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CONTROLLED DRUG RELEASE FOR POORLY WATER SOLUBLE DRUGS- A ROLE OF POLYMERIC NANOPARTICLES

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ABSTRACT: In the treatment of health related dysfunctions, it is desirable that the drug reaches its site of action at a particular concentration and that this therapeutic dose range remains constant over a sufficiently long period of time to alter the process. Delivery of hydrophobic molecules and proteins has been an issue to poor bioavailability following administration. Thus, micelle carrier systems are being investigated to improve drug solubility and stability. Due to problems with toxicity and immunogenicity, biodegradable polymers are being explored as substitutes for synthetic polymers in the development of new micelle system. By grafting hydrophobic moieties to the biodegradable polymer backbone, self-assembled micelles can be readily formed in aqueous solution. The mechanisms involved in controlled release require polymers with a variety of physicochemical properties. Thus several polymers have been tested as potential drug delivery systems, including nano- and micro-particles, dendrimers, nano- and micro- spheres, capsosomes and micelles. In all these systems, drugs can be encapsulated or conjugated in polymer matrices. This review will provide an overview of the biodegradable polymeric micelles that have been developed for controlled delivery of poorly soluble drugs.

INTRODUCTION: Over the past few decades, there has been considerable interest in developing biodegradable nanoparticles (NPs) as effective drug delivery device. Various polymers have been used in drug delivery research as they can effectively deliver the drug to a target site and thus increase the therapeutic benefit, while minimizing side effects [1].

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Therapeutic nanoparticle (NP) technologies have the potential to revolutionize the drug development process and change the landscape of the pharmaceutical industry [2-6]. Nanoparticles could also improve the bioavailability of water insoluble drugs, carry large payloads, protect the therapeutic agents from physiological barriers, as well as enable the development of novel classes of bioactive macromolecules.

Additionally, the incorporation of imaging contrast agents within nanoparticles can allow us to visualize the site of drug delivery or monitor the *in vivo* efficacy of the therapeutic agents [7-8]. The controlled release (CR) of pharmacologically active agents to the specific site of action at the

therapeutically optimal rate and dose regimen has been a major goal in designing such devices. Polymeric micelles have been used as potential drug carriers instead of conventional dosage forms because of their unique advantages which include ability to protect drugs from degradation, target the drug to the site of action and reduce the toxicity or side effect [9].

Polymeric nanoparticles can encapsulate drugs and release them at sustained rates in the optimal range of drug concentration, thus enhancing the *in vivo* therapeutic efficacy, maximizing patient compliance, and facilitating the use of highly toxic, poorly soluble, or relatively unstable drugs [10-11].

Biodegradable polymer: A polymer that loses its weight over time in the living body is called an absorbable, resorbable, or bioabsorbable polymer as well as biodegradable polymer regardless of its degradation mode for both enzymatic and no enzymatic. In other words biodegradable polymers are defined as those which are degraded in biological environment not through thermal oxidation, photolysis, or radiolysis but through enzymatic or non-enzymatic hydrolysis [12].

Biodegradable polymers are becoming increasingly important in pharmaceutical applications especially in the field of drug delivery. Polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions; can also be used as film coatings,

- To disguise the unpleasant taste of a drugs,
- To enhance drug stability and
- To modify the release characteristics [13-14]

Biodegradable polymer is that they are broken down into biologically acceptable molecules that are metabolized and removed from the body by a normal metabolic pathway however biodegradable material do produced degradation by products that must be tolerated with little or no adverse reactions within the biological environment .The degradation products-both desirable and potentially non desirable - must be tested thoroughly ,since there are a number of factors that will affect the biodegradable of original material [15].

Polymeric nanoparticles: Nanostructure materials are materials with sizes in the 1-100 nm range, which demonstrate unique properties and function s due to ”size effect” [16]. Since most biologically active macromolecules and agents such as viruses, membranes and protein complexes are natural nanostructures [17]. The size and structure of nanoparticles also makes it easier for these materials to be integrated into a number of biomedical devices with in past few years, rapid developments have been made to use nanomaterials in a wide variety of applications in various fields of medicine such as cardiovascular and orthopedic. In medicine, nanomaterials have been used in specific application s such as tissue engineered scaffolds and devices, site specific drug delivery systems, cancer therapy and clinical bioanalytical diagnostics and therapeutics [18-20].

Polymer based nanoparticles are submicron –sized polymeric colloidal particles in which a therapeutic agent of interest can be embedded or encapsulated within their polymeric matrix or adsorbed or conjugated onto the surface [21]. These nanoparticles serve as an excellent vehicle for delivery of a number of biomolecules, drugs, genes and vaccines to the site of interest *in vivo*. NPs can be used to safely and reliably deliver hydrophilic drugs, hydrophobic drugs, proteins, vaccines and other biological macromolecules in the body. They can be specifically designed for targeted drug delivery to the brain, arterial walls, lungs, tumor cells, liver and spleen. They can also be designed for long-term systemic circulation within the body. In addition, nanoparticles tagged with imaging agents offer additional opportunities to exploit optical imaging or MRI in cancer diagnosis and guided hyperthermia therapy [22].

Biodegradable polymer in pharmaceutical and bio medical applications

Biodegradable polymers have been used as a main tool to control the drug release rate from the formulations. They are also increasingly used as taste-masking agent, stabilizer and protective agent in oral drug delivery [23]. New technological development in polymer-based encapsulations and controlled drug release system offers possibilities for optimizing the administration of drugs.

These improvements contribute to make treatment more efficient and to minimize side effects and other types of inconveniences for patients [24]. The pharmaceutical applications of polymers range from their use as binders in tablets to viscosity and flow controlling agents in liquids, suspensions and emulsions. Biodegradable polymers can be used as film coatings to disguise the unpleasant taste of a drug, to enhance drug stability and to modify drug release characteristics. Biodegradable polymers are widely used to achieve taste masking; controlled release (e.g., extended, pulsatile, and targeted), enhanced stability, and improved bioavailability [25].

(a) Water-soluble synthetic polymers:

- Poly (acrylic acid): cosmetic, pharmaceuticals, immobilization of cationic drugs, base for carbopol polymer
- Poly (ethylene oxide) coagulant, flocculent, very high molecular-weight up to a few millions, swelling agent
- Poly (ethylene glycol) Mw<10,000; liquid (Mw<1000) and wax (Mw>1000), plasticizer, base for suppositories
- Poly(vinyl pyrrolidone)used to make betadine (iodine complex of PVP) with less toxicity than iodine, plasma replacement, tablet granulation
- Poly (vinyl alcohol) water-soluble packing, tablet binder, tablet coating
- Polyacrylamide gel electrophoresis to separate protein based on their molecular weights coagulant, absorbent
- Poly (isopropyl acrylamide) and poly (cyclopropyl methacrylamide)
- Thermogelling acrylamide derivatives, its balance of hydrogen bonding and hydrophobic association changes with temperature [26-28].

(b) **Cellulose based polymer:**

- Ethyl cellulose insoluble but dispersible in water, aqueous coating system for sustained release applications
- Carboxy methylcellulose super disintegrate, emulsion stabilizer
- Hydroxyethyl and hydroxypropyl celluloses Soluble in water and in alcohol, tablet coating
- Hydroxylpropyl methyl cellulose binder for tablet matrix and tablet coating, gelatin alternative as capsule material
- Cellulose acetate phthalate enteric coating [29]

(c) Hydrocolloids:

- Algenic acid oral and topical pharmaceutical products; thickening and suspending agent in a variety of pastes, creams ,and gels, as well as a stabilizing agent for oil in water emulsions ; binder and disintegrant
- Carrageenan modified release, viscosifier
- Chitosan cosmetics and controlling drug delivery applications, mucoadhesive dosage forms, rapid release dosage forms
- Hyaluronic acid reduction of scar tissue, cosmetics
- Pectinic acid drug delivery

(d) Water-insoluble biodegradable polymer:

- (lactide-co-glycolide) polymers microparticle-nanoparticle for protein delivery

(e) Starch based polymers:

- Starch glidant, a diluents in tablets and capsules, a disintegrant in tablets and capsules, a tablet binder
- Sodium starch glycolate super disintegrant for tablets and capsules in oral delivery [30].

(f) Plastics and rubbers:

- Polyurethane transdermal patch backing (soft, comfortable, moderate moisture transmission), blood pump, artificial heart, and vascular grafts, foam in biomedical and industrial products
- Silicones pacifier, therapeutic devices, implants, medical grade adhesive for transdermal delivery
- Polycarbonate case for biomedical and pharmaceutical products
- Polychloroprene septum for injection, plungers for syringes, and valve components
- Polyisobutylene pressure sensitive adhesives in surgery, a drug carrier in nano- and micro particles
- Poly(vinyl acetate) binder for chewing gum

- Polystyrene petridishes and containers for cell culture
- Polypropylene tight packing, heat shrinkable films, containers
- Poly(vinyl chloride) blood bag hoses and tubing
- Polyethylene transdermal patch backing for drug in adhesive design, wrap, packaging, containers
- Poly(methyl methacrylate) hard contact lenses
- Copolymers with desirable hydrophilic/ hydrophobic interactions.
- Block or graft copolymers
- Complexation networks responding via hydrogen or ionic bonding
- Dendrimers or star polymers as nanoparticles for immobilization of enzymes, drugs, peptides or other biological agents
- New biodegradable polymers
- New blends of hydrocolloids and carbohydrate based polymer [31].

Types of Nanoparticles:

(a) Liposomes: Liposomes are concentric bilayered vesicles in which an aqueous volume is entirely enclosed by a membranous lipid bilayer mainly composed of natural or synthetic phospholipids. Liposomes are characterized in term of size, surface charge and number of bilayers. It exhibits number of advantages in term of amphiphilic character, biocomptability and ease of surface modification rendering it a suitable candidate delivery system for biotech drugs.

Liposomes have been used successfully in the field of biology, biochemistry and medicine since its origin. There alter the pharmacokinetic profile of loaded drug to a great extent especially in case of protein and peptides and can be easily modified by surface attachment of poly ethylene glycol units(PEG)making it as stealth liposome's and thus increase its circulation half-life [32].

Liposomes are formed by the self assembly of phospholipids molecule in an aqueous environment. Amphiphilic phospholipids molecules from a closed bilayer sphere in an attempt to shield their hydrophobic groups from aqueous environment while still maintaining contact with aqueous phase via hydrophilic head group. The resulting closed sphere may encapsulate aqueous soluble drugs within the central aqueous compartment or lipid soluble drugs within bilayer membrane [33].

Unfortunately, are rapidly taken up by liver macrophages [34]. This problem was overcome by coating surface of liposomes with liposome surface ligand, such as monosialoganglioside [35] or polyoxyethylene [36-37], which are called stealth liposomes (stealth liposomes of about 100 nm in size passively target solid tumors by extravasation into their intracellular space upon i.v. administration

(b) **Dendrimers:** Dendrimers are synthetic, branched macromolecules with a well-defined chemical structure, consisting of an initiator core and multi layers with active terminal groups [38-39]. Their specific molecular structure enables Dendrimers to carry various drugs via covalent conjugation to the multivalent surfaces or encapsulation in cavities of the cores through hydrophobic interaction, hydrogen bond, or chemical linkage [40-41]. Besides, Dendrimers can also carry bioactive macromolecules such as DNA by condensing them through electrostatic interactions [42].

The rigidity and the density of the branched units of Dendrimers affect drug release kinetics. By use of pH or enzyme-sensitive linkages, stimulus-responsive dendrimers can be generated [43]. Dendrimers are emerging as an important class of nanoparticles carrier for therapeutic delivery.

Frechet *et al*. have developed a biodegradable polyester dentritic drug delivery system with different architectures and molecular weights, for the delivery of doxorubicin [44]. Dendrimers composed of poly (amidoamine) (PAMAM) polymer have also been extensively investigated for the effective delivery of small molecular drugs [45]. Besides, the cationic nature of PAMAM, dendrimers allow them to effectively deliver macromolecular drugs such as DNA across cellular and subcellular barriers (e.g., cell membrane and endosome) [46]. Attaching targeting ligands to their surface could further enhance the potential of PAMAM dendrimers in drug delivery. A case in hand is a floate-conjugated, methotrexate-loaded PAMAM (G5) dendrimer, which has demonstrated a tenfold reduction in tumor size and exhibited less systemic toxicity, compared to free methotrexate [47].

(c) **Lipid polymer hybrid nanoparticles:** The success of polymeric nanoparticles and liposome's has also motivated the devel9opment of lipid- polymer hybrid nanoparticles, which could integrate the unique advantages of both polymeric nanoparticles and liposome systems, while overcoming some of their limitations. Thus far, several important lipid –polymer hybrid nanoparticles have been developed. For example, lipid coated polymeric nanoparticles comprising a PLGA core, a PEG shell, and a lipid monolayer at the interface were recently described and characterized [48 -53].

The PLGA core is capable of carrying poorly water soluble drugs, while the PEG shell helps to decrease biofouling and increase circulation half life. The lipid monolayer that resides at the interface between PLGA core and PEG shell acts as a molecular fence, promoting drug retention and sustained release from the polymeric core [49, 53]. In another example, a liposome – enveloped PLGA nanoparticles, known as "nanocell" was developed in a multistep manner for the effective treatment of cancers. The nanocell has a PLGA core encapsulating the PLGA-conjugated anticancer drug doxorubicin, and a lipid multilayer shell containing the anti angiogenic agent, combrestastatin. The synergistic effect of the two drugs is obtained through temporally controlled release, where combrestastatin is first released to reduce vascularization, while the sustained release of doxorubicin from the nanocell directly kills the tumor cells [54].

(d) **Polymeric micelles:** Micelles are self-assembled, nanosized colloidal particles with a hydrophobic core and hydrophilic shell [55]. The specialized structure makes micelles suitable carrier for poorly water soluble drugs that account for approximately 25% of conventional, commercially available therapeutics and nearly 50%of candidates identified through screening techniques [56-57]. Insoluble drugs often are characterized by poor bioavailability and rapid clearance after administration, characteristics that are associated with low therapeutic efficacy and high toxicity [58]. Thus using amphiphilic, solubilizing agents, Cremophor EL, can increase water solubility. However a number of problems associated with its use were overcome by developing poly (N-vinylpyrrolidone) - block- poly (D, L-lactide) copolymer that formed polymeric micelles in water and solubilized anticancer drugs [59] (paclitexal, docetaxel, teniposide and etoposide).

Doxorubicin was physically loaded into micelles prepared from polyethylene glycol (PEG)-POLY (β-benzyl-L-aspartate) block copolymer by an o/w emulsion method with a substantial drug loading. This system showed high antitumor activity compared to free doxorubicin [60]. Drug solubility has been greatly improved because of the hydrophilic shell of the micelle; and due to the tunable size of micelles, drugs can be directed to tissue where permeability is enhanced, particularly tumor and

inflammatory tissue. Moreover, when modified by functional molecules that recognize molecular cues specific to diseased sites, micelles can achieve higher tissue specificity and cellular uptake [61-62]. To date, numerous micelle drug delivery systems have been developed, with some achieving clinical testing. However, some concerns, including material toxicity, immunogenicity, low cellular uptake, short half life, and tissue accumulation, have arisen [63].

Degradation of Polymer: Polymer degradation is a change in the properties-tensile strength, colour, shape, etc- of a polymer or polymer based product under the influence of one or more environmental factors such as heat, light or chemicals. Deteriorative reactions occur during processing, when polymers are subjected to heat, oxygen and mechanical stress, and during the useful life of the materials when oxygen and sunlight are the most important degradative agencies. In more specialized applications, degradation may be induced by high energy radiation, ozone, atmospheric pollutants, mechanical stress, biological action, hydrolysis and many other influences. The mechanisms of these reactions and stabilization processes must be understood if technology and application of polymer s are to continue to advance. The study of all these processes has made extensive use of modern instrumental analytical methods and the thermal analysis techniques have been particularly prominent. Various routes of degradation of polymers are given in **Figure 1**.

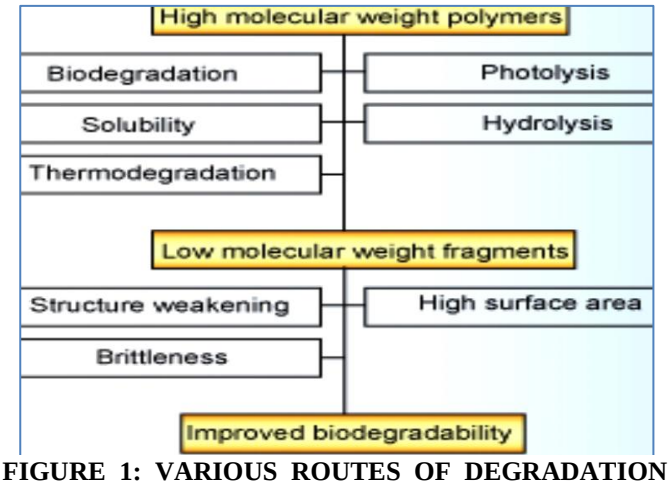

FIGURE 1: VARIOUS ROUTES OF DEGRADATION OF POLYMERS

Factors affecting Bio-degradation of Polymer:

- Chemical structure
- Chemical composition
- Distribution of repeat units in multimers
- Presence of ionic groups
- Presence of un expected units or chain defects
- Configuration structure
- Molecular weight
- Molecular weight distribution
- Annealing
- Morphology(amorphous/semi-crystalline, microstructures, residual stresses
- Presence of low molecular weight compounds
- Processing conditions
- Sterilization process
- Storage history
- Shape
- Site of implantation
- Adsorbed and absorbed compounds (water, lipids, ions, etc.)
- Physicochemical factors(ion exchange, ionic strength, and pH)
- Physical factors (shape and size changes, variations of diffusion coefficients, mechanical stresses, stress and solvent-induced cracking etc.)
- Mechanism of hydrolysis (enzymes verses water [64].

Classifications of poorly water soluble drugs: The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [65]. It allows for the prediction of *in vivo* pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form [66-67].

1. **Class I:** The drugs of this class exhibit high absorption number and high dissolution number. The rate-limiting step is drug dissolution, and if dissolution is very rapid, then the gastric-emptying rate becomes the rate-determining step. These compounds are well absorbed, and their absorption rate is

usually higher than the excretion rate [68]. Examples include metoprolol, diltiazem, verapamil, and Propranolol.

2. **Class II:** The drugs of this class have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than for Class I and occurs over a longer period of time.

   In vitro–in vivo correlation (IVIVC) is usually accepted for Class I and Class II drugs. The bioavailability of these products is limited by their solvation rates. Hence, a correlation between the *in vivo* bioavailability and the *in vitro* solvation can be found. Examples include glibenclamide, phenytoin, danazol, mefenamic acid, nifedinpine, ketoprofen, naproxen, carbamazepine and ketoconazole.
3. **Class III:** Drug permeability is the rate-limiting step for drug absorption, but the drug is solvated very quickly. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. If the formulation does not change the permeability or gastrointestinal duration time, then Class I criteria can be applied. Examples include cimetidine, ranitidine, acyclovir, neomycin B, atenolol, and captopril.
4. **Class IV:** The drugs of this class are problematic for effective oral administration. These compounds have poor bioavailability. They are usually not well absorbed through the intestinal mucosa, and a high variability is expected. Fortunately, extreme examples of Class IV compounds are the exception rather than the rule, and these are rarely developed and marketed. Nevertheless, several Class IV drugs do exist [69]. Examples include hydrochloro-thiazide, taxol, and Furosemide

Drug Delivery System: A system that formulates or device that delivers therapeutic agent(s) to desired body location(s) and/or provides timely release of therapeutic agent(s), such a system by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived and concentrations above or below this range can be toxic or produce no therapeutic benefit at all.

On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues.

From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, bio recognition, and efficacy of drugs were generated. These new strategies, often called Drug Delivery Systems (DDS), are based on interdisciplinary approaches that combine pharmaceutics, polymer science, analytical chemistry, bioconjugate chemistry, and molecular biology [70-71].

Controlled drug delivery Controlled drug delivery is the use of formulation components and devices to release a therapeutic agent at a predictable rate *in vivo* when administered by an injected or non-injected route. To do this, pharmacist and analyst skills are needed to develop and measure release from the formulation, *i.e.* a polymer or device construction.

Controlled Drug Delivery (CDD) occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predesigned manner. The release of the active agent may be constant over a long period, it may be cyclic over a long period, or it may be triggered by the environment or other external events. In any case, the purpose behind controlling the drug delivery is to achieve more effective therapies while eliminating the potential for both under and overdosing [72]. An example of Controlled drug delivery was shown in **Figure 2.**

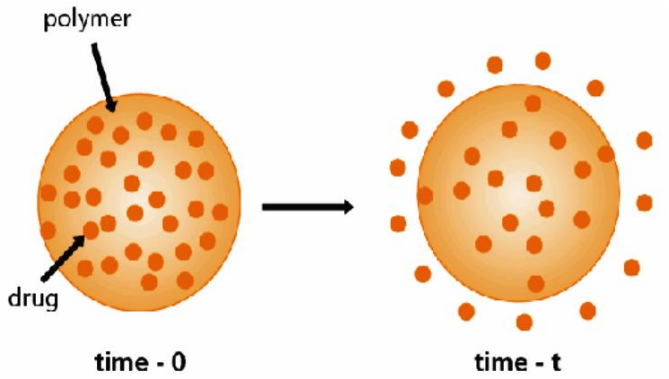

FIGURE 2: CONTROLLED DRUG DELIVERY

Advantages of controlled release drug delivery systems:

- Reduced dosing frequency
- Dose reduction
- improved patient compliance
- Constant level of drug concentration in blood plasma
- Reduced toxicity due to overdose
- Reduces the fluctuation of peak valley concentration
- Night time dosing can be avoided [73]

CONCLUSION: As drug carrier systems, biodegradable polymeric nanoparticles have shown potential to improve hydrophobic drug and protein delivery through enhanced solubility, increased stability, and controllable drug release properties. The action of the drug is limited by their degradation, interaction with other cells, and inability to penetrate tissues due to their chemical nature. Therefore, administration of relatively high doses is required to obtain the desired concentration at the site of action, thus leading to undesirables toxicological and immunological processes.

For, these reasons, research efforts are devoted to designing new formulations, being of particular interest polymeric system of drug carrier, to achieve a higher desired pharmacological response. These polymeric systems are suitable for site-specific and timed controlled delivery of drugs.
Controlled drug delivery can be achieved depending on the features of polymer. From a polymer chemistry perspective, it is important to appreciate that the mechanism of controlled – release require polymer with a variety of physic-chemical properties. Several types of polymers have been tested as potential drug delivery systems, including nano-and micro- particles, Dendrimers, nano-and microspheres, capsosomes and micelles. In these systems, drugs can be encapsulated or conjugated into polymer matrices.
The chemical nature of the many types of polymeric rug carriers available facilitates the distribution and interaction of drugs with their tissue. These carriers also protect their drug cargo from degradation and prevent their side effects.

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