MICROSPHERES: A UNIQUE DRUG DELIVERY SYSTEM WITH IMMENSE BIOPHARMACEUTICAL SOLICITATIONS

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ABSTRACT

Term microspheres defined as “free flowing particle with size range 50nm to 2 mm containing the API”. Generally, the terms microspheres & microcapsules are used synonymously. Although other various terms like “microbeads” & spherical particles (for larger particles) also used. Ideally the size of microspheres considers less than 200µm. In these spheres the drugs are either in dispersed or dissolved in polymeric matrix uniformly which has capable to control release the drug to desired rate. This system achieved greater attention not only because of prolonged release but also for the delivering the anticancer drugs to desired site. Moreover, microsphere is modestly adopted by human body and these microspheres easily diagnosis the diseases. Microspheres, due to high surface area and low particle size significantly increase the absorption rate and bio-availability. They are also useful to provide the controlled release or sustained release and site specific drug delivery. In future by combining various other strategies microsphere will find a central place in advanced drug delivery, particularly in diagnostics, diseased cell sorting, gene and genetic material delivery, targeted and effective in-vivo delivery. The present review explains the methodology of preparation of microspheres and their recent applications and also updates the recent research on microspheres.

KEYWORDS: Microspheres, Sustained release, polymers, drug delivery.

1. INTRODUCTION

The concept of advanced drug delivery system has been revolutionized. The reason behind revolution was delivering the drug to specific site at the rate & concentration, which produce optimum therapeutic effects & minimized the ADRs. In the ADDS, the delivery systems
offering sustained & controlled release of drug at desire site had been attained greater attention than other system. In 1940s & 1960s the chemical micro capsulation technology was an alternative way to delivering the drugs. Later in 1980s polymer membrane technology replaced former technology. In continued, the process of targeting or site specific delivery could be achieved by attaching biomolecules with liposomes, various particulate carriers like microspheres & nanoparticles, niosomes, resealed erythrocytes, implant etc. From the drug delivery system, the microspheres accepted as reliable one to delivering the drug to specific site & easy to maintain the drug concentration in required site in body.\[1-3]\n
2. Types of Microspheres
a) Bio adhesive microspheres: Microspheres made up with water soluble polymer having properties to adhere to the mucus membrane of GIT, buccal, nasal & ocular and release the drugs for longer period.\[4]\n
b) Magnetic microspheres: This type of microspheres is prepared by incorporation of magnetic carrier along with the polymers to localize the drugs to the disease sites in the body.\[5]\n
c) Floating microspheres: these are the low density system which are lighter than the gastric fluid and remain buoyant in it. This increases the gastric residence in stomach and release drugs for longer times. It reduces sticking and dose dumping thus improve the therapeutic effects.\[6]\n
d) Radioactive microspheres: These types of microspheres are formulated by incorporation of radioisotopes which do not release out from delivery system but they emit \(\alpha\), \(\beta\) & \(\gamma\)-radiation to cure the various disease like tumours.\[7]\n
e) Polymeric microspheres: there are two types of polymer widely used in the microspheres formulations.

A. Biodegradable polymeric microspheres: they are natural polymer like chitosan, gelatin, starch etc. They are capable to degrade in the body and having bioahesion properties. These polymers are having high swellability so controlling the release rates and drug loading cause difficulty during formulation.\[7,8]\n
B. Synthetic polymeric microspheres: The synthetic polymers are widely used in the clinical science. They are quite safe, easy to formulate & easy to control the drugs release rates.\[8]
3. Polymer Commonly Used for Microparticles Formulation

There are three broad categories of polymers used in microspheres formulation.\(^ {13,9}\)

a) Natural polymers
b) Semi-synthetics polymer
c) Synthetic polymers

A. Natural polymers: These are natural in origin, capable to degrade in the body and water solubility & bioadhesion are properties of choice for microspheres formulations. Single emulsification technique is used for preparation of microspheres consisting natural polymers.

a) **Proteins:** Albumin, Gelatin, collagen
b) **Carbohydrates:** Starch, Agarose, carrageenan, chitosan
c) **Chemically modified carbohydrates:** DEAE Cellulose, poly (acryl) dextran, poly (acryl) starch.

B. Semisynthetics polymers: These polymers are obtained after chemical modification of natural polymer to obtain desired polymer properties. They are widely used in ADDS as delivery vehicles. Examples. Hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC), Sod. Carboxymethylcellulose (Sod. CMC), HPC etc.

C. Synthetic polymers: This includes two categories


4. Microspheres: Method of preparation.\(^ {10}\)

a. Single emulsion technique
b. Double emulsion technique
c. Polymerization technique
d. Solvent extraction
e. Phase separation coacervation technique
f. Spray drying and spray congealing
g. Quassi emulsion solvent diffusion
A. Single emulsion technique
Polymers of natural origin like proteins & carbohydrates are converted into microspheres by single emulsion technique. In this method the polymers are dissolved in aqueous medium followed by oily medium. This will form the small globules of aq. Polymer solution. Second step is cross linking by means of temperature or chemical agent like Glutaryldehyde, formaldehyde, di acid chloride etc.[11]

B. Double emulsion technique
This method is suitable for water soluble drugs, proteins, vaccine & peptide using natural or synthetic polymers. The microspheres formulation included preparation of multiple emulsions like W/O/W. The water soluble drugs dissolved in water phase followed by dissolved in polar organic solvent with continuous stirring, this form the primary emulsion. This primary emulsion undergoes homogenization before adding it to aq. Solution of PVA. This gives the double emulsion formation. Later this emulsion subjected to solvent removal either solvent evaporation or solvent extraction method.[11]

![Fig.6- Emulsification technique](image)

C. Polymerization technique.[11]
This technique conventionally used for formulation of the microspheres. Broadly Classified as:

- Normal polymerization
- Interfacial polymerization
Normal polymerization: In this technique monomer or a mixture of monomers along with the initiator or catalyst are dissolved in bulk & polymerization is usually initiate by heating. Polymer obtained in the form of microspheres. Drug loading done during the process of polymerization. Normal polymerization is done using different techniques as bulk, suspension, precipitation, emulsion and micelle polymerization processes. Suspension polymerization is also known as pearl polymerization which carried out by heating the monomers as droplets in continuous phase. Bulk technique gives pure polymers.

Interfacial polymerization: this includes the reaction of various monomers at the interface of two immiscible liquid phases to form a film of polymer that essentially envelops the dispersed phase.

A. Solvent extraction
This method involved evaporation of organic volatile solvent from polymer solution which dispersed in an aqueous phase. The temperature of water, amount of water in emulsion and solubility profile of polymers determine the rate of solvent evaporation.\(^{[12]}\)

The summery of this method a described in follow figure.

![Solvent evaporation method](image)

**Fig. 7- Solvent evaporation method**

B. Phase separation coacervation technique
This method is based on the fact that the solubility of polymer decreases in a solvent to form a polymer rich phase which is known as coacervate. The drug particles are dispersed in the polymer solution, now addition of incompatible polymer to former mixture cause phase separation of first polymer and engulfing of drug particles by newer polymer solution. Incorporation of non-solvents causes hardening of polymer mixture resulting formation of
microspheres. Process variables like rate of coacervate formation determine the particle size, agglomeration of the formed particles & distribution of the polymer film.\textsuperscript{[11,13]}

![Image](https://www.wjpr.net/Vol 4, Issue 11, 2015. 2062)

**Fig.8- phase separation technique**

**C. Spray drying and spray congealing**

These are the commercial method of microspheres formation. In this method polymers are dissolved in organic volatile solvent followed by addition of drug to polymer solution like chloroform, acetone or dichloromethane. This formed dispersion than atomized in the hot air stream which causes formation of small droplets or fine mist. Instantaneous solvent evaporation from these droplets cause formation of microspheres size range 1-100µm, remaining traces of solvent separated by vacuum drying and particles by means of cyclone separator. On the basis of removal of the solvent or cooling of the solution, the processes respectively known as spray drying and spray congealing.\textsuperscript{[11]}

![Image](https://www.wjpr.net/Vol 4, Issue 11, 2015. 2062)

**Fig.9- Spray drying and spray congealing**
D. Quassi emulsion solvent diffusion: In this method the drug & polymer dissolved in an organic solvent and resulting mixture incorporate in the aq. solution of PVP (0.2%) under high stirring speed (500-800). The drug-polymer solution converted in droplet form & solidification of resulting microspheres done by the solvent evaporation.

Fig.10- Quassi emulsion solvent diffusion

Tab. 2- EVALUATION PARAMETER

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<td>Electron spectroscopy for chemical analysis (ESCA)</td>
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<td>Drug loading efficiency</td>
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<td>Swelling index</td>
<td>Weighing method</td>
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<tr>
<td>Surface carboxylic residue</td>
<td>Radioactive glycine</td>
</tr>
<tr>
<td>Surface amino acid residue</td>
<td>Radioactive $^{14}$c- acetic acid conjugate</td>
</tr>
</tbody>
</table>

5. Characterization of Microspheres

1. Micromeritic properties

a. Particle size and shape

The light microscopy (LM) and scanning electron microscopy (SEM) are two commonly used methods to evaluate the particle size and surface properties of microspheres. With help of LM microspheric structures can be visualized before and after coating. But SEM provides higher resolution and allows investigations of the microspheric surfaces and after
particles are cross-sectioned. Other methods like Laser light scattering and multi size coulter counter are also used for this purpose.[22]

b. Bulk density
Specific amount of sample weighed and filled in a measuring cylinder and volume occupied by microspheres consider as initial volume (V0). The bulk density calculated by following formula.[14]

\[
\text{Bulk density} = \frac{\text{Mass of the microspheres (W)}}{\text{Initial vol. of microspheres (V0)}}
\]

c. Tapped density
Specific amount of sample weighed and filled in a measuring cylinder and cylinder tapped against a wooden surface at regular interval for 100 times, than note the volume of microspheres after tapped and tapped density can be calculate as follow[14]

\[
\text{Tapped density} = \frac{\text{Mass of the microspheres (W)}}{\text{Tapped vol. of microspheres (Vf)}}
\]

d. Compressibility index
CI indicates the flowability of microspheres and the % compressibility can be determined by given formula.

\[
\% C = \frac{P_b - P_u}{P_b} \times 100
\]

Where
‘P_b’ is tapped bulk density and ‘P_u’ is loose bulk density

e. Flow properties
Angle of repose commonly used to determine the flow properties of microspheric formulations, for this purpose the funnel method used. The height and diameter of heap noted and the angle of repose can be calculated as follows[15].

\[
\tan \theta = \frac{2H}{D}
\]

Where,
H = Height,
D = diameter of heap
Tab. 8-Angle of repose

<table>
<thead>
<tr>
<th>Angle of repose (θ)</th>
<th>Type of flow</th>
</tr>
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<tbody>
<tr>
<td>&lt;20</td>
<td>Excellent</td>
</tr>
<tr>
<td>20-30</td>
<td>Good</td>
</tr>
<tr>
<td>30-34</td>
<td>Passable</td>
</tr>
<tr>
<td>&gt;34</td>
<td>Very poor</td>
</tr>
</tbody>
</table>

1. Encapsulation efficiency
The drug encapsulation of drug within microspheres can be determined by washing microspheres to lyse. The lysated microspheres than subjected to determine the amount of drug as per method mention in pharmacopoeial monographs. The per cent of drug encapsulation within microspheres can be calculated by following formula,[15, 25, 16]

\[
% \text{ drug Entrapment} = \left( \frac{\text{Actual content}}{\text{Theoretical content}} \right) \times 100
\]

2. Electron spectroscopy for chemical analysis
The surface chemical properties of microspheres generally determined by using the electron spectroscopy (ESCA). The surficial degradation of biodegradable microspheres can be determined by spectra obtained by ESCA, because it determined the atomic composition of microspheric surface.[13]

✓ Attenuated total reflectance Fourier-Transform- Infrared Spectroscopy: FT-IR used to evaluate the degradation pattern of polymeric matrix of microspheres. The alternated total reflectance (ATR) investigates, to evaluate the surface of microsphere. The In the FT-IR, IR beam passing through the ATR cell reflected many times through the sample to provide IR spectra mainly of surface material, which reveal the detail the surface properties of the microspheres depend of manufacturing procedures and sample condition.[11]

✓ Isoelectric point
The electrophoretic mobility of microspheres can be measure by micro electrophoresis, from which the isoelectric point can be determined. The mean velocity at different pH values ranging from 3-10 is calculated by measuring the time of particle movement over a distance of 1 mm. The electrophoretic mobility related with surface contained charge, ionisable behaviour or ion absorption nature of the microspheres.[11]
✓ **Surface carboxylic acid residue**

The radioactive glycine used to determine the surface carboxylic acid residue. The reaction of C\textsuperscript{14}-glycine ethyl ester hydro chloride with the microspheres formed the radioactive glycine conjugates, than the radioactivity of conjugate is then determined using liquid scintillation counter. The free carboxylic acid residue measures for hydrophobic or hydrophilic of the microspheres.\textsuperscript{[11]}

✓ **Surface amino acid residue**

This is measured by radioactive C\textsuperscript{14}-acetic acid conjugate. The amino acid residue can be determined indirectly by measuring the carboxylic residue. 1- ethyl-3 (3-dimethyl amino propyl) carbдиiimide (EDAC) is used to condense the amino group and the C\textsuperscript{14}–acetic acid carboxylic acid residue. This method used to measure both the free amino or the free carboxylic acid residues on the base of indirect estimation.\textsuperscript{[11]}

✓ **Stability study**

The protocols regarding stability study mention in the ICH ‘Q1AR2’ guidelines. According to the ICH protocols the stability study should determine at 40 ± 2\textdegree C and 75 ± 5% RH for two month. The testing carried out at 0, 20, 40 & 60 days for accelerated storage condition.\textsuperscript{[16]}

✓ **In -vitro method**

In–vitro method is one of the tools which used to determine the release characteristics and permeability of a drug through membrane. There are numbers of in-vitro and in-vivo techniques used for evaluating the drug release profile. Based on effects of technologically defined conditions and difficulty in achieving the simulating in-vivo conditions, there are numbers of in-vitro release methods have been development. The standard USP or BP dissolution apparatus commonly used to determine in- vitro release study, both rotating elements paddler or basket. The dissolution medium and rotating speed specify in the pharmacopoeias,\textsuperscript{[17,19]}

6. **Relevant studies in the field and outcomes**

1. **Sohail M. F., et al. (2014)** formulated modified release microcapsules of Flurbiprofen for sustained release and reduced gastrointestinal side effects. Microspheres were developed by co-polymer containing Eudragit RS 100 and hydroxypropyl methylcellulose (HPMC) in different drug/co-polymer ratios and method used was emulsion solvent evaporation (MESE) technique. The encapsulation efficiency was 65 - 85 % while regression
coefficient (R2) values from kinetic analysis showed that release followed Korsmeyer-Peppas model with “n” > 1 indicating release mechanism followed super case II transport. The study concluded the MESE technique using Eudragit RS 100/HPMC polymer blend is a suitable approach to development of modified release Flurbiprofen microcapsules.\textsuperscript{[20]}

2. Sudheer P., et al. (2014) formulated the nifedipine microspheres using chitosan as a polymer for mucoadhesive drug delivery. The nifedipine microspheres were prepared by using by o/w/o emulsification cross linking method. The formulations were evaluated for various properties like its drug loading, surface properties, in-vitro release profile and mucoadhesion properties was evaluated in using modified USP disintegration test apparatus model. In -vivo study was done in rabbit model which controlled blood level as compare to pure nifedipine. The conclusion of study was, the microspheres obtained were uneven surface which help in the increasing mucoadhesive properties, all parameters are satisfactory and in- vitro showed controlled and increased drug release microsphere.\textsuperscript{[21]}

3. Bashir S., et al. (2014) formulated and evaluated microspheres of Nateglinide. The ultimate goal was to formulate sustained release microspheres which help to enhance patient compliance. The microsheres were formulated by using varying proportions of biodegradable polymers i.e., Olibanum gum and Guar gum. The method used was calcium chloride/sodium alginate ionic gelation method. The result of this study was drug release was sustained at simulated intestinal fluid (pH 7.2) up to 10 to 12 hrs and olibanum gum retards the drug release for prolong time period. Drug release pattern was Higuchi kinetics model with non-fickian diffusion.\textsuperscript{[22]}

4. Hongfei Liu et al. (2014) formulated the novel pH sensitive microsphere of ion exchange resin. The prime objective of study was to evaluate the biocompatibility and in-vivo pharmacological & toxicological profile. This study also evaluated the possibility of pH sensitive ion exchange resin microsphere for clinical utilizations. The study was concluded that novel pH sensitive ion exchange resin showed that the LD50 after oral administration was more than 18.84 g·Kg.\textsuperscript{[23]}

5. Goudanavar P., et al. (2013) prepared and evaluated the floating microspheres of Esomeprazole magnesium trihydrate (EMT) for prolongation of the gastric retention time for oral delivery. The EMT floating microspheres were prepared by double emulsion
solvent diffusion method by using Ethyl cellulose and different grades of HPMC like K4M, K15M, using Dichloromethane and alcohol solvent systems. The conclusion of study as entrapment efficiency, percentage of yield and particle size improved with combination of Ec+HPMC K15M than Ec+HPMC k4M. The FTIR and DSC studies revealed that no interaction between drug and polymer. Based on the entrapment efficiency, in vitro release of F5 containing ethyl cellulose (300mg) & HPMC (100mg) was found to be best formulation.[24]

6. Muruges S., et al. (2013) developed microsphere carrier system loaded bupivacaine for buccal delivery. Chitosan was used as carrier system which entrapped the bupivacaine and deliver to buccal cavity. The method used to formulate the microspheres was emulsification technique based on glutaraldehyde cross-linking which later coated with polyglycolic acid film. This study concludes that microspheres can potentially be used for controlled release of of bupivacaine for the management of dental pain in the buccal cavity. The microspheres were evaluated and In vitro results show that in the presence of lysozyme, 39 % of the drug was released from the microspheres after 4.5 days while maximum drug release (42.5 %) was achieved on day 1, maximum drug released in the absence of lysozyme.[24]

7. Shivhare U.D., et al. (2013) prepared mucoadhesive microspheres. They used the polymer sodium alginate alone and guar gum. The study was concluded that microspheres prepared with three concentrations of the sodium alginate 0.5% w/v, 1% w/v and 1.5% w/v, showed that method and polymers used were suitable for mucoadhesive microspheres formulations.[25]

8. Shahzad M.K., et al. (2012) formulate the microspheres celecoxib with employing response surface methodology (RSM) for statistical optimization of formulation factors. The method used was solvent evaporation method and polymers used were Eudragit L-100 and polyvinyl pyrrolidon. In this study influence of two independent variables (i.e., the concentration of the two polymers used) on four dependent variables (i.e., recovery, encapsulation efficiency and % drug released) were examine. A celecoxib-loaded microsphere formulation was successfully formulated with optimum recovery, entrapment efficiency and release behavior was proposed.[26]
9. Kumar K., et al. (2012) were formulate and evaluate the floating microspheres of curcumin, to prolonged gastric residence of drug and increase its bioavailability. The microspheres were formulated by using emulsion solvent diffusion method. Polymer used to prepare the formulation were HPMC, ethyl cellulose (EC), Eudragit S 100 in varying ratios. The solvent system consisting of mixture of DCM and ethanol in 1:1 ratio. The conclusion of this study that curcumin microspheres were good approach for prolong its action and increasing it bioavailability.\textsuperscript{[27]}

10. Garud N., et al. (2012) prepared and evaluated the microspheres metformin to achieved its prolong release formulation. The prolong release microspheres were prepared by using polymers like ethyl cellulose, HPMC, carbopol 934 and chitosan and method used was non-aqueous solvent evaporation. The effects of process variables such as drug & polymer ratio, stirring speed, polymer type on various characteristic of polymer were studied. This study conclude that as the stirring speed increased, size of microspheres decrease and drug release rate increase and microspheres made by chitosan showed prolong release up to 15 hrs.\textsuperscript{[28]}

11. Karthikeyan K., et al. (2012) formulated the carbopol gel incorporating drug loaded gelatine microspheres. The objective of this formulation was, to achieve the bioadhesive formulation for drug periodontal delivery. Diclofenac sodium and metronidazole hydrochloride were loaded in gelatin microspheres using Glutaryldehyde cross-linking. Formulated microspheres were evaluated for its various properties such as drug loading, drug entrapment or encapsulation efficiency, particle size, drug release, SEM and DSC. Microspheres were incorporated into carbomer gel and evaluated for drug release.\textsuperscript{[29]}

12. Gowda D.V., et al. (2012) prepared Microspheres of Sugar Cane Wax Containing indomethacin. The method used was melt-emulsified dispersion and cooling-induced solidification. The microspheres were characterized by differential scanning calorimetric and scanning electron microscopy, drug loading and in vitro & in vivo release in albino sheep were also included in evaluation tests. Sugar Cane Wax was chosen because it has physical properties suitable for preparing gastro-resistant, as well as biocompatible and biodegradable microspheres which release entrapped drug in intestinal lumen. Microcid SR capsule was taken as reference and prepared microspheres were showing bioequivalent based on in-vitro and in-vivo data obtained. So it concluded that
indomethacin microspheres encapsulated in sugar wax microspheres by melt method showed good potential for controlled drug delivery systems.\textsuperscript{[30]}

13. Shwetha S., et al. (2012) developed the floating microspheres of a proton pump inhibitor Rabeprazol, to increase the residential time of drug in stomach. The method used was emulsion solvent evaporation and polymers were HPMC K15M and ethyl cellulose. All formulation were evaluated and conclusion of study was as polymer concentration increased, various properties like particle size, percentage yield, percentage buoyancy and in vitro drug release affected. The formulation containing HPMC K15M showed excellent Micromeritic properties and in vitro drug release in comparison to ethyl cellulose. The polymers and method used to prepare the microspheres found suitable and consider alternative to conventional dosage forms.\textsuperscript{[31]}

14. Keerthi T.S., et al. (2012) formulated and evaluated losartan potassium microspheres using solvent evaluation method. The polymer used to formulated the microspheres was natural polymer i.e., Sodium alginate. These formulations were found to be spherical, free- flowing and their morphology (SAM), particle size, drug entrapment efficiency and in-vitro drug release were evaluated. The production yield was found to be maximum in case of solvent evaporation method and the range of the spheres were 50 to 250 μm. The formulations were releases drug up to 12 hrs, that was extended. This study was concluded that losartan microspheres prepared by solvent evaporation method, were suitable to deliver the losartan potassium in a controlled release manner for extended time period, so it can be adopted as a suitable oral delivery of losartan.\textsuperscript{[32]}

15. Patel B., et al. (2012) developed the ethyl cellulose microspheres by using emulsification solvent evaporation method and tween 80 as an emulsifying agent. The effect of various processing parameters like solvent mixture and composition, concentration of emulsifying factor and stirring speed had been examined. The various microspheric properties also evaluated. The smooth surface Spherical microspheres having required encapsulation efficiencies were obtained. The acetone used as oil phase reduces the particle size and the study concluded that the processing factor significantly affect the microsphere size, drug loading capacity and drug release study.\textsuperscript{[33]}

16. Sahoo S.K., et al. (2011) prepared theophylline microspheres using solvent evaporation method with cellulose acetate and evaluate the effect of various processing factors on
their characteristics. The solvent system was acetone/liquid paraffin system which contains Span 80 as a surfactant. Two processing factors effect i.e., drug/polymer ratio (1:1, 1:2, 1:3) and temperature (10 and 35 °C) on microsphere characteristics and drug release were examined. Conclusion of study was as combination of three suitable factors - Span mixture (with HLB value of 4.3), processing temperature of 10 °C and drug/polymer ratio of 1:3 - produced a suitable controlled release theophylline microsphere formulation.

17. Chella N., et al. (2010) prepared the microspheres of diclofenac sodium and evaluated for various properties like drug entrapment efficiency, Size and Size distribution, In-vitro drug release study etc. The microsheres were prepared by novel W/O/O emulsion method using Ethyl Cellulose as polymer to sustained drug action. Formulation & processing parameters such as drug & polymer ratio, volume and concentration of processing medium were optimized to maximize the entrapment efficiency. Loading of drug up to 51.2% in the formed microspheres. The microspheres also evaluated for their kinetic release and best fit release kinetics was achieved with Higuchi plot followed by zero order and first order.\[34\]

18. Chudiwal P.D., et al. (2009) performed a study which title was Statistical Evaluation and Optimization of Influence of Viscosity and Content of Polymer on Floating Microspheres of Clarithromycin. The purpose of study was to develop an optimized gastroretentive drug delivery system (GRDDS) of clarithromycin floating microspheres by the optimization technique. The clarithromycin microspheres were prepared by non-aqueous solvent evaporation method using different grades of hydroxylpropyl methylcellulose (HPMC) such as HPMC 15M (15cps), HPMC K4M (4000cps), HPMC 100LV (100cps) and ethyl cellulose (EC).3^2 factorial design was employed in formulating the GRDDS with different viscosity grades of HPMC (X1) and polymer to polymer ratio Ethyl cellulose: HPMC (X2) as independent variables. Four dependent variables were percentage of yield, drug entrapment efficiency, buoyancy percentage and percentage of cumulative drug release of microspheres after 12 hrs. The results demonstrate that feasibility of the model in the development of GRDDS.\[35\]

19. Deepa M.K., et al. (2009) formulates and evaluates the microspheres of Cefpodoxime proxetil using non-aqueous solvent evaporation method. The polymer used to prepare the microsheres were HPMC K 15 M and ethyl cellulose in different combinations. The
prepared microspheres was floating in nature and this study was concluded that as the polymer-drug ratio increased, the entrapment efficiency, percentage yield as well as buoyancy percentage improved.\textsuperscript{[36]}

20. Kamila M.M., et al. (2009) developed the multiunit floating drug delivery system containing rosiglitazone maleate. The encapsulating agent was Eudragit\textsuperscript{®} RS100 and method used was non-aqueous emulsification-solvent evaporation. The formulation were evaluated and the result concluded that the formulated floating microspheres was successfully prepared with satisfactory percentage yields (69–75%), high drug entrapment (78–97%), narrow size distribution and required target release with the help of statistical design of experiments.\textsuperscript{[37]}

21. Behera B.C., et al. (2008) formulated and evaluated microencapsulated glipizide using the emulsion – solvent evaporation method. The microspheres were prepared using polymethacrylate polymers like Eudragit\textsuperscript{®} RS 100 and RL 100 and characterized for their micromeritic properties and drug loading, FTIR and scanning electron microscopy. In vitro release studies were performed in phosphate buffer (pH 7.4).The conclusion of study was Eudragit microspheres containing glipizide prepared successfully by using an emulsion solvent evaporation technique, which will not only sustain the release of drug but also manage the complicacy of the diabetes in a better manner.\textsuperscript{[38]}

22. Trivedi P., et al. (2008) prepared and characterized the microsphere of anti-inflammatory drug aceclofenac. The ultimate goal behind this formulation was to minimized the drug release in upper GI region and thus avoid its local side effect. The drug targeted to colon by encapsulation within Eudragit S100, RS 100 & RL100 and method used to formulate the microspheres was O/W emulsion-solvent evaporation. All formulations undergo various evaluations, and result shows that the drug- polymer concentration in dispersed phase effect particle size i.e., as concentration increase particle size increase and drug release pattern was matrix higuchi model.\textsuperscript{[39]}

23. Pachuau L., et al. (2008) formulated and evaluated the matrix microspheres for simultaneous delivery of salbutamol sulphate and theophylline. The major objective of formulation was simultaneous delivery of two anti-asthmatic drugs Salbutamol sulphate and Theophylline. The polymer used was ethyl cellulose and method used was emulsion solvent evaporation using acetone/light liquid paraffin system. The microspheres showed
drug-loaded 67-91% of entrapment and release was extended up to 6 to 8 h. The matrix microspheres able for the prolongation and simultaneous delivery of the anti-asthmatic drugs.\[40\]

24. Basu S.K., et al. (2008) prepared and characterized the Nitrendipine loaded eudragit RL 100 Microspheres by using an emulsion-solvent evaporation method. The solvent system used was ethanol/ liq. Paraffine. The ultimate goal of microspheres was to sustain the release of nitrendipine. The drug release was influence by polymer concentration and particle size; the microspheres showed poor drug release at pH 1.2 and extended up to 8 hrs. The conclusion of study was nitrendipine-loaded Eudragit RL 100 microspheres showed good sustained release characteristics under optimized conditions.\[41\]

7. Conclusion and Future Prospects

Microsphere as its name suggests that it is a tiny particle just micron in diameter. It can be design in various shape and size. It can contain various core materials which released the medicines at their target. Microspheres have very broad application in every field of biological science and in targeted drug delivery system. It can be concluded that coated or uncoated microsphere carry a sufficient amount of drug with excellent flow rate and good timing for drug release. Thus enhancing the sustained release at site of action. Moreover, microsphere is modestly adopted by human body and these microspheres easily diagnosis the diseases. Microspheres, due to high surface area and low particle size significantly increase the absorption rate and bio-availability. They are also useful to provide the controlled release or sustained release and site specific drug delivery. In future by combining various other strategies microsphere will find a central place in advanced drug delivery, particularly in diagnostics, diseased cell sorting, gene and genetic material delivery, targeted and effective in-vivo delivery.

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