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A Review on Ocular Microspheres as a Controlled Drug Delivery System

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Abstract: *The eye is one of the intricate anatomical structures in the mortal body which hold multiple physiological barricades that restricts the entry of foreign particles into the eye which makes ocular drug delivery most challenging drug delivery system. These barriers reduce bioavailability of the drugs. This makes it important to developed newer and effective techniques which provide ocular drug delivery with high therapeutic efficacy and better bioavailability. These techniques include iontophoresis, liposome, bio adhesive gels, ocular insert, contact lenses & especially microspheres. Microspheres are a well-developed controlled drug delivery system which can overcome the difficulties of conventional drug delivery system and improve the therapeutic efficacy of the drug. The methodology of delivering a drug to the targeted site of action in a controlled and sustained mode and better bioavailability in ocular delivery system can be achieved.*

Key Words: *Ocular Bioavailability, Microspheres, Sustained or Controlled release, Therapeutic efficacy, Polymers, CDDS (Controlled drug delivery system), LM (Light Microscope), SEM (Scanning Electron Microscope), ER (Extended Release).*

1. INTRODUCTION:

Controlled Drug Delivery System:

Since, the costs and issues included in the marketing of new medicines have increased, with the simultaneous identification of the therapeutic benefits of CDDS, greater attention being paid on the development of this field. The main aim of developing CDDS is to minimize frequency of dosing, reducing the dose and providing uniform and prolong drug delivery at the desired targeted site. So that this system releases drug continuously in predestined pattern for particular period of time to the target organ. [1,2] Controlled release dosage formulations offer several advantages in comparison with the conventional dosage forms such as increased patient safety and patient compliance by reducing the dosing frequency through an increased in the therapeutic duration for a given dose of drug.

Controlled release system means any system that maintains adequate and desired release of drug over an extended time period hydrophilic polymer matrix is broadly used for formulating a controlled dosage form. The goal of controlled release is to provide proper amount of drug at regular interval of time. The use of reservoir system is also known for controlled drug release. [2, 8]

1.1.1 Advantages of CDDS:

1. To upkeep drug concentration within a desired extent.
2. Fast release of drugs having low solubility.
3. To lower dosing frequency and increased patient compliance.
4. To avoid over dose or under dose of the medication.
5. Prevention of side effects and reduction in health care cost.
6. Efficacy in the treatment is enhanced.
7. Reduction in adverse side effects and improvement in tolerability. [3,4,5]

1.1.2 Disadvantages of CDDS:

1. Onset of action of drug is delayed.
2. Possibility of dose discarding in the case of a poor formulation strategy.
3. Potential for first pass metabolism is enhanced.
4. More dependence on gastrointestinal residence time of dosage form.
5. In some cases, there is a possibility of less accurate adjustment of the dose.
6. Cost is higher as compared to conventional doses.
7. All drugs are not suitable to manufacture into dosage forms for extended release. [6,7]

1.2 CONTROLLED OCULAR DRUG DELIVERY SYSTEM

In the case of ocular drug delivery, the main problem regarding to this route is rapid and excessive loss of conventional dosage forms such as eye drops from the eye. This problem leads to very less extent of drug penetrates the corneal layer and get to internal tissue of the eye. The main cause of drug loss includes lachrymal drainage and dilution by tears. This superfluity retards the ocular bioavailability and results into toxicity and side effect. The features need to optimize ocular drug delivery systems

1. It should have good corneal penetration.
2. Contact time of drug with corneal tissue should be prolonged.
3. It should be easy for installation and removal for the patient.
4. It should be non-irritant and at ease form.
5. It should have appropriate rheological characteristics and concentration of viscolyzer.

Since two decades much attention is to be paid on developing sustained and controlled release drug system. The focus of such system based on localization on site of action so as to reduce frequency of dose and efficacy of the drug. [9]

1.2.1 Advantages of Controlled ODDS:

1. To increase accurate dosing of the drug.
2. To conquer the side effects caused by pulse dosing produced by conventional systems.
3. To maintain release of drug in sustained and controlled manner.
4. To increase ocular bioavailability of drug by improving the corneal contact time. This can be attained by effective adherence to corneal surface.
5. To provide targeting within the ocular globe so as to prevent the loss to other ocular tissues.
6. To circumvent the defensive barricades like drainage, lacrimation and conjunctive absorption.
7. To enhance medicine efficacy. [10]

Self-medication, thus improving patient compliances compared to parenteral routes.
Good penetration of hydrophilic and low molecular weight drugs can be obtained through the eye.
Avoidance of hepatic first pass metabolism and thus amount of dose is reduced as compared to oral drug delivery. [11]

1.2.2 Disadvantages of Controlled ODDS: -

Physiological limitation is the low permeability of cornea resulting into poor absorption of ophthalmic preparations.
Systemic side effects may appear because major portion of the administered dose drains into the lacrimal duct.
Tear flow and eye blinking cause rapid elimination of the drug through the eye results in a short duration of action. [11,12]

1.3 Recent Trends in ODDS: -

- Ocular inserts.
- Corneal shields.
- Artificial tear inserts.
- Hydrogels.
- Ophthalmic iontophoresis.
- Muco-adhesive dosage forms
- Phase transition systems.
- Microspheres and Nano-particles. [13]

2. Anatomy of the Eye: -

The human eye is the complex structure and demonstrates architectural wonders of the human body. Eye is a spherical structure with a wall made up of three layers; the inner portion of nervous tissue layer, the middle part composed of choroid layer, cilia body and iris and the outer part is consist of sclera.

The human eye is a challenging and complex organ for topical administration of drugs as it consists of multiple barriers for the drug molecule to cross. The basis of this can be found in the anatomical organization of the surface tissues and in the permeability of the cornea. The protective function of the eyelids and lachrymal system is such that there is rapid removal of material introduced into the eye. [13]

2.1.1 Cornea: -

The translucent bulge cornea located at the anterior site of the eye that carries images to the back of the nervous system. In adults, the radius of cornea is approx. 7-8mm that covers about 1/6th of the total surface area of the eye ball which is a vascular tissue that provides nutrient and oxygen are delivered by means of lachrymal fluid and aqueous humor as well as from blood vessels of the junction between the cornea and sclera. [14, 15]

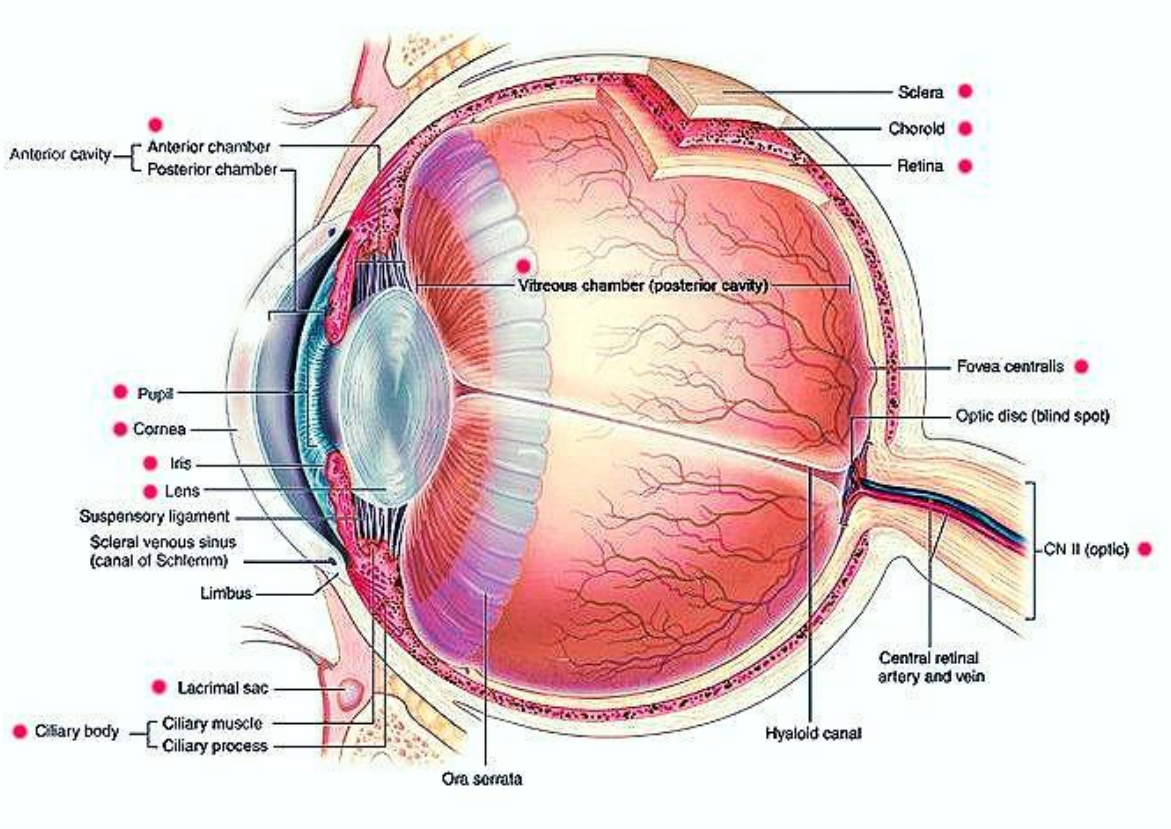

Fig no. 1 Structure of the Eye

2.1.2 Conjunctiva: -

The conjunctiva defends the eye and also involved in the formation and conservation of the precorneal tear film. The conjunctiva is a thin transparent membrane lies in the inner surface of the eyelids and reflected onto the globe. The conjunctiva is made up of an epithelium, substantial propria and sub-mucosa. The conjunctival membrane covers outer surface of the white portion of the eye and the inner aspects of the eyelids. It is loosely attached and hence permits free movement of the eyeball. Other than cornea, the most exposed portion of eye is conjunctiva. [14, 16]

2.1.3. Sclera: -

Sclera has the microcirculation, which nurtures the tissues of this anterior part of eye and is usually white.

2.1.4. The ciliary body: -

The ciliary body includes orbicularis ciliaris, ciliary processes, and ciliary muscle. [13]

2.1.5. Nasolacrimal Drainage: -

Most of the administered drugs are lost through nasolacrimal drainage instantly after administration. The drainage allows drug to be absorbed systemically across the nasal mucosa and the gastrointestinal tract leading to various effects. This system consists of three parts. The secretory portion consists of the lacrimal gland that secretes tears. The distributive system have the eyelids and tear meniscus around the edges of the eyelid of the open eye that spread tears over the ocular surface by blinking; it prevents dry areas from developing. The excretory part consists of the lachrymal puncta, the superior, inferior and common canaliculated; the lachrymal sac, and the nasolacrimal duct. [14]

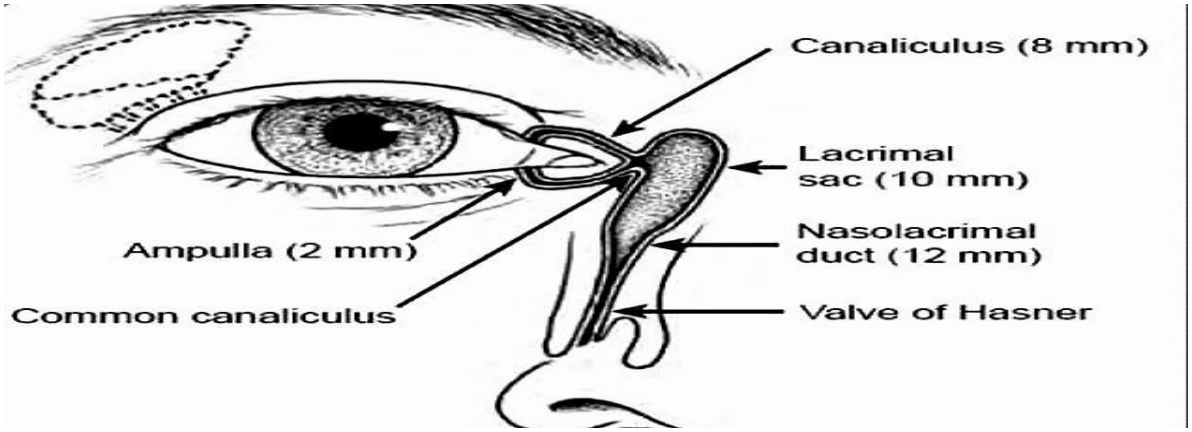

Fig no. 2 Nasolacrimal drainage system

2.1.6. Tear Film:

A thin fluid layer is enclosed the visible part of the eye called as pre-corneal tear film. The mean pH of normal tears is about 7.4. Diurnal forms of pH alter the pH of tear, which is a general shift from acid to alkaline throughout the day. Mean surface tension of tear film is around 44 mN/m. The buffer capability of the tear fluid is investigated by bicarbonate ions, proteins and mucins. Tears demonstrate a non-Newtonian rheological behaviour. [14]

2.2 Physiological Barriers of Ophthalmic Drug Delivery Systems

1. Drug drainage and ocular region: - The lachrymal turnover rate is 1µl/min; therefore, the drug gets washed by lachrymal fluid to the nasolacrimal duct within few minutes. The nasolacrimal drainage is the main reason for reduced bioavailability.

2. Corneal barrier: - The corneal epithelium is made up of epithelial cells which comprises of tight junctions that hampers the Para-cellular transport of drug molecules. Hydrophilic drugs cannot penetrate through the corneal tight junction due to its lipophilic nature, lipophilic drugs can easily penetrate through the barrier.

3. Blood ocular barrier: - This is a physical barrier that separates the local blood capillaries with the parts of eye usually comprising of iris or retina. Blood ocular barrier can be further subdivided into anterior blood aqueous barrier and posterior blood retina barrier.

4. Blood aqueous barrier: - This barrier is composed of endothelial cells which inhibit passage of hydrophilic drugs from plasma to aqueous humor. In the state of inflammation, the permeability of the barrier can be compromised.

5. Blood retinal barrier: - This barrier is composed of retinal capillaries and retinal epithelium which easily allows the drugs to the choroid extravascular space. Despite of easy permeability the drug cannot reach the retina because of limited distribution of capillaries into retina. [18, 19]

2.2.1 Mechanism of Controlled and Sustained Release of Drug into the Eye: -

- The major mechanism of absorption for the most conventional ocular therapeutic entities is corneal absorption.
- For absorption of non-erodible ocular insert with dispersed drug, passive diffusion mechanism plays important role.
- Gradual dissolution regulates the controlled release of solid dispersed drug as a result of inward diffusion of aqueous solution. [10]

3. MICROSPHERES

Microspheres are small sphere-shaped particles, with diameters in the micrometre size range (typically 1 µm to 1000 µm). Microspheres are also called as micro-particles. Microspheres are prepared from various natural and synthetic polymers. Microcapsules and microspheres both are often used as synonyms. [30] There are two common type of polymer microspheres. Polyethylene and polystyrene microspheres. Polystyrene microspheres are often used in biomedical applications. [25]

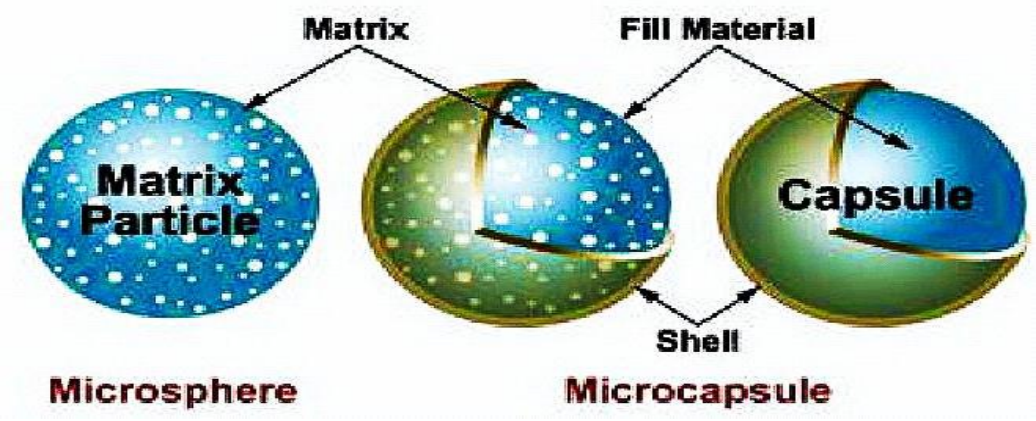

Fig no. 3 Microspheres and Microcapsules

3.1. Microspheres in Ocular Delivery

Major problem involved in ocular drug delivery is the rapid elimination of conventional liquid eye drops from the eye is still remains unsolved. The factors like, rapid tear turnover leads to precorneal loss, irritation caused by drug preparation and relatively large volume of administered eye drop lead to induction of tear flow and high extent of lacrimal drainage. Due to resulting elimination rate, the precorneal half-life of drugs is considered to be between about 1-3 min applied by these pharmaceutical formulations. As a result, small amount of approximately 1-3% of dose literally penetrates into cornea and is get to intraocular tissues. On the other hand, high extent of dose of drug drained into the nose or into the gut. Not only nose but the gut also a very important organ of the body for absorption. This in turn results in high systemic absorption and leads to toxic effects of drugs. While these difficulties have been identified for a long time, amazingly very less attempts have been made by pharmaceutical industries to upgrade this condition and only few substitutes for ocular drug delivery are available in the market. One probability for such systems is the usage of small particles. These colloidal particles have an advantage that they can be applied in liquid form just like eye drop solutions. Suitable small particle systems include microspheres, microcapsules as well as nanoparticles and Nano-capsules. Micro-particles have size above 1μm.

Microspheres are rigid particles having porous, solid polymer matrix and microcapsules composed of polymeric membrane surrounded by solid or liquid drug reservoir. Nanoparticles having particle size in the nanometre size range below 1 μm. Monolithic micro-particles or nanoparticles comprise the drug either dissolved in the polymer matrix in form of a solid solution or suspended in form of a solid dispersion. Simultaneously, drug can be adsorbed to the particle surface. It is necessary to remember that the particle size for ophthalmic applications should not exceed 10 μm because particles with larger size, scratching might occur. Therefore, reduced particle size improves patient's comfort during administration. [20, 21, 22]

The major advantages of the microsphere formulation prepared by dispersing drug loaded microspheres:

- Easy in administration.
- It should have better biocompatibility and biodegradability.
- Variation of drug release rates and durations by carefully influencing the type of microspheres used in the dispersion.
- Minimal migration of particles in vitreous.
- Frequent re-administrations possible without need of removal of previous implants. [24]

3.2 Methods of Preparation of Ocular Microspheres

3.2.1. Single Emulsion Solvent Evaporation Technique:

In this process dissolution of polymer in organic solvent along with the emulsification of aqueous phase having the emulsifying agent. The formed emulsion is stirred for few hours in atmospheric conditions and allows the solvent to evaporate afar this it is washed, rinsed and dried in the desiccators. Designed and manufactured drugs are entrapped in the microspheres with polymers by diffusion-evaporation method with emulsion solvent. [32]

Fig no. 3.1 Single Emulsion Solvent Evaporation Technique

3.2.2. Double Emulsification Method:

This technique involves preparation of double emulsion either w/o/w or o/w/o. The aqueous drug solution is distributed in a continuous manner in lipophilic phase. The continuous phase contains polymer solution which is later encapsulates the medication which containing dispersed aqueous phase to produce primary emulsion. The previously formed emulsion undergoes homogenization or sonication. The microspheres entrapped the drug and intended for prolonged the release of the medication by the mechanisms like diffusion and erosion. [31,32]

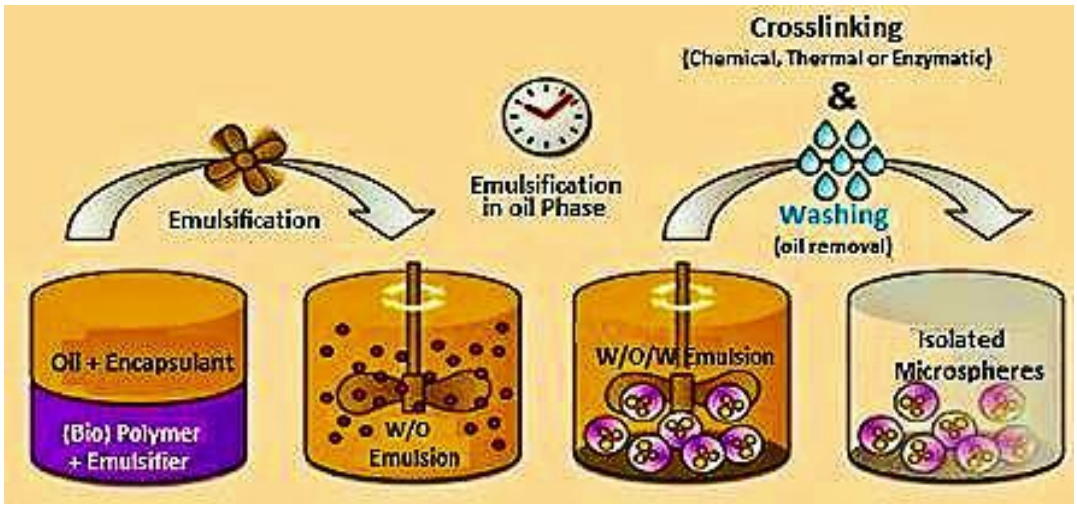

Fig no. 3.2 Double Emulsification Method

3.2.3 Spray Drying Technique:

This technique was used to produce polymer blended microsphere which is loaded with the drug. This requires dispersing raw substance into liquidize coating liquid, then spraying mixture into air for solidification of surface along with the instant solvent evaporation. Organic solvents and polymer solutions are prepared and sprayed in different ratios of weight and drug in the particular laboratory conditions producing microspheres which are filled with medications. This is fast but the crystallinity may loss because of rapid drying. [33]

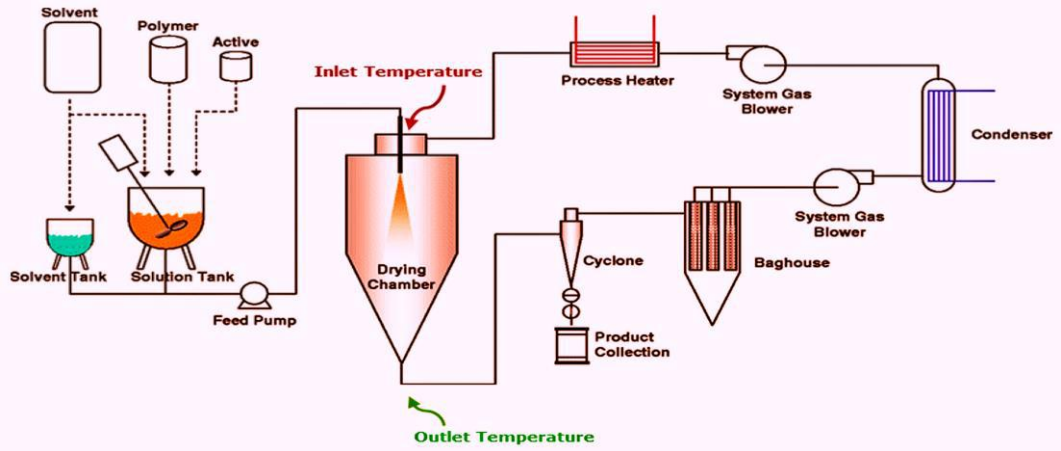

Fig no. 3.3 Spray Drying Technique

3.2.4 Coacervation:

This technique is the direct separation of macromolecular fluid into the two types of immiscible material, a thick coacervate layer, comparatively liquefied in macromolecules and a distilled layer of equilibrate. This method is referred as basic coacervation, in the presence of just one macromolecule. When two or more oppositely charged macromolecules are involved and they are regarded as a complex coacervation. The formation is caused by particular factors like temperature shift. Use of non-solvent or micro-ions contribute to the dehydration in macromolecules, as they promote the interactions between polymer and polymer through polymer solvent interactions. [33]

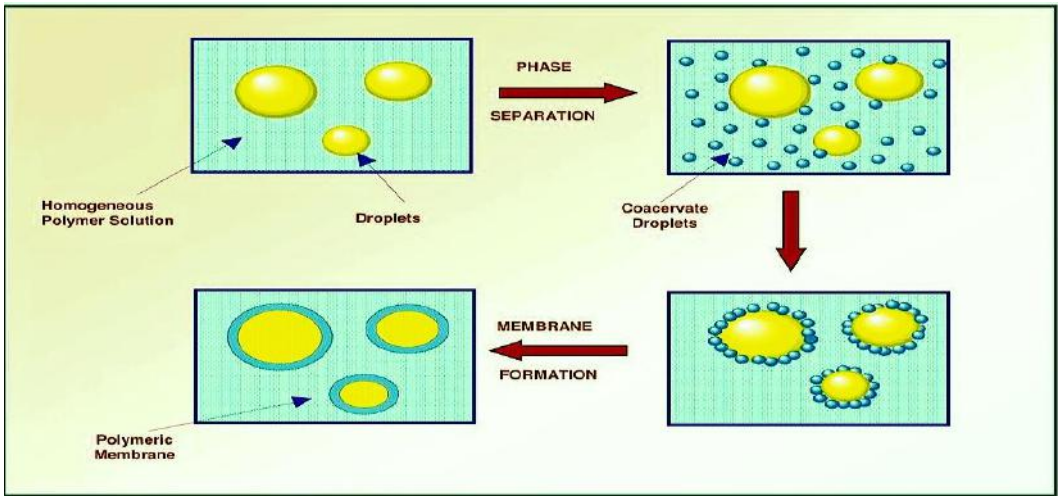

Fig no. 3.4 Coacervation and Phase Separation

3.2.5 Precipitation:

It is a modified form of the evaporation technique. In the emulsion polar droplets are dispersed in non-polar medium. The use of co-solvent can withdraw solvent from droplets. Successive increase in concentration of polymers involves precipitation to produce a microspheres suspension. [35]

3.2.6. Solvent Evaporation:

The technique of solvent evaporation has also been broadly used in formation of PLA (polylactic acid) and PLGA (polylactic-co-glycolic acid) microspheres which consists of many drugs. Some factors were remarkably affect microspheric characteristics such as solubility of drug, internal morphology, type of solvent, diffusion rate, temperature, polymer composition, viscosity and drug loading. The potency of the solvent evaporation system to create microspheres depends on the effective intricacy of active constituent into the particles, and therefore this process is specifically capable with drugs that are either insoluble or partially soluble in the liquid medium that composed of the constant phase. [34]

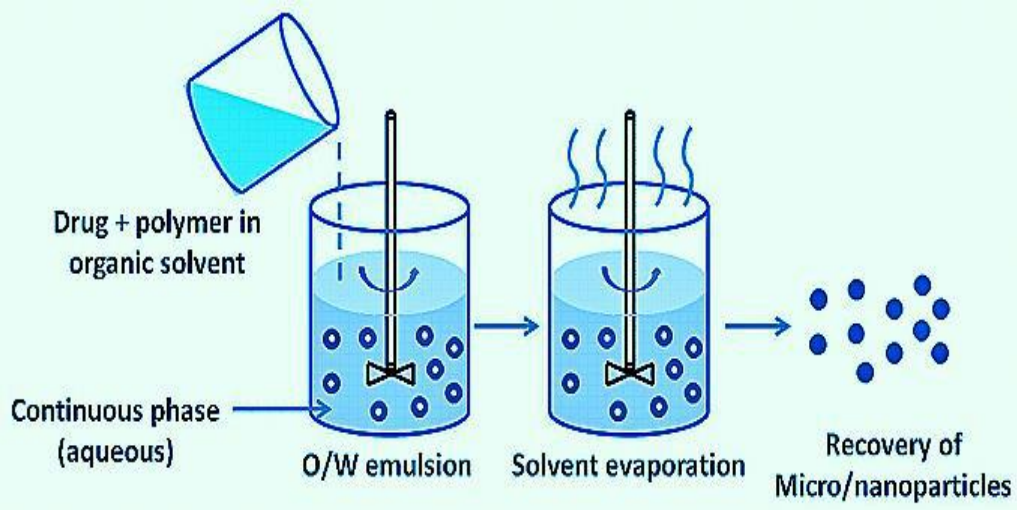

Fig no. 3.5 Solvent Evaporation Technique

3.2.7. Ionic gelation method:

Inotropic gelation is dependent on the capacity of polyelectrolytes to cross connect to produce hydrogel beads often termed as gelispheres in existence of counter ions. Gelispheres are circular cross linked polymeric hydrophilic agent are capable of considerable gelation and thickening in model biological fluids and drug release is regulated by polymer relaxation through it. The hydrogel beads prepared by dumping a heavily loaded polymeric solution into polyvalent cations aqueous solution. The cations migrate through the heavily loaded drug hydrophilic compounds, creating a three-dimensional lattice the moiety is ionically cross-linked. Biomolecules also be placed into these gelispheres to retain their three dimensional structure under the moderate situation. [26]

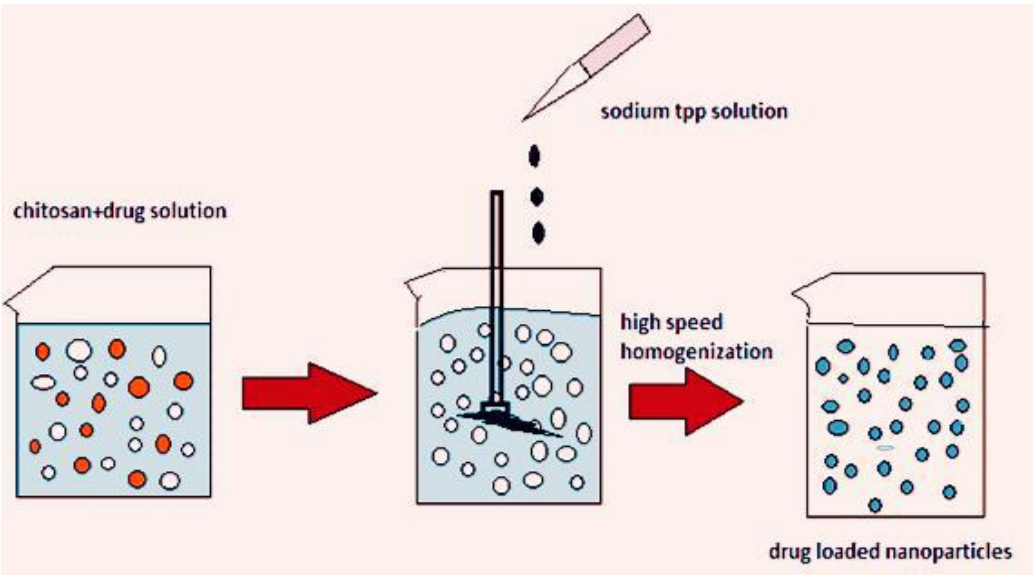

Fig no. 3.6 Ionic Gelation Method

3.2.8. Polymerization:

Polymers show appreciative biological behaviour like bio-adhesion and permeability enhancing properties make it suitable material for designing ocular drug delivery medium. Polymer hydrogels have elastic properties hence it provides better acceptability with regarding to the semisolid or solid preparation. For ocular drug delivery, the formulations like suspensions, ointments, chitosan gel enhance mucin adhesion that covers the corneal surface and conjunctiva of the eye and this causes to increase the residence time. [25,26] Microspheres for ocular drug delivery produced from synthetic polymers (i.e. poly (alkyl cyanoacrylates) have been mainly produced by emulsion polymerization. In this procedure, a poorly soluble monomer is dissolved in the continuous phase which can be aqueous

or organic. The polymerization is initiated chemically by pH shift, or by treatment with gamma-rays, ultraviolet (UV) or visible light. Location of polymerization is in continuous phase where dissolved monomers react with each other and grow until particle formation by phase separation occurs. Additional monomers diffuse to resulting growing polymer particles and maintain the polymerization. [6]
Materials used in microsphere formulation mainly are polymers, they are classified as follows.[27,28,29]

➢ **Synthetic Polymers**

a) Non-biodegradable polymers Ex- Poly methyl methacrylate (PMMA), Acrolein Glycidyl methacrylate, Epoxy polymers
b) Biodegradable polymers Ex- Lactides, Glycolides and their co polymers, Poly alkyl cyano acrylates, Poly anhydrides.

➢ **Natural polymers**

They are mainly obtained from the different sources like proteins, carbohydrates and chemically modified carbohydrates. They are also used proteins like Albumin, Gelatin, and Collagen, Carbohydrates like Agarose, Carrageenan, Chitosan, Starch and also chemically changed carbohydrates used like Poly dextran, Poly starch.

Table no. 1 Polymers used in ophthalmic preparations [16]

Drugs	**Polymers**
Amikacin	Poly(butyl)cyanoacrylate
Betaxolol	Poly(epsilon)caprolacton Poly(isobutyl)cyanoacrylate, Polylactic-co-glycolic acid
Carteolol	Poly(epsilon)caprolacton
Chloramphenicol	Polylactic acid
Hydro-cortisone	Albumin
Indomethacin	Poly(epsilon)caprolacton
Pilocarpine	Albumin Cellulose-acetate hydrogen phthalate Gelatin Poly(butyl)cyanoacrylate Poly(hexyl)cyanoacrylate Polylactic acid, Poly(methyl)methacrylate acrylic-acid-copolymer, Poly(methyl)methacrylate, Polyamide, Poly phthalamide
Progesterone	Poly(hexyl)cyanoacrylate Poly(butyl)cyanoacrylate
Timolol	Poly(alkyl)cyanoacrylate

3.3 Evaluation Techniques for Microspheres:

3.3.1. Particle Size and Shape

It is the most commonly used techniques for visualization of micro-particles are typical light microscopy (LM) and scanning electron microscopy (SEM). Both of the methods used to estimate shape and outer structure of micro-particles. LM regulates the coating parameters in double walled microspheres. The microspheres structure can be visualized before and after coating and difference can be measured microscopically. SEM allows investigation of double walled system. Confocal fluorescence microscopy is used for structure identification of multiple walled microspheres. Scattering of laser light is used for the determination of size, shape and morphology of microspheres. [36]

3.3.2. Capture Efficiency

The capture efficiency of microspheres is percentage of drug entrapment in the microspheres. Percent entrapment can be estimated by allowing microspheres to lyse after washing. The lysate is then used for the estimation of active components as per the requirement of the monograph. The percent of entrapment can be calculated by using following formula:

% Entrapment = Actual content/Theoretical content x 100

3.3.3. Angle of Contact

Angle of contact is used to determine wetting property of micro particle carriers. It is used to estimate hydrophilic and hydrophobic nature of microspheres. The presence of adsorbed component affects the thermodynamic property which is particular to solid. Angle of contact is measured at the interface of solid/air/water. The increasing and decreasing angle of contact can be measured by putting a droplet in a circular cell arranging the above objective of inverted microscope. Angle of contact is measured at 200^0C in a minute of deposition of microsphere. [36]

3.3.4. Flow Properties

The flow properties of the powders can evaluate by determining the Carr's compressibility index, Hausner's ratio and by the angle of repose. [37] Angle of repose can be calculated by using formula:

$$\text{Angle of repose} = \tan^{-1}(h / r)$$

3.3.5. Thermal Analysis

Thermal analysis methods are used to analyse changes regularly by applying planned difference in temperature for heating and cooling, as well as applying defined atmospheres and pressures. The most commonly observed properties include subtle difference in heat and enthalpy, weight loss or weight gain, Young's modulus, thermal expansion or shrinkage and evolution of gas. [38]

3.3.6. Determination of Percentage Yield

The percentage yield can be calculated by measuring the amount of the product and the polymers used in formulation of the microspheres and the sum of microspheres produced. [39]

3.3.7. Drug Content

The mixture should be kept aside to allow particles to sediment and then washed. Then 1mL was transferred into the volumetric flask from filtrate, and volume was balanced with 0.1N NaOH. Drug was measured spectrophotometrically after the correct dilution. [40]

3.3.8. Determination of Drug Loading

Loading ability is the amount of drug entrapped per unit weight of the nanoparticle which gives the percentage of nanoparticle weight that is attached to the encapsulated materials. Loading capacity (LC percent) can be determined by total amount of drug entrapped is divided by total weight of nanoparticles. In the drug delivery, yield is given in the form of percentage which represents the amount of drug delivered per amount. [41]

3.4. Mechanism of Microspheres :-

Majority of drug delivery can be achieved using micro particles avoids the establishment of a matrix-like internal solid dispersion and morphological structure. The medication may be insoluble in polymeric matrix and is released during erosion. Initially water get diffuses into matrix and resulting it to dissolve towards the device's surface. The osmotic pressure is relieved by creating channel to the surface and releasing a predetermined amount of medicine. [23]

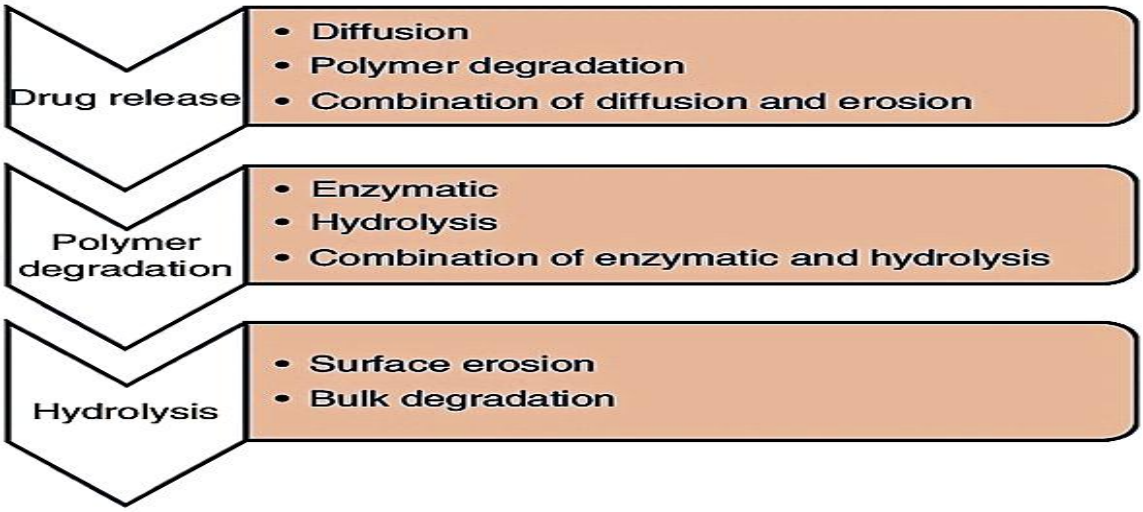

Fig no. 3.7 Mechanism of Drug release in Microspheres

4. SIGNIFICANCE OF MICROSPHERES IN OCULAR DRUG DELIVERY

Many of the researches and the published data recommends that in the ophthalmic drug delivery, it requires accurate particle size and particles with the narrow size range which ensures less irritation, adequate bioavailability and

compatibility with ocular tissues it should be pursued for every suspended drug. An ideal ocular drug delivery system should be the one which can be delivered in the dosage form like eye drops, it should not cause blurred vision or irritability and wouldn't require doses more than one to two doses per day.

Though the optical drug delivery anterior segment of eye is mainly achieved, very less amount of topically applied drug approach to the posterior segment of eye. This made administration of some drugs like antiglaucoma drugs, corticosteroids and certain antibiotics systemically. However, small fraction of dose reaches to ocular tissues which following systemic administration. Through this route the doses need to give the therapeutic effects. Since it can result in substantial side effects. The use of nanotechnology based drug delivery system has results in various solubility-related issues of low soluble drugs (like dexamethasone, budesonide, ganciclovir and many more) in the solution.

Mononuclear phagocyte systems can be also used to permit region specified drug delivery and reduced side effects in other organs. Apart from this, depending on their particle charge, surface properties and relative hydrophobicity, nanoparticles are designed in such a way that it could be successfully overcome the retinal barriers. Additionally, drugs encapsulated in the nano-spheres and liposomes can give protection to the drugs which results in the prolonged action and controlled release of the drug. The drugs which are based on the nanotechnology are capable in crossing membrane barriers, like blood retinal barrier present in eye. The drug delivery systems centered on nanotechnology may established as the best way for drug delivery for some chronic ocular diseases, in which frequency of drug dosing is more like in the case of ophthalmic diseases like chronic cytomegalovirus retinitis (CMV) the topical drug delivery like ganciclovir (GCV) is avoided and intravitreal delivery is preferred. As the half-life of ganciclovir by intravitreal administration is 13 hrs. Hence, to maintain therapeutic levels frequent injections are needed. Therefore, for the long term therapy GCV intravitreal implants are used which can release drug for 6-8 months, but it may cause side effects vitreous hemorrhage and also need surgery to withdraw implants which adversely restricts their use. To overcome these problems nanoparticles having small size and controlled release properties can be used which are made up of various natural polymers like albumin. When drugs are delivered to eye, these nanoparticles didn't cause any inflammation to retinal tissue or didn't disturb the organization and function of surrounding ocular tissues.
Therefore, the use of microspheres and other nanotechnology based drugs are preferred over the conventional drug delivery systems. [42]

5. DRUG LOADING AND DRUG RELEASE KINETICS [43]

For the loading of active constituents over the microspheres mainly two methods are used where first is during the preparation of microspheres and another is after formation of microspheres in which they are incubate with the drug/protein. The loading of the active component is done by the means of:

- Physical entrapment
- Chemical linkage
- Surface adsorption.

The method of preparation and nature of drug or polymer (monomer if used) are the factor on which entrapment is largely depends. By incorporation of drug during time of preparation helps in achieving maximum loading but it can get affected by the other process factors like method of preparation, presence of additives (e.g. cross-linking agent, surfactant stabilizers, etc.) heat of polymerization, agitation intensity, etc. In case of microspheres the release of active constituent from the microsphere is the most important consideration. The nature of polymer used in the preparation and the nature of active drug determines the release profile of the drug. The drug release from both the type i.e. biodegradable and non-biodegradable microspheres is affected by the structure and micro-morphology of the carrier and the features of polymers itself.
The drugs release from the microsphere is followed by the three mechanisms:

- Osmotically driven burst mechanism: - In this method, water get diffuse into core through coating which creates as much pressure that ruptures the membrane.
- Pore diffusion mechanism: - In this method, as name indicates the water continuously penetrates towards the core and the drugs get released.
- Erosion or Degradation of polymers: - In this method the loss of polymer takes place. The polymer erosion initiates with the change in microstructure of the carrier because of penetration of water inside resulting to the plasticization of the matrix

Table no. 2 Microparticles and Nanoparticles involved in ocular drug delivery.

Drug	Prodrug	Evaluation	Ref.
Vancomycin	PLGA	*In-vitro* & *in-vivo* studies	48
Calcein	Starch acetate	*In-vivo* studies	49

Colecoxib	PLGA-PEG	*In-vitro* studies	50
Ketorolac	NIPAAM, VP, AA	*In-vitro* studies	51
Cyclosporine- A	Chitosan	*In-vitro & In-vivo* studies	52
Acyclovir	PEG-PECA	Tolerance & Bioavailability studies	53
Rhodamine /Nile red	Polylactide	Ocular kinetics	54
Ganciclovir	Albumin	Tolerance studies	55
Fluorescein	Chitosan	*In-vitro & In-vivo* studies	56
Betamethasone phosphate	Poly (lactic acid)	*In-vivo* studies	57
LHRH agonist Deslorelin and transferrin	Polystyrene	Surface modification	58
Gatifloxacin	Chitosan-Sodium Alginate	*In-vitro* studies	59
Dexamethasone Acetate	PLGA	*In-vitro & In-vivo* studies	60
Indomethacin	Chitosan	Bioavailability Studies	61
Dorzolamide & Pramipexole	Chitosan	*In-vitro* studies	62
Gene delivery (GFP,RFP)	Chitosan. PCEP	Transfection & toxicitystudies	63
Cyclosporine A	Hyaluronic acid (PECA)	*In-vitro* studies	64
Pilocarpine	Albumin	I- vivo or in-vitro studies	17

6. Recent Studies in Ophthalmic Drug Delivery Using Microspheres

Egg albumin microspheres of pilocarpine nitrate are prepared by using the technique called heat stabilization method. The factors which affect the size and the ability of encapsulation were optimized to produce microspheres in size range 1 to 12 in to make them invisible by eyes and sufficient to entrap drug efficiently. The ability of encapsulation of egg was found to be 63.4%. In the preparation of microsphere gel Carbopol-940 polymer is used. [44]

It is reported that the muco-adhesive microspheres can be formulated by different methods and was evaluated for their muco-adhesion properties. The microsphere formulated by glutaraldehyde (as a cross-linking agent) and thermal cross linking displayed good stability in HCl as compared with microsphere prepared by tripolyphosphate and emulsification ionotropic gelation technique. In controlled and targeted drug delivery system, microspheres are used because it overcomes the difficulties associated with conventional drug delivery like poor absorption, less contact time and poor bioavailability. [45]

The PLGA (poly lactide-co-glycolide) microspheres serve as carriers for topical ocular delivery of a peptide drug vancomycin. In this experiment microspheres were prepared by emulsification/spray-drying technique that can be proposed as an alternative to double emulsion method for production of peptide-loaded micro particles. The drug encapsulation efficiencies were evaluated that was close to theoretical values (84.2–99.5%); average particle size was about 11 mm. The microspheres were able to modulate in-vitro drug release of vancomycin with behaviour dependent on their composition: highest drug content corresponded to highest drug release rate. In-vivo studies were carried out by determining pharmacokinetic profile of Visual acuity in aqueous humor of rabbits after topical administration of aqueous suspensions of microspheres. [47]

The Pectin microspheres are evaluated as an ophthalmic carrier for piroxicam. Microspheres were prepared by spray-drying technique; Scanning Electron Microscope (SEM) is employed for investigation of their morphological characteristics and their In-vitro release behaviour was determined at pH 7.0 USP buffer using a flow-through device. Px loaded in pectin microspheres displayed an earlier In-vitro dissolution rate regarding the solid micronized drug. The precorneal retention of fluorescein-loaded microspheres was determined In-vivo in albino rabbits: an aqueous dispersion of fluorescent microspheres showed a remarkably enhanced residence time in eye (2.5 vs. 0.5 hr.) than fluorescein solution. Hence, it is concluded that bioavailability is increased. In-vivo tests in rabbits of dispersions of Piroxicam-loaded microspheres also indicated a significant enhancement in Piroxicam bioavailability in aqueous humour (2.5-fold) when compared with commercial Piroxicam eye drops. [46]

It is reported that nanoparticles and microspheres are served as promising drug carriers for ophthalmic applications. The binding of drugs depends on physicochemical properties of drugs and polymer used, as well as nano and micro-particle material and also on the manufacturing procedure for these particles. After absolute drug binding to these particles, the ocular bioavailability of a number of drugs is considerably improved in comparison to normal or conventional aqueous eye drop solutions as increased solubility. Generally, smaller particles are better tolerated by the patients than larger particles (no irritation). For this purpose, exclusively, nanoparticles are preferred for long-acting

ocular drug delivery systems, since, larger micro particles displayed slower elimination kinetics from the precorneal compartment. [11]

7. CONCLUSION: -

It can be concluded that the microspheres are promising drug carriers for an ophthalmic administration which assures the controlled and prolonged drug delivery. By the use of microsphere, ocular bioavailability of many of the drugs is improved considerably in comparison to conventional eye drops. Generally, conventional systems of drug delivery possess larger particle size which leads to irritation in eye. While, microspheres have smaller particle size and smaller particles are better tolerated than the particles with larger size. As per the consideration of patient's compliance microspheres are preferred over the conventional route for prolonged and sustained action. According to the future perspective the microsphere based formulation for ocular drug delivery have great scope and application with increased bioavailability, less drug loss and minimal side effects as compared other routes of drug delivery.

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