Asian Journal of Scientific Research

ISSN 1992-1454

science alert
http://www.scialert.net

ANSInet
an open access publisher
http://ansinet.com

Asian Journal of Scientific Research 4 (1): 1-15, 2011
ISSN 1992-1454 / DOI: 10.3923/ajsr.2011.1.15

Colloidosomes an Advanced Vesicular System in Drug Delivery

Swarnlata Saraf, Rahul Rathi, Chanchal Deep Kaur and Shailendra Saraf
University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (CG) 492010, India

Corresponding Author: Dr. Swarnalata Saraf, University Institute of Pharmacy, Pt. Ravishankar Shukla University, Raipur (CG) 492010, India Tel: 0771-2262832 Fax: 0771-2262832

ABSTRACT

The application of colloidal drug delivery system in biomedical field has changed the definitions of diagnosis and treatment. Colloidal drug carriers such as liposomes, ethosomes, lipospheres, transferosomes, nanoparticles, microspheres etc. are used to improve the therapeutic index of both existing and new drug molecules by modifying their distribution and thus increase their efficacy and reduce their toxicity. Such delivery systems are widely used in gene delivery, targeting to tumor, targeting to brain, oral formulations, in stability and permeability problem of drug also. In the series of these vesicular systems, colloidosomes is the advanced tool in drug delivery. Colloidosomes are the hollow shell microcapsules consisting of coagulated or fused particles at interface of emulsion droplets. Colloidosomes have exciting potential applications in controlled release of drugs, proteins, vitamins as well as in cosmetics and food supplements. Colloidosomes have a great encapsulation efficacy with a wide control over size, permeability, mechanical strength and compatibility. This review focuses on the types, properties fabrication techniques, characterization and stability of colloidosomes.

Key words: Colloidosomes, emulsion droplets, fused particles, microcapsules

INTRODUCTION

In the past decades a renaissance of the colloidal science and technology has occurred due to expanding field of vesicular carrier system in biomedical field (Rill *et al*., 2008). In the recent years, vesicles have become the vehicle of choice in drug delivery. Vesicles were found to be of value in immunology, membrane biology, diagnostic techniques, cosmetics, food supplements and most recently in genetic engineering. Vesicles can also play a major role in modeling biological membranes and in the transport and targeting of active agents.

Vesicular delivery system provides an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. Vesicular drug delivery reduces the cost of therapy by improved bioavailability of medication, especially in case of poorly soluble drugs. They can incorporate both hydrophilic and lipophilic drugs. In the past few decades, consequently a number of lipid based systems like lipospheres (Rawat *et al*., 2008; Rawat and Reader, 2008, Rawat and Saraf, 2008) liposomes, (Chanchal and Swarnlata, 2008) niosomes, ethosomes, transferosomes were developed (Elsayed *et al*., 2006). Such delivery systems are used for delay drug elimination of rapidly metabolizable drugs and function as sustained release systems. This system also solves the problem of insolubility, instability, rapid degradation and widely used in specialized areas like protein delivery, gene delivery, targeting to brain, tumor targeting (Biju *et al*., 2006). Novel technology has shown great potential for improving the effectiveness and

efficiency of delivery of nutraceuticals and bioactive compounds. Recent advances in nanotechnology show their promise as potential cosmetics for poorly soluble, poorly absorbed and labile herbal extracts and phytochemicals (Chanchal and Swarnlata, 2008). Other than vesicular systems nanoparticles (Saraf, 2009; Jain and Saraf, 2009) and microspheres (Rawat and Reader, 2008) have also gained importance in colloidal systems. In the series of vesicular system, colloidosomes are used as advanced tool for encapsulation of various materials such as drugs, dyes, cosmetics, biomaterials as filler in catalysis and waste removal (Ofoegbu, 2003).

Colloidosomes is a novel class of microcapsules whose shell consists of coagulated or fused colloid particles at interface of emulsion droplets (Noble *et al*., 2004). The particles self assemble on the surface of droplets in order to minimize the total interfacial energy forming colloidosomes (Pieranski, 1980). Such structures were produced for first time by Velev *et al*. (1997) by templating latex particles adsorbed on the surface of octanol-in-water emulsion drops and subsequent removal of oil after fusing the particles monolayers (Ashby *et al*., 2004a). Similar structures have also been obtained by templating water-in-oil emulsions (Yi *et al*., 2002). Caruso *et al*. (2001) and Caruso and Mohwald (1999) and templated solid nanoparticles on the surface of solid sacrificial microparticles based on electrostatic attraction and layer by layer assembly of multilayer shells consisting of alternating positively and negatively charged nanoparticles or polyelectrolytes. The final hollow shells are obtained by removal of central, sacrificial colloidal particles (Yi *et al*., 2002). Dinsmore *et al*. (2002) produced colloidosomes by assembly of polymer latex colloidal particles into shells around water-in-oil emulsion drops followed by partial fusion of shell and centrifugal transfer into water to yield stable capsules in which the shell permeability can be controlled by adjustment of partial fusion conditions. Noble *et al*. (2004) created hairy colloidosomes whose shell consists of microrod particles. They designed and fabricated novel colloidosome capsules that consist of aqueous gel core and shells of polymeric microrods. This has been achieved by templating water-in-oil emulsions stabilized by rod like particles followed by gelling of the aqueous phase, dissolution of oil phase in ethanol and redispersion of obtained colloidosome microcapsules in water.

Samanta *et al*. (2009) co-assembled alkyne- and azide-functionalized iron oxide nanoparticles at the water-oil interface and covalently linked using click chemistry under ambient conditions to create stable magnetic colloidosomes. (Samanta *et al*., 2009). Despite the importance of colloidosomes (Fig. 1) as a novel and promising encapsulation vehicle, very little experimental work

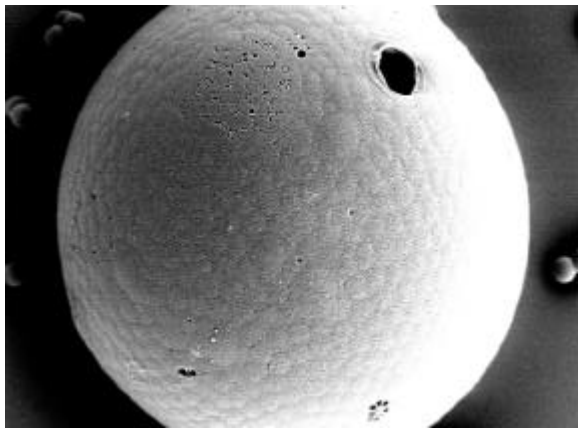

Fig. 1: Scanning electron microscope image of a colloidosomes encapsulating oil in aqueous solution

has been reported investigating the phenomena occurring as particle monolayers adsorbed on liquid templates (drops) transfer through the oil–water interface and how this process leads to the formation of a colloidosome membrane. Very recently, scientists reported the bridging of water drops densely coated with latex particles in an oil phase with a planar oil-water interface. The liquid surfaces strongly adhere to each other but do not coalesce due to the formation of a stable oil film whose surfaces are bridged by the latex particle monolayer (Ashby *et al*., 2004a).

POTENTIAL BENEFITS OF COLLOIDOSOMES

It is a versatile technique should provide efficient encapsulation in structures whose size, permeability, mechanical strength and compatibility can be easily controlled.

- Control of the size allows flexibility in applications and choice of encapsulated materials
- Colloidosome membrane offer great potential in controlling the permeability of the entrapped species and allow the selective and time release
- Control of the mechanical strength allows the yield stress to be adjusted to withstand varying of mechanical loads and to enable release by defined shear rates
- Control of compatibility allows encapsulation of fragile and sensitive ingredients, such as biomolecules and cells. Precise control of its features would allow the strategic design of possible release mechanisms. Ideally, ease to construct colloidosome capsules from a wide variety of inorganic, organic, or polymeric materials to provide flexibility in their uses (Dinsmore *et al*., 2002)

LIMITATIONS

A major problem in the colloidosome manufacture is the poor yield of particles. If the shell locking is inefficient then the colloidosomes simply coalesce and fall apart on transfer into water. In addition a large proportion of the colloidosomes seem to be lost on the transfer from organic to water media (Laib and Routh, 2008).

CLASSIFICATION OF COLLOIDOSOMES

Colloidosomes are the spherical capsules fabricated from the controlled selfassembly of colloidal particles onto the emulsion droplets. For these colloidosomes, colloidal particles in aqueous solution adsorb onto the emulsion droplets in order to minimize the total interfacial energy and act as bridge between particles, locking them together and stabilizing the structure to allow removal of initial templating interfaces (Gibbs *et al*., 1999). So, the colloidosomes are classified on the basis of emulsion used. They are classified as follows:

- Water-in-oil emulsion based colloidosomes
- Oil-in-water emulsion based colloidosomes
- Water-oil-water emulsion based colloidosomes

Water-in-oil emulsion based colloidosomes: Aqueous solution is emulsified in oil in presence of colloidal particles to produce water-in-oil emulsion. Particles are adsorbing onto the surface of the droplets to reduce the surface energy. These particles are subsequently locked together by addition of polycations, by Vander Waals forces or by sintering the particles. These colloidal particles help in producing water-in-oil stabilized emulsion (Gibbs *et al*., 1999; Velev *et al*., 1996a, b, 1997).

Then water-in-oil based colloidal dispersion is obtained. The two different ways to transfer them into water is suggested. They are centrifugation approach and filtration approach. In centrifugation approach, the obtained colloidosomal dispersion is diluted with non aqueous phase (ethanol, dodecane) and then allowed to centrifuge to separate them from the supernatant. The obtained water core colloidosomes are washed with ethanol and water and redispersed in water. The second transfer approach is to filter the oil suspension on the hydrophobic milipore membranes. At the end of filtration, a small amount of water containing a small proportion of ethanol is added to top of the membrane, removing the oil interface and resuspending the colloidosomes in water. This water core colloidosomes (W/O emulsion based) seem to be a suitable encapsulating agent for the drugs, dye, fragrances because of their mechanical resistance of their shell, the tunable porosity and the easy mass transfer potential due to absence of chemical barrier (Cayre *et al.*, 2004).

Oil-in-water emulsion based colloidosomes: In such type, oil is emulsified in aqueous solution containing particles in presence of a surfactant to produce oil-in-water emulsion. This colloidal particle in presence of surfactant is used to stabilize the oil/water interface. This introduces an electrostatic driving force to take the colloidal particles to the emulsion interface. Then Oil-in-water emulsion based colloidosomal dispersion is obtained. The obtained colloidosomal dispersion added to non aqueous phase (ethanol) and allowed to centrifuge to separate them from the supernatant. The obtained oil core colloidosomes are washed with ethanol and finally redispersed in water (Velev *et al.*, 1996a, b, 1997).

Water-oil-water emulsion based colloidosomes: Pendant drop of an aqueous suspension of latex particles is formed in an oil phase. A closely packed particle monolayer adsorbed on the drop surface by multiple infusion and withdrawal of the particle suspension through the capillary in the oil phase. Finally, the pendant water drop in oil, densely coated with adsorbed particles, is transferred through a planar oil-water interface (free of particles) to form a giant pendant colloidosome, which consists of a spherical water/oil/water film supported by latex particles possibly bridging both surfaces (Ashby *et al.*, 2004b). Nanoparticle colloidosomes with selective permeabihty are generated by using water-in-oil-in-water (W/O/W) double emulsions as templates (Lee and Weitz, 2008).

GENERAL METHOD OF PREPARATION OF COLLOIDOSOMES

Colloidosomes are microcapsules with shells consisting of coagulated or partially fused colloid particles. It has been recognized that the colloidosome membranes offer a great potential in controlling the release rate of entrapped species. Their major advantage is that the membrane pores size can be varied by varying the size of the particles and by controlling their degree of fusion. Novel colloidosomes microparticles consist of solid colloidal microparticles and aqueous gel cores. Generally the colloidosomes are developed by gel trapping techniques for monolayers at liquid surfaces by gelling the aqueous subphase. The basics of versatile fabrication method of novel colloidosomes microcapsules which is based on the following 3 stages (Fig. 2) (Paunov *et al.*, 2005):

- Hot aqueous solution of gelling hydrocolloid is emulsified in suitable oil in the presence of solid polymer particles dispersed in the aqueous phase to produce a water-in-oil emulsion stabilized by the solid particles and the system is cooled off to set the gel

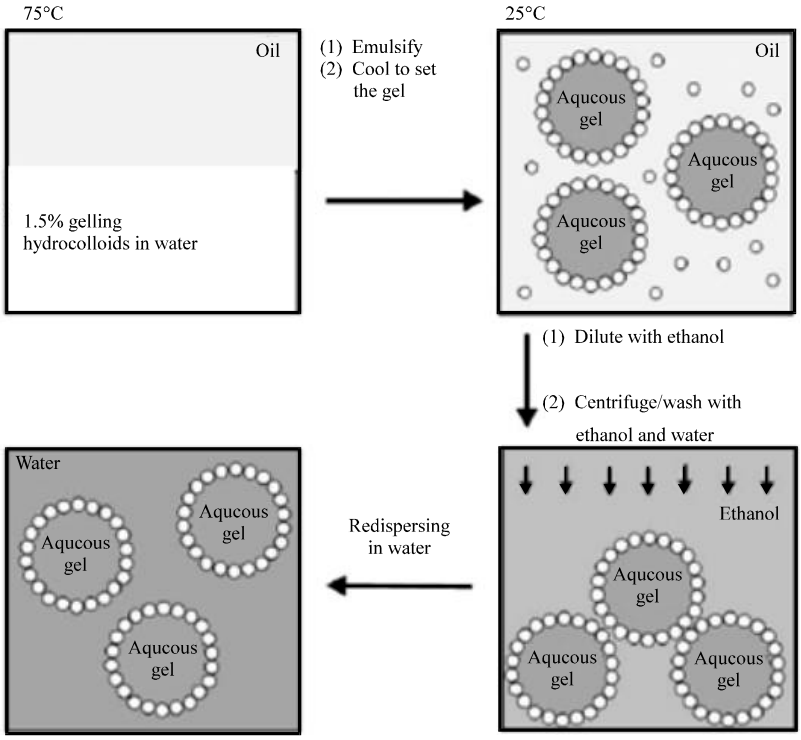

Fig. 2: Schematic of method for preparation of the colloidosomes microcapsules of polymeric particles and aqueous gel cores

- The produced suspension of aqueous gel microcapsules coated with a particle monolayer is separated by filtration to remove the oil phase
- The microcapsules are washed and collected into water. This methodology allows us to produce colloidosome microcapsules of diameters varying between several tens of micrometers to several hundreds of micrometers. The function of the gel cores was to support the particle shell around them and to give the microcapsules enough stiffness to be separated from the oil phase by filtration

FACTORS AFFECTING COLLOIDOSOMES FORMATION

There are several factors that might be expected to affect the formation of stable colloidosomes. Consider a system consisting of a mixture of small and large spherical colloidal particles that have opposite electrical charges (Fig. 3). The small particles will be attracted to the surfaces of the large particles due to electrostatic attraction. When the concentration of small particles is insufficient to completely saturate the surfaces of the large particles, then bridging flocculation will tend to occur between a positive patch on one large particle and a negative patch on another large particle. On the other hand, when the concentration of small particles exceeds some critical value, the surfaces of the large particles will be completely saturated with small particles and colloidosomes will be formed. If the concentration of small particles is increased further, they may generate a sufficiently high depletion attraction between the colloidosomes to promote their flocculation. The purpose of this section is to mathematically examine some of the key factors that are likely to influence the formation of stable colloidosomes.

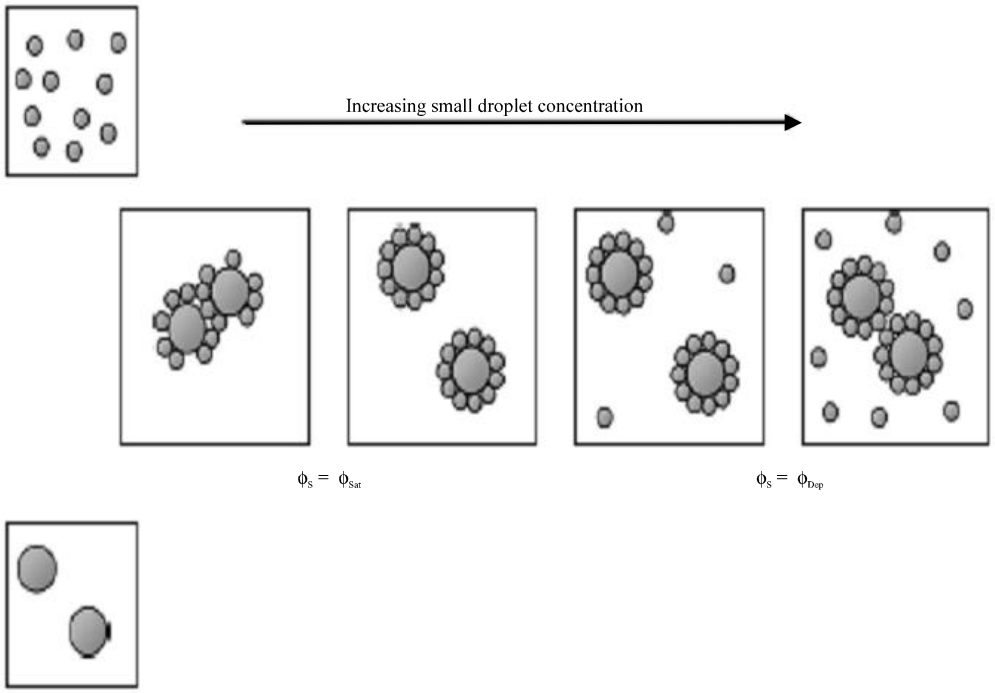

Fig. 3: Schematic diagram of the formation of colloidosomes by mixing colloidal dispersions containing large and small particles that are attracted to one another

Critical saturation concentration: Simple geometric considerations can be used to calculate the volume fraction of small particles required to completely saturate the surfaces of a given concentration of large particles. If it is assumed that the population of small spherical particles is monodisperse and that the particles are incompressible, then the maximum number of small particles required to saturate the surface of a single large spherical particle (assuming hexagonal packing) is given by the following expression (Yates *et al.*, 2005):

$$n_{S,Sat} = \frac{2\pi}{\sqrt{3}}\left(1+\frac{1}{R}\right)^2 \tag{1}$$

where, R (= d_S/d_L) is the ratio of the diameters of the small and large particles. If it is assumed that the population of large spherical particles is also monodisperse and that the attraction between the large and small particles is extremely strong (so that all small particles added to the system bind to the surface of the large particles), then the following expression can be obtained for the minimum volume fraction of small particles required to completely saturate the surfaces of all the large particles present:

$$\phi_{S,Sat} = \frac{2\pi}{\sqrt{3}} R\left(1+R\right)^2 \phi_L \tag{2}$$

$$\varnothing_S = \varnothing_{Sat}$$

where, $Ø'_L$ is the volume fraction of the large particles present. This equation shows that the volume fraction of small particles required to saturate the surfaces of the large particles increases as R increases, i.e., as the small particles increase in size relative to the large ones.

Critical depletion concentration: Once the surfaces of the large particles have become completely saturated with small particles, then any additional small particles added to the system will remain free in the continuous phase and therefore they will generate a depletion attraction between the large particles (Fig. 3). If this depletion attraction is strong enough to overcome any repulsion interactions, then the large particles will tend to flocculate. The following expression gives the strength of the depletion interaction between two large particles dispersed in a continuous phase containing non-adsorbed small particles (McClements, 2000):

$$\frac{w_{Dep}}{k_B T} = \phi_S(1+2\phi_S)\left[\frac{3}{2R}+1\right] \quad (3)$$

where, w_{Dep} is the strength of the depletion attraction when the surfaces of the two large particles are directly in contact with each other. The strength of this depletion attraction increases with increasing small particle concentration and decreasing R. The fraction of large particles that are flocculated due to the presence of the small particles can be estimated by assuming that the depletion attraction is constant from h = 0 to d_S (w_{Dep}), but is zero at greater particle separations and that the only other interaction is an infinitely strong short-range repulsion. Hence, the large particles partition between the flocculated state (low free energy) and the non-flocculated state (high free energy) according to the depth of the secondary minimum w_{Dep}/k_BT and the relative volume fractions of the flocculated (θ_{Low}) and non-flocculated (θ_{High}) states:

$$F=100\times\left[\frac{\theta_{High}}{\theta_{Low}}\exp\left(-\frac{w_{Dep}}{k_B T}\right)+1\right]^{-1} \quad (4)$$

Where:
$\theta_{High} = 1-Ø_L(1+3R)^3$
$\theta_{Low} = Ø_L[(1+3R)^3-(1+2R)^3]$

where, F is the percentage of particles in the system that is flocculated, i.e., in the low free energy state. The values of θ_{Low} and θ_{High} were calculated from the volumes occupied by the depletion zone and that occupied by the continuous phase minus that occupied by the depletion zone, respectively. In this analysis, it was assumed that the surface of the large droplets was saturated with small droplets so that the effective diameter of the colloidosomes was $d_L + 2d_S$. If it is assumed that 50% of the particles in the emulsions are flocculated, then a critical value of the depletion attraction can be calculated:

$$\left(\frac{wDep}{k_B T}\right)_{Crit} = -\ln\left(\frac{\theta_{High}}{\theta_{Low}}\right) \quad (5)$$

For a particular colloidal system, it is possible to calculate the amount of free small particles ($Ø_S$;Dep) required to promote depletion flocculation (i.e., F = 50%) by inserting the values of θ_L and

R into the equations for θ_{Low} and θ_{High} given above and calculating $(W_{Dep}/k_BT)_{Crit}$ and then inserting this value into Eq. 3. The resulting quadratic equation can then be solved:

$$\varnothing_{S,\,Dep} = -\frac{1}{4} + \frac{1}{2}\sqrt{\frac{1}{4} + \frac{4RW}{3+2R}} \tag{6}$$

where, $W = (W_{Dep}/k_BT)_{Crit}$, as given by Eq. 5. Since some of the small particles added to the system are adsorbed to the surfaces of the large particles, then the overall concentration of small particles required to promote depletion flocculation is given by

$$\varnothing^{*}_{S,\,Dep} = \varnothing_{S,\,Dep} + \varnothing_{S,\,Sat} \tag{7}$$

In reality, the emulsion system would become unstable to depletion flocculation at a somewhat lower concentration than $\varnothing^{*}_{S,\,Dep}$, since visible instabiity of an emulsion is likely to be observed when less than 50% of the droplets had been flocculated.

Critical adsorption concentration: Another important factor that influences the stability of the colloidosomes against aggregation during formation is the time taken for the surface of the large particles to be saturated (τ_{Sat}) with small particles relative to the time between collisions of the large particles (τ_{col}). If the surfaces of the large particles are not completely saturated with small particles when the large particles encounter each other ($\tau_{col} < \tau_{Sat}$), then it is likely that the large particles will aggregate with some small particles acting as bridges between them (Fig. 3). It is therefore useful to examine the relationship between tSat and tCol. If it is assumed that the dominant mechanism for the collisions of large particles is Brownian motion, then the average time between collisions is (Walstra, 2003):

$$\tau_{Col} = \frac{\pi d_L^3}{8k_B}\frac{n_C}{T\varnothing_L} \tag{8}$$

where, η_C is the viscosity of the continuous phase. To a first approximation, the adsorption of spherical particles to a planar interface can be given by the following expression:

$$\tau_{Ads} = \frac{10T_{\infty}^2}{C_s^2 D_s} \tag{9}$$

where, c_S (= Øsñs) is the concentration of small particles in the continuous phase (in kg m^{-3}), D_S is the translation diffusion coefficient of the small particles through the continuous phase (in m^2 sce^{-1}) and _ is the surface load of the small particles at the interface (in kg m^{-2}), i.e., the mass of small particles per unit surface area of large particles. This characteristic adsorption time is the time required for the surface to be 90% saturated with the spherical particles. It assumes that the attraction between the small and large particles is very strong so that no particle desorption occurs. The surface load at saturation is given by the total mass of small particles required to saturate a large particle divided by the surface area:

$$T_{\infty} = \frac{\pi}{3\sqrt{3}} d_{sps} (1+R)^2 \tag{10}$$

Hence,

$$\frac{\tau_{Ads}}{\tau_{Col}} = \left(\frac{80\pi^2}{9}\right) R^3 (1+R)^4 \frac{\varnothing_L}{\varnothing_S^2} \tag{11}$$

The value of τ_{ads}/τ_{col} should therefore increase as the size ratio of small-to-large droplets (R) increases, the concentration of small particles ($\varnothing_S$) decreases or the concentration of large particles ($\varnothing_L$) increases. In other words, the adsorption time decreases relative to the collision time (i.e., less expected large particle aggregation) as R decreases, $\varnothing_S$ increases or $\varnothing_L$ decreases. We can estimate a critical volume fraction of small particles ($\varnothing_{S,Ads}$), where the adsorption time is faster than the collision time, by letting $\tau_{ads} = \tau_{col}$,

$$\varnothing_{S,Ads} = \sqrt{\left(\frac{80\pi^2}{9}\right) R^3 (1+R)^4 \varnothing_L} \tag{12}$$

If, $\varnothing_S > \varnothing_{S,Ads}$ then we would expect the adsorption time to be faster than the collision time between large particles and therefore little aggregation to occur. The above equation indicates that critical adsorption concentration should increase as R or $\varnothing_L$ increases.

Overall considerations determining stability: To produce colloidosome particles that are stable to flocculation, it is necessary to ensure that $\varnothing_{S,sat} < \varnothing_S < \varnothing_{S,dep}$ i.e., there are enough small particles present to completely saturate the surfaces of the large particles, but not too many to promote depletion flocculation. In addition, it is also important that the time required for the large particles to be completely covered by small particles is less than the time between large particle-large particle collisions, $\tau_{ads} < \tau_{col} < 1$. Using the various equations derived above for $\varnothing_{S,sat}$, $\varnothing_{S,dep}$ and $\varnothing_{S,ads}$, it is possible to generate a stability map for formation of composite particles. In order to have a stable system, one should use a small particle concentration ($\varnothing_S$) that is lower than $\varnothing'_{S,dep}$ but higher than $\varnothing'_{S,sat}$ and $\varnothing'_{S,ads}$ for the particular R value used. Thus, for a system containing 2% of large particles ($\varnothing'_L$ = 0-02) with a diameter five times greater than that of the small particles (R = 0:1), we would predict that stable composite particles can be produced between 2 and 12 wt. % small particles ($\varnothing_L$ = 0:02-0.12).

Effect of cosolvents: In order to improve the packing of the colloidal particles at the water/oil interface, some cosolvent (like ethanol) introduced into colloidal suspension before mixing with oil. The ethanol as a cosolvent seems to induce colloid al particle aggregation and coalescence. Laib and Routh (2008) determined the critical ethanol concentration is found to be around 25 wt. % for a 11.25 wt. % colloidal suspension. To define the effect of the ethanol itself on the particles stability, the colloidal particle/ethanol (3/1 v/v) suspension is air-dried and analyzed by SEM. The images show some aggregates of fused particles. This implies that the latex particles are fusing, presumably due to plasticization by the ethanol (Gu *et al.*, 2007).

Effect of surfactants: Aqueous suspensions of various colloidal particle concentrations (<10 wt% in aqueous phase) is mixed with oil, with an aqueous volume fraction of 1/50. In such case, no stable emulsion is observed, which shows that the colloidal particles are not an appropriate emulsifier for water-in-oil droplets. To better drive the particles to the edge of the water droplets, surfactant is added to the oil phase prior to introducing the colloidal suspension. nonionic surfactant with a hydrophobic tail and a polar head, which can stabilize water-oil droplets. A cationic surfactant could also have been appropriate, since the colloidal particles are negatively charged (Gu *et al*., 2007).

Effect of sintering time: The sintering time has greatly affected the colloidosome stability. By increasing the sintering time the stability of the shell is significantly higher and therefore the yield of colloidosomes increases. If continuous stirring is not maintained during the sintering step the shells tend to sinter with neighboring particles and the colloidosome shells coalesce before the fusion of the particles is complete (Gu *et al*., 2007).

Effect of electrolyte: Surfactant having efficiency to produce a high yield of colloidosomes. The presence of surfactant at the colloidosome external surface and its high affinity for oil, makes removal of the oil interface very difficult. This can limit the potential applications of the colloidosomes. Simply removing the surfactant from the formulation does not permit formation of a stable emulsion, with the colloidal particles. The presence of an electrolyte in a particle-stabilized emulsion can induce particle aggregation at the water/oil interface and the resulting system can remain stable (Gu *et al*., 2007).

Effect of volume fraction of water: With increase in volume fraction of water, the shape and stability of colloidosomes get altered. With increase in volume fraction, colloidosomes tend to non spherical shape and even broken for some colloidosomes (Liu *et al*., 2008). Volume of fraction of water $\emptyset' = 0.1$ produced an emulsion template of highest stability.

CHARACTERIZATION OF COLLOIDOSOMES

The characterization of colloidosomes including particle size measurement, zeta potential measurement, gravitational separation, small droplet concentration, optical microscopy, surface are a are as follows:

- **Particle size analysis:** The particle size distribution of the emulsions is measured using a laser diffraction particle size analyzer. This instrument measures the angular dependence of the intensity of light scattered from a stirred dilute emulsion. The particle size distribution is then calculated using Mie theory to obtain an optimal analysis of this light energy distribution. To avoid multiple scattering effects the emulsions were diluted with buffer prior to making the light-scattering measurements. The emulsions were stirred continuously throughout the measurements to ensure the samples were homogenous. Dilution and stirring are likely to disrupt any flocculated droplets or break up any free oil into droplets, hence particle size data on highly flocculated or coalesced samples should be treated with caution. A refractive index ratio of 1.08 is used by the instrument to calculate the particle size distributions. Measurements are reported as the volume-surface mean radius:

$$d_{32} = \frac{\sum d_i n_i^3}{\sum d_i n_i^2}$$

where n_i is the number of droplets of diameter d_i. The particle size measurements are reported as the average and standard deviation of measurements made on two freshly prepared samples, with two readings made per sample. The size of the latex particles was measured by dynamic light scattering and the Tg by differential scanning calorimetry (Gu *et al*., 2007)

- **Zeta potential measurements:** Emulsions are diluted using a buffer solution prior to analysis to avoid multiple scattering effects. Diluted emulsions are injected directly into the measurement chamber of a particle electrophoresis instrument. The zeta (ζ) -potential was then determined by measuring the direction and velocity of droplet movement in a well-defined electric field. The ζ-potential measurements are reported as the mean and standard deviation of two separate injections, with five readings made per injection. All measurements are made on at least two freshly prepared samples. The ζ-potential measurements are used to monitor the adsorption of colloidal molecules onto the surfaces of large emulsion-coated droplets (Gu *et al*., 2007)
- **Gravitational separation:** Emulsions is poured into glass tubes (100 mm height, 16 mm i.d.), covered and stored at room temperature for 24 h before the heights of any separated layers were measured manually using a ruler. Different kinds of layers are observed depending on emulsion type, e.g., a clear oil layer at the top, an opaque emulsion layer in the middle and/or a transparent serum layer at the bottom. We defined the serum layer to be the sum of the turbid and transparent layers. The total height of the emulsion (H_E) and the height of the serum layer (H_S) are measured. The extent of creaming is characterized by a creaming index =100X (H_S/H_E). The creaming index provided indirect information about the extent of droplet aggregation in an emulsion. All measurements were made on at least two freshly prepared samples (Gu *et al*., 2007)
- **Free small droplet concentration:** The concentration of small droplets that is not adsorbing to the surfaces of the large droplets is determined by using a gravitational separation and turbidity method. The composite emulsions is allowed to stand at room temperature for 24 h, which meant that any large droplets creamed to the surface while the small droplets remained in the lower layer. A sample of the lower phase containing the free small droplets was then collected and the turbidity measured (after appropriate dilution). The small droplet concentration is determined from a previously prepared calibration curve of turbidity (at 600 nm) versus small droplet concentration (Gu *et al*., 2007)
- **Optical microscopy:** The microstructure of selected emulsions is determined using optical microscopy. Emulsions were gently agitated in a glass test tube before analysis to ensure that they were homogeneous. A drop of emulsion was then placed on a microscope slide, covered by a cover-slip and observed at a magnification of 40X using an optical microscope (Gu *et al*., 2007)

APPLICATIONS OF COLLOIDOSOMES

Colloidosomes have widely used as encapsulating agent with endless application in industries and medicines. There is strong interest in encapsulation and controlled release of materials like drug delivery, proteins, vitamins, fragrances and flavors in food to molecules produced by sensitive biomaterials as living cells, catalytic material or even living cells are of increasing

importance to biomedical, pharmaceutical and cosmetic industries. Colloidosomes are selectively permeable to particles of different sizes, making them appropriate for controlled release applications (Caruso *et al*., 2001; Gu *et al*., 2007). The mechanical deformation and rapture of colloidosomes are also of interest in possible encapsulation applications as well as being of intrinsic interest. Shah *et al*. (2010) introduced a novel and versatile technique to fabricate monodisperse stimuli-responsive colloidosomes using stimuli-responsive microgel particles as building blocks, aqueous droplets as templates and microfluidic devices to control the assembly (Shah *et al*., 2010). It exhibited 80% decrease in volume when actuated; thus, they can be of immense potential in applications that require targeted pulsed-release of active materials. Colloidosomes may be used for following range of therapeutic and pharmaceutical applications (Vyas and Khar, 2002):

- Colloidosomes as drug/protein delivery carrier
- Colloidosomes for controlled and sustained drug release
- Colloidosomes for enhanced drug solubilization
- Colloidosomes for altered pharmacokinetics and biodistribution
- Colloidosomes for encapsulation of enzymes
- Colloidosomes in tumor therapy
- Colloidosomes in antimicrobial, antifungal, antiviral therapy
- Colloidosomes in cosmetics and dermatology
- Colloidosomes in ocular drug delivery
- Colloidosomes in brain delivery
- Colloidosomes in DNA delivery
- Colloidosomes in enzyme immobilization

FUTURE PERSPECTIVES

Colloidosomes have been exploited in various diverse applications like pharmaceutics, cosmetics and food industries. It shall be now possible to design colloidosomes for protracted drug release, effective immunization and in development of bio-implantable, bio-chips, bio-sensors. In future by combining various other strategies, colloidosomes will find the central place in novel drug delivery particularly in diseased cell sorting, diagnostics, gene and genetic materials, safe targeted and effective in vivo delivery, which may have its implications in gene therapy, genetic customization and supplements as miniature version of diseased organ and tissues in the body. In future there is a plan to incorporate the colloidosome with composite rods that are made up of alternate layers of metals. These rods will have the properties of both metals an ultimately we can manipulate the colloidosomes using external forces as well as chemically. For example, a nanorod made of up alternate layers of Nickel and gold will have the magnetic properties of Nickel but the gold part can be functionalized to direct the colloidosome based on the affinity of the attached functional group for the molecules in the site of release.

CONCLUSION

Colloidosomes that consist of large droplets surrounded by a layer of small droplets can be produced by mixing coarse and fine emulsions that containing oppositely charged droplets together. Colloidosomes are the solid hollow capsules with precise control size, permeability, mechanical strength and compatibility, therefore may have applications in products that are consumed by humans, ex- beverages, food, pharmaceuticals, flavors, fragrances, cosmetics industries. It may be

possible to reduce their susceptibility to gravitational separation to control their stability to environmental stresses, to develop novel controlled or triggered release system, to compartmentalize active agents or to control certain chemical reactions. The capsules are fabricated by the self-assembly of colloidal particles onto the interface of emulsion droplets. After the particles are locked together to form elastic to elastic shells, the emulsion droplets are transferred to a fresh continuous phase fluid that is the same as that inside the droplets. The resultant structures are called colloidosomes are hollow, elastic shells whose permeability and elasticity can be precisely controlled. The generality and robustness of these structures and their potential for cellular immunoisolation are demonstrated by the use of a variety of solvents, particles and contents. Colloidosomes successfully meet many of the key requirements for encapsulation: Emulsification provides a simple means of producing capsules from a wide variety of fluids and with controlled sizes ranging from submicrometer to several millimeter. Furthermore, because the internal and external fluids remain completely separate until the final step, materials can be encapsulated efficiently with minimal loss. The choice of different colloidal particles allows for additional flexibility. We show that the permeability and rupture stress of the capsules can be controlled through the size of the coating particles and through postfabrication treatment by sintering or, alternatively, by further filling of the holes with smaller particles or polymers. A variety of release strategies may be feasible, either through control of their permeability for slow but sustained release, or through control of their rupture stress for shear-induced breakup. This flexibility will allow a wide range of potential applications to be explored.

REFERENCES

Ashby, N.P., B.P. Binks and V.N. Paunov, 2004a. Formation of giant colloidosomes by transfer of pendant water drops coated with latex particles through an oil-water interface. Phys. Chem. Chem. Phys., 6: 4223-4225.

Ashby, N.P., B.P. Binks and V.N. Paunov, 2004b. Bridging interaction between a water drop stabilized by solid particles and a planar oil/water interface. Chem. Comm., 21: 436-437.

Biju, S.S., S. Talegaonkar, P.R. Mishra and R.K. Khar, 2006. Vesicular system: An overview. Ind. J. Pharm. Sci., 68: 141-153.

Caruso, F. and H. Mohwald, 1999. Preparation and characterization of ordered nanoparticle and polymer composite multilayers on colloids. Langmuir, 15: 8276-8281.

Caruso, F.J., X.Y. Shi and R.A. Caruso, 2001. Fabrication of nanoporous silica nanotubes by inorganic and organic double templates. Adv. Matter, 13: 740-740.

Cayre, O.J., P.F. Noble and V.N. Paunov, 2004. Fabrication of novel colloidosome microcapsules with gelled aqueous cores. J. Mater. Chem., 14: 3351-3355.

Chanchal, D. and S. Swarnlata, 2008. Novel approaches in herbal cosmetics. J. Cosmet. Dermatol., 7: 89-95.

Dinsmore, A.D., M.F. Hsu, M.G. Nikolaides, M. Marquez, A.R. Bausch and D.A. Weitz, 2002. Colloidosomes: Selectively permeable capsules composed of colloidal particles. Science, 298: 1006-1009.

Elsayed, M.M.A., O.Y. Abdullah, V.F. Nagar and N.M. Khalafallah, 2006. Deformable hposome and ethosome: Mechanism of enhanced skin delivery. Int. J. Pharm., 322: 60-66.

Gibbs, B.F., S. Kermasha, I. Alli and C.N. Mulligan, 1999. Encapsulation in the food industry: A review. Int. J. Food Sci. Nutr., 50: 213-224.

Gu, Y.S., E.A. Decker and D.J. McClements, 2007. Formation of colloidosomes by adsorption of small charged oil droplets onto the surface of large oppositely charged oil droplets. Food Hydrocolloids, 21: 516-526.

Jain, S. and S. Saraf, 2009. Repaglinide-loaded long-circulating biodegradable nanoparticles: Rational approach for the management of type 2 diabetes mellitus. J. Diabetes, 1: 29-35.

Laib, S. and A.F. Routh, 2008. Fabrication of colloidosomes at low temperature for the encapsulation of thermally sensitive compounds. J. Colloid Interface. Sci., 317: 121-129.

Lee, D. and D.A. Weitz, 2008. Double emulsion-templated nanoparticle colloidosomes with selective permeability. Adv. Mater., 20: 3498-3503.

Liu, H., C. Wang, Q. Gao, X. Liu and Z. Tong, 2008. Fabrication of novel core-shell hybrid alginate hydrogel beads. Int. J. Pharm., 351: 104-112.

McClements, D.J., 2000. Food Emulsions: Principles, Practice and Techniques. 2nd Edn., CRC Press, USA., pp: 632.

Noble, P.F., O.J. Cayre, R.G. Alargova, O.D. Velev and V.N. Paunov, 2004. Fabrication of Hairy colloidosomes with shells of polymeric microrods. J. Am. Chem. Soc., 126: 8092-8093.

Ofoegbu, O., 2003. Force measurements on nanorods-enriched sintered colloidosomes. Gordon Mckay Laboratories: Harvard University Summer, pp: 2-9. http://eduprograms.seas.harvard.edu/reu03_papers/Ofoegbu.O.FinReport03.pdf.

Paunov, V.N., P.F. Noble, O.J. Cayre, R.G. Alargova and O.D. Velev, 2005. Fabrication of novel types of colloidosome microcapsules for drug delivery applications. Mater. Res. Soc. Symp. Proc., 845: 279-283.

Pieranski, P., 1980. Two-dimensional interfacial colloidal crystals. Phys. Rev. Lett., 45: 569-572.

Rawat, M. and S. Saraf, 2008. Liposphere: Emerging carriers in the delivery of proteins and peptides. Int. J. Pharm. Sci. Nanotechnol., 1: 207-214.

Rawat, M. and S.S. Reader, 2008. Formulation optimization of double emulsification method for preparation of enzyme-loaded Eudragit S100 microspheres. J. Microencapsulation, 26: 306-314.

Rawat, M., D. Singh, S. Saraf and S. Saraf, 2008. Lipid carriers: A versatile delivery vehicle for proteins and peptides. Yakugaku Zasshi, 128: 269-280.

Rill, C., M. Bauer, H. Bertagnolli and G. Kickelbick, 2008. Microemulsion approach to neodymium, europium and ytterbium oxide/hydrocolloids-Effect of precursors and preparation parameters on particle size and crstallinity. J. Colloid Interface Sci., 325: 179-186.

Saraf, S., 2009. Process optimization for production of nanoparticles for drug delivery applications. Expert Opin. Drug Deliv., 6: 187-196.

Shah, R.K., J.W. Kim and D.A. Weitz, 2010. Monodisperse stimuli-responsive colloidosomes by self-assembly of microgels in droplets. Langmuir, 3: 1561-1565.

Velev, O.D., K. Furusawa and K. Nagayama, 1996a. Assembly of latex particles by using emulsion droplets as templates. 1. Microstructured hollow spheres. Langmuir, 12: 2374-2384.

Velev, O.D., K. Furusawa and K. Nagayama, 1996b. Assembly of latex particles by using emulsion droplets as templates. 2. Ball-like and composite aggregates. Langmuir, 12: 2385-2391.

Velev, O.D., K. Furusawa and K. Nagayama, 1997. Assembly of latex particles by using emulsion Droplets. 3. Reverse (water in oil) systems. Langmuir, 13: 1856-1859.

Vyas, S.P. and R.K. Khar, 2002. Targeted and Controlled Drug Delivery- Novel Carrier Systems. 1st Edn., CBS Publisher, New Delhi.

Walstra, P., 2003. Physical Chemistry of Foods. 1st Edn., Marcel Decker, New York.

Yates, P.D., G.V. Franks, S. Biggs and G.J. Jameson, 2005. Heteroaggregation with nanoparticles: Effect of particle size ratio on optimum particle dose. Colloids Surf. A: Physicochem. Eng. Aspects, 255: 85-90.

Samanta, B., D. Patra, C. Subramani, Y. Ofir, G. Yesilbag, A. Sanyal and V.M. Rotello, 2009. Stable magnetic colloidosomes via click-mediated crosslinking of nanoparticles at water-oil interfaces. Small, 5: 685-688.

Yi, G.R., V.N. Manoharan, S. Klein, K.R. Brzezinska, D.J. Pine, F.F. Lange and S.M. Yang, 2002. Monodisperse micrometer-scale spherical assemblies of polymer particles. Adv. Matter, 16: 1137-1140.