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A Review on Mucoadhesive Microspheres

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Abstract : Several approaches have been developed to prolong the residence time of the dosage forms at the absorption site and one of them is the development of controlled release mucoadhesive system.
Mucoadhesive polymers have recently gained interest among pharmaceutical scientists as a means of improving drug delivery. Microspheres are small in size and due to this small size they have efficient carrier capacity. They generally have the potential to be used for targeting and controlled release of the drug. The binding of mucoadhesive properties to the microspheres has additional benefits such as much more intimate contact with the mucus layer, effective absorption and increased bioavailability of the drugs due to a large ratio of surface area to volume. This review gives an overview about the potential uses of mucoadhesive microspheres as a novel carriers for improving drug delivery through various modes of administration such as oral, nasal, ocular, topical, vaginal and rectal administration or for systemic effects and also focuses on the types of mucoadhesive polymers, method of preparation of microspheres and their evaluation in vitro and in vivo respectively.
Keywords: Mucoadhesion, Mucoadhesive polymers, Microspheres.

Introduction

Drug delivery through oral route is the most convenient and preferred route of delivering drugs

However, their short circulating half-life and limited absorption through a certain segment of the small intestine has challenged the scientists to develop new methods of drug delivery. There is a continuous need to develop new drug delivery systems with enhanced efficacy and minimum side effects. An approach to improve bioavailability, pharmacokinetic and pharmacodynamics profile of a drug is to release it in a predetermined controlled manner is required. So, mucoadhesive medication are conveyance frameworks which use the property of bio adhesion of specific polymers which wind up cement on hydration[1] and henceforth can be

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utilized for focusing on a medication to a specific district of the body for broadened times of time[2]. Mucoadhesion is a topic of current interest in the design of drug delivery systems. Mucoadhesive drug delivery systems improves the therapeutic activity of drug by forming intimate contact of the dosage form with the main absorbent surface and thus enhancing the residence time of drug. Various dosage forms include tablets - oral, sublingual; plasters, films, gels, pastes, liposomes, microcapsules, nanoparticles, emulsion systems and the like.

Bioadhesion is an interfacial wonder in which two materials, no less than one of which is organic, are held together by methods for interfacial forces[3]. The connection could be between a simulated material and an organic substrate, for example, grip between a polymer and a natural film. On account of polymer appended to the mucin layer of a mucosal tissue, the expression "Mucoadhesion" is utilized. The body contains various mucosal layers like gastrointestinal tract, the urogenital tract, the aviation routes, the ear, nose and eye. Binding of drug to Mucoadhesive layers will help in increase of drug release and their by enhancing its efficacy with minimum dose of drug. This review focus on mechanism, theory of mucoadhesive drug delivery, mucoadhesive polymers, and mucoadhesive microspheres etc., mucoadhesive microspheres is rapidly expanding technology. Microspheres are strict in sense, spherical empty particles. They are characteristic free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature and ideally having a particle size less than 200nm.

Mucoadhesive Drug Delivery Systems

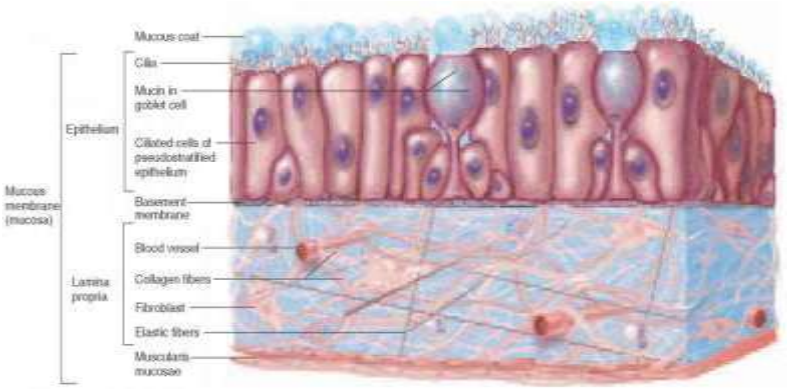

Figure 1: Structure of mucous membrane

Mechanism of Mucoadhesion

For bio adhesion to happen, a progression of wonders, whose part relies upon the idea of the bio adhesive, is required. The main stage includes an intimate contact between a bioadhesive and a film, either from a decent wetting of the bioadhesive surface, or from the swelling of the bioadhesive. In the second stage, after contact is built up, infiltrations of the bioadhesive into the cleft of the tissue surface or interpenetration of the chains of the bioadhesive with those of the bodily fluid happen. Low concoction bonds would then be able to settle.

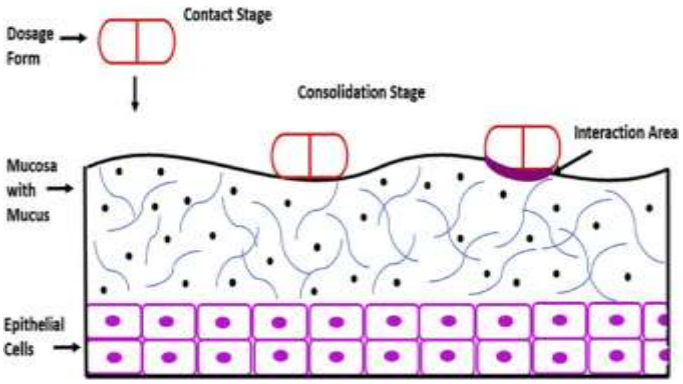

Figure 2: Mechanism of mucoadhesion

On a molecular level, mucoadhesion can be clarified in view of molecular interactions. The connection between two molecules is made out of attraction and repulsion. Attractive interactions arise from Vander waals forces, electrostatic attraction, hydrogen bonding and hydrophobic interaction. Repulsive collaborations happen in light of electrostatic and stearic aversion. For mucoadhesion to happen, the attractive interaction should be bigger than nonspecific repulsion.

Theories of Mucoadhesion[4]

A few speculations have been proposed to clarify the essential mechanism(s) of adhesion. In a specific framework at least one speculation adds to the development of bioadhesive bonds. In any case, there are four classic hypotheses of bioadhesion.

1) Electronic theory:

The glue polymer and bodily fluid ordinarily have diverse electronic attributes. At the point when these two surfaces come in contact, a double layer of electrical charge shapes at the interface, and then adhesion develops due to the attractive force from electron transfer across the electrical double layer.

2) Adsorption theory:

In the adsorption theory, the bioadhesive polymer adheres to mucus due to secondary surface forces, such as Vanderwaal forces, hydrogen bonds, or hydrophobic interactions. For a bioadhesive carboxyl group polymer, it is believed that the hydrogen bond is the dominant force of the interface. On the other hand, hydrophobic interactions may explain the fact that the bioadhesive material may bind more closely to the hydrophobic substrate than to the hydrophilic surface.

3) Wetting theory:

Generally applicable to liquid bioadhesive systems, the wetting theory emphasizes the intimate contact between adhesive and mucus. Thus, the wet surface is controlled by the structural resemblance, the degree of crosslinking of the adhesive polymer or the use of a surfactant.

$S_{AB} = \gamma_B - \gamma_A - \gamma_{AB}$

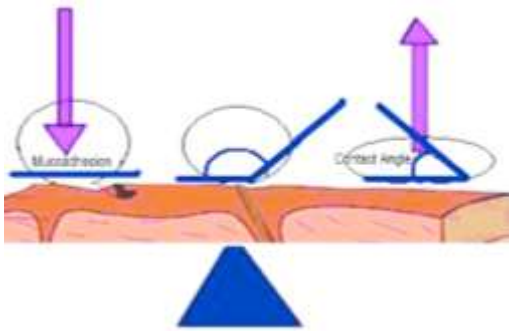

Figure 3: Influence of contact angle on mucoadhesion

4) Diffusion theory:

The essence of this theory is that the glue and substrate chains intertwine to a depth sufficient to create a semi-permanent adhesive bond. The degree of penetration depends on the diffusion coefficients of the two interacting polymers. The diffusion coefficient is known to depend on the molecular weight and crosslinking density of the polymer. In addition, the mobility of the segments, the flexibility of the bioadhesive polymer, the mucosal glycoprotein and the expanded nature of the two networks are important parameters to be taken into account.

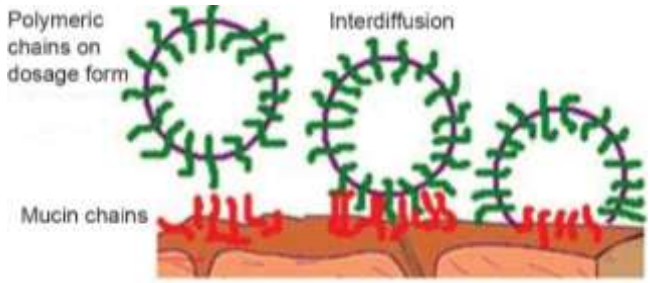

Figure 4: Secondary interaction between mucoadhesive device and of mucus

Factors Affecting Mucoadhesion

The mucoadhesive power of a polymer is affected by the nature of the polymer and also by the nature of the surrounding media.

Bio adhesive polymer-related factors

(1) Molecular weight[5]
(2) Concentration[6]
(3) Chain flexibility[7]

Environment related factors

(1) pH[8]
(2) Initial contact time[9]
(3) Swelling[10]

Physiological variables[11]

Mucin properties, turnover, and disease states

Mucoadhesive Polymers

Mucoadhesive polymers are water-insoluble and water-soluble polymers that are inflatable meshes associated with crosslinking agents. The polymer must have an optimal polarity to ensure that it is sufficiently moistened by the mucus and an optimal fluidity that allows mutual adsorption and mutual penetration of the polymer and mucus. The ideal polymer for the mucoadhesive drug delivery system should have the following characteristics[12].

The polymer and its degradation products must be non-toxic and non-absorbable by the gastrointestinal tract.

- Must be non-irritating to the mucous membranes.
- They should bind efficiently with surfaces of mucin epithelial cells.
- Drug should be easily encapsulated
- They should not interfere with the drug release
- The polymer should not decompose during its shelf life.
- The cost of the polymer should be economical

Mucoadhesive polymers reported in the literature were summarized in Table 1.

Table 1: Mucoadhesive polymers

Polymer	**Bio adhesive Property**[13]
Sodium carboxy methylcellulose	Excellent
Polycarbophil	Excellent
Carbopol	Excellent
Hydroxy propyl methyl cellulose	Excellent
Tragacanth	Excellent
Sodium alginate	Excellent
Hydroxy ethyl cellulose	Excellent
Poly (acrylic acid / divinyl benzene)	Excellent
Gelatin	Fair
Guar gum	Fair
Gum karaya	Fair
Pectin	Poor
Polyvinyl pyrrolidone	Poor
Polyethylene glycol	Poor
Acacia	Poor
Psyllium	Poor
Hydrox propyl cellulose	Poor
Hydroxyethyl methacrylate	Poor

Advantages of Mucoadhesive Delivery Systems

Mucoadhesive systems have three advantages different from conventional dosage forms.

1. Mucoadhesive systems are easily located in the area used to improve and improve the bioavailability of drugs. Greater bioavailability of pibritade, testosterone and its esters[14], vasopressin[15], dopamine, insulinand gentamicin has been observed by mucoadhesive assay systems.
2. Modifies the permeability of the tissues for the absorption of proteins and peptides.
3. Incorporation of permeation enhancers, such as sodium glyucocholate, sodium taurocholate and choline L-fosfatidil (LPC) and protease inhibitor in mucoadhesive dosage forms leads to better uptake of peptides and peptides.
4. Due to increase residence time of drug at the absorption site mucoadhesive formulations can be given once or twice.

Mucoadhesive Drug Delivery Formulations

Mucoadhesive Microcapsules

The mucoadhesive microcapsules with a diameter of 1-1000 µm consist entirely of a mucoadhesive polymer or have an outer coating covering the drug particles. By binding the mucoadhesive properties to microcapsules, offers additional advantages like

1. Effective absorption
2. Increased bioavailability of drugs
3. Providing intimate contact with the mucus layer,
4. Specific targeting of the drug at the absorption site

Localized and systemic effects can be achieved by mucoadhesive microcapsules as they can be adapted to adhere to any mucosal tissue, including those found in the eye, nasal cavity, urine and gastrointestinal tract. The administration of mucoadhesive microcapsules in the mucous membranes of the ophthalmic cavity, stomach and colon is used to administer localized drugs.

Thereby dose frequency is reduced and thus improved patient compliance.

Due to the mucolytic clearance of drugs adhering to the nasal mucosa in case of intra nasally administered drugs. Microcapsules selectively pass the M cell uptake of Peyer's patches into the gastrointestinal (GI) mucosa. This uptake mechanism is used to deliver protein and peptide drugs, vaccine antigens, and gene therapy plasmid DNA. Mucoadhesive microcapsules improve the absorption and oral bioavailability of drugs such as furosemide and riboflavin by keeping the drugs near the absorption window of the GI tract. Another application of mucoadhesive microcapsules is non-invasive, single dose, mucosal immunization concept.

Microspheres

Microspheres are small spherical particles with diameters from 1 μm to 1000 μm. They are free-flowing spherical particles consisting of proteins or biodegradable synthetic polymers. There are two types of microspheres, microcapsules and micromachines, which are described as "microcapsules", are those in which the trapped substance is clearly distinct from a separate wall of the capsule and micrometres in which the entrapped substance is dispersed throughout the matrix. Microspheres are sometimes called microparticles. They are made up of polymers, of natural and synthetic origin. The microsphere plays an important role in improving the bioavailability of conventional drugs and in reducing side effects.

Types of Microspheres

Generally microspheres are classified in to Bioadhesive microspheres, Magnetic microspheres, floating microspheres, radioactive microspheres, Polymeric microspheres are categorized in to Biodegradable polymeric microspheres and Synthetic polymeric microspheres

Bioadhesive microspheres:

Bio membership is defined as sticking of the drug to biological membrane like buccal, ocular, rectal, nasal, using the water sticking property of soluble polymers. Microspheres have an extended residence time on the application site and gives intimate contact with the site of absorption and give better therapeutic action[16,17].

Magnetic microspheres:

This delivery system is one of the most appropriate drug delivery system for locating the drug at the site of the disease. The drug can be either encapsulated in a magnetic microsphere or conjugated on the surface of the microsphere. Accumulation of the carrier in the target object allows delivering the drug locally[18]. In this technique free circulating drug can be replaced by small amount of magnetically directed drug. When they are administered intravenously accumulation occurs within the area where magnetic field is applied and accumulation leads to localize the drug in that particular area. Embedded materials used for magnetic microspheres are chitosan, dextran and so on[19]. These can be used for diagnostic purpose also.

Floating microspheres:

For floating species, the apparent density is lower than that of gastric fluid. So, it retains in stomach without affecting the rate of gastric emptying. As the low density systems floats on the contents of stomach leads to slow release of the drug reduces fluctuations in plasma levels, increase in patient's compliance. It also reduces the chances of dose quenching and dosing and produces prolonged therapeutic effect.

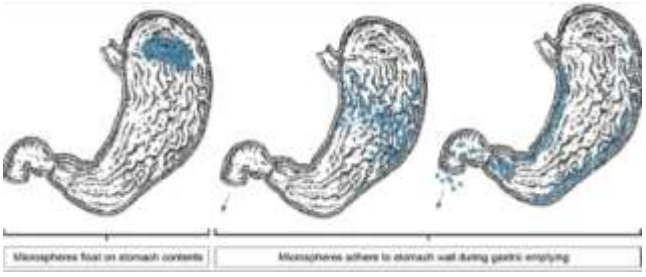

Figure 5: Floating microspheres

Radioactive microspheres:

In this therapy microspheres larger than the diameter of the capillaries are injected in to the arteries, to a tumour site and a high dose of radiation was given to the targeted area without disturbing the surrounding area. These radioactive microspheres are very stable. Types of radioactive microspheres are α emitters, β emitters, γ emitters.

Polymeric microspheres:

Polymeric microspheres are classified as biodegradable polymeric microspheres and synthetic polymeric microspheres.

Biodegradable polymeric microspheres:

These polymers are biodegradable, biocompatible and bio-adhesive in nature. Due to increased swelling properties causes increased residence and contact time with the mucosa. Constant concentration of the polymer and release pattern controls the rate of drug release. However, they offer a broad spectrum of application in the treatment of microspheres.

Synthetic polymeric microspheres: Synthetic polymeric microspheres are used clinically, in addition to being used as a volume agent, fillers, embolic particles, and media for drug delivery. They are biocompatible and safe, but the main disadvantage of this type was they tend to migrate away from the injection site and drive at the possible risk, embolism and additional organ damage[20].

Materials and Methods

Microspheres are usually made up of polymers. They are classified into two types:

1. Synthetic Polymers : They are of two types

a) Non-biodegradable polymers: Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate, Epoxy polymers

b) Biodegradable polymers: Lactides, Glycolides & their co polymers, Poly alkyl cyanoacrylates, Poly anhydrides

2. **Natural Polymers**

Obtained from different sources like proteins, carbohydrates and chemically modified carbohydrates.

Proteins: Albumin, Gelatin, Collagen

Carbohydrates: Agarose, Carrageenan, Chitosan, Starch

Chemically modified carbohydrates: Poly dextran, Poly starch

Preparation of Mucoadhesive Microcapsules

Mucoadhesive microcapsules may be prepared by using the following techniques.

Solvent evaporation:

This is the most widely used microencapsulation method described for the first time by Ogawa et al., 1988. Under heavy agitation the buffer or the ordinary aqueous solution of the drug (may contain a viscosity or a stabilizing agent) is added to an organic phase consisting of the polymer solution in solvents such as dichloromethane (or ethyl acetate or chloroform). The formed emulsion is then added to a large volume of water containing an emulsifier, such as PVA or PVP, to form multiple emulsions (w/o/w). The double emulsion thus formed is stirred continuously until the bulk of the organic solvent is evaporated, leaving solid

microcapsules. The microcapsules thus obtained was washed, centrifuged and lyophilized to obtain dried microcapsules.

Hot melt microencapsulation:

This method is reported by Mathiowitz, E. and Langer, R., in 1987 for the preparation of polybis (p-carboxyphenoxy) propane anhydride polyanhydride copolymer microcapsules with sebacic acid. In this method, the solid drug particles are dispersed in melted polymer and obtained mass was sieved at less than 50 µ. The mixture is suspended in an immiscible solvent (such as silicone oil), continuously stirred and heated to 5°C above the melting point of the polymer. Once the emulsion was stabilized, cooled until the polymer particles are solidified. The resulting microcapsules are washed by decantation with petroleum ether. Microcapsules a diameter of 1 to 1000 µ can be obtained and the particle size distribution can be easily controlled by changing the stirring speed. The main problem for the development of this process is to provide a suitable method for the microencapsulation of water labile polymers, such as field anhydride. Disadvantage of this method was the moderate temperature at which the formulation is exposed.

Solvent removal:

It is a non-aqueous microencapsulation method, particularly suitable for water-resistant polymers such as polyanhydrides. In this method, the drug is dispersed or dissolved in a solution of the selected polymer solution (volatile organic solvent such as methylene chloride). This mixture was then suspended in a silicone oil containing[21]andmethylene chloride. After suspending petroleum ether was added and stirred for complete solvent extraction. The resulting microcapsules can then be dried under vacuum.

Hydrogel microcapsules:

Microcapsules based on gel-like polymers such as alginate can be prepared by dissolving the polymer in an aqueous solution, suspending the active ingredient by mixing and extrusion through a precision machine, to obtain microspheres. As droplets fall into the cured bath, which has been stirred slowly, the curing bath usually comprises a calcium chloride solution, wherein the calcium ions divide the polymer to form gelled micro-capsules. The process includes an aqueous system, which removes residual solvents in the microcapsules.

Lim and Moss have developed this method to encapsulate living cells because they do not include harsh conditions that can kill cells. The surface of these microcapsules can be further modified by coating with polycation polymers such as polylysine after manufacture. By using extruders of various sizes or by changing the flow rates of the polymer solution the size of microcapsules can be controlled.

Spray drying:

In this process, the drug may be dissolved or dispersed in the polymer solution and spray-dried. By the addition of suitable plasticizers (citric acid), the coalescence of the polymer of the drug particles was stimulated and thus promoting the formation of spherical microcapsules and are coated smoothly and quality microcapsules can be obtained.

By controlling the spray rate, drug delivery rate, nozzle size, and drying temperature size of microcapsules can be controlled. This method is less dependent on the solubility characteristics of the drug and polymer. This technique is simple, reproducible and easy to scale.

Phase inversion microencapsulation:

It contains a solution of the polymer (1 - 5%, v / v in the case of chlorine of methyl). The mixture is poured into a solvent-free bath with solids (petroleum ether) insoluble in a solvent / solvent ratio of 1: 100, which is 0.5 to 5.0 microns in size. Then filtered, washed with petroleum ether and air-dried.

Preparation of Mucoadhesive Microspheres

Inclusion of solid, liquid or gaseous substances in one or more polymer coatingscan be made by a microencapsulation technique. The methods used to obtain different microspheres depend on the size of the particles, the duration of release of the drug, the speed indications, the method of crossing, binding, cross

linking drug, evaporation time, co-precipitation, and so on. The different methods of preparations should satisfy certain criteria

1. Ability to include acceptable high drug concentrations.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersion in aqueous vehicles for injection.
4. Release the active reagent with good control over a long period of time.
5. Biocompatibility with controlled biodegradability
6. Sensitivity to chemical modification.

Emulsion solvent evaporation technique[20]:

In this technique, the drug is dissolved in a polymer solution (Eudragit dissolved in chloroform) and the resulting solution was added to an aqueous phase containing 0.2% sodium PVP as an emulsifier. The obtained mixture was stirred at 500 rpm and drug was added. The polymer (Eudragit) is transformed into fine droplets, which solidify forming solid microspheres by evaporation of the solvent, then collected by filtration and washed with demineralised water and dried at room temperature for 24 hours. The microspheres of aceclofenac were prepared by this technique.

Emulsion cross linking method:

In this method, the drug was dissolved in a preheated (1hour at 40 °C) aqueous gelling solution. The resultant solution was added drop wise to liquid paraffin while stirring the mixture at 1500 rpm for 10 minutes at 35° C gives a w / o emulsion. Further stirring is continued for 10 minutes at 15°C. The microspheres thus obtained were washed three times with acetone and Isopropyl alcohol respectively. Then they were air dried and dispersed in 5 ml of aqueous glutaraldehyde[22]. A solution of toluene saturated at room temperature for 3 hours used[36] for cross linking, and then treated with 100 ml of 10µ glycine solution containing 0.1% w / v Tween 80 at 37 °C for 10 minutes to block the glutaraldehyde.

Coacervation method

Thermal change:

It is carried out by dissolving ethyl cellulose in cyclohexane with vigorous stirring at 80 °C. The drug is finely pulverized and added with vigorous stirring to the above solution, and the phase separation is carried out by reducing the temperature by using an ice bath. The above product is then washed twice with cyclohexane and air-dried and then passed through a sieve (No. 40 sieve) to obtain microcapsules.

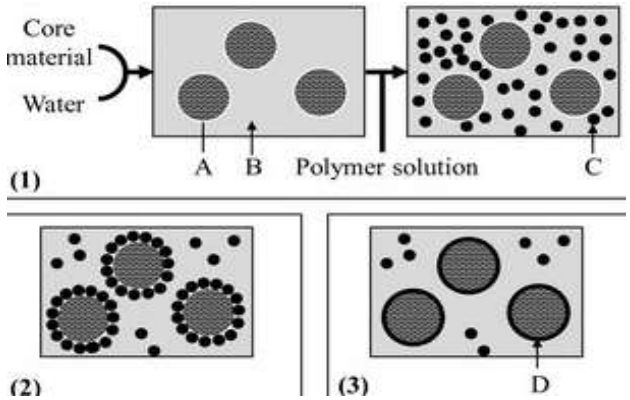

Figure 6: scheme of microencapsulation process by coacervation

Spray drying technique:

This is used to produce a mixed polymer microsphere loaded with a drug. In it the base material is dispersed in a liquefied roofing material, and the mixture is sprayed in an environment to harden the coating, followed by rapid evaporation of the coating solvent. Organic solution of poly (epsilon caprolactone) (PCL) and

cellulose acetate butyrate (CAB) in different weight ratios and drug and are dispersed in different experimental state, realizing microspheres loaded with a drug. It's fast, but it can be loosen the crystallinity due to the fast drying process[23].

Emulsion-solvent diffusion technique:

Floating microparticles of ketoprofen were prepared by using emulsion diffusion solvent technique. The drug was dissolved in a polymer mixture of ethanol and dichloromethane (1: 1). The mixture was then added drop wise to a solution of sodium lauryl sulphate (SLS) and stirred with a shaker at room temperature at 150 rpm for 1 hour. In this manner, the formed floating microspheres were washed and dried in a desiccator at room temperature. The obtained microparticles were sieved and collected[23].

Multiple emulsion method:

Oral administration with a controlled release medicament of indomethacin is prepared by this technique. The initial powdered medicine is dispersed in solution (methylcellulose), followed by emulsifier in a solution of ethyl cellulose in ethyl acetate. The first emulsion was again emulsified in an aqueous medium. In the optimized state, discrete microspheres are present generated during this phase.

Ionic gelation:

By this methodthe alginate / chitosan particle system for the release of sodium diclofenac is obtained. Diclofenac sodium 25% (w / v) was added to a 1.2% (w / v) aqueous solution of sodium alginate. Agitation is done to attain complete solution and then it was added drop wise to a solution containing Ca 2+ / Al 3+ and a solution of chitosan in acetic acid. The formed microspheres are stored in the original solution for 24 hours for internal gelation followed by separation and filtration. Complete release is achieved at pH 6.4-7.2, but the drug is not released at acidic pH.

Hydroxyl appetite (HAP):

Hydroxyapatite (HAP) microspheres with peculiar spheres-in-sphere morphology by dispersing the organic phase (sodium diclofenac containing 5% by weight of EVA and an appropriate amount of PAH) in the aqueous phase of a surfactant, an initial oil / water emulsion is obtained. The organic phase is dispersed in the form of small droplets surrounded by molecules of a surfactant which prevents the co-dissolution of the droplets and helps them to remain individual droplets. While stirring, the dichloromethaneslowly evaporates and the droplets are individually hardened to become microspheres[24].

Polymerization techniques:

The polymerization techniques conventionally used for preparing the microspheres are mainly classified as: Normal polymerization and Interfacial polymerization. Both are carried out in liquid phase[25, 26].

Normal polymerization:

It is carried out by using different techniques as bulk, suspension, precipitation, emulsion and micellar polymerization methods. In bulk, a monomer or a combination of monomers along with the initiator or catalyst is usually heated to initiate polymerization. Polymer so obtained may be moulded as microspheres. Drug loading may be done during the polymerization process. Suspension polymerization also referred as bead or pearl polymerization. It is carried out by heating the monomer or composition of monomers as droplets dispersion in a continuous aqueous phase. Droplets may also contain an initiator and other additives. Emulsion polymerization deviates from suspension polymerization as due to the presence initiator in the aqueous phase, which afterwards diffuses to the surface of micelles. Bulk polymerization has merits of formation of pure polymers.

Interfacial polymerization:

This involves the reaction of various monomers at the interface between the two immiscible liquids to form a film of polymer that essentially envelops the dispersed phase.

Optimization Techniques[27, 28, 29]

Based on the principal of design of experiments (DOE), the methodology encompasses the use of various types of experimental designs, generation of polynomial equations, and mapping of the response over the experimental domain to determine the optimum formulation(s). The technique requires minimum

experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating dosage forms.

Evaluation of Mucoadhesive Microcapsules

The best approach for assessing mucoadhesive microcapsules/microspheres is to evaluate the effectiveness of the mucoadhesive polymer to prolong the drug residence time in site uptake, thereby increasing the absorption and bioavailability of the drug. The methods used to evaluate mucoadhesive microcapsules and microspheres are[30]:

1. Particle size and shape: The most widely used procedures to visualize microparticles are conventional light microscopy (LM) and scanning electron microscopy (SEM).

2.Micromeritic study[31, 32]**:**

a) ***Angle of repose*****:** Angle of repose of each batch was carried out by glass funnel method.

Angle of repose was calculated by the formula, $\theta = \tan^{-1}(h/r)$.

b) ***Bulk density*****:** Bulk density of known mass of microspheres in graduated measuring cylinder. The bulk density was calculated by taking ratio of weight of microspheres in gram to bulk volume of microspheres in cm^3.

c) ***Tapped density*****:** Tapped density is the volume of powder determined by tapping using measuring cylinder containing pre-weighed amount of sample. Tapped density of microspheres was calculated as microspheres in gram to volume of microspheres after tapping in cm^3.

d) ***Carr's index*****:**

Carr's compressibility index = (Tapped density- Bulk density)/ Tapped Density× 100

3. Electron spectroscopy for chemical analysis: The surface chemistry of the microspheres can be determined using the electron spectroscopy for chemical analysis (ESCA).

4. Density determination: The density of the microspheres can be measured by using a multi volume pycnometer.

5. Isoelectric point: The micro electrophoresis is used to measure the electrophoretic mobility of microspheres from which the isoelectric point can be determined.

6. Angle of contact: The angle of contact is measured to determine the wetting property of a micro particulate carrier.

7. ***In vitro*** **methods:** Release studies for different type of microspheres are carried out by using different suitable dissolution media, mostly by rotating paddle apparatus (USP / BP).

8. Drug entrapment efficiency[33]**:**

Drug entrapment efficiency can be calculated using following equation,

% Entrapment = Actual content/Theoretical content x 100.

9. Swelling index: The swelling index of the microsphere was calculated by using the formula,

Swelling index= (mass of swollen microspheres - mass of dry microspheres/mass of dried microspheres) 100

10.*In vitro* wash off test[34]

In vitro bioadhesive properties of microspheres were evaluated with piece of stomach mucosa of goat was tied on glass slide using thread. A Fixed number of microspheres were spread on this mucosa and allowed to wet by mucus for 5min. This glass slide was hanged in grove of USP disintegration test apparatus containing

hydrochloric acid buffer of pH 2.2 and operated for regular up and down movements. After 15 min number of microspheres remain adhered on the mucus membrane were counted and further percentage was calculated.

% mucoadhesion = Number of adhered microspheres/Total number of applied microspheres× 100

Applications of Mucoadhesive Microspheres[35]**(**HemlataKaurav, S. L et al., 2012)

1. Controlled and sustained release dosage forms
2. Enteric coating dosage forms can be prepared
3. Protects drug from environmental hazards
4. Can be used for separation of incompatible substances
5. The hygroscopic properties of many core materials may be reduced by microspheres
6. Microencapsulated drugs reduce gastric irritation
7. Therapeutic magnetic microspheres can be used to deliver the drug to liver tumour
8. Radioactive microspheres are used for imaging of liver, spleen, lung, bone marrow etc.,

Conclusion

Mucoadhesive drug delivery systems are used to enhance drug absorption in a site –specific manner. Mucoadhesive polymers have recently raised interest among pharmaceutical scientists as a means of improving drug delivery by enhancing the residence time and contact time of the dosage form with mucous membranes. Mucoadhesive microspheres can be modified to adhere to any mucosal tissue including those found in eye, nasal cavity, and rectal, urinary and oral mucosal delivery, thus providing the potential for localized as well as systemic controlled release of drugs.

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