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Review Article

MICROENCAPSULATION: AN INDISPENSABLE TECHNOLOGY FOR DRUG DELIVERY SYSTEM

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ABSTRACT
In this review, the various new and well established technologies relevant to the controlled and targeted drug delivery systems have been precisely discussed. A perfectly designed controlled drug delivery system can be of huge advantage towards solving problems concerning to the targeting of drug to a specific organ or tissue and controlling the rate of drug delivery at the target site. Novel drug delivery systems have various advantages over other conventional drug therapy. In which microencapsulation is one approach for achieving the novel drug delivery dosage forms such as sustained release and controlled release, though the development of oral controlled release systems has been a challenge to formulation scientist due to their inability to restrain and focus the system at targeted areas of gastrointestinal tract. Microparticulate drug delivery systems are an interesting and promising option when developing an oral controlled release system. Our objective is to take a closer look at microparticles as drug delivery devices for increasing efficiency of drug delivery, improving the release profile and drug targeting. In order to elucidate the application of microcapsules in drug delivery, some fundamental aspects are briefly reviewed.
Keywords: Microencapsulation, microcapsule, microsphere, coacervation, polymerization.

INTRODUCTION

Microencapsulation is one of the most promising fields in the area of pharmaceutical technology since its inception many years ago. Nowadays the microencapsulation is extensively studied inside major pharmaceutical companies and universities as well as research institutes. Polymeric drug delivery devices are focusing on the encapsulation of large molecules, e.g., peptides, proteins, and DNA/RNA for potential use as vaccines or as long-acting release drug formulations. Importantly, some of these initiatives led to important pharmaceutical products and most of them are still on the market (e.g., Lupron Depot®, Zoladex®, Decapeptyl®, Eligard®, Enantone®, Trenantone®, Nutropin Depot®, and Profact®). [1] In addition, encapsulation for controlling the release of highly water soluble drugs has received much attention. This article reviews the current state of the art in emulsion solvent evaporation/extraction based microencapsulation technologies. It is focused on the formulation, optimization and the drug delivery related aspects rather than equipments and machinery, as described in the most recent and early pioneered patents and the most related articles in the literature. Both, well-established and more advanced technologies are reviewed. Microencapsulation processes based on solvent removal from emulsions have been reviewed in various books [2-4] and review articles.[5-10]

Micro-encapsulation is a process in which tiny particles or droplets are surrounded by a coating to give small capsules with many useful properties. In a relatively simplistic form, a **microcapsule** is a small sphere with a uniform wall around it. The material inside the microcapsule is referred to as the core, internal phase, or fill, whereas the wall is sometimes called a shell, coating, or membrane. Most microcapsules have diameters between a few micrometers and a few millimeters.[11]

The microencapsulation procedure was firstly discovered by Bungen burg de Jon and Kan in 1931 and which were deal with the preparation of gelatin spheres through a coacervation process. During the past decades, there has been an increasing interest in optimizing the efficiency of existing drugs through the use of better-designed drug delivery systems. The majority of these systems are based on polymers that differ in their permeability, rate of dissolution, degree of swelling and erodibility.

It is generally accepted that microencapsulation products (microparticles) are larger than 1 micrometer in diameter and can be up to 1000 micrometers. Commercial microparticles have a diameter range 3 to 800 micrometers and contain 10-90% w/w core. A wide range of core materials has been encapsulated, including adhesives, agrochemicals, live cells, active enzymes, flavors, fragrances, pharmaceuticals and ink. Morphologically, two general structures exist: **microcapsules** and **microspheres**. A **microcapsule** is a reservoir-type system with regular or irregular shapes that contains a well defined core and envelope. The core can be solid, liquid, or gas; the envelope is made of a continuous, porous or nonporous, polymeric phase created by one or more polymers. Alternatively, a **microsphere** is a homogeneous or monolithic structure made of a continuous phase of one or more miscible polymers in which particulate drug is dispersed throughout the matrix, at either the macroscopic (particulates) or molecular (dissolution) level.

Classification

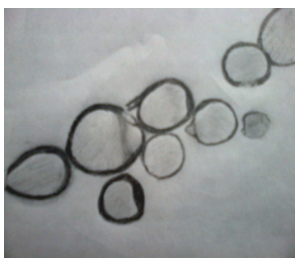
Microcapsules can be classified on three basic categories, they are as follows:

1. Mononuclear
2. Polynuclear
3. Matrix types

Mononuclear (core-shell) microcapsules contain the shell around the core, while Polynuclear capsules have many cores enclosed within the shell. In matrix encapsulation, the core material is distributed homogeneously into the shell material. In addition to these three basic morphologies, microcapsules

can also be mononuclear with multiple shells, or they may form clusters of microcapsules.[12]

The scanning electron microscopy (SEM) has revealed the structural features of microcapsules as to be varying and complex. The walled prototype may be mononuclear as shown in Figure 1(a) or may have multiple core structure [13] and also double or multiple concentric coating may be present. [14] Aggregated microcapsules greatly vary in size and shape [Fig. 1(b)] and may also posses additional external wall. The perfect microcapsules are obtainable by using the liquid cores or forming the microcapsules as a liquid dispersed phase prior to the solidification.[15] Although microstructure of both membrane and interior can be detected by SEM of surfaces or sections [Fig. 1(c)][16] their physical quality is difficult to characterize quantitatively in microcapsules involving measurements of porosity, tortuousity and crystallinity, though some of progress has been made and efforts are continuing to calculate permeability and porosity from release data, dimensions, densities, and core/wall ratios.[17] The effect of size and shape distribution has only been studied recently.



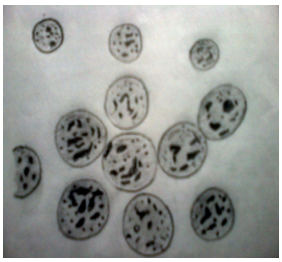


Figure 1(a): Mononuclear microcapsule
Figure 1(b): Polynuclear microcapsule

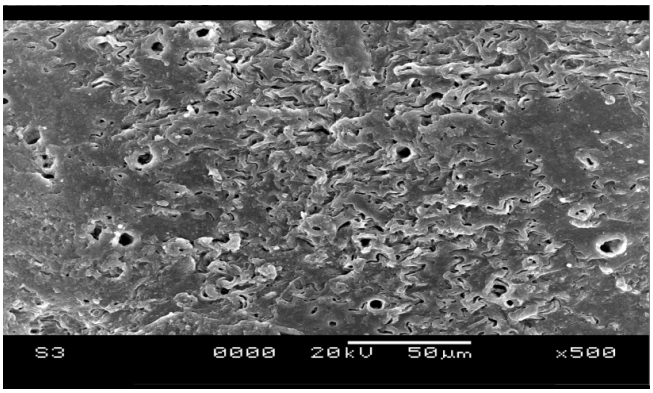


Figure 1(c): Cross sectional view microbeads.

Reasons for Microencapsulation

The main reason for microencapsulation is for sustained or prolonged release of the drug.

- This technique has been widely used for masking the organoleptic properties like taste and odor of many drugs and thus improves patient compliance e.g. Paracetamol, nitrofurantoin for masking the bitter taste.
- By using microencapsulation techniques the liquid drugs can be converted in a free flowing powder.
- The drugs can be protected by microencapsulation which is sensitive to moisture, light and oxygen, such as nifedipine is protected from photo instability.
- Microencapsulation technique also helpful to prevent the incompability between drugs
- The drugs which are volatile in nature may vaporize at room temperature like Aspirin and peppermint oil can be prevented by microencapsulation.
- Reduction in toxicity and GI irritation including with KCL and ferrous sulphate can be achieved by microencapsulation
- Microencapsulation has also been employed to change the site of absorption. This application has been useful for those drugs which have the toxicity at lower pH.
- Bakan and Anderson were reported that microencapsulated vitamin A palmitate had enhanced stability, as prevent from oxidation.
- Microencapsulation method has also been employed to prepare intrauterine contraceptive device. [18]

MATERIALS USED FOR MICROENCAPSULATION

Preparation of microspheres should satisfy certain criteria, like basic understanding of the general properties of microcapsules, such as the nature of the core and coating materials.

Core Material

The core material defined as the specific material to be coated can be liquid or solid in nature. The composition of the core material is varied, as the liquids core can include dispersed and/or dissolved material. The solid core can be a mixture of active constituents, stabilizers, diluents, recipients and release-rate retardants or accelerators. The ability to vary the core material composition provides definite flexibility and utilization of this characteristic often allows effectual design and development of the desired microcapsule properties.

Coating Materials

The coating material should be capable of forming a film that is cohesive with the core material; be chemically compatible and nonreactive with the core material; and provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability. The coating materials used in microencapsulation methods are amenable, to some extent, to in-situ modification.

The selection of a given coating often can be aided by the review of existing literature and by the study of free or cast films, although practical use of free-film information often is impeded for the following reasons:

1. Cast or free films prepared by the usual casting techniques yield films that are considerably thicker than those produced by the microencapsulation of small particles; hence, the results obtained from the cast films may not be extrapolate to the thin microcapsule coatings.
2. The particular microencapsulation method employed for the deposition of a given coating produces specific and inherent properties that are difficult to simulate with existing film-casting methods.
3. The coating substrate of core material may have a decisive effect on coating properties. Hence, the selection of a particular coating material involves consideration of both classic free-film data and applied results.
4. The coating material should be capable of forming a film that is cohesive with the core material.
5. Be chemically compatible and nonreactive with the core material.
6. Provide the desired coating properties, such as strength, flexibility, impermeability, optical properties, and stability. [19]

The different coating materials used in microencapsulation are classified into following categories:

1. Vegetable Gums: such as, gum Arabic, agar, sodium alginate, and carrageenan and dextran sulphate.
2. Celluloses: such as, ethyl cellulose, nitrocellulose, carboxy methylcellulose, cellulose acetate phthalate and cellulose acetate butyrate phthalate.
3. Condensation polymers: such as nylon, Teflon, polymethane, polycarbonate, amino resins, alkyl resins and silicone resins.
4. Homopolymer: such as, poly vinyl chloride, polyethylene, polystyrene, poly vinyl acetate and poly vinyl alcohol.
5. Copolymers: such as maleic anhydride copolymer with ethylene or vinyl methyl ether, acrylic acid copolymers and methacrylic acid co-polymers (eudragit).
6. Proteins: such as collagen, gelatin, casein, fibrinogen, hemoglobin and poly amino acids. Waxes: such as wax, paraffin, rosin shellac, tristerium, monoglyceride, bees wax, oils, fats and hardened oils.
7. Curable polymers: such as, epoxy resins, nitro paraffin and nitrated polystyrene. [20]

Methods used for microencapsulation:

1. Air suspension
2. Coacervation phase separation
3. Centrifugal Extrusion process
4. Spray drying and congealing
5. Pan coating
6. Solvent evaporation techniques
7. Polymerization

1. Air suspension

Air-suspension coating of particles by solutions or melts gives better control and flexibility. The particles are coated while suspended in an upward-moving air stream. They are supported by a perforated plate having different patterns of holes inside and outside a cylindrical insert. Just sufficient air is permitted to rise through the outer annular space to fluidize the settling particles. Most of the rising air (usually heated) flows inside the cylinder, causing the particles to rise rapidly. At the top, as the air stream diverges and slows, they settle back onto the outer bed and move downward to repeat the cycle. The particles pass through the inner cylinder many times in a few minutes methods. The air suspension process offers a wide variety of coating materials candidates for microencapsulation. The process has the capability of applying coatings in the form of solvent solutions, aqueous solution, emulsions, dispersions or hot melts in equipment ranging in capacities from one pound to 990 pounds. Core materials comprised of micron or submicron particles can be effectively encapsulated by air suspension techniques, but agglomeration of the particles to some larger size is normally achieved [21].

2. Coacervation phase separation

The general outline of the processes consists of three steps carried out under continuous agitation.

i) Formation of three immiscible chemical phases: A liquid manufacturing vehicle phase, a core material phase, and a coating material phase. To form the three phases, the core material dispersed in a solution of the coating polymer, the solvent for the polymer being the liquid manufacturing vehicle phase. The coating material phase, an immiscible polymer in a liquid state, is formed by utilizing one of the methods of the methods of phase separation-coacervation, i.e., by changing the temperature of the polymer solution; or by adding a salt, nonsolvent, or incompatible polymer to the polymer solution; or by inducing a polymer-polymer interaction.

ii) Deposition of the coating: It consists of depositing the liquid polymer coating upon the core material. This is accomplished by controlled, physical mixing of the material in the manufacturing vehicle. Deposition if the liquid polymer coating around the core material occurs if the polymer is adsorbed at the interface formed between the core material and the liquid vehicle phase, and this adsorption phenomenon is a prerequisite to effective coating. The continued deposition of the coating material is promoted by a reduction in the total free interfacial energy of the system, brought about by the decrease of the coating material surface area during coalescence of the liquid polymer droplets.

iii) Rigidization of the coating: It involves rigidizing the coating, usually by thermal, cross-linking, or desolvation techniques, to form a self-sustaining microcapsules. [19]

3. Centrifugal extrusion

Liquids are encapsulated using a rotating extrusion head containing concentric nozzles. In this process, a jet of core liquid is surrounded by a sheath of wall solution or melt. As the jet moves through the air it breaks, owing to Rayleigh instability, into droplets of core, each coated with the wall solution. While the droplets are in flight, a molten wall may be hardened or a solvent may be evaporated from the wall solution. Since most of the droplets are within ± 10% of the mean diameter, they land in a narrow ring around the spray nozzle. Hence, if needed, the capsules can be hardened after formation by catching them in a ring-shaped hardening bath. This process is excellent for forming particles 400–2,000μm (16–79 mils) in diameter. Since the drops are formed by the breakup of a liquid jet, the process is only suitable for liquid or slurry. A high production rate can be achieved, i.e., up to 22.5 kg (50 lb) of microcapsules can be produced per nozzle per hour per head. Heads containing 16 nozzles are available. [21]

4. Spray drying and Congealing

Spray drying serves as a microencapsulation technique when an active material is dissolved or suspended in a melt or polymer solution and becomes trapped in the dried particle. The main advantages is the ability to handle labile materials because of the short contact time in the dryer, in addition, the operation is economical. In modern spray dryers the viscosity of the solutions to be sprayed can be as high as 300mPas.

Spray drying and spray congealing processes are similar in that both involve dispersing the core material in a liquefied coating substance and spraying or introducing the core - coating mixture into some environmental condition, whereby, relatively rapid solidification (and formation) of the coating is affected. The principal difference between the two methods is the means by which coating solidification is accomplished. Coating solidification in the case of spray drying is affected by rapid evaporation of a solvent in which the coating material is dissolved. Coating solidification in spray congealing methods, however, is accomplished by thermally congealing a molten coating material or by solidifying a dissolved coating by introducing the coating - core material mixture into a nonsolvent. Removal of the nonsolvent or solvent from the coated product is then accomplished by sorption, extraction, or evaporation techniques.

In practice, microencapsulation by spray drying is conducted by dispersing a core material in a coating solution, in which the coating substance is dissolved and in which the core material is insoluble, and then by atomizing the mixture into air stream. The air, usually heated, supplies the latent heat of vaporization required to remove the solvent from the coating material, thus forming the microencapsulated product. The equipment components of a standard spray dryer include an air heater, atomizer, main spray chamber, blower or fan, cyclone and product collector.

Microencapsulation by spray congealing can be accomplished with spray drying equipment when the protective coating is applied as a melt. General process variables and conditions are quite similar to those already described, except that the core material is dispersed in a coating material melt rather than a coating solution. Coating solidification (and microencapsulation) is accomplished by spraying the hot mixture into a cool air stream. Waxes, fatty acids and alcohols, polymers and sugars, which are solids at room temperature but melt at reasonable temperatures, are applicable to spray congealing techniques. Typically, the particle size of spray congealed products can be accurately controlled when spray drying equipment is used, and has been found to be a function of the feed rate, the atomizing wheel velocity, dispersion of feed material viscosity, and variables. [19]

5. Pan coating

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly.

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles or tablets. The particles are tumbled in a pan or other device while the coating material is applied slowly with respect to microencapsulation, solid particles greater than 600 microns in size are generally considered essential for effective coating, and the process has been extensively employed for the preparation of controlled - release beads. Medicaments are usually coated onto various spherical substrates such as nonpareil sugar seeds, and then coated with protective layers of various polymers.

In practice, the coating is applied as a solution, or as an atomized spray, to the desired solid core material in the coating pans. Usually, to remove the coating solvent, warm air is passed over the coated materials as the coatings are being applied in the coating pans. In some cases, final solvent removal is accomplished in a drying oven. [19, 21]

6. Solvent Evaporation Techniques

Solvent evaporation techniques are performed in a liquid manufacturing vehicle (O/W emulsion) which is formed by agitation of two immiscible liquids. In this process microcapsule coating (polymer) is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dispersed in the coating polymer solution. To obtain the microcapsule of appropriate size the core and coating material mixture is dispersed in the liquid manufacturing vehicle phase with agitation. The agitation of system is constant till the solvent partitions into the aqueous phase and aqueous phase is removed by evaporation. Various process variables that could affect the process of microencapsulation include methods of forming dispersions, evaporation rate of the solvent for the coating polymer, temperature cycles and agitation rates. Important factors that must be considered when preparing microcapsules by solvent evaporation techniques include choice of vehicle phase and solvent for the polymer coating, as these choices greatly influence microcapsule properties as well as the choice of solvent recovery techniques .This technique to produce microcapsules is applicable to liquid and solid core material. Water soluble or water insoluble materials are used as core materials. A variety of film forming polymers can be used as coating materials. [19]

7. Polymerization

i) Interfacial polymer

In Interfacial polymerization, the two reactants in a polycondensation meet at an interface and react rapidly. The basis of this method is the classical Schotten Baumann reaction between an acid chloride and a compound containing an active hydrogen atom, such as an amine or alcohol, polyesters, polyurea, polyurethane. Under the right conditions, thin flexible walls form rapidly at the interface. A solution of the pesticide and a di-acid chloride are emulsified in water and an aqueous solution containing an amine and a polyfunctional isocyanate is added. Base is present to neutralize the acid formed during the reaction. Condensed polymer walls form instantaneously at the interface of the emulsion droplets.

ii) In-situ polymerization

In a few microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface. In one process, e.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rates are about 0.5μm/min. Coating thickness ranges 0.2-75μm. The coating is uniform, even over sharp projections.

iii) Matrix polymer

In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple method of this type is spray-drying, in which the particle is formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix also can be caused by a chemical change. [21]

RELEASE MECHANISMS

Mechanisms of drug release from microspheres are

1. Degradation controlled monolithic system:

The drug is dissolved in matrix and is distributed uniformly throughout. The drug is strongly attached to the matrix and is released on degradation of the matrix. The diffusion of the drug is slow as compared with degradation of the matrix

2. Diffusion:

It's the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores.[22] Thus, the overall release depends on, (1) the rate at which dissolution fluid penetrates the wall of microcapsules, (2) the rate at which drug dissolves in the dissolution fluid, and (3) the rate at which the dissolved drug leak out and disperse from the surface. [23]

The kinetics of such drug release obeys Higuchi's equation [24] as below:

$$Q = [D/J\,(2A - \varepsilon C_S)\,C_S\,t]^{1/2}$$

Where Q is the amount of drug released per unit area of exposed surface in time t; D is the diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; C_S is the solubility of drug in permeating dissolution fluid; ε is the porosity of the wall of microcapsule; J is the tortuosity of the capillary system in the wall. The above equation can be simplified to **Q = vt** where **v** is the apparent release rate.

i) **Diffusion controlled monolithic system:**

Here the active agent is released by diffusion prior to or concurrent with the degradation of the polymer matrix. Rate of release also depend upon where the polymer degrades by homogeneous or heterogeneous mechanism.

ii) **Diffusion controlled reservoir system:**

Here the active agent is encapsulated by a rate controlling membrane through which the agent diffuses and the membrane erodes only after its delivery is completed. In this case, drug release is unaffected by the degradation of the matrix.

3. Osmosis:

The polymer coat of microcapsule acts as semi permeable membrane and allows the creation of an osmotic pressure difference between the inside and the outside of the microcapsule and drives drug solution out of the microcapsule through small pores in the coat.

4. Erosion:

Erosion of the coat due to pH and enzymatic hydrolysis causes drug release with certain coat material like glyceryl mono stearate, beeswax and stearyl alcohol etc.

Based on various studies concerning the release characteristics, the following generalizations can be made:

1. Drug release rate from microcapsules conforming to reservoir type is of zero order.

2. Microcapsules of monolithic type and containing dissolved drug have release rates that are $t_{1/2}$ dependant for the first half of the total drug release and thereafter decline exponentially.

3. However, if a monolithic microcapsule containing large excess of dissolved drug, the release rate is essentially $t_{1/2}$ dependant throughout almost the entire drug release.

In monolithic capsules the path traveled by drug is not constant; the drug at the center travels a large distance than the drug at the surface. Therefore, the release rate generally decreases with time. [25]

Applications of microcapsules and microspheres

There are huge numbers of applications of microencapsulation; some of them are as follows:

1. Prolonged release dosage forms. The microencapsulated drug can be administered, as microencapsulation is perhaps most useful for the preparation of tablets, capsules or parenteral dosage forms.
2. Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament will be selectively absorbed in the intestine rather than the stomach.
3. It can be used to mask the taste of bitter drugs.
4. Microencapsulation has been used to overcome problems inherent in producing tablets from tacky granulations. This was done by improving the flow properties. For example, the non-flowable multicomponent solid mixture of niacin, riboflavin, and thiamine hydrochloride and iron phosphate may be encapsulated and made directly into tablets.
5. It has been used to protect drugs from environmental hazards such as humidity, light, oxygen or heat. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation. [26]
6. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing. [27]
7. Microencapsulation can be used to decrease the volatility. [28]
8. Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. [29]
9. The hygroscopic properties of many core materials may be reduced by microencapsulation. [30]
10. Many drugs have been microencapsulated to reduce gastric irritation.
11. Microencapsulation method has also been proposed to prepare intrauterine contraceptive device.
12. In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles.

Table 1: Some microencapsulated drugs [31,32]

Sl No.	Drug material	Purpose	Product
1	Acetaminophen	Taste masking.	Tablet
2	Aspirin	Taste masking, sustained release, reduce gastric irritation & incompatibilities.	Tablet or capsule
3	Islet of Langerhans	Sustained normalization of diabetic condition.	Injectables
4	Isosorbide dinitrate	Sustained release capsules.	Capsules
5	Menthol	Reduction of volatility.	Lotion
6	Progesterone	Sustained release.	Varied
7	Potassium chloride	Reduced gastric irritation.	Capsules
8	Urease	Perm selectivity of enzyme, substrate & and reaction product.	Dispersion
9	Vitamin A palmitate	Stabilization to oxidation.	Dry powder
10	5-fluorouracil	Reduced irritation.	Cream
11	Retinol (pure)	Enhanced potency & reduced irritation.	Cream (microsponge)
12	Salicylic acid	Target particular area.	Microcrystal

CONCLUSION

Microencapsulation refers a phenomenon in which drug compounds are safely encapsulated as a small capsule in order to achieve a most stable product. This technology brings a huge impact in arena of pharmaceutical research, which also offers special appearance in controlled and target drug delivery system. This approach is not only able to deliver the drug to target organ or tissue but also lowers drug concentration in other sites as well as minimizes the adverse effects of same drug. In other hand, it provides protection for labile compounds before and after administration and until it appears to the specified location for action.

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