Review Article

A Review on Various Techniques of Microencapsulation

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ABSTRACT

The formulation of natural substances together with a biocompatible or biodegradable carrier material to form composites or encapsulates has a great relevance for pharmaceutical, cosmetic and food industries. The main objective of this article is taking a look at microencapsulation as a novel drug delivery system. Its scope extends beyond conventional microcapsules to all other small particulate systems such as self-assembling structures that involve preparative manipulation. The review covers encapsulation materials, techniques of preparation, physics of release through the capsule wall, characterization of microcapsules and the many uses to which microcapsules are put. The review of State of Art of Microencapsulation of Microcapsule Preparation Process Technology is a well established dedicated to the preparation, properties and uses of individually encapsulated novel small particles, as well as significant improvements to tried-and-tested techniques relevant to microcapsules and their use in a wide variety of industrial, engineering, pharmaceutical, biotechnology and research applications.

Keywords: Microencapsulation, Jet Excitation, SCF method, Coacervation.

1. INTRODUCTION

Microencapsulation is the process in which small droplets or particles of liquid or solid material are surrounded or coated by a continuous film of polymeric materials (Ipemtech, 2009), (Figure 1). The microencapsulation procedure was introduced by Bungen burg de Jon and Kan, (1931), and particle size below 200 µm (Vyas and Khar, 2002). Microencapsulation process helps in converting the liquids to solids, changing the colloidal and surface properties, providing environmental protection, enhanced bioavailability and controlling the release characteristics of different coated materials (Bakan, 1991; Khawala, 1996a, 1996b). Microencapsulated products (microparticles or microcapsules) are small entities that have an active agent know as the core material surrounded by a shell known as the coating material or embedded in a matrix structure. Most of the microparticle shells consist of organic polymers, but waxes and lipids are also used. The microencapsulated products have a size range from 1 to 1000 µm in diameter. Commercially available microparticles contained 10-90% w/w core. A large number of core materials can be encapsulated like live cells, adhesives, flavours, agrochemicals, enzymes, pharmaceuticals etc (Kreitz et al. 2000). The scanning electron microscopy is used to reveal the structural features of microcapsules as these are to be varied and complex. The walled prototype may be mononuclear or may have multiple core structure (Jegat and Taverdet, 2000) and there may also be double or multiple concentric coating present (Benita and Donbrow 1982). As aggregated microcapsules have an additional external wall and thus vary in shape and size. Although, the microstructure of membrane and the interior can be detected by SEM of surfaces of microcapsule but their physical quality is not easily characterized quantitatively. The porosity and permeability can be calculated from release data, densities, dimensions, and core/wall ratios (Sachan, 2005; Reis et al. 2004).

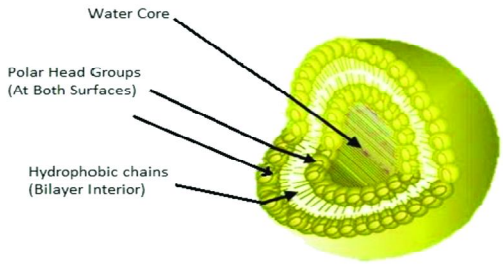

Fig. 1: Photographic depiction of microcapsules

2. Rationale for Microencapsulation

- To attain the sustained or prolonged release of the drug.
- For masking the organoleptic properties like taste and odour of many drugs and thus improve patient compliance.

- The liquid drugs can be converted into a free flowing powder.
- The drugs which are sensitive to moisture light and oxygen can be protected by microencapsulation.
- Microencapsulation technique is also helpful to prevent the incompatibility between drugs.
- The drugs, which are volatile in nature and vaporize at room temperature, can be prevented by microencapsulation.
- Reduction in toxicity and GI irritation including with KCL and ferrous sulphate can be achieved by microencapsulation
- Microencapsulation can be employed to change the site of absorption. This application has been useful for those drugs which have the toxicity at lower pH.
- Microencapsulation of vitamin A palmitate provides the enhanced stability, as prevents from oxidation (James, 2007).

3. Mechanism and Kinetics of Drug Release

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

Diffusion

The most common mechanism of drug release (core material) in which the dissolution fluid penetrates the shell then the core material comes into the contact with the dissolution fluid and leak out through the interstitial channels or pores (Korsmeye et al. 1983). The drug release depends on the rate of drug dissolution in the dissolution fluid, rate of penetration of dissolution fluid to the microcapsules and rate at which the dissolved drug escapes from the microcapsule (Gunder, 1995).The kinetics of such drug release follows Higuchi's equation (Higuchi, 1963):

$Q = [D/J (2A – \varepsilon CS) CS t]^{1/2}$ where, Q is the amount of drug released per unit area of exposed surface in time t; J is the tortuosity of the capillary system in the wall; D is the diffusion coefficient of the solute in the solution; A is the total amount of drug per unit volume; ε is the porosity of the wall of microcapsule; CS is the solubility of the drug in permeating dissolution fluid.

Dissolution

The release rate of the drug from the microcapsule depends on the dissolution rate of polymer coat, when the coat is soluble in the dissolution fluid (Korsmeye et al. 1983). The solubility in the dissolution fluid and thickness of coat influence the release rate (Costa and Lobo, 2001).

Osmosis

Another method of drug release is through osmosis. The essential requirement of osmosis is semi permeable membrane and in microcapsule polymer coat serve the purpose. As the process progress an osmotic pressure is created between the outside and the inside membrane of microcapsule which result in release of drug through small pores**.**

Erosion

Erosion of coat generally occur due to pH or enzymatic hydrolysis and causes drug release with certain coat materials like bee's wax, stearyl alcohol and glyceryl monostearate (Sachacht and Van, 1987). The drug release from microcapsules has become complex because of great diversity in physical forms of microcapsules with size, shape and arrangement of the core and coat materials (Nokhodchi et al. 2002; Haznedar and Dortue, 2004). The physiochemical properties of core materials like solubility, diffusibility and partition coefficient and of coating materials like variable porosity, thickness and inertness which makes difficult to modeling of drug release. However, on the basis of various studies concerning with the release characteristics, the following considerations can be made:

- Drug release rate from microcapsules follow the zero order kinetic.
- Microcapsules of monolithic type have the $t_{1/2}$ dependant release rate for the first half of the total drug release and thereafter turn down exponentially.
- Microcapsules of monolithic type containing excess of dissolved drug, the release rate are $t_{1/2}$ dependant throughout almost the entire drug release.
- The path traveled by drug is not constant in monolithic capsules; as the drug at the center travels a large distance than the drug at the surface. Therefore, the release rate in monolithic capsules generally decreases with time (Bakan, 1991).

4. Development of microcapsules

Core Materials

The core material can be liquid or solid in nature. The composition of the core material can be varied, as the liquid core can include dispersed and/or dissolved materials. The solid core be active constituents, stabilizers, diluents, excipients, 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 (Bakan, 1991).

Coating Materials

The coating material should be capable of forming a film that is cohesive with the core material ; to 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 (Bakan, 1991). The ideal characteristics of coating material are as stabilization of core material, inert toward active ingredients, controlled release under specific conditions, film forming, pliable, tasteless, stable and non-hygroscopic, no high viscosity, and economic, soluble in an aqueous media or solvent and melting and the coating should be flexible, brittle, hard, thin etc. Examples of coating materials are:

Synthetic polymers

(a) Non-biodegradable polymers e.g. Poly methyl methacrylate (PMMA), Acrolein, Glycidyl methacrylate Epoxy polymers (Kreuter et al. 1983; Margel and Wiesel, 1984).

(b) Biodegradable polymers e.g. Lactides, Glycolides & their co polymers (Wakiyama, 1981) Poly alkyl cyanoacrylates Polyanhydrides.

Natural polymers

(a) Proteins: albumin, gelatin and collagen (Yoshioka et al. 1981) (b) Carbohydrates: agarose, carrageenan, chitosan, starch (Russel, 1983) and (c) Chemically modified carbohydrates: poly dextran, poly starch (Jain, 2002).

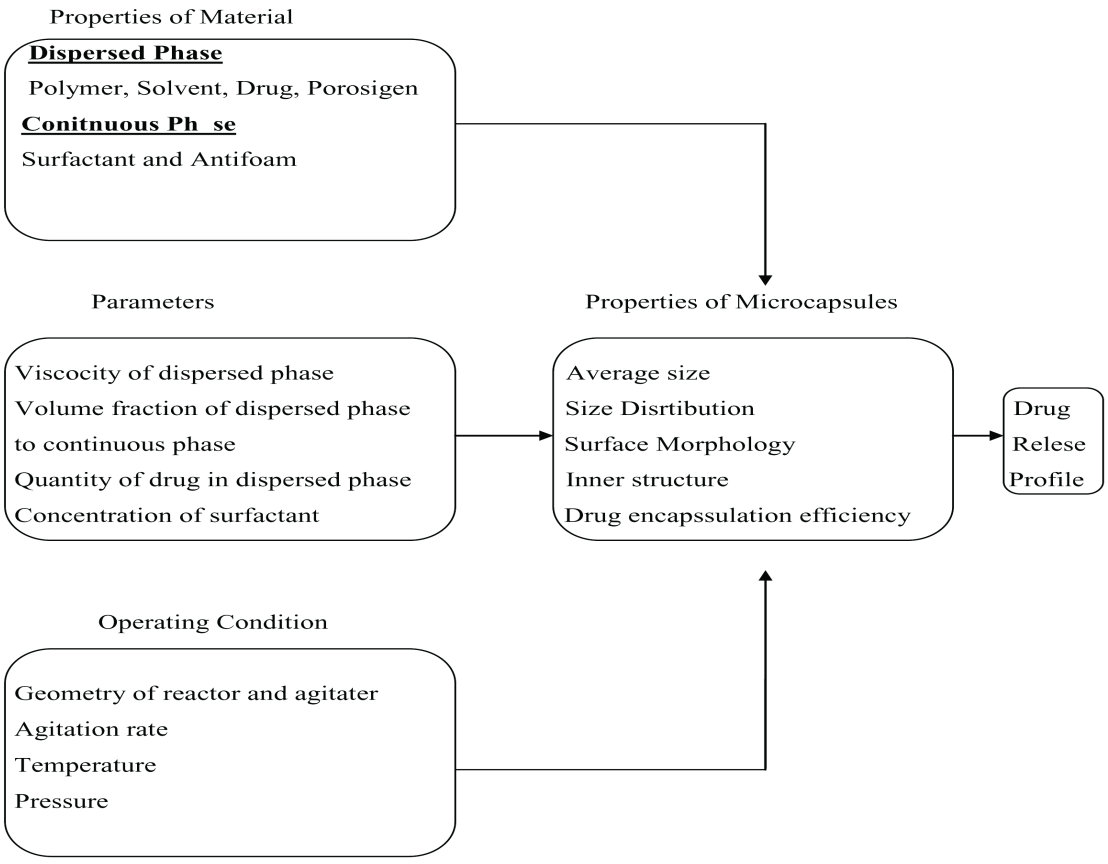

Fig. 2: Schematic representation of the factors influencing the properties of microcapsules

5. Techniques for microcapsules fabrication

Air-suspension method

The air suspension technique involves the dispersion of the core materials in a supporting air stream and the spraying of coating material in the air suspended particles. The moving air stream suspends the particles on an upward within the coating chamber. The design of the coating chamber and its operating parameters should be in such a way that could affect the flow of the particles through the coating zone of chamber, where a coating material (polymer solution) is applied to the moving particles. As the moving particles passed through the coating zone repeatedly, the core material receive more of coating material. The cyclic process is repeated about several times depending on the desired coating thickness or whether the particles of core materials are thoroughly encapsulated. The encapsulated product is air dried. The rate of drying are directly depends on to the temperature of the supporting air stream. The process variables that can affect the process are (Bakan, 1991). concentration of the coating material or if in solid form then melting point , solubility, surface area, density, melting point , volatility of the core material, application rate of coating material, temperature of air stream and the amount of air required to fluidize the core material (Bansode et al. 2010).

Coacervation Method

During this process the core material is dispersed in the solution of coating material. The core material should not react or dissolve in solvent of coating material maximum solubility is 2%. The particle size is defined by dispersion parameters, such as stirring speed, stirrer shape, surface tension and viscosity. The particle size range varies from 2µm - 1200µm. Coacervation starts with a change of the pH value of the dispersion, e.g. by adding H2SO4, HCl or organic acids. The result is a reduction of the solubility of the dispersed phase (shell material). The shell material (coacervate) starts to precipitate from the solution. The shell material forms a continuous coating around the core droplets. The shell material is cooled down to harden and forms the final capsule. Hardening agents like formaldehyde can be added to the process. The microcapsules are now stable in the suspension. The suspension is then dried in a spray dryer or in a fluidized bed dryer. Spray Drying is a suitable method for heat sensitive products (Bansode et al. 2010).

Coacervation Phase Separation method

This process of microencapsulation is generally referred to The National Cash Register (NCR) Corporation and the patents of B.K. Green. This process consists of three steps (Bansode et al. 2010). (a) Formation of three immiscible phases; a liquid manufacturing phase, a core material phase and a coating material phase (b) Deposition of the liquid polymer coating on the core material and (c) Rigidization of the coating material

The first step involves the formation of three immiscible chemical phases: a liquid vehicle phase, a coating material phase and a core material phase. The three phases are formed by dispersing the core material in a solution of coating polymer, the vehicle phase is used as a solvent for the polymer. The coating material phase consists of polymer in liquid phase which is formed by using one of the methods of phase separation- coacervation i.e. by changing the temperature of the polymer solution, by adding a solution, or by inducing a polymer- polymer interaction (Bakan, 1991). In step II involves the deposition of the liquid polymer coating upon the core material by controlled mixing of liquid coating material and the core material in the manufacturing vehicle. The liquid coating polymer deposited on the core material if the polymer is adsorbed at the interface formed between the core material and liquid phase. Reduction in the total free interfacial energy of the system help to promote the deposition of the coating material, brought by the decrease of the coating material surface area during coalescence of the liquid polymer droplets (Bansode et al. 2010). In step III rigidization of the coating material is done by the thermal, cross linking or desolvation technique, to form a self-supporting microcapsule. The process of phase separation and coacervation is depicted in (Figure 2).

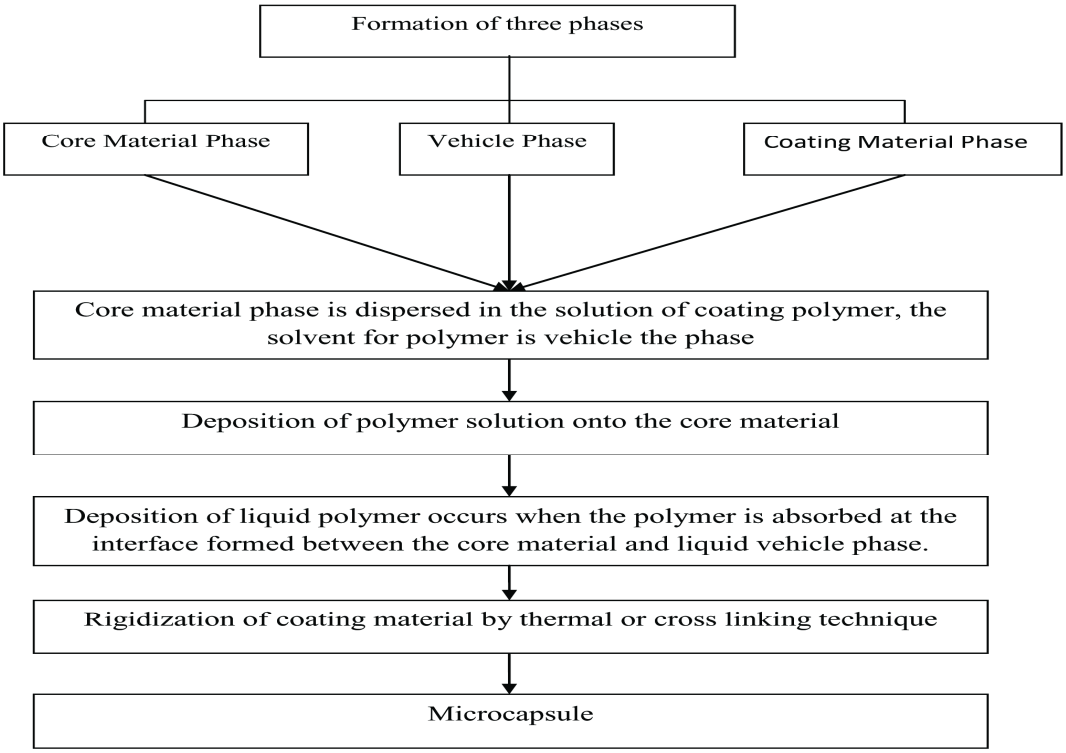

Fig. 3: Microencapsulation by coacervation phase separation process

Centrifugal extrusion method

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, into droplets of core, each coated with the coating material solution. While the droplets are in flight, molten coating material may be hardened or a solvent may be evaporated from the coating material 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 (Bansode et al. 2010).

Pan coating method

The pan coating process, widely used in the pharmaceutical industry, is among the oldest industrial procedures for forming small, coated particles. The particles are tumbled in a pan while the coating material is applied slowly. With respect to microencapsulation, solid particles greater than 600 µm in size are generally considered essential for effective coating. In practice, the coating is applied as a solution or as an atomized spray to the desired solid core material in the coating pan. 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 drying oven (Kasturagi et al. 1995).

Spray drying spray congealing method

Spray drying is a unit operation by which a liquid product is atomized in a hot gas current to instantaneously obtain a powder. The gas generally used is air or more rarely an inert gas as nitrogen. The initial liquid feeding the sprayer can be a solution, an emulsion or a suspension. Spray-drying produces, depending on the starting feed material and operating conditions, a very fine powder (10-50 lm) or large size particles (2-3 mm). 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 thermo 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 300 mPa.s (mili Pascal second) Spray drying and spray congealing processes are similar in that both

involve dispersion of 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 effected 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 (Re, 1998; Eduard, 2010; Boza et al 2004).

Single emulsion method

This method has been primarily used to encapsulate hydrophobic drugs through oil-in-water (o/w) emulsification process. The polymer is dissolved in a water-immiscible, volatile organic solvent such as dichloromethane, and the drug is dissolved or suspended in the polymer solution. The resulting mixture is emulsified in a large volume of water in the presence of an emulsifier (Jain, 2000; Hombreiro et al 2000; Passerini and Craig, 2002). The solvent in the emulsion is removed by either evaporation at elevated temperatures or extraction in a large amount of water, resulting in formation of compact microparticles. The rate of solvent removal is reported to affect the final morphology of microparticles. The solvent removal rate is determined by the temperature of the medium, the solubility characteristics of the polymer, and the solvent used (Hombreiro et al 2000; Passerini and Craig, 2002; Arshady, 1991). This method, however, is only available for the hydrophobic drugs because the hydrophilic drugs may diffuse out or partition from the dispersed oil phase into the aqueous phase, leading to poor encapsulation efficiencies (Hombreiro et al 2000; Arshady, 1991). In an attempt to encapsulate hydrophilic drugs (e.g. Peptides and proteins), an oil-in-oil (o/o) emulsification method has recently received considerable attention (Carrasquillo, 2001; Jiang and Schwendeman, 2001a, 2001b). In this method, the water miscible organic solvents are employed to dissolve the drug and polymer, whereas hydrophobic oils are used as a continuous phase of the o/o emulsion. The microparticles are obtained by removing the organic solvents through evaporation or extraction process (Figure 3).

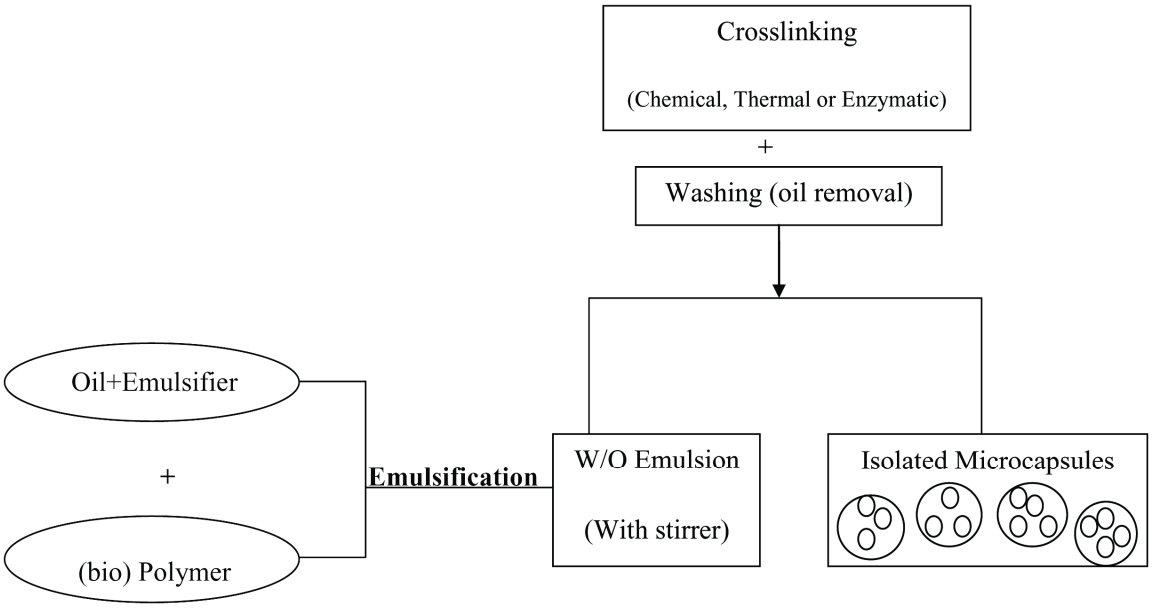

Fig. 4: Method of Preparation of Microcapsules by single emulsion technique

Double emulsion method

Most water-soluble drugs have been encapsulated by water-in-oil-in-water (w/o/w) methods. The aqueous solution of the water-soluble drug is emulsified with polymer-dissolved organic solution to form the water-in-oil (w/o) emulsion. The emulsification is carried out using either high speed homogenizers or sonicators. This primary emulsion is then transferred into an excess amount of water containing an emulsifier under vigorous stirring, thus forming a w/o/w emulsion. In the subsequent procedure, the solvent is removed by either evaporation or extraction process. One advantage of this method is encapsulation of hydrophilic drugs in an aqueous phase with the high encapsulation efficiency. For this reason, the w/o/w emulsion system has been used widely for the development of protein delivery systems (Sinha and Trehan, 2003; Crotts and Park, 1998; Okochi and Nakano, 2000). The characteristics of the microspheres prepared by the double emulsion method are dependent on the properties of the polymer (such as composition and molecular weight), the ratio of polymer to drug, the concentration and nature of the emulsifier, temperature, and the stirring/agitation speed during the emulsification process and depicted in (Crotts and Park, 1998; Okochi and Nakano, 2000) (Figure 4).

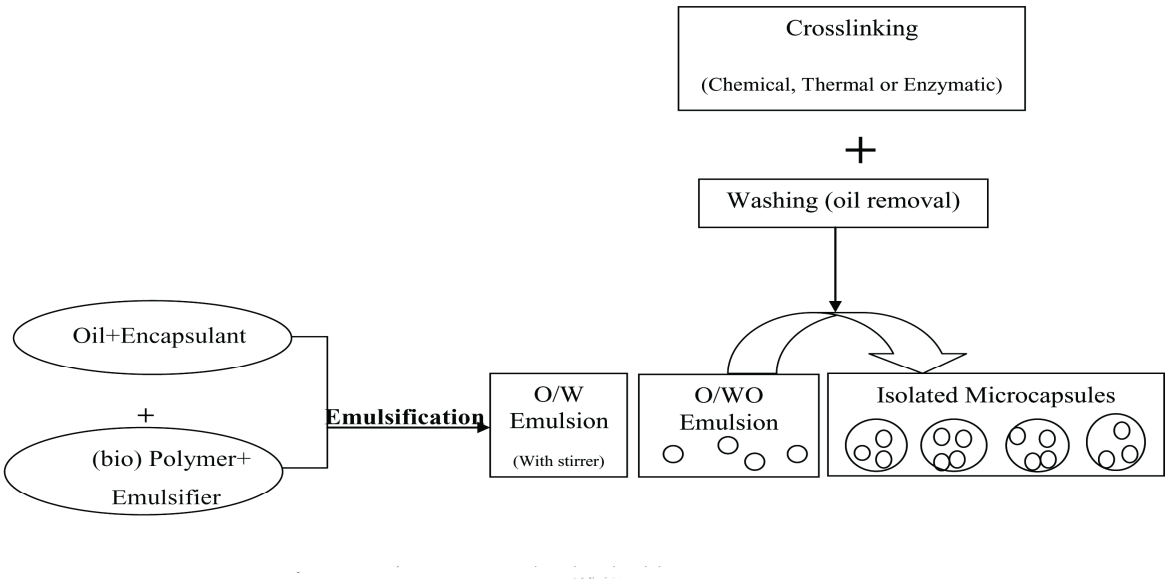

Fig. 5: Microcapsule Preparation by double emulsion Technique

Jet excitation

The vibration of a liquid jet for its disruption into droplets was originally studied by Lord Rayleigh as early as in the late 19th century (Rayleigh, 1879; Rayleigh, 1882). A longitudinal oscillation imposed on a liquid stream causes periodic surface instabilities, which break up the liquid into a chain of uniform droplets. Lord Rayleigh found that uniform droplets are produced from a range of excitation wavelengths corresponding to 7 to 36 times the liquid jet radius. This principle was recently used to produce uniform PLGA micro particles (Berkland et al. 2001; Berkland et al. 2002). A 5% (w/v) solution of PLGA in DCM was fed through a nozzle to form a cylindrical jet while the nozzle was excited by an ultrasonic transducer of adjustable frequency (Fig. 5). The particles were collected in 1% (w/v) PVA solution for solvent extraction/evaporation. Very uniform microspheres of 45 to 500 Am diameter were produced by jetting the polymer solution from nozzles of different orifice size. Generally, 95% of the microspheres were within 1.5 Am of the average diameter. At a fixed feed rate (2–3 ml/min; 60 Am nozzle), the microsphere size could be adjusted between 70 and 130 Am by decreasing the frequency from 70 to 19 kHz. Augmenting the feed rate at fixed excitation frequencies from 2 to 3 ml/min resulted in a 30% increase in the microsphere diameter. Predetermined size distributions were obtained by switching the excitation frequency during production. Generally, the size of the microspheres was slightly larger

than the diameter of the nozzle. Therefore, particle sizes below 25 Am are difficult to achieve with this technique as the pressure drop across the orifice opening rapidly increases, as does the risk of orifice clogging. Scale-up is achieved using multiorifice nozzles (Berkland et al. 2002). Multiorifice nozzles with nonuniform openings were designed to yield desired microsphere size distributions (Brenn et al. 1996). The jet of drug/matrix dispersion may be surrounded by an annular stream of extraction fluid or any other suitable fluid immiscible with the drug/matrix dispersion (Fig. 5). The biphasic jet is then again vibrated and disintegrated into biphasic droplets (Berkland et al. 2001; Brenn, 2000). The outer layer of fluid around the droplets of drug/matrix dispersion protected the latter from deformation upon impact with the collection/extraction fluid bath (Hatcher and Fulwyler, 1979; Lombardo and Natale, 1983). Feeding the outer stream at a higher velocity than the inner stream of drug/matrix dispersion stretched and thinned the latter due to the friction between the two phases. Subsequent vibration of the biphasic jet yielded uniform particles as small as 5 Am produced from a nozzle of much larger diameter (Berkland et al. 2001). The combined control of exciting frequency and annular sheath stream velocity allowed for a wide range of particle sizes manufactured from a single nozzle. The annular stream may alternatively be employed to dissolve a second matrix material, allowing for the manufacture of core/ (multi)shell microspheres (Brenn, 2000; Lombardo and Natale, 1983).

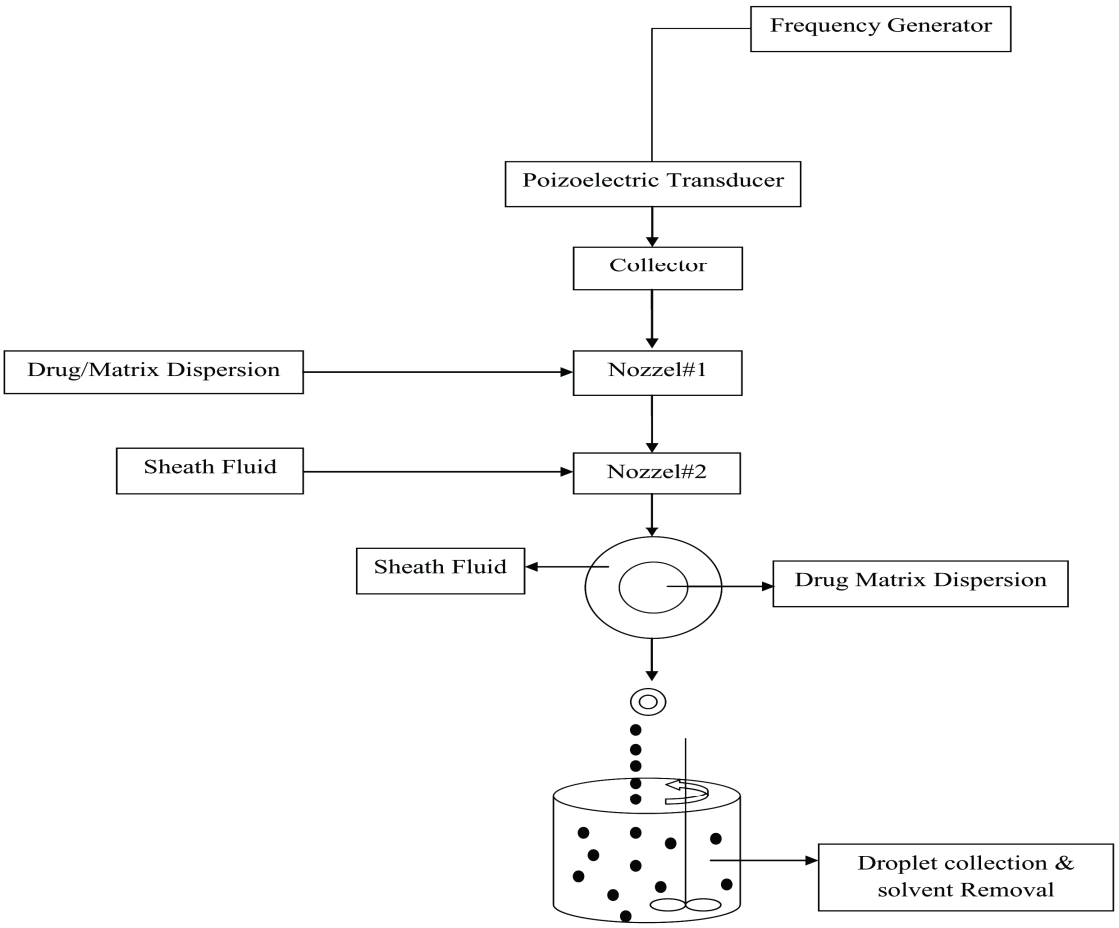

Fig. 6: Microencapsulation by jet excitation

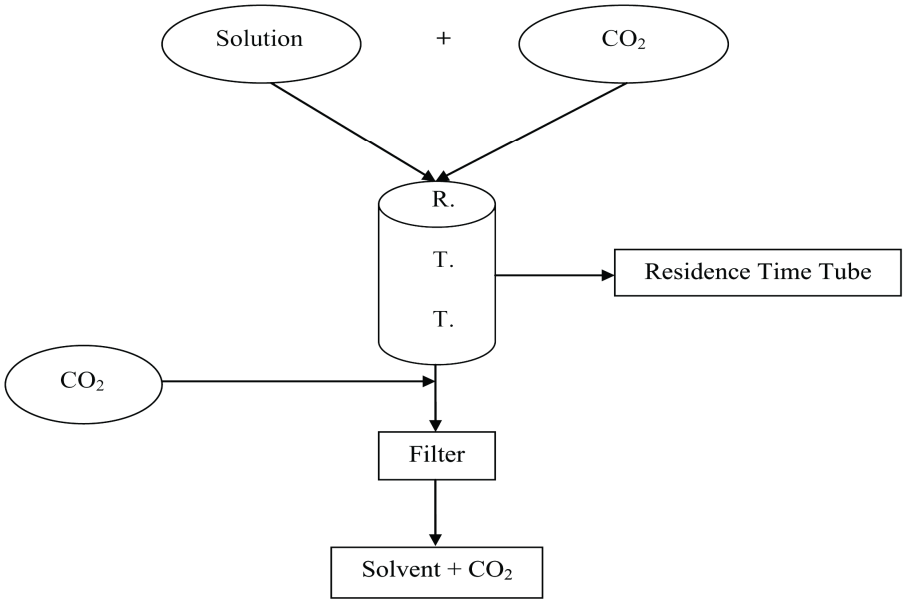

Fig. 7: Schematic flow sheet of the modified PCA process

Super critical fluid micronization(SCF) techniques

The application of supercritical fluids as an alternative to all conventional precipitation processes has been an active field of research and innovation during the past two decades (Kyekyoon et al. 2002; Jung and Perrut, 2001; Shariati and Peters, 2003). The main motivation for this is the possibility of exploiting the peculiar properties of supercritical fluids, and in particular of supercritical carbon dioxide (sc-CO2), the most used supercritical fluid for precipitation processes. The properties of supercritical fluids are often described as intermediate between those of a liquid and a gas; moreover these properties can be easily changed with changes in pressure and temperature (Martin and Cocero, 2008). In the case of carbon dioxide, the supercritical region can be achieved at moderate pressures and temperatures (Tc = 304.2 K, Pc = 7.38MPa); therefore, working with sc-CO_2 it is possible to carry out the process at near-ambient temperatures, avoiding the degradation of thermolabile substances. sc-CO_2 also provides an inert medium suitable for processing easily oxidable substances. Additionally, the use of the supercritical fluid eliminates or reduces the use of toxic or contaminant organic solvents in the process, the separation of the supercritical fluid from the product can be easily accomplished by a depressurization, and the high solubility of most organic solvents in supercritical fluids allows obtaining solvent-free products (Bertucco and Vetter, 2001). For this reason, several precipitation processes based on supercritical fluids have been developed. These processes can be classified according to the role of the supercritical fluid in the process (Kyekyoon et al. 2002; Miguel, 2006) as solvent, anti solvent, co-solvent or solute, or even propellent gas.

Solvent Evaporation

This technique has been adopted by various companies to produce microcapsules. The process is carried out in a liquid manufacturing vehicle. The coating material is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. A core material to be microencapsulated is dissolved or dispersed in the coating polymer solution. With agitation, the core and coating material mixture is dispersed in the liquid manufacturing vehicle phase to obtain the microcapsule of appropriate size. The mixture is heated (if necessary) to evaporate the solvent of the polymer and if the core material is dispersed in the polymer solution, polymer shrinks around the core and if the core material is dissolved in the coating polymer solution, a matrix - type microcapsule is formed. Once all the solvent of polymer is evaporated, the liquid vehicle temperature is reduced to ambient temperature (if required) with continued agitation (Bakan, 1991). At this stage, the microcapsules can be used in suspension form, coated on to substrates or isolated as powders. The solvent evaporation technique is applicable to a wide variety of liquid and solid core materials. The core

materials may be either water - soluble or water - insoluble materials. A variety of film - forming polymers can be used for coating (Youan et al. 2003).

Polymerization

(a) Interfacial polymer: In interfacial polymerization, the two reactants in a polycondensation process meet at an interface and react rapidly. This method is based on the Schotten Baumann reaction in which an acid chloride and a compound containing an active hydrogen atom, such as amine alcohol, polyesters, polyurea or polyurethane react. Under proper conditions, thin flexible walls form rapidly at the interface. A solution of pesticide and diacid chloride is emulsified and an aqueous solution containing an amine and a polyfunctional isocyanate is added. Presences of a base neutralize the acid, formed during the reaction. Condensed polymer walls form instantaneously at the interface of the emulsion droplets. (b) In situ polymerization: In certain microencapsulation processes, the direct polymerization of a single monomer is carried out on the particle surface e.g. Cellulose fibers are encapsulated in polyethylene while immersed in dry toluene. Usual deposition rate is about 0.5µm/min. Coating thickness ranges from 0.2 to 75µm. The coating is uniform, even over sharp projections. (c) Matrix polymerization: In a number of processes, a core material is imbedded in a polymeric matrix during formation of the particles. A simple example of this type is spray-drying, in which the particle are formed by evaporation of the solvent from the matrix material. However, the solidification of the matrix can also be done by a chemical change. Using this phenomenon, prepares microcapsules containing protein by incorporating the protein in the aqueous diamine phase (Jackson and Lee, 1991).

6. Coating materials

The coating material must fulfill several requisites: its biocompatibility and lack of toxicity are of course important considerations. It should also provide a suitable medium for preserving the properties and activity of the active substance (e.g. the activity of pharmaceutical proteins (Martin and Cocero, 2008). Additionally, it should be easy to process with the selected precipitation technique. Most frequently, natural or synthetic biopolymers are used as coating materials, although other materials as fats (Martin and Cocero, 2008) or sugars (Jovanovic et al. 2008) can also be used. Yeo and Kiran (2005) and Tomasko et al (2003) presented extensive reviews of the supercritical processing of polymers. Starch-based polymers often are a blend of starch and other plastics, which allows for enhanced biological and environmental properties. On the other hand, some bio-polyesters as polylactic acid (PLA) and polyglycolic acid (PGA) were the first polymeric materials successfully used as sutures, and their degradation pathways are well known and do not produce toxic products and other aliphatic polyesters and particularly of polycaprolactones (PCL). PCLs degrade slower than PLA and PGA and therefore they are more suitable for long-term delivery systems. Some nonbiodegradable but biocompatible polymers can also be used in drug delivery systems, including polyethylene co-vinyl acetate (EVA), polyethylene glycol (PEG), and some acrylic polymers (Bouchard et al. 2008; Li, 2006; Yeo and Kiran, 2005).

7. Characterization of Microcapsules

Particle size distribution: Particle size analysis12 of the microcapsules was done by sieving method using Indian Standard Sieves # 16, #20, #30, #40, #60 and #80 (Indian Pharmacopoeia. 1996). The amounts retained on different sieves were weighed. The values of Particle Size are depicted (Prakash et al., 2007) in (Table 1)

Shape and surface morphology

The shape and surface morphology of the microcapsules was studied by using scanning electron microscope (JSMT330A, JEOL). Microcapsules were mounted directly onto the SEM sample stub using double-sided sticking tape and coated with gold film (thickness 200 nm) under reduced pressure (0.001 mm of Hg) (Chowdary and Srinivasa, 2003).

Carr's Index & Hausner's Ratio

The static angle of repose was measured according to the fixed funnel and free standing cone method. The bulk density of the mixed microcapsules was calculated in determining the Hausner's ratio and Carr's index from the pored and tapped bulk densities of a known weight of the sample using a measuring cylinder (Hausner, 1967; Carr, 1965). The following formulas were used for calculating carr's index:

Carr's Index = [Tapped Density-Bulk Density/Tapped Density] ×100

The Hausner ratio of the microcapsules manufactured using different formulations was computed according to the following relationship (Kumar et al. 2002):

$HR=\rho_T/\rho_B$ where ρ_T is tapped density and ρ_B is bulk density.

Bulk density

Accurately weighed microcapsules (Wm) were transferred into a 100ml graduated cylinder to obtain the apparent volumes (V) of between 50 and 100 ml. The bulk density was calculated in gram per milliliter by the following formula:

Bulk Density (ρρ)= [Weight of Microcapsules (g) (M) / Bulk Volume (ml) (V)]

where, M = mass of the powder, V_o = volume of the powder

Angle of repose

A funnel was fixed on a stand in such a way the top of the funnel was at a height of 6cm from the surface. The microcapsules were passed from the funnel so that they form a pile. The height and the radius of the heap were measured and the angle of repose was calculated using the equation (Aulton, 1988):

Tan θ= h/r where h is the height of the heap and r is the radius of the heap.

Determination of drug loading, encapsulation efficiency and microcapsule yield

The average drug content was determined by extraction of a 20-mg sample of microcapsules with methanol. Following filtration and appropriate dilution with additional methanol, the resultant concentration was determined using UV spectrophotometry, and the percent drug loading was calculated using the following equation:

% Loading= weight of the drug / weight of microcapsules

The encapsulation efficiency of the process was calculated using the following equation:

% Encapsulation Efficiency = [% Actual drug content/% Theoretical drug content] ×100

The percentage yield of the microcapsules was determined for each drug candidate and was calculated using the following equation (El-Kamel, 2006).

Yield =M/M_0 ×100 where M is the weight of microcapsules and Mo is the total expected weight of drug and polymer.

Table 1: Physical characteristics of microcapsules

Particle Size Distribution	Percent retained				
Formulation code	F-1	F-2	F-3	F-4	F-5
10/20 (1242 µ)	9 ± 0.25	6 ±0.29	9 ±0.22	12 ±0.21	5 ±0.11
20/30 (666.5 µ)	5 ±0.11	72 ±2.33	78 ±1.78	65 ±1.23	81 ±2.63
30/40 (445 µ)	7 ±0.23	2 ±0.19	3 ±0.21	9 ±0.21	6 ±0.12
60/80 (225 µ)	7 ±0.22	20 ±0.11	11 ±0.37	14 ±0.18	8 ±0.22

Drug Release Kinetics

To investigate the mechanism of drug release from the microcapsules, the release data were analyzed using zero-order kinetics (Donbrow and Samuelov, 1980), Higuchi (Higuchi, 1961; Higuchi, 1963), Korsmeyer–Peppas (Korsmeyer et al. 1983), Kopcha (Kopcha et al. 1991), and Makoid–Banakar (Pais, 2001) models in (Table 2).Modeling was performed using Graph Pad Prism Software Version 4.0 (Graph Pad Prism Software, San Diego, CA, USA). The software estimates the parameters of a nonlinear function that provides the closest fit between experimental observations and the nonlinear function. The best-fit solution was identified by evaluating the coefficient of determination (R2), where the highest R2 value indicates the best fit (El-Kamel, 2006).

Table 2: Mathematical Representation of Models Used to Describe the Release Profiles from the Microcapsules

Models for Drug Release	Mathematical Equation
Zero-order	$Qt = Q_o + K_o t$
Higuchi	$Qt = Q_o + K_H t^{1/2}$
Korsmeyer–Peppas	$Qt = K_{KP} t^n$
Makoid–Banakar	$Qt = K_{MB} t^n e^{(-ct)}$

Qt = amount of drug released in time t, Qo=initial amount of the drug in the solution, Ko= is the zero order release constant,KH= Higuchi's dissolution constant and KMB= Makoid-Banakar Coefficient.

Thickness of coating

Thickness of aceclofenac microcapsules was determined by the method of Luu. et. al (1973) using equation:

h = r (1-p) d1 / 3[pd2 + (1-p) d1] whereas: h = wall thickness of microcapsules,r = arithmetic mean radius,d1 = density of core material, d2 = density of coating material, p = proportion of medicament in microcapsules. The values of wall thickness are depicted in Table 3 (Yadav et al. 2009).

Table 3: Characterization of ethyl cellulose coated microcapsules

Particle Size (µm)	% Entrapment Efficiency	% Yield	Coating Thickness (nm.)
1350	24.56% (1.23)	29.69 (1.03)	168.32
855	32.54% (1.16)	30.55 (0.8)	123.45
532.5	41.45% (1.34)	40.34 (1.45)	66.32

8. Applications of Microencapsulation

Some of the applications of microencapsulation are shown in (Table 4) and illustrated as below:

- Microencapsulation can be used to prepare enteric-coated dosage forms, so that the medicament can be selectively absorbed in the intestine rather than the stomach.
- It can be used to mask the taste of bitter drugs.
- From the mechanical point of view, microencapsulation has been used to aid in the addition of oily medicines to tableted dosage form. This has been used to overcome problems inherent in producing tablets from tacky granulations. This was accomplished through improved flow properties. For example, the nonflowable multicomponent solid mixture of niacin, riboflavin, thiamine hydrochloride, and iron phosphate may be encapsulated and compress directly into tablets.
- 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 factors can be provided. For example, vitamin A and K have been shown to be protected from moisture and oxygen through microencapsulation.
- he separations of incompatible substances, for example, pharmaceutical eutectics have been achieved by encapsulation. The stability enhancement of incompatible Aspirin-Chlorpheniramine maleate mixture can be accomplished by microencapsulating both of them before mixing.
- Microencapsulation can be used to decrease the volatility. An encapsulated volatile substance can be stored for longer times without substantial evaporation.
- 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.
- The hygroscopic properties of many core materials may be reduced by microencapsulation.
- Many drugs have been microencapsulated to reduce gastric irritation.
- In the fabrication of multilayered tablets for controlled release of the medicament contained in medial layers of tableted particles (Simon, 1996; Thies, 1983).

Table 4: Examples of some microencapsulated drugs

Active moiety	Purpose of encapsulation
Aspirin	Taste masking, sustained release, reduced in gastric irritation,
Paracetamol	Taste masking
Cells of Islet of Langerhans	Sustained normalization of diabetic condition
Isosorbide dinitrate	Sustained release
Progesterone	Sustained release
Menthol	Reduction in volatility, Sustained release
Potassium chloride	Reduction in gastric irritation
Urease	Permselectivity (restriction of permeation of macromolecules across a glomerular capillary wall on the basis of molecular size, charge, and physical configuration.) of enzyme, substrate and reaction
Vit.A palmitate	Stabilization to oxidation
Nifedipine	Prevention from photo instability

9. CONCLUSION AND FUTURE TRENDS

The widespread interest in microencapsulated drugs brought forth the need to prepare such particles in larger quantities and in sufficient quality suitable for clinical trials and commercialization. The most frequently described solvent extraction/evaporation-based technology using simple beaker/stirrer setup is unappropriate for producing larger amounts of microspheres in an economic, robust and well controlled manner. Static mixers warrant continuous production and simple scale-up, while the extrusion through porous membranes or micro channels, integrated in small-scaled equipment that is easy to operate and sterilize, additionally offers improved control of the microsphere size distribution as compared to classical mixing processes. Further, jet excitation is powerful in combining productivity and size control of microspheres. Solvent removal by evaporation may be accelerated using elevated temperatures or reduced pressure. The rapid solvent extraction may require relatively larger amount of processing fluids and their subsequent recycling. Therefore, combined extraction and evaporation represents a compromise in terms of both time and waste-efficient microsphere production. Microencapsulation technology has developed from a simple immobilization or entrapment to sophisticated and precise micro capsule formation. The advances in this field have been tremendous with nutraceuticals and food ingredients; however, as to the micro-encapsulation of live probiotic bacterial cells, the technology seems to be not well developed. The delivery of viable micro encapsulated probiotic bacteria will become important in the near future. In future multiple delivery may be developed, such as co-encapsulating prebiotics and probiotics as well as nutraceuticals, thus a new area of more complex nutritional matrices will need to be investigated. In food processing industry, preservation, storage, and micro-encapsulation will increasingly play a role to protect the viability and enhance the survival of bacteria against adverse environmental conditions. New food regulations may specify labeling including the strain and the number of viable probiotic bacteria at the end of shelf life of a food or supplement claimed to be probiotic.

10. ACKNOWLEDGEMENT

The corresponding author would like to acknowledge ADINA Institute of Pharmaceutical Science Sagar (AIPS) for providing substantial efforts in providing financial and logistic support. The author would like to thank Associate Professor Ashish K. Jain (AIPS/INDIA) for his contributions in the manuscript. The author would like also to thank Director Sunil K. Jain (AIPS/INDIA) for his continuous support and encouragement in performing this work.

11. Declaration of interest

The authors report no conflicts of interest. The Correspond author alone is responsible for the content and writing of the paper.

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