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An Overview on Microspheres and Microcapsules as Promising Drug Carriers

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Abstract

Microspheres are tiny sphere-shaped particles with sizes under 200 nm. The analysis focuses on the microspheres of its qualities, forms, preparation, outcomes, and application of process variables. This article discusses a cutting-edge drug delivery technology.

It overcame a number of issues with other dosing forms. The various kinds of microspheres are employed in a variety of ways to increase therapeutic efficacy and bioavailability. Investigations are being done into how process factors affect drug release, drug trapping, and particle size. Microspheres are typically free-flowing powders made of synthetic polymers that are naturally biodegradable. A medication is located in the centre of a microsphere, where it is protected by a unique polymeric membrane.

keywords: Microspheres; Drug Delivery; Particle Size; Controlled Release

Introduction

Due to factors including patient compliance, convenience of administration, and formulation flexibility, oral delivery of medications is by far the preferred route of drug delivery.

Traditional drug preparations, such as tablets and capsules, are designed to release the active ingredient as soon as possible to achieve quick and thorough systemic absorption of the drug. By providing a specific dose and at a specific frequency, the traditional dosage form keeps the plasma drug concentration constant over an extended period of time. The half-life or mean residence time (MRT) and therapeutic index of any medicine determine the frequency of administration or the dosage interval. The dose interval is typically significantly shorter than the drug's half-life, which has a variety of drawbacks.

History of Extended Release System

- Early in the 1950s, Smith Kline and French created an oral formulation of dextroamphetamine sulphate by putting the drug in pellets covered in wax. This was the beginning of the extended

release technique [1].

- Since the late 1970s, the number of new extended release formulations has increased experimentally. Specific reasons for this progress include the development of new materials, methods for manufacturing and analytical techniques and better understanding of the influence of the physiology on the performance of dosage forms [1].
- Between 1940s and 1960s, the concept of chemical microencapsulation technology began as an alternative means of delivering drugs [4].
- In 1980s polymer / membrane technology came to be known as forefront [4].

Terminology [5]

- *Controlled Release denotes systems* which could optimise some control, it can be either of temporal or spatial nature, or both, releasing drug in the body.
- *Prolonged release or sustained release systems* only prolong therapeutic blood or tissue levels of the drug for an extended period of time.
- *Rate controlled drug delivery systems* are able to accurately specify the release rate and duration in vivo on the basis of straightforward in vitro studies.

In general, controlled delivery attempts to

1. *Sustain drug action at a predetermined rate* by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects associated with a sawtooth kinetic pattern.
2. *Localize drug action*. Localise drug effect by spatially locating a rate-controlled controlled release device close to or inside the sick tissue or organ.
3. Deliver medication that targets pharmacological action using carriers or chemical derivatization.
4. *Target drug action* by using carriers or chemical derivatization to deliver drugs to a particular 'target' cell type.

There are three types of controlled drug delivery systems available [5]

1. *Passive preprogrammed*, in which the release rate is predetermined and is irresponsive to the external biological environment.
2. *Active preprogrammed*, whose release rate can be altered by a source external to the body (include most metered insulin pumps).
3. *Active, self - programmed*, modulate release rate of the drug in response to information, registered by a sensor, on the changing biological environment, such as blood sugar level in diabetes.

Some Rationales for Modifying the Release Kinetics of the Drug from the Dosage Form [4]

1. To sustain the pharmacological effect.
2. To achieve a flatter blood level curve, thus avoiding toxic peak levels and subtherapeutic valley levels of drug.
3. To increase the extent of absorption, e.g.
   i) To avoid stability problems in specific regions of the GI tract (as asythermycin degrade in the stomach's acidic environment) or
   ii) When uptake occurs only in limited region in GI tract (as Vit. B12)
4. To programme release of active ingredient.
5. To avoid a direct or adverse pharmacological action in GI tract (e.g. gastric irritation).

Advantages of Extended-Release System [6]

1. Reduction in drug blood level fluctuations.
2. Frequency reduction in dosing.
3. Enhanced patient convenience and compliance.

4. Increased safety margin of highly potent drugs.
5. Reduction in adverse side effects.
6. Reduction in overall health care costs.

Disadvantages [6]

1. Loss of flexibility in adjusting the drug dose and / or dosage regimen.
2. Increased risk of sudden and total drug release or dose dumping due to failure of technology of the dosage unit.
3. Decreased systemic availability due to incomplete release, site specific absorption etc.
4. Poor in vitro - in vivo correlation.
5. Possibility of dose dumping.
6. Higher cost of formulation.

Drug Candidates for Extended-Release Products [6]

Not all drugs are suitable candidates for formulation as prolonged action medication. Table - 1 lists specific drug characteristics that would preclude formulation in peroral sustained release forms.

Characteristics	***Examples of Drugs***
Not effectively absorbed in lower intestine	Riboflavin, ferrous salts
Absorbed and excreted rapidly; shortbiologic half-lives (<1 hr)	Penicillin G, Furosemide
Long biologic half-lives (>12 hr)	Diazepam, phenytoin
Large doses required (> 1g)	Sulfonamides
Cumulative action and undesirable sideeffects; drugs with low therapeutic indices	Phenobarbital, digitoxin
Precise dosage titrated to individual isrequired	Anticoagulants, cardiac glycosides
No clear advantage for sustained releaseformulation	Griseofulvin

Table 1: Characteristics of drugs unsuitable for peroral sustained release forms.

Biological factors influencing design and performance of sustained / controlled release products [5]

1. Absorption.
2. Distribution.
3. Metabolism.
4. Duration of Action.
5. Side effects.
6. Margin of safety.
7. Role of disease state.
8. Role of circadian rhythm.

Physicochemical properties of a drug influencing design and performance of Sustained / Controlled Release products [5]

1. Aqueous solubility.
2. Partition co-efficient and molecular size.
3. Drug stability.
4. Protein binding.

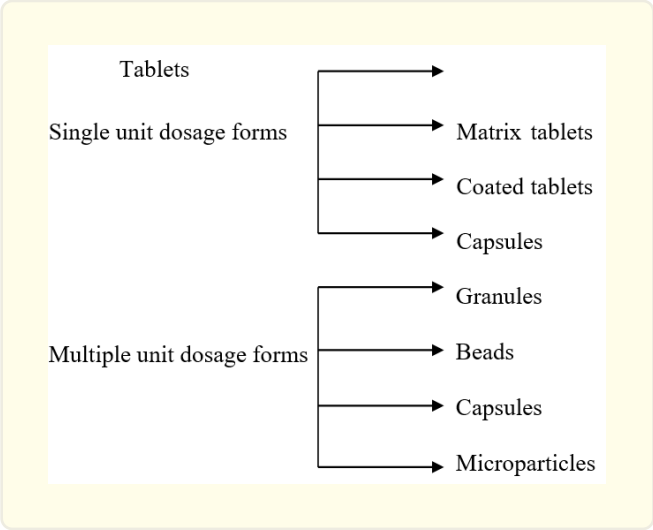
The aqueous solubility and intestinal permeability of drug compounds are paramount importance. According to the *Biopharmaceutics Classification System* (BCS), drug substances are classified as follows: [7]

Class I - High permeability, high solubility.
Class II - High permeability, low solubility.
Class III - Low permeability, High solubility.
Class IV - Low permeability, Low solubility.

Class Boundaries

- ***Highly Soluble*** when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.
  Highly Permeable when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- *Rapidly Dissolving* when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

Types of Oral Sustained Release Dosage Forms



Different Oral Sustained Drug Delivery Systems [5]

1. Dissolution Controlled Release.
2. Diffusion Controlled Release.
3. Diffusion and Dissolution Controlled Release.
4. Ion - Exchange Resins.
5. pH - Independent Formulations.
6. Osmotically Controlled Release.
7. Altered Density Formulations.

Microspheres and Microcapsules

The term microparticles refer to a particle with a diameter of 1-1000 mm, irrespective of the precise interior or exterior structure [8].

Microparticles cover two types of forms:

→ Microspheres: micrometric matrix systems.

→ Microcapsules: micrometric reservoir systems.

Microspheres are solid, spherical particles of protein or polymer based matrix which comprised of a fairly homogeneous mixture of polymer and active agents.

Microcapsules are microparticles which have a core surrounded by a material which is distinctly different from that of core. The core may be solid, liquid or even gas.

The major difference between these two types of microgranules is the different release profiles of microspheres and microcapsules. Microspheres usually have diffusion controlled release profiles with a permanent release rate that is controlled kinetically by the particle size, whereas microcapsules usually have diffusion or dissolution controlled release profiles or both. Microcapsules expel their content by a single high burst as the shell breaks or slow releases [9].

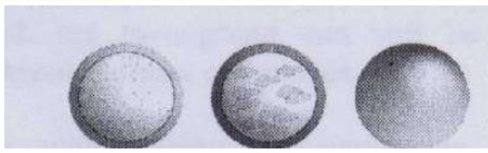


Figure 1: From left to right: Microcapsules with solution as core, Microcapsule with cell suspension as core, Microsphere with matrix encapsulated active agent.

Advantages of Microspheres

Microsphere is one of the multiple unit dosage forms. The growing interest for multiple unit dosage forms and their increasing share of the pharmaceutical product market are claimed by their proponents to stem from some advantages. Microspheres for oral use offer following advantages as compared to single unit dosage forms [10].

- Microspheres spread out more uniformly in the gastro-intestinal (GI) tract, thus avoiding exposure of the mucosa to high concentrations of drug, thereby ensuring more reproducible drug absorption.
- The risk of dose dumping also seems to be considerably lower than with a single unit dosage form.
- Preparation of the multiple unit dosage form of drug which has nonlinear pharmacokinetic characteristics as Verapamil provides an advantage as regards to its decreasing inter and intra subject variability of absorption [11].
- Multiple unit microparticulate dosage forms avoid the vagaries of gastric emptying and different transit rates, and thereby, release the drugs more uniformly (K12).
- With multiple unit dosage forms, the intestinal retention of polymeric material can be avoided [13].

Dosage Forms of Microspheres [14]

The multiparticulates can be filled into hard gelatin capsules or compressed into tablets. The compression of multiparticulates into tablets is becoming more popular.

Hard gelatin capsules are very elegant dosage forms, but have the disadvantages of higher production cost, lower production rate and tampering potential when compared to compressed tablets. Microspheres have been tableted to control or modify the release of

the drug. The tablet manufacturing process from microspheres will create a single unit from a multi-particulate system in order to produce compact forms that disintegrate into many subunits soon after ingestion to attain more uniform concentrations of the drug in the body. Reduced risk of tampering, a higher dose strength per unit and higher production rate of the tablet process can be listed among the advantages of tabletting.

Polymers Used to Prepare Microspheres [4]

I. Synthetic polymers

A. Non-Biodegradable

- Polymethyl methacrylate (PMMA).
- Polymethacrylate (Eudragit).
- Acrolein.
- Glycidyl methacrylate.
- Epoxy polymers.

B. Biodegradable

- Lactides and glycolides and their copolymers.
- Polyalkyl Cano acrylates.
- Polyanhydrides.

II. Natural polymers

A. Proteins

- Albumins.
- Gelatin.
- Collagen.

B. Carbohydrates

- Starch.
- Agarose.
- Carrageenan.
- Chitin and chitosan.

C. Waxes and lipids

- Paraffin.
- Stearic acid.
- Bees wax.
- Carnauba wax.

D. Chemically modified carbohydrates

- Ethyl cellulose.
- Poly (acryl) dextran and Poly (acryl) starch.

Methods of Preparation of Microspheres [8]

I. Polymer Phase - Separation Methods.
II. Solvent Evaporation (Emulsification - Evaporation) Method.
    - Oil-in-Water Emulsion.
    - Multiple Emulsion: Water-in-Oil-in-Water.
    - Nonaqueous Emulsions.
III. Solvent Extraction (Emulsification - Extraction) Method.
IV. Spray Drying Method or Nebulization.
V. Methods Using Fluids Under Supercritical Conditions.
VI. Milling Methods.

Different methods used for preparation of Microspheres

Polymer phase - separation Method

Polymer phase - separation, in non-aqueous media, by non-solvents or polymer addition is also referred to as coacervation.

This method is specially designed for preparing the reservoir type of the system, i.e. to encapsulate water soluble drugs such as peptides, proteins etc. But under certain circumstances, it has been demonstrated that this process leads to the production of microspheres, i.e. matrix type device, particularly when the drug is hydrophobic in nature, e.g. steroids.

Solvent Evaporation Method

This technique was fully developed at the end of 1970s.

General description

This technique is based on the evaporation of the internal phase of an emulsion by agitation. Initially, the polymeric supporting material is dissolved in a volatile organic solvent. The active medicinal principle to be encapsulated is then dissolved in the organic solution to form a solution. In the following step, the organic phase is emulsified under agitation in a dispersing phase, consisting of a non-solvent of the polymer, which is immiscible with the organic solvent, which contains an appropriate tensioactive additive.

When the emulsion is stabilised, agitation is kept up, and the solvent diffuses through the continuous phase before dissolving. The result is the creation of solid microspheres. The microspheres held in suspension in the continuous phase are recovered by filtration and are washed and dried.

Oil-in-Water Emulsion

Water is preferred as non-solvent to the polymer. In this system, polymer active principle are dissolved in an organic solvent. Then the entire mixture is emulsified in an aqueous solution containing an appropriate surfactant.

Disadvantage

- This technique is particularly suitable for lipophilic active principles.

Multiple Emulsions - Water-in-Oil-in-Water

- This process proves much more effective when water solubility of the medicine is high (>900 mg/ml) and partitioning between the organic phase is disfavorable.
- This process is particularly suitable for active principles in weak doses, which are strongly water soluble (e.g. hormones) and antigens.

Non-aqueous Emulsion (Oil-in-Oil Emulsion)

This technique is also known as oil-in-oil emulsion, in which continuous phase is oil. Naturally, the dispersed phase (also of an oily nature) needs to be totally immiscible with the continuous phase. The dispersing medium can be constituted by a mineral or vegetable oil or a non-volatile organic solvent.

Advantages

- This process gives elevated microencapsulated yields for water soluble components.
- This process can prevent the hydrolysis of the medicine or polymer

Disadvantage

- Expensive due to the use of non-aqueous solvents.

Solvent Extraction (Emulsion - Extraction) Method

In the emulsification - evaporation method, the organic solvent of the dispersed phase of the emulsion is eliminated in two stages:

1. Diffusion of the solvent in the dispersing phase (solvent extraction)
2. Solvent evaporation is the elimination of the solvent at the dispersing phase-air contact.

In theory, if one uses a continuous phase which will immediately extract the solvent(s) of the dispersed phase, the evaporation stage is no longer necessary in the formation of microspheres. In practice, this can be achieved by using large volumes of dispersing phase with respect to the dispersed phase or by choosing a dispersed phase consisting of cosolvents of which at least one has a great affinity for the dispersing phase.

Advantage

- This method prevents the development of active principle crystals at the microparticle surface.

Disadvantage

- This method leads to decreased efficiencies in incorporation of medicines.

Spray Drying Methods or Nebulization

The principle of spray drying by nebulization rests on the atomization of a solution (containing the product to be dried) by compressed air or nitrogen through a desiccating chamber and drying across a current of warm air.

Advantages

This method can be used to prevent the oxidation of delicate compounds (such as fish oils, essential oils, vitamins, and colourants).

Methods using Fluids Under Supercritical Conditions

This technique is based upon placing of a fluid at a temperature and pressure exceeding its critical point and using it as an extractant.

This process involves

- Solvation of compounds.
- Precipitation of pure compounds.
- Crystallization of pure compounds.
- Formation of microparticles.

This method should be used where there is need of modifications of the physical properties of drugs.

Milling Methods

This technique is preceded by the fusion of the polymer powder and can be completed by a spheroniztion step.

The main advantage is that it is a solvent free technology.

Basis of Selection of Solvent Evaporation (Emulsification - Evaporation) Method for Preparation of Microspheres (Advantages)

The solvent evaporation method is a commonly and widely employed technique for the preparation of polymeric microspheres. It is preferable to the other preparation methods due to following reasons.

- It requires only mild conditions such as ambient temperature and constant stirring [15].
- A stable emulsion can be formed without compromising the activity of drugs [15].
- This method neither requires elevated temperatures nor phase separation - inducing agents [16].
- Controlled particle sizes in the nano - to micrometer range can be achieved [16].
- This technique provide elevated incorporation yield.
- This process prevents the hydrolysis of active component or polymer.

Basis of Selection of Solvent in Solvent Evaporation Process

Chlorinated solvents like dichloromethane and chloroform have been used as dispersing solvent in the preparation of microspheres. But, the use of such solvents is of environmental concern and challenges human safety [17].

In order to overcome this, mix solvent system is used. The mixed solvent system comprise of acetone and methanol which has been extensively utilized as a dispersed medium.

Advantages

- Mixed solvent system solubilize the drug and polymer extensively [15].
- Uniform evaporation of solvent occurs during emulsification.
- In order to prevent the usage of more single solvent, a mixture of acetone and methanol can be used [11].

Basis of Selection of Dispersing Solvent

When a solvent with a dielectric constant about 10 or above is used, non-polar liquid paraffin is preferred as dispersing medium [11].

Dispersing Agent or Droplet Stabilizer in Solvent Evaporation Method [18]

When using solvent evaporation technique for microspheres preparation dispersing agents play an important role.

Mechanism of Dispersing Agent

Dispersing agents decrease the interfacial tension between the liophilic and hydrophilic phases of the emulsion and simplify formation of the microspheres. During the process of droplet formation in the solvent evaporation, the gradual removal of the solvent from the polymer droplets is accompanied by a corresponding decrease in the volume and the viscosity of the individual droplets increases. In particular, highly viscous droplets coalesce much faster than they can redivide. Droplet coalescence and particle coagulation can usually be overcome by the use of a small amount of a suitable droplet / particle stabilizer (dispersing agent). The dispersing agent provides a thin protective layer around the droplets and hence reduces the extent of their collision and coalescence.

Dispersing agents used can be various polymeric materials, proteins or surfactants. Dispersing agents used in w/o systems are especially metallic soaps (Magnesium stearate, aluminium tristearate). Sorbitan fatty esters (spans, tweens, arlacels) and polyoxyethlene fatty esters. Sucrose esters have also been proposed as dispersing agents.

Variables Influencing the Final Product [19]

Although the solvent - evaporation method is conceptually simple, many variables can influence the final product. These include;

- Drug / polymer ratio.
- Emulsion stirring rate.
- Phase ratio of emulsion system.
- Drug and polymer concentration.
- Solubility of drug.
- Type of organic solvent.
- Type and concentration of emulsifier.
- Rate of solvent diffusion.
- Apparatus design.

Evaluation Parameters for Microspheres

- Percentage yield value.
- Incorporation efficiency.
- Particle size and distribution measurement.
- Flow property.
- Scanning electron microscopy (SEM).
- FTIR.
- Differential Scanning Calorimetry (DSC).
- Differential Thermal Analysis (DTA).
- In-vitro dissolution tests.

Views of different authors

- *Ceyda T. Sengel, Canan Hascicek, and Nursin Gonul* worked on Development and in-vitro evaluation of modified release tablets including ethylcellulose microspheres loaded with diltiazem hydrochloride [14].
  In their study, ethylcellulose microspheres were prepared by emulsion- solvent evaporation technique. The influence of emulsifier type and drug/polymer ratio on production yield, encapsulation efficiency, particle size, surface morphology and in-vitro release characteristics of the microspheres was evaluated.
  It was found that increasing the polymer amount in the formulation resulted in a decrease in the dissolution rate as a result of the increase in matrix thickness formed by the polymer.
- *Iskandar S. Moussa, and Louis H. Cartilier* performed Evaluation of cross-linked amylose press-coated tablets for sustained drug delivery [20].
  They made the cores by mixing cross linked amylose (CLA) with the model drug diltiazem.HCl in different proportions and then compressed. The cores were coated manually by compression coating, consisting of either pure CLA or a mixture of CLA with a small proportion of solute. They found that for the same core composition, decreasing the coating thickness or incorporating small amounts of NaC1 in the shell shorten the release lag time and increase the release rate.
- *T. Kristmundsdottir, O.S. Gudmundsson, and K. Ingvarsdottir* studied Release of diltiazem from Eudragit microparticles prepared by spray-drying [21].
  Microparticles containing diltiazem hydrochloride were prepared by the spray-drying technique using acrylatemethacrylate co-

polymers, Eudragit RS and Eudragit RL, as coating materials. It was observed that the release of diltiazem hydrochloride from Eudragit RS microspheres increases with increasing proportion of the drug.

- *Anurag Sood, and Ramesh Panchagnula* performed Drug release evaluation of diltiazem CR preparations [22].
  The objectives of this study was to evaluate the effects of dissolution medium pH and dosage form structural integrity on the release mechanisms and kinetics of Diltiazem HCl (DTZ) from peroral CR:SR preparations(4 marketed products). From the solubility studies performed, the solubility of DTZ was found to be fairly independent of the pH of the media.
- *M.C. Bonferoni, S. Rossi, F. Ferrari, G.P. Bettinetti, and C. Caramella* carried out Characterization of a diltiazem-lambda carrageenan complex [23].
  In the study, the interaction between lambda carrageenan, a natural sulphated polysaccharide, and diltiazem HCl, was studied. Dialysis equilibria were performed to quantify the binding capacity of lambda carrageenan for diltiazem. They showed that the amount of drug going into solution from the complex was not significantly affected by the pH of the medium (in the range 1.8-6.8), while it was increased by increasing ionic strength.
- *Udaya S. Toti, and Tejraj M. Aminabhavi* prepared Modified guar gum matrix tablet for controlled release of diltiazem hydrochloride [24].
  Polyacrylamide-grafted-guar gum (pAAm-g-GG) was prepared by taking three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5). Tablets were prepared by incorporating diltiazem hydrochloride. In-vitro drug release was carried out in simulated gastric and intestinal conditions. Effect of drug loading on release kinetics was evaluated.
- *Nicolas Follonier, Eric Doelker, and Ewart T. Cole* studied Various ways of modulating the release of diltiazem hydrochloride from hot-melt extruded sustained release pellets prepared using polymeric materials [25].
  Sustained release pellets of Diltiazem hydrochloride were prepared using the continuous process of hot-melt screw extrusion. Firstly, the release profiles from extrudates varying in their polymer to drug ratio were analyzed. Then, to optimize the release profile of the drug the influence of different parameters, such as polymer type, addition of pore-forming additives and hydrophilic polymers, or size of the pellets was studied.
- *Ian R. Wilding, Stanley S. Davis, Robert A. Sparrow, John A. Ziemniak, and Donald L.* Heald performed Pharmacoscintigraphic evaluation of a modified release (Geomatrix ®) diltiazem formulation [26].
  The gastrointestinal transit and in - vivo release behaviour of a modified release (Geomatrix®) diltiazem formulation was evaluated by the combined technique of gamma scintigraphy and pharmacokinetic assessment (pharmacoscintigraphy) in eight healthy male subjects under fasting and fed conditions.
  It was observed that the variable transit of the tablets through the GI tract does not appear to affect the sustained release properties of the dosage form following oral administration under fasted conditions suggesting that DTZ is uniformly absorbed throughout the GI tract.
- *Eiji Fukui, Katsuji Uemura, and Masao Kobayashi* carried out Studies on applicability of press-coated tablets using hydroxypropylcellulose (HPC) in the outer shell for timed-release preparations [27].
  Press-coated tablets, containing diltiazem hydrochloride (DIL) in the core tablet and coated with hydroxypropylcellulose (HPC) as the outer shell were prepared. Besides in-vitro tests, in-vivo tests were performed in beagle dogs.
  The dissolution of Diltiazem appeared not to be affected by the gastrointestinal pH, and this system seemed to be more useful than the disintegrating tablets coated with the pH-dependent polymer.
- *S. S. Bhalerao, J. K. Lalla and M. S. Rane* performed Study of processing parameters influencing the properties of diltiazem hydrochloride microspheres [28].
  Diltiazem hydrochloride - ethylcellulose microspheres were prepared by the water-in-oil emulsion-solvent evaporation technique. The effect of various processing parameters such as temperature, light to heavy liquid paraffin ratio, speed of agitation, drug - polymer ratio was evaluated.
- *H. El-Kamel, O. M. N. Al-Gohary and E. A. Hosny* worked on Alginate-diltiazem hydrochloride beads: optimization of formulation factors, in vitro and in vivo availability [29].
  Conclusion: Microspheres and microcapsules are most promising systems for site specific drug delivery .In these types of system

drug is placed centrally surrounded by polymer system. They have future applications in treatment of several diseases with effectivessness.

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