

REVIEW ARTICLE

CONTROLLED DRUG DELIVERY THROUGH MICROENCAPSULATION

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An appropriately designed controlled release drug delivery system can be a major advance towards solving problems concerning to the targeting of drug to a specific organ or tissue and controlling the rate of drug delivery to the target site. The development of oral controlled release systems has been a challenge to formulation scientist due to their inability to restrain and localize 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. The objective of this paper 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 appreciate the application possibilities of microcapsules in drug delivery, some fundamental aspects are briefly reviewed.

Keywords: Drug delivery systems, Microcapsules, Controlled release, Microencapsulation

INTRODUCTION

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. Intensive interdisciplinary research efforts have led to a variety of advanced dosage forms. The majority of these systems are based on polymers that differ in their permeability, rate of dissolution, degree of swelling and erodibility (Khan 2001). An important class of polymer mediated drug delivery systems that are applied for controlled drug delivery is the microcapsules. Microencapsulation provides the means of converting liquids to solids, of altering colloidal and surface properties, of providing environmental protection and controlling release characteristics or availability of coated materials (Bakan 1986). The recent research has been heavily involved particularly

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on how the distribution of release controlling parameters among the individual microcapsules of the batch alters the release profile.

Although the word capsule implies a core and shell structure, the term microcapsules admits not only membrane enclosed particles or droplets but also dispersion in solid matrix lacking a distinctive external wall phase as well as intermediate types (Kramer 1974). The size range (2 to 2000 μm approximately) distinguishes them from the smaller nanoparticles or nanocapsules.

Microcapsules according to the French Pharmacopoeia are solid material consisting of a solid envelope containing a liquid or solid or a pasty substance. The microcapsules occur in the form of powder with particles less than 1250 μm in diameter.

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 (Jegat and Taverdet 2000). Also double or multiple concentric coating may be present (Benita and Donbrow 1982). Aggregated microcapsules greatly vary in size and shape [Fig. 1(b)] and may also possess 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 (Thies and Bissery 1983). Although microstructure of both membrane and interior can be detected by SEM of surfaces or sections [Fig. 1(c)] (Ramarao 2005), their physical quality is difficult to characterize quantitatively in microcapsules involving measurements of porosity, tortuosity and crystallinity, though some progress has been made and efforts are continuing to calculate permeability and porosity from release data, dimensions, densities, and core/wall ratios (Reis *et al.* 2004). The effect of size and shape distribution has only been studied recently (Berkland *et al.* 2004).

The standard pharmaceutical dosage forms are employed, such as hard gelatin capsules, which also may be enteric coated, soft gelatin capsules, or suspensions in liquids, all of which allow dispersion of individual microcapsules on release.

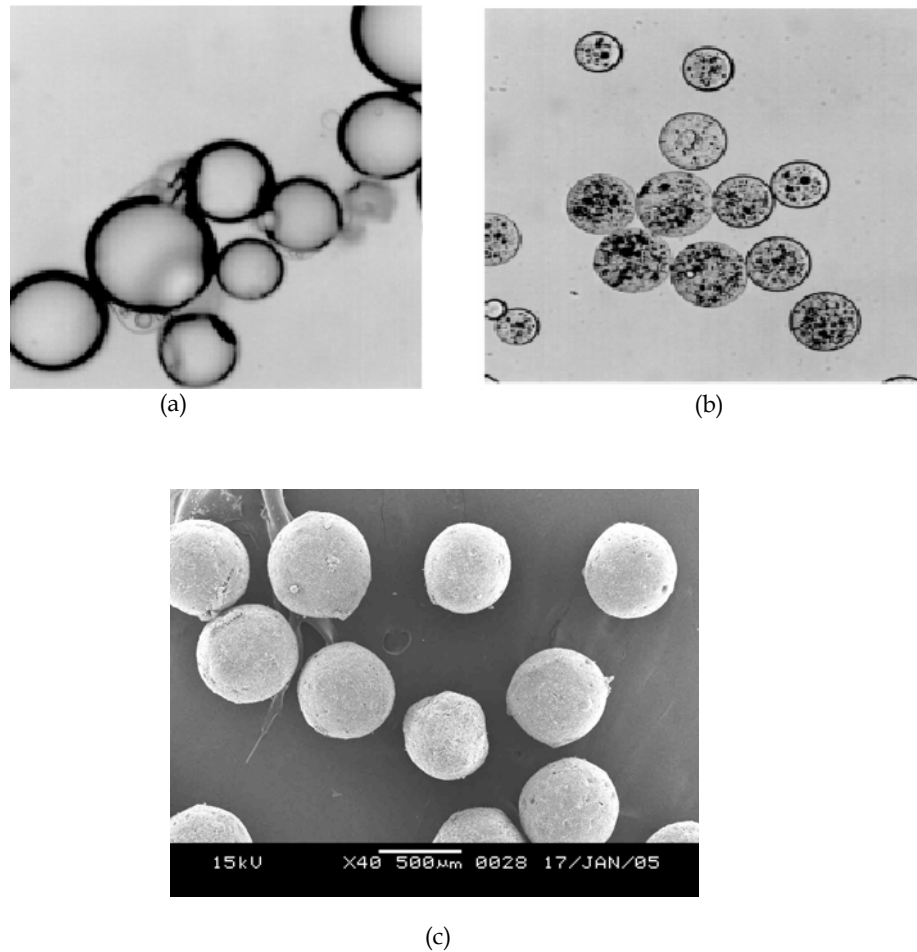


Fig. 1: Scanning electron micrographs ($\times 100$) of (a) mononuclear, (b) multinuclear microspheres, and (c) surface of the microspheres

There has been some recent interest in tableted microcapsules (Farid and Nokhodchi 1991), which will however, only restore the original microcapsules if suitably formulated to undergo complete disintegration. Several publications deal with non-disintegrating tablets, intended to extend release time particularly of soluble drugs and in fact doing so, but to greatly varying extent (Davis *et al.* 1984; Chaumeil, Chemtob and N'Dongo 1986; Farid and Nokhodchi 1991; Lee 2003). The release is affected by many factors (excipients, compaction pressure, and usual tableting factors). The advantage of using costlier microcapsules as opposed to conventional mixtures of drug and polymer in sustained

release matrix type tablets is no means clear, except when microencapsulation offer additional benefits.

Microcapsules continue to be of much interest in controlled release based partly on relative ease of design and formulation and partly on the advantages of microparticulate delivery systems. The latter include sustained release from each individual microcapsule and offer greater uniformity and reproducibility (Hsieh 1988). Additional advantage over monolithic systems containing multiple doses is the greater safety factor in case of a burst or defective individual in subdivided dosage form. Finally, it has been argued that multiple particle systems are distributed over a great length of gastrointestinal tract, which should result in, (a) lowered local concentrations and hence toxicity or irritancy, and (b) reduced variability in transit time and absorption rate (Davis *et al.* 1984).

MATERIALS AND METHODS FOR MICROENCAPSULATION

Coating Materials

A wide variety of coating materials are available for microencapsulation. Some patent innovative coating polymers have also been developed for some special applications particularly among the bioadhesives and mucoadhesives. However, many traditional coating materials are satisfactory for the use in the gastrointestinal tract. They include inert polymers such as ethyl cellulose and pH sensitive ones, such as carboxylate and amino derivatives, which swell or dissolve according to the degree of cross-linking (Deasy 1984).

The selection of appropriate coating material from a long list of candidate materials needs consideration of following general criteria by the research pharmacist (Bakan 1986):

1. What are the specific dosage forms or product requirements, such as stabilization, reduced volatility, release characteristics, and environmental conditions?
2. What coating material will satisfy the product objective and requirements?
3. What microencapsulation method is best suited to accomplish the coated product objectives?

The proper selection of coating material dictates to a major degree, the resultant physical and chemical characteristics of microcapsules. The coating material should be capable of producing a cohesive film with the core material, be chemically compatible and not reactive with the core material, and provide the desired coating properties such as strength, flexibility, impermeability, optical properties and stability.

The non-toxic polymethacrylate co-polymers have recently been applied as wall material and include inert and swellable types of varying porosity as well as solubility in selected pH ranges (Majeti and Kumar 2000). Natural latex from the peduncle of jackfruit was studied and found to be a promising candidate as a coating polymer for muco-adhesive microspheres (Bal 2005). The coating material used in microencapsulation methods are amenable, to some extent, to *in situ* modification. For example, colorants may be added to achieve product elegance or masking; or coating may be plasticized or altered chemically by cross-linking, for instance to achieve controlled release or permeability. Addition of a magnetic component has enabled the magnetic localization at certain sites (Ahuja, Khar and Ali 2004). Auxiliary coats have been used either to seal pores or to overcome body defense by providing anionic, cationic, and hydrophobic, mucoadhesive, immunospecific, or masking groups (Vyas and Khar 2004). Chemical cross-linking insolubilizes proteins and carbohydrates or in proteins heat denaturation, and new derivatives include the poly acryl starches. Synthetic polymers that have been used include polylactides, polyacrylamides and poly alkyl α -cyanoacrylates (Majeti and Kumar 2000). The hydrolysable groups may be of those used for cross-linking and insolubilization or the polymer backbone itself (Jayakrishan and Lata 2002). Finally, the development of a wall polymer and techniques for microencapsulating live cells without loss of viability was based on polyelectronic complexes such as polylysine alginate; nylon polymerization has given fruitful results (Donbrow 1987). Also the natural latex from different sources has been found to be potential biocompatible, biodegradable, and mucoadhesive coating polymer. 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 (Pathak, Nikore and Dorle 1985), shellac, tristearin, monoglyceride, bees wax, oils, fats and hardened oils.
7. Curable polymers: such as, epoxy resins, nitro paraffin and nitrated polystyrene.

Core Materials

The core material is the material over which coating has to be applied to serve the specific purpose (Chien 1982). Core material may be in form of solids or droplets of liquids and dispersions (Bakan 1986). The composition of core material can vary and thus furnish definite flexibility and allow effectual design and development of the desired microcapsule properties. A substance may be microencapsulated for a number of reasons. Examples may include protection of reactive material from their environment (Patel *et al.* 2000), safe and convenient handling of the materials (Gutcho 1979) which are otherwise toxic or noxious, taste masking, means for controlled or modified release properties (Lin and Wu 1999) means of handling liquids as solids (Peyre *et al.* 2003), preparation of free flow powders and in modification of physical properties of the drug (Alireja *et al.* 2005).

Available Technologies for the Preparation of Microcapsules

The microcapsules were prepared by a variety of methods. The first research leading to the development of microencapsulation procedures for pharmaceuticals was first published by Bungenburg de Jong and Kaos in 1931, which dealt with the preparation of gelatin spheres and the use of gelatin (Robinson and Lee 1987) coacervation process for coating. The

method of preparation and techniques employed for microencapsulation overlap considerably. The various microencapsulation processes can be divided into chemical, physiochemical, and electrostatic and mechanical processes. Chemical processes include the interfacial and *in-situ* polymerization methods. Physiochemical processes include coacervation-phase separation, complex emulsion, meltable dispersion and powder bed methods. Mechanical processes include the air-suspension method, pan coating, and spray drying, spray congealing, micro-orifice system and rotary fluidization bed granulator method. Also the spheronization is some times included under the mechanical process of microencapsulation. In addition to classical spheronizing equipment, the Rotocoil[®] from Aeromatic. Inc., equipment has been used to form the spheres from extrudates of varying size that are dried and coated with fluid bed unit (Kondo 1979). Kawashima, Niwa and Takeuchi (1992) prepared hollow microspheres [microballoons] loaded with drug in enteric acrylic polymer shell by using a novel emulsion solvent diffusion method. Sustained release polymers microcapsules containing drug with various solubility characteristics were prepared with colloidal polymer dispersion in a completely aqueous environment as an alternative to the conventional microencapsulation technique.

The microencapsulation techniques used for newer polymers are, except for some minor modifications, largely the classical ones comprising mainly the coacervation phase separation, interfacial polymerization, electrostatic methods, and mechanical methods.

The microencapsulation by coacervation-phase separation generally consists of three steps carried out under continuous agitation: (1) formation of three immiscible chemical phases, (2) deposition of coating, and (3) rigidization of the coating. The coacervation-phase separation has been classified into two categories, simple coacervation and complex coacervation (Feld *et al.* 1988). The former implies addition of a strongly hydrophilic substance to a solution of colloid. This added substance causes two phases to be formed [Fig. 2(a)]. The complex coacervation is principally a pH dependant process. The acidic or basic nature of the system is manipulated to produce microcapsules. Above a certain critical pH value, the system depending upon its acidic or basic nature may produce microcapsules. Below that pH value they will not form. Usually complex coacervation deals with the system containing more than one colloid [Fig. 2(b)].

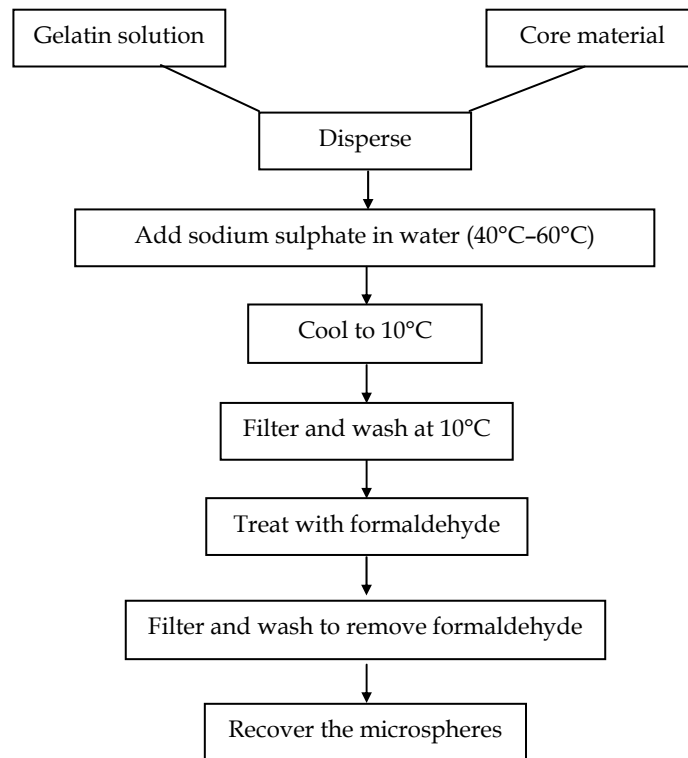


Fig. 2(a): Microencapsulation by simple coacervation

Interfacial polymerization, the microencapsulation by this method is a process whereby a monomer is made to polymerize (Torres *et al.* 1990) at the interface of two immiscible substances. If the internal phase is a liquid, it is possible to disperse or solublize the monomer in this phase and emulsify the mixture in the external phase until the desired particle size is reached. At this point a cross-linking agent may be added to the external phase. Since there is usually some migration of the monomer from the internal to external phase, and since it is preferred that the cross-linking agent does not transfer to the internal phase, the bulk of any polymerization will take place at the interface.

The electrostatic methods of microencapsulation involve triggering together the wall material and the material to be encapsulated when both are aerosolized. The wall material must be liquid during encapsulation stage and must be capable of surrounding the core material. The aerosols produced must be oppositely charged. Three chambers are used for the process, two for atomization of wall and core material and the third for

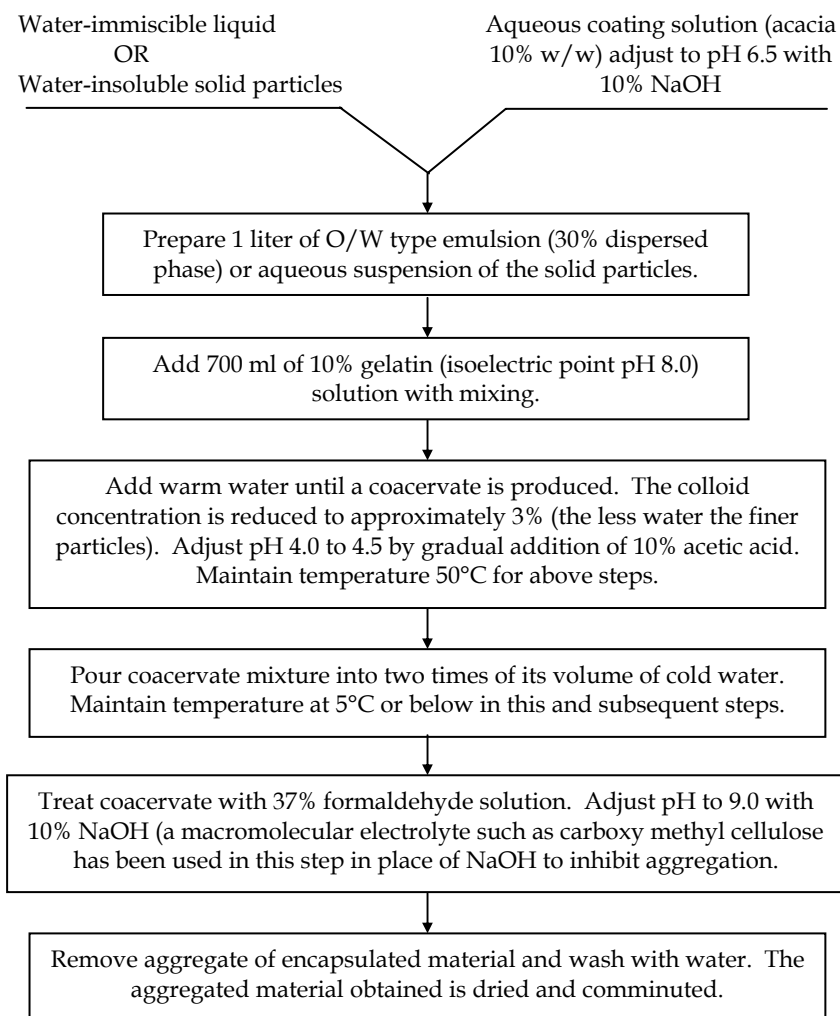


Fig. 2(b): Microencapsulation by complex coacervation

mixing. Oppositely charged ions are generated and deposited on the liquid drops while they are atomized (Feld *et al.* 1988).

Mechanical methods used for microencapsulation utilize the special equipments for their own. The microcapsules produced result from mechanical procedures rather than from a well-defined physical or chemical phenomenon. The most commonly employed mechanical methods for the preparation of microcapsules and microspheres (Arshady 1990) are: (1) multiorifice-centrifugal process, (2) air suspension

coating (wurster), (3) vacuum coating, (4) spray drying, (5) spray congealing, (6) pan coating, (7) rotary fluidized bed granulator, and (8) spheronization.

The techniques used to prepare microcapsules or microspheres have been detailed over the last few decades, so that the concept of the wide use of microencapsulation has now become a reality (Chowdary, Koteswara and Malathi 2004). Several developments have contributed to this reality, but in fact none of encapsulation system is ideal. Many authors pointed the fact that several of the encapsulation systems may be altered and/or combined to meet a specific need and that each job requirement must be met with in-depth approach.

Mechanism and Kinetics of Drug Release

Major mechanisms of drug release from microcapsules (Brazel and Peppas 2000) include diffusion, dissolution, osmosis and erosion.

1. *Diffusion* is the most commonly involved mechanism wherein the dissolution fluid penetrates the shell, dissolves the core and leak out through the interstitial channels or pores (Korsmeyer *et al.* 1983). 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 (Gunder, Lippold and Lippold 1995). The kinetics of such drug release obeys Higuchi's equation (Higuchi 1963) 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 $Q = v\sqrt{t}$ where v is the apparent release rate.

2. *Dissolution*: Dissolution rate of polymer coat determines the release rate of drug from the microcapsule when the coat is soluble in the

dissolution fluid (Korsmeyer *et al.* 1983). Thickness of coat and its solubility in the dissolution fluid influence the release rate (Costa and Lobo 2001).

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 coat due to pH and/or enzymatic hydrolysis causes drug release (Sachacht and Van Bos 1987) with certain coat materials like glyceryl monostearate, bee's wax and stearyl alcohol.

Attempts to model drug release from microcapsules have become complicated due to great diversity in physical forms of microcapsules with regard to size, shape and arrangement of the core and coat materials (Nokhodchi *et al.* 2002; Haznedar and Dortue 2004). The physiochemical properties of core materials such as solubility, diffusibility and partition coefficient, and of coating materials such as variable thickness, porosity, and inertness also makes modeling of drug release difficult. However, 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.

Applications of Microcapsules and Microspheres

Some of the applications of microencapsulation can be described in detail as given below:

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. From the mechanical point of view, microencapsulation has been used to aid in the addition of oily medicines to tableted dosage forms. This has been used to overcome problems inherent in producing tablets from otherwise tacky granulations. This was accomplished through improved 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. Microencapsulation does not yet provide a perfect barrier for materials, which degrade in the presence of oxygen, moisture or heat, however a great degree of protection against these elements can be provided. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation (Trindade and Grosso 2000).
6. The separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. This is a case where direct contact of materials brings about liquid formation. The stability enhancement of incompatible aspirin-chlorpheniramine maleate mixture was accomplished by microencapsulating both of them before mixing (Robinson and Lee 1987).

7. Microencapsulation can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation (Gulden *et al.* 2002).
8. Microencapsulation has also been used to decrease potential danger of handling of toxic or noxious substances. The toxicity occurred due to handling of fumigants, herbicides, insecticides and pesticides have been advantageously decreased after microencapsulation (Conick, Walker and Geynes 1983; Fravel *et al.* 1985).
9. The hygroscopic properties of many core materials may be reduced by microencapsulation (Bakan 1986).
10. Many drugs have been microencapsulated to reduce gastric irritation.
11. Microencapsulation method has also been proposed to prepare intrauterine contraceptive device (Rosilio *et al.* 1991).
12. In the fabrication of multilayered tablet formulations for controlled release of medicament contained in medial layers of tableted particles.

CONCLUSION

Microfabricated system offers potential advantages over conventional drug delivery systems. Microspheres and microcapsules are established as unique carrier systems for many pharmaceuticals and can be tailored to adhere to targeted tissue systems. Hence, microcapsules and microspheres can be used not only for controlled release but also for targeted delivery of drugs to specific site in the body. Although significant advances have been made in the field of microencapsulation, there are still many challenges ahead in this field. Of particular importance are the development of cheaper biopolymers for the microencapsulation technology and the development of universally acceptable evaluation methods especially for bioadhesive microspheres. Therefore, the development of safe and efficient particular systems will require, in the future, in-depth investigations of both the biological and technological aspects of these systems.

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