RELATIONSHIP BETWEEN POLYMERS AND DRUG DELIVERY: AN OVERVIEW

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Abstract: The surface and bulk features of polymers make them ideal for use in medication delivery. They are being integrated into pharmaceutical products and medication delivery systems. These systems for administering drugs gradually might be implantable medical gadgets. Small particle colloidal drug carrier systems made from polymers have several benefits as drug delivery systems due to their optimized drug loading and releasing property. The purpose of this article is to examine the production of polymeric particles and learn more about polymer drug conjugation. Polymeric drug carriers and their drug loading are also discussed. The research shows that the optimized drug loading and releasing feature of polymers employed in colloidal drug carrier systems (which consist of microscopic particles) is a major benefit in drug delivery systems. Safeness, effectiveness, hydrophilicity, lack of immunogenicity biological inactivity, sufficient pharmacokinetics, and the presence of functional groups for covalent conjugation of drugs, targeting moieties, or formation of copolymer are some of the general characteristic features that make the polymer a potential candidate for drug delivery.

Keywords: polymer, controlled drug delivery, , co polymer, novel drug, delivery, polysaccharides , biodegradable polymers.

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Introduction:

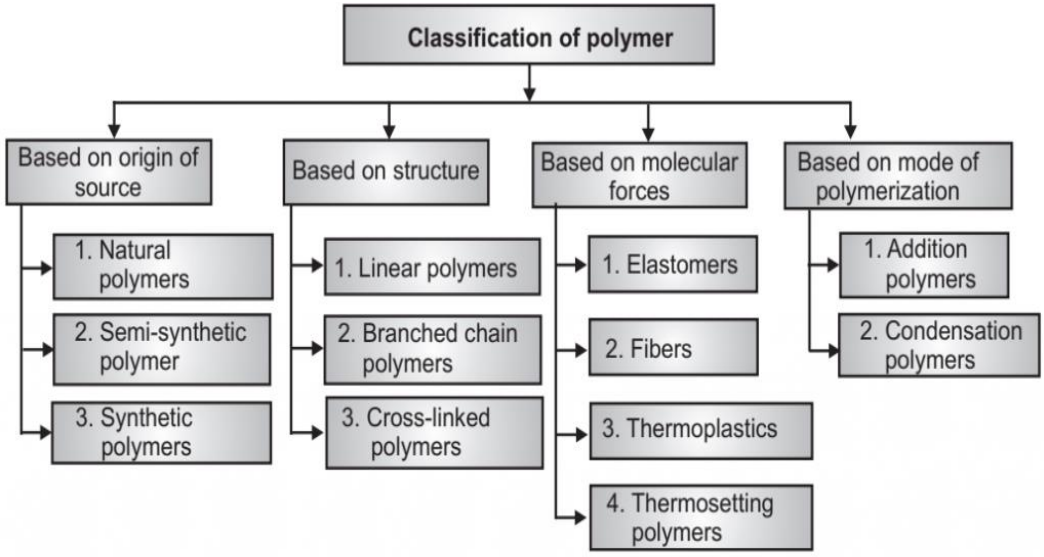
Since the last few decades, drug delivery and drug targeting have been the area of prime importance to researchers. The drug delivery systems to be used in drug targeting are being designed keeping in mind the physiological and biochemical nature of targeting site and the physico-chemical properties of the drugs to be delivered. Depending upon their physical state, the drug carriers can be broadly classified into two types, viz., particle based carriers and soluble carriers. The particle based carriers include liposomes, lipid particles (LDL and HDL), microspheres, nanoparticles, and polymeric micelles, whereas the soluble carriers include monoclonal antibodies, modified proteins, peptides, polysaccharides and biodegradable polymers of various chemical composition. Moreover, even the viral vectors and whole cells are being used for site specific delivery of DNA leading to altered expression of genes.

Polymer is defined as a naturally occurring or synthetic compound consisting of large molecules made up of a linked series of repeated simple monomer units. Based on their origin polymers can be broadly divided into three categories: (a) Natural polymers (b) Synthetic polymers (c) Semi- synthetic/ Semi- natural polymers.

(a)Natural Polymers Naturally occurring biopolymers mainly include proteins, carbohydrates, and nucleic acids which are majorly found in the biological systems. These polymers are very well suited for biomedical applications; however, one of their major drawbacks is change in their properties in response to even small changes in the external environment.

(b) Synthetic Polymers Synthetic polymers are macromolecules synthesized out of monomers or derived from preformed polymers to suit the specific needs. Last few years saw emergence and then extensive usage of synthetic polymers in drug delivery formulations. Synthetic polymers are advantageous over natural polymers and lipids

(c) Semi-Synthetic / Semi- Natural Polymers These macromolecules are blends or combination of a synthetic as well as a naturally occurring polymeric moiety.



Besides the origin polymers have also been categorized on the basis of their structure or the arrangement of the monomers in the polymer backbone. The properties exhibited by the polymers are also depends largely on the structure of the polymer itself which includes chain linearity, size, monomers units, their arrangement and chirality of the same. Polymers synthesized using only one type of monomers is called homo-polymers and those containing different monomers are largely called copolymers. ***(Omanathanu Pillai, Ramesh,2001)***

Significance of the Study:

Capsules and tablets, which are created by compressing, coating, and encapsulating bioactive drug molecules, are often used in conventional drug delivery methods [2]. Polymers have several uses in traditional pharmaceutical formulations, such as film coating agents for tablets, viscosity enhancers for emulsions and suspensions, and binding agents in capsules. Polymers may be conjugated to certain drugs to serve as inert carriers. The use of polymer as an inert carrier has several benefits, including improving the biopharmaceutical's pharmacological and pharmacokinetic characteristics. In this regard the present study will be very useful for the chemists, druggists, scholars and all others concerned.

Objectives: The current study has been undertaken with the following objectives-

- To study the Polymer drug conjugation
- To analyze the synthesis of polymeric particles
- To discuss the drug loading in polymeric drug carriers

Method: The current study is descriptive in nature. Therefore the researcher has followed secondary sources of information in the forms of journals, articles and internet sources.

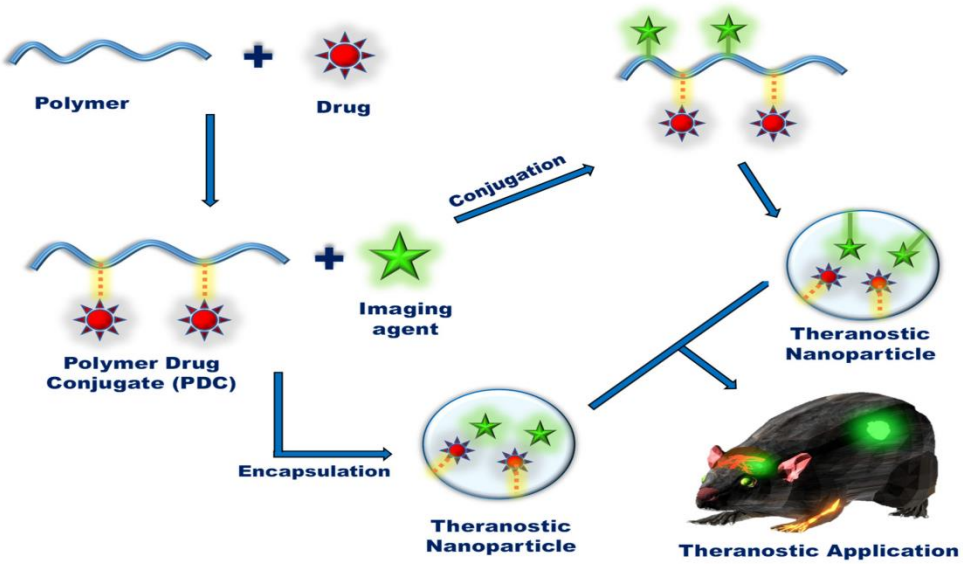
Polymer-Drug Conjugation

Drug delivery systems made from synthetic polymers may have better control over nanoscale structure creation via the use of biological (peptide/protein) conjugation. Different conjugates are:

Polymer-Drug Conjugates: These are conjugates of highly potent cancer drugs with that of polymers.108 Following, pro-drug concept these systems bind the drug till it reaches its site of activity and also, keep its toxicity minimal before reaching the target site. Polymer drug conjugates are most effective as cancer chemotherapeutics.

Polymer-biopolymer conjugates (a):

Polymer- protein/ peptide conjugates are highly acclaimed in the area of pharmaceutics as covalent linking saves these biopolymers from bodily degradation by enzymes like peptidases and other chemical changes. Successful therapy of Hepatitis C has been carried out however severe side effects have been reported and are being worked upon. (b) Polymer-Nucleic acid conjugates: as in case of proteins and peptides covalently linked polymers and oligonucleotides circumvent the difficulty of delivering nucleic acids. Polymer conjugation improves the oligonucleotides' solubility and may prevent their rapid destruction by nucleases. The medicinal uses of self-assembled polymer-nucleic acid complexes are mostly focused on their use in gene therapy. Somatic cell delivery and expression of therapeutic genes are the cornerstones of gene therapy.



Synthetic polymers have been conjugated with these bio-polymers to provide targeted delivery, eliminating the need for the medications to be systemically dispersed. The capacity of cationic peptide sequences to bind and condense DNA and oligonucleotides is the basis for the development of non-viral vectors for gene-delivery based on synthetic polymeric hybrid materials.

Micro-Electro Mechanical Systems:

Micro electro- mechanical systems or MEMS are micro fabricated devices with the ability to store and release multiple chemical substances on demand. These micro systems range from miniature medical devices to a lab on-a-chip systems. The advantages of these systems include storage and release of multiple chemicals, targeted delivery of potent drugs, simultaneous-constant and pulsatile release patterns can be achieved. Also, as water penetration can be avoided in these systems stability of protein-based drugs with limited shelf-life is enhanced and lastly these can act as drug reservoirs. Formulation and effective usage in the world of pharmacy is the ultimate goal of researches being carried out on the field of drug delivery. As the main focus of this thesis is standardization of the protocol for the development of stimuli responsive thermo (microgel and nanogel) and pH-sensitive (as enteric coating materials) polymers hence, the

synthesis of these polymeric carriers are given in detail.

SYNTHESIS OF POLYMERIC PARTICLES

Synthesis of Microgel Particles:

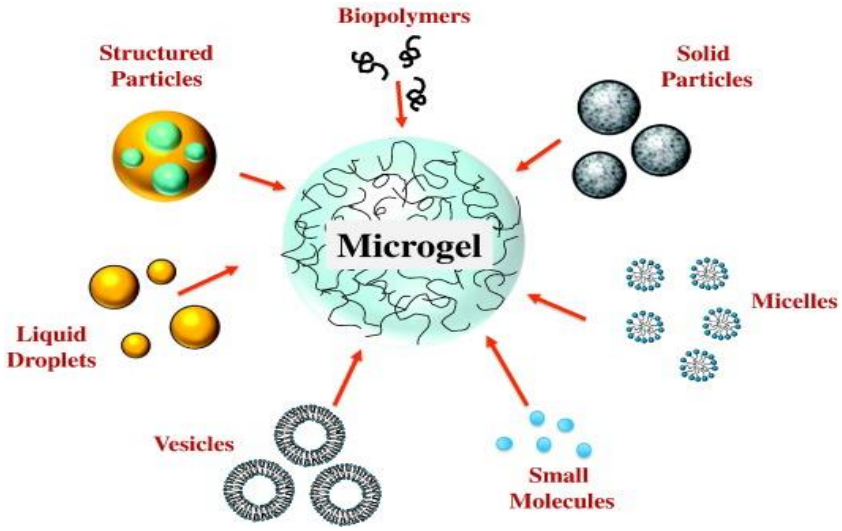
Phase Separation Method: A solution of polymer along with the drug is added to an organic non-solvent like silicon oil under continuous stirring. Gradually, soft co-acervate droplets containing drug are generated. Addition rate of the non solvent determines the size of micro gel particles, encapsulation of the drug and dispersity in size. Final characteristics of the micro gel are determined by molecular weight of the polymer, viscosity of the non-solvent and polymer concentration. Formation of large aggregates is a disadvantage for this method.

Spray Drying: spray drying is an advantageous method over other techniques for synthesizing microgel particles. This method involves drug dispersed polymer solution with volatile solvents being subjected to a heated air as a stream. Size of the microparticles is controlled by the atomizing conditions. Yield of the final product is low in the case of spray drying process due to adhesion of microparticles to the spray dryer. Aggregate formation is also one of the disadvantages of this process.

Single Emulsion Method: Single emulsion method involves dissolving polymer in an organic solvent along with the drug and then emulsifying it with large quantities of water in the presence of an emulsifying agent. The solvent is then removed by extraction or evaporation resulting in microparticle formation. This method is suitable for formulation of hydrophobic drugs.

Double Emulsion Method:

In this method an aqueous solution of a hydrophilic drug is emulsified with polymer dissolved organic solution to form a water-in-oil microemulsion. This emulsion is then transferred into an excess amount of water along with an emulsifier with vigorous stirring, thus forming w/o/w emulsion, subsequently solvent is removed and micro particles are isolated. Synthesis of Nanogel Particles Nanogel particles may be synthesized either through dispersed pre-formed polymers or from the polymerization of the monomers.



Dispersion of pre-formed polymers

Solvent evaporation method:

Polymer and drug are dissolved in an organic solvent and then this mixture is emulsified into an aqueous solution to make o/w emulsion by using a surfactant/ emulsifying agent. The organic solvent is then evaporated to yield the final product. Water soluble drug loaded nanogel particles have also been synthesized using w-o-w systems.

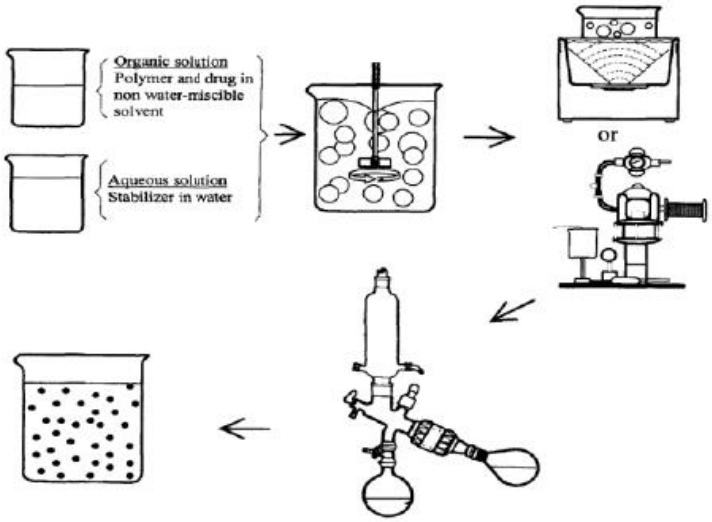


Fig.1. representation of solvent evaporation method

Spontaneous emulsification/ Solvent diffusion method: Oils both polar and non-polar were utilised.116 smaller particles arise as a result of interfacial turbulence brought about by the spontaneous diffusion of a water- soluble solvent between two phases. The concentration of the water-soluble solvents has a linear relationship with particle size.

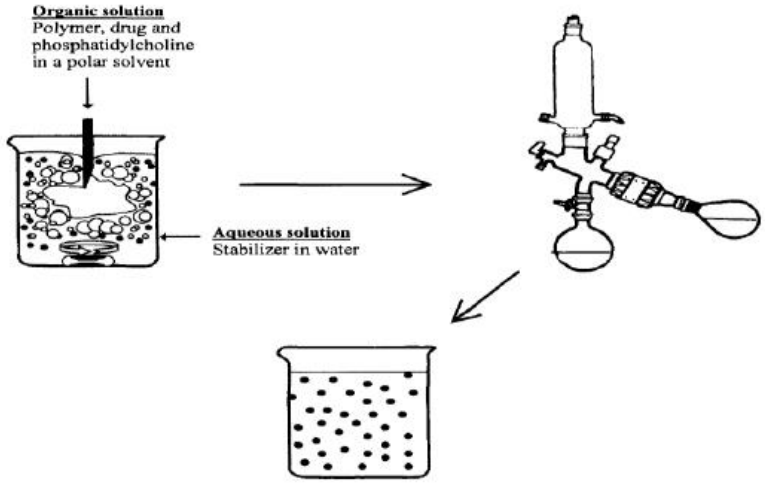


Fig. 2. representation of spontaneous emulsification/ solvent diffusion method

Salting Out: This technique uses the salting-out action to separate the water-miscible solvent from the aqueous solution.117 A solvent such as acetone is used to dissolve the polymer and drug, and then the mixture is emulsified in an aqueous gel with a colloidal stabilizer and salting-out agent by vigorously stirring. Nanogel particles are formed when this emulsion is diluted with enough water so that acetone may more easily diffuse into the aqueous phase.

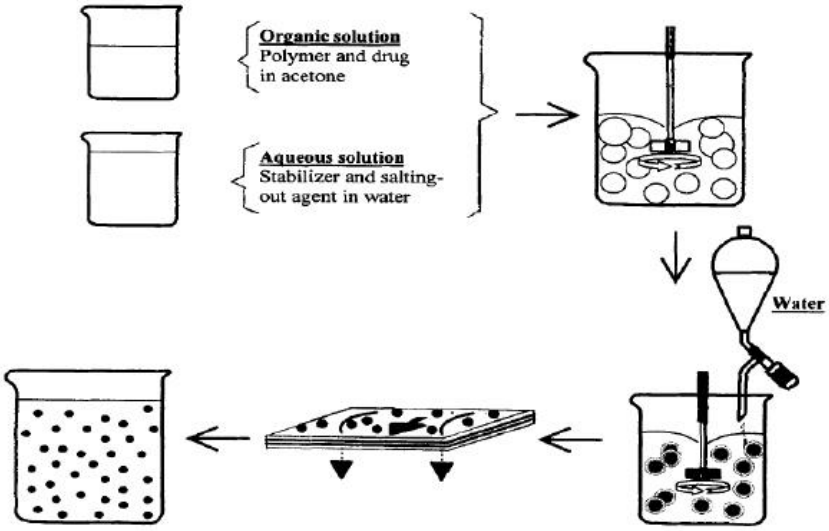


Fig.3. representation of synthesis of nanoparticles by salting out technique

Emulsification-diffusion method:
This technique entails dissolving the polymer in a solvent that is only partly soluble in water, with the aim of maintaining the thermodynamic equilibrium between the two liquids at the outset.118 This organic phase is emulsified in an aqueous solution containing a stabiliser, and the mixture is agitated vigorously. When water is added to the system, the solvent diffuses into the exterior phase, leading to nanoparticle production.

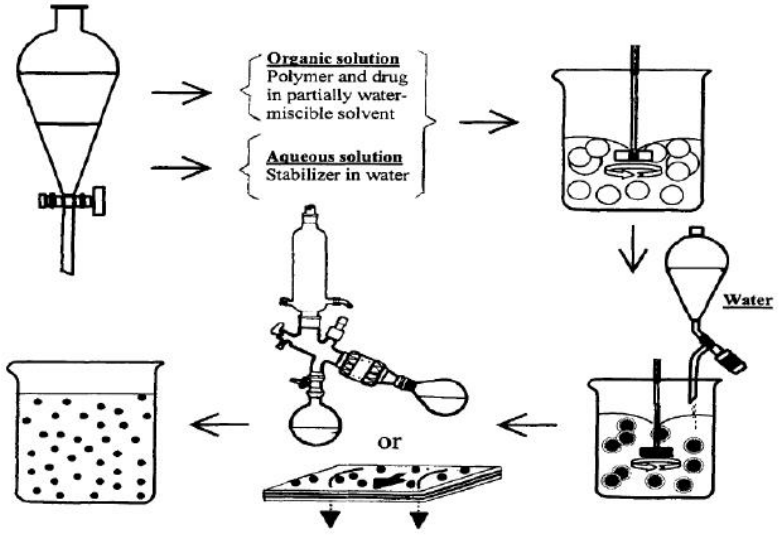


Figure .4. Schematic representation of synthesis of nanoparticles by emulsification-diffusion technique

Synthesis of pH Sensitive Polymers:
pH-sensitive polymers have been synthesized successfully through conventional techniques involving radical polymerization and ionic polymerization. However emulsion polymerization is the most successful kind of polymerization technique employed for synthesis of such polymers. Emulsion polymerizations are easily carried in the essential presence of monomers, water, initiator and an emulsifier (surfactant). The drawback of this system is use of emulsifier. ***(Vicky V. Mody,2010)*** At the end of the reaction removal of emulsifier is required which may lead to changes in the physical appearance and behaviour of the polymer. Surfactant free emulsion polymerizations have also, been carried out however, the yield of the polymer is decreased two folds. Modified procedures followed for emulsion polymerization are of instant interest. These methods include batch emulsion polymerization, semi-batch polymerization and seeded semi-batch emulsion polymerization. Controlled polymerization techniques have also, been introduced recently to synthesize well- defined pH- sensitive polymers. These include stable free radical polymerization

(SFRP), atom transfer radical polymerization (ATRP) and nit oxide mediated polymerization (NMP) and reversible addition fragmentation chain transfer.

After successful synthesis of polymeric drug delivery vehicles the first and the most important aspect of making a polymer into a formulation is effective and optimum drug loading. The aspect of drug loading and type of disease targeted are combined with the kind of drug release behaviour expected from a polymeric system. Hence, drug loading and drug release behaviour are explained further in order to get a better understanding of the drug delivery vehicles.

DRUG LOADING IN POLYMERIC CARRIERS:

Drug loading in a vehicular system is dependent on the type of delivery system being used. The drug can be either encapsulated (mostly includes passive diffusion of drugs into the polymeric matrix through a drug-solvent mix or by application of pressure), entrapped (in-situ drug loading during the polymerization process), covalently conjugated or physically adsorbed on the surface of the polymeric material, based on the methods of preparation of the polymer. Stabilized surface properties are also a pre-requisite for the delivery system to function properly affecting the biocompatibility and bio-distribution of the polymer-drug vehicle. Also, the functionalities and chemical properties of the drugs is one of the factors in choosing the drug delivery vehicle as the loading efficiency, stability and shelf life of a formulation are dependent on the polymer-drug interaction. Lastly, the drug loading should be analyzed and assessed keeping in mind the release profiles to be achieved or aimed at from the formulations delivering in the biological systems. Different loading processes lead to varied concentrations of a drug in formulations. Adsorption of drugs leads to lower concentration of drugs whereas encapsulation of drugs leads to drug reservoirs coated with a polymer lining. However, incorporation of drug during the polymerization procedure is a preferred method as it leads to higher concentrations of uniformly distributed drug in the polymeric matrix following an optimum release profile.

DRUG RELEASE FROM POLYMERIC CARRIERS:

Drug release from polymeric materials is the most important aspect of a formulation which renders it useful for the pharmaceutical purposes. Drug release is mostly a function of the structure of the polymeric material. Owing to the structure, these release mechanisms can be divided into following types as: drug release by diffusion or osmotic pressure in case of membrane/capsule or reservoir based systems, release by desorption in case of surface bound drugs by either diffusion or matrix erosion as in case of matrix based systems. Drug release is also chemically controlled in case where drug is covalently conjugated to the polymer matrix and also, from the systems where matrix swelling or de- swelling is controlled by the stimuli

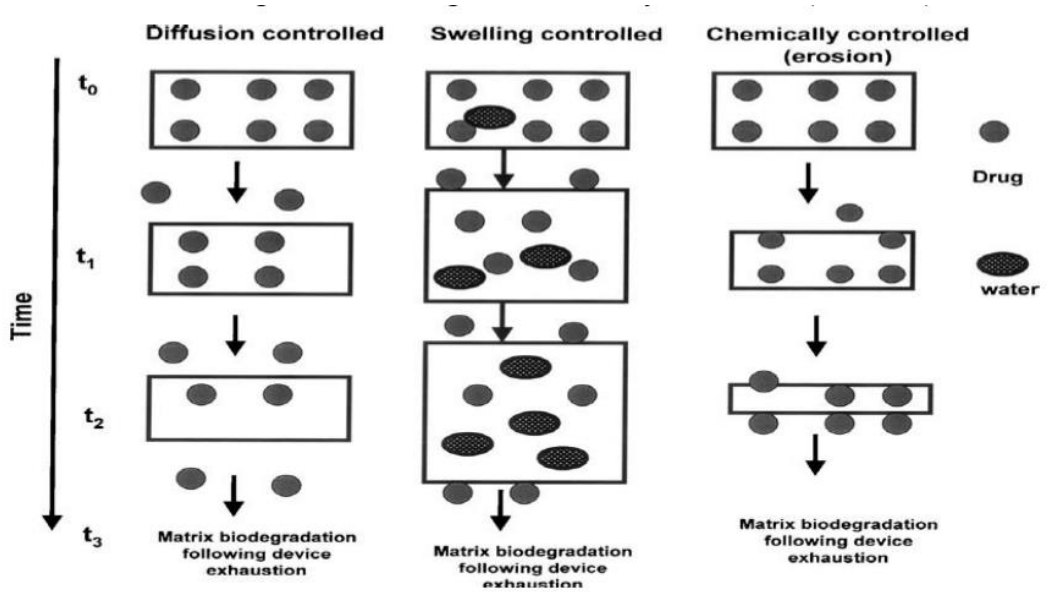


Fig. 5. Representation of three types of drug release from controlled release devices

CONTROLLED RELEASE OF DRUG FROM POLYMERIC MATERIALS:

Controlled drug release is a very important factor for developing the successful formulations. For achieving this, various targeted and controlled release drug delivery systems have been developed. The different oral and parenteral methods exclusively used to deliver drugs proved to be extremely inefficient and poorly controlled. To overcome these limitations the need for controlled release system is rapidly gaining importance due to the numerous advantages it offers. The goal of controlled release is to provide a medicine at a specified rate, at a specific time, or with a specific release profile into the patient's body. A controlled release system's release profile is mostly determined by the system's design and is not affected by environmental factors. Every controlled-release device is designed with one goal in mind: making medication treatment more efficient.120,121 This enhancement may come in the form of increased therapeutic action relative to the degree of the adverse effects, fewer drug administration's necessary throughout therapy, or the elimination of the necessity for specialized medication delivery (for example, multiple injections). The benefits of these systems include higher efficiency, lower toxicity, and more convenient use for the patient.

POLYMERS IN HUMAN BODY:

Finally, the in vivo and in vitro destiny of a polymer under consideration throughout its design and manufacture for distribution applications. Several polymeric systems have been employed to transport medicines and therapeutic proteins in the form of particles (both micro and nano).140-143 There is a growing demand for data on the effects of these polymeric nonmaterial's on human and environmental health because of their vast use. In vitro and in vivo studies with mammalian test systems have shown that the same properties that make nonmaterial's so attractive from a commercial application standpoint (such as nanoparticle size and increased surface area) can also be potentially responsible for undesirable health effects, with the focus thus far having been on the potential impacts on human health.144-148 However, there have been no definitive correlations found between manmade nanoparticles and a biological or health effect, and there is not yet enough information to draw broad conclusions regarding the biocompatibility or safety of nanomaterials. More research is needed to determine whether PNIPAM and its derivatives are cytotoxic. Very little is known about the toxicity of this polymer. After intravenous treatment, Matsumaru et al.149 found that PNIPAM was safe for mice. In a recent study, Fujimoto et al. found that at concentrations of 4 mg/ml or less, a copolymer of NIPAM and N-methacryloyloxys uccinimide was noncytotoxic to U-937 cells***(Krushnakumar J Gandhi, Subhash V Deshmane, Kailash R Biyani,2012)***

Conclusion:

Controlled drug release systems and sustained release formulations are being created with the use of polymers by chemical engineers, pharmacologists, and scientists. Micelles, dendrimers, liposome's, polymeric nanoparticles, cellular phantoms, microcapsules, and lipoproteins are all examples of novel drug delivery methods. Recent developments in polymer-based encapsulations and controlled drug release systems aid in managing medication administration by avoiding either under- or over-dosing. These cutting-edge methods have great potential for enhancing bioavailability and reducing the number of undesirable effects on patients. Research into polymers' surface and bulk properties is necessary since these characteristics dictate how the materials may be put to use. To address several future challenges in medication delivery, polymers will play an increasingly important role. Drug administration optimization may depend on a number of factors, such as the ability to target particular sub cellular organelles for drug delivery and making full use of the medication's chemical, physical, and biological characteristics.

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