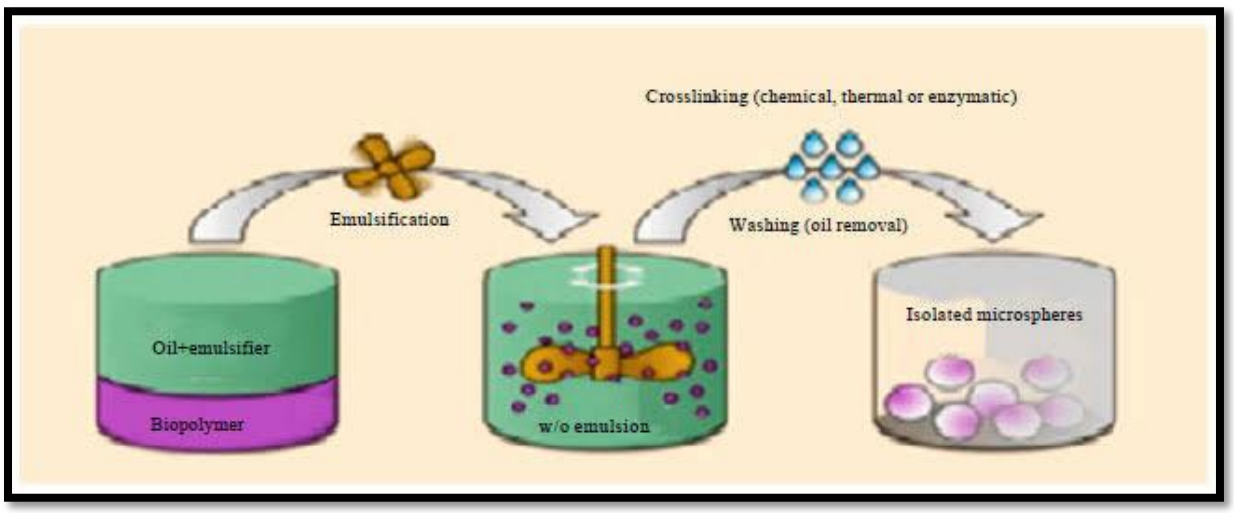

FIGURE 04 -: SINGLE EMULSION TECHNIQUE

"DOUBLE EMULSION TECHNIQUE"- This method of microspheres preparation involves formation of multiple emulsion or double emulsion of type w\o\w and is best suited to the watersoluble drugs, peptides, proteins, and vaccines.

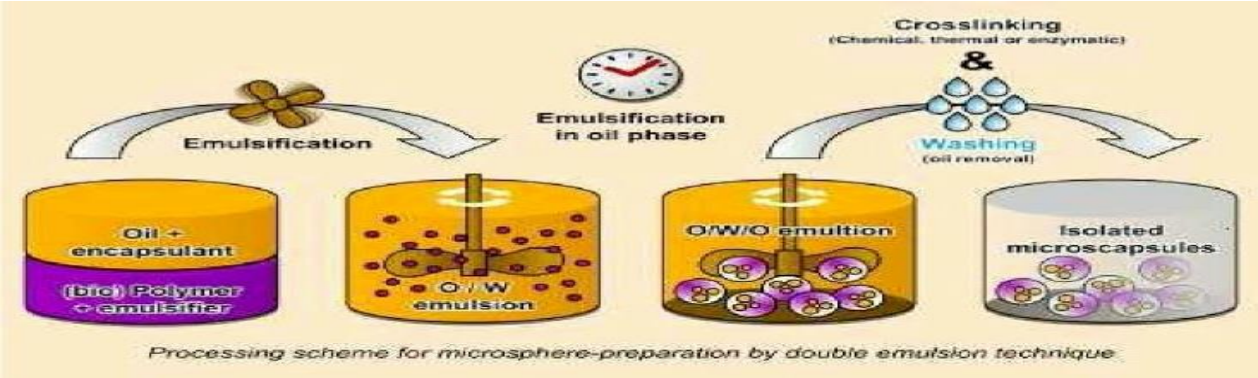

FIGURE 05 -: DOUBLE EMULSION TECHNIQUE

This method can be used with the both natural as well as synthetic polymers. The aqueous protein solution is dispersed in the lipophilic organic continuous phase. This solution may contain the active constituent. [17,19]

"IONOTROPIC GELATION" – This is the potential of poly-electrolytes which makes a cross ling using counter-ions results in formation of beads (Hydrogel). For encapsulation of pharmaceuticals various components are used such as CMC, Chitosan, Gellan, Alginate in this process. Natural polyelectrolytes have certain anions in their chemical composition, which allows for coating core of drug that employ retard in release rate. These anions create meshwork structures with cations(polyvalent) which induces gelation through binding particularly to blocks of anion. By reducing polymeric solution having loaded drug into the cations(poly-valent) solution having high aqueous concentration, hydrogel beads are created. Because the negative charge ions migrate in formulation, the ionically linked moiety forms a three-dimensional lattice. Bio-molecules can put in these beads keeping the 3D form under mild circumstances [20].

APPLICATIONS [21].

- "Multiparticulate delivery system".[22]
- "Transdermal drug delivery".[23]
- "Peroral drug delivery".[24]
- "Vaginal drug deliver".[25]
- "Colonic drug delivery".[26]
- "Gastrointestinal drug delivery".[27]
- "Nasal drug delivery".[28]
- "Gene delivery".[29]
- "Oral drug delivery".[30]
- "Buccal drug delivery".[31]
- "Ophthalmic drug delivery".[32]

"Multiparticulate delivery system"- Using extrusion/spheronization technology, H.Steckle and F.Mandermann-Nogly created chitosan pellets. As an additive, microcrystalline cellulose was employed in concentrations ranging from 0 to 70%. Water was used to extrude the powder combination, which decreases the concentration of acetic acid in different ratios (liquid: powder). This gives the clarification about, using demineralized water as a granulating fluid, pellets of chitosan can be manufactured. If acetic acid used in less concentrated form in the process of granulation the fraction of mass (chitosan) enhanced in the pallets. [22]

"Transdermal drug delivery"- The film-forming characteristics of polymer are excellent. The membrane thickness & the film (crosslinking) have an impact on release of drug from implement. Natural preparation of alginate polyelectrolyte complex in the beads and in the microspheres has been done for possible use in encase, CR systems (controlled release) and dressings of wound. These polymeric beads of gels are bio-compatible & bio-degradable medium in local inflammation treatment with medications for example Prednisolone, shown to have a prolonged release effect that improves therapeutic efficacy. The type of membrane utilised was discovered to affect the rate of drug release. [23]

"Peroral drug delivery" – Because the polymer and various derivatives having mucoadhesive property, peptide (presystemic) metabolism could be significantly enhanced bioavailability of several perorally administered peptide medicines like Buserelin, calcitonin. For peptide medicines, high permeation effect can only be showed by non-changed chitosan. By mixing chitosan glyceryl mono-oleate with polymer gel, the mucoadhesive property can be increased by three to seven folds. A matrix diffusion-controlled mechanism, controlled drug release from the gel. When compared to granules, nifedipine encapsulated in the matrix of chitosan in bead has a longer deliverance time.[24]

"Vaginal drug delivery" - Clotrimazole, an imidazole derivative, is a chemical influencer on addition with thio-glycolic acid with main groups (Amino) of chemicals. Myotic infection in urinary tract frequent treated with this drug delivery. The adhering behaviour of natural & synthetic polymers influences when thiol groups are introduced. Through this vaginal mucosa tissue, the time of residence increase ensuring controlled form of release of drug and adhesion qualities polymer(vaginal) tablet contains drug were satisfactory.[25]

"Colonic drug delivery" - Insulin administration to the colon has been achieved using polymer. Apart from insulin, capsules of chitosan covered by HPMC (an enteric coating polymer) and having numerous other enhancers (absorption) & enzyme inhibitors. From prior studies it was cleared that the capsule first dissolved in the region of colon. These disintegrations were thought to be caused by either a lesser pH in colon (ascending) in compare to ileum (terminal) or bacterial enzyme presence can be able to destroy the chemical polymer. absorption enhancers and enzyme inhibitors.[26]

"Gastrointestinal drug delivery" - when polymer granules with interior voids generated through the process of de-acidification were put to neutral & acidic environments, they floated and released prednisolone in a controlled manner. Melatonin was delivered in floating hollow microcapsules that were gastro-retentive and controlled-release. In simulated stomach fluid, the release from microcapsules are considerably delayed, lasting 1.75-6.7 hours. Most mucoadhesive microcapsules, such as glipizide-loaded chitosan microsphere & metoclopramide, are maintained in thye stomach for than 10 hours.[27]

"Nasal drug delivery" – Mucosa of the nose is the best place where bio-adhesion delivery of drug works well. Polymer based DDS (drug delivery system) e.g. gels/liposomes/microspheres were get in contact with nasal mucosa demonstrated to have great bio-adhesion qualities and time of residence. Different salts of polymers like chitosan (lactate/glutamate) and hydrochloride of chitosan are viable option. Nasal release (sustained) of hydrochlorides of vancomycin. Microparticles of chitosan which will be delivered from nasal route promote enhanced "IgG" synthesis along with local immune response against toxoids of Diphtheria.[28]

"Gene delivery" – Gene DDS include polycation complex, cationic(liposomes), viral vectors and systems specifically which are microencapsulated. Viral vectors are excellent for delivering genes, because they are too efficient and can target a great range of cells. However, in-vivo, they result in both an immunological reaction and carcinogenic effects. The shortcoming of viral vectors are being addressed by research into non-viral delivery methods for gene therapy. Preparations are easy, targeting cell/tissue.[29]

"Oral drug delivery" – Diazepam coated with polymer film were tested on Rabbits to see if they might be utilised as oral delivery device. According to research the film is composed in this ratio 1:0.5 i.e. drug with polymer this could be a practical dosage form that is on par with current solid dosage form. Chemicals (polymers) could be utilised to make dosage form (film) as an alternative to pharmaceutical tablet because of its ability to form films. Polymer are often used in oral medication administration.[30]

"Buccal drug delivery" - Because of its muco/bioadhesive characteristics and abilities to act as an absorption enhancer, polymer is ideal for buccal delivery. Chitosan MS dependent buccal tablets contains, chlorohexidine diaconate provide extended drug release in the buccal cavity, enhancing the drug`s antibacterial effectiveness. The antibacterial action of polymer microparticle without drugs is attributed to chemical (polymer). Bilayer buccal devices (palavered tablets, bi-laminated films,) containing these drugs mixture these two drugs are (propranolol hydrochloride & nifedipine) along with chitosan either by or without cross linking polymer i.e. (gellan gum & sodium alginate) show promise regulated distribution in the oral cavity.[31]

"Ophthalmic drug delivery" - Polymers are a suitable for ocular delivery of drug vehicle design because they have exciting physico-chemical characteristics, such as bio-adhesion and permeability-enhancing qualities. Ophthalmic chitosan gels increase precorneal drug residence duration, reducing drug elimination through the lachrymal flow, and improve adherence to the conjunctiva layer (mucin) and cornea of eye. Additionally, its increased penetration allows for lower pharmacological doses and more targeted effects. On the other hand,

polymer-based colloidal systems were found to accelerating transport of drug to inner part of eye, drug transport to the inner eye or by accumulating in the corneal on junctional epithelial layer (Chitosan nanoparticulate containing Cyclosporine). The topical delivery of acyclovir via microscopic particles appears to be a promising option. Using chitosan with a high molecular weight extended the efficacy of Ofloxacin.[32]

OTHER APPLICATIONS OF ENTERIC COATING MICROSPHERES

1. Enteric coated microspheres help in reducing gastric discomfort like gastric burning, gastric irritation etc. which caused by drugs [33].
2. The enteric coated microspheres permit the dosage form to tolerate a hostile, low pH environment without degrading [34].
3. Bioavailability of drug also increases by increase in solubility through enteric coating [35].
4. Through enteric coating target site can be achieved mainly small intestine [36].
5. By enhancing gastric retention time, solubility of poorly soluble drug also increased by using enteric coating [37].

CHARACTERIZATION OF ENTERIC COATING MICROSPHERES

1. **"Particle size analysis"-** The dried microspheres were measured with a calibrated optical micrometre using a microscopic method; conventional light microscopy is the most widely used technique for visualising micro-particulars (LM) [38-39].

2. **"Scanning electron microscopy (SEM) study"-** The sample were investigated using a scanning electron microscope (SEM), which was highly qualified for image processing and conducting x-ray diffraction analysis (EDXA) for elemental structure determination where specific elements had been found. The material was inspected in lines by using electron beam (centred) in this approach. Formulation were put on holder for analysis, which was preceded by a sputter coater covered by a metal having good conductive properties such as platinum, zirconium. Directed, fine electron beam was then used to scan the material. The secondary electron lost from the sample surface were used to calculate the sample`s surface characteristics [40].

3. **"Flow properties" -** Flow properties of enteric coating microspheres can be determined by using 1. Hausner ratio, 2. Angle of repose. 3. Carr`s compressibility index for assessing densities (bulk as well as tapped) a volumetric cylinder was used [41].

4. **"Determination of percentage (%) yield" -** This calculated by calculating the products amount(measured) and polymer used in the formulation [42].

% Yield = Practical Yield / Theoretical Yield × 100

5. **"Drug content" -** Allow for sedimentation and then wash the mixture. 1ml of the mother liquid was poured to a flask, and then volume of liquid was maintained with 0.1 normal NaOH. Lastly after the proper dilutions, the sample was measured using spectrophotometer [43].
6. **"FTIR Analysis"-** To study the compatibility between the drug and polymer [44].
7. **"DSC" -** To determine whether there are interactions between drug-polymer [45].
8. "**Drug Entrapment Efficiency" -** To estimate drug entrapped in the microspheres [46].

DEE= (amount of drug actually present/theoretical drug load expected×100)

9. **"In-Vitro Drug Release Study" –** By using dissolution media of [pH 1.2 HCl and Phosphate buffer pH 7.6 (SIF)] [47]**.**

CONCLUSION -:

Microspheres which are enteric coated are better drug delivery system than rest of the others. Enteric coated microspheres improve drug bioavailability by enhancing their solubility, increases gastric retention time, and also provides the targeted drug delivery, hence reduces the side effects. There are various methods explained for preparing enteric coated microspheres and their characterization. These enteric coated microspheres give more potency, which gives enhanced results in in-vivo delivery system.

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