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ARTICLE

LIPID MICROSPHERES: EMERGING TRENDS IN PHARAMCEUTICAL TECHNOLOGY

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Abstract:

Recent advances in the isolation techniques, medicinal chemistry, biotechnology and the capacity for screening new drug compounds have been able to produce several lead molecules. More than likely many potential drugs have lost because of inadequate formulation strategies during different stages of evaluation. In many cases, the loss could have been due to solubility problems. To maximize the drug potential of all molecules, there has been a renewed effort to find formulation strategies for compounds inadequately soluble in water. Many different drug delivery systems for lipid soluble compounds have been suggested, but lipid microsphere (LM) drug delivery system has great potential. The system is time tested, safe and stable at room temperature, easily mass- produced yet cheaper. The drug distribution and targeting can be achieved by manipulating size, surface charge and surface legands of LM. At present, commercially available lipid microsphere formulation are few but in future this system will find considerable share in the market.

Keyword: Lipid microsphere (LM), Solubility, surface charge and surface legands.

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Introduction

The past 30 years have seen enormous activity in drug delivery and targeting research, and in particular the use of colloidal drug delivery systems, for vascular, subcutaneous, intramuscular and oral administration. A wide range of colloidal materials have been studied, including polymeric microspheres and cross-linked proteins such as albumin, which can be used to prepare solid particles of varying sizes. The production of these particles is often complex, involving processes such as solvent evaporation, coacervation and removal of untrapped drug. In contrast, emulsion delivery systems have many advantages. They can be prepared easily in a single dispersion step; for correctly chosen drug candidates, entrapment can be high, and they can be easily administered in liquid form without the need for reconstitution by the user.

Triglyceride lipid emulsions have a number of additional advantages. They have been studied widely for parenteral feeding, and consequently their preparation, stability and biopharmaceutics are well understood [1-10]. The droplet size of triglyceride emulsions normally lies in the range 200-400 nm, and consequently they are suitable for intravenous administration. The most significant drawback of emulsion delivery systems is that they cannot easily be adapted to the delivery of water-soluble drugs. Oil-soluble drugs can be dissolved in the oil phase of the emulsion, and surface-active drugs can be adsorbed to the emulsion surface; however the only viable approach to the delivery of a hydrophilic drug is to synthesize a hydrophobic prodrug, or analogue. This approach has been used, for example, to formulate emulsions containing hydrophobic mitomycin C derivatives. [11]

Drugs such as prostaglandins [12,13], Cytokines and many active peptides show strong physiological activities, develop a local effect in the body and are rapidly metabolized. Therefore, a large dose of drug must be administered. As a result, the reaction spreads throughout the entire body, causing adverse reactions to develop [14]. Local adverse reactions, such as pain and inflammation at the administration site, are also observed. In order to overcome these problems, pharmaceutical devices such as drug delivery systems (DDS), particularly targeted delivery, need to be developed. Many studies of pharmaceutical devices have been carried out to develop drug carriers that are suitable for delivering a drug to the injured site. These pharmaceutical devices have been studied on delivery using liposome [15-17], polysaccharide-coated liposomes [18,19], micelle- forming polymers [20,21] and a virus [22]. As a result, prolongation of the effect, as well as the safety of a drug, has been improved with liposomes. However the sterilization that is essential for the injections and the stability of the emulsion on the shelf has still to be improved with liposomes. Furthermore, the safety of the raw materials used for the drug carrier

needs to be improved further, especially for toxicity problems such as the hemolytic property. Considering these problems, the lipid microsphere (LM), formed by dispersion of the LM particles in aqueous solution, appears to be a safe and excellent drug carrier [23-29].

Since LM was first used as a DDS pharmaceutical around 1970. Jeppsson applied it to barbituric acid [30], and further applications to nitroglycerin and cyclandelate [31] were examined [32]. Reviews of its use with pharmaceuticals have been reported by Collins-Gold et al. [33]; on its metabolism by Skeie et al. [34] and Illum et al. [35]; and on its clinical application by Mizushima [36,37] and by Mizushima and Hoshi [38]. Figure 1 shows morphology of LM. The effect of LM is characterized by the passive targeting of the drug into the disease site, such as inflammatory and arteriosclerotic lesions, with much clinical efficacy [39, 40], such as relieving the adverse effects of the drug. Prostaglandin E_1, (PGE_1) [41], dexamethasone palmitate (corticosteroid) [42-45] and flurbiprofen axetil (nonsteroidal sedative) are presently the only drugs available as LM pharmaceuticals on the market. Lipo-PGE_1, which is a LM formula of PGE_1, shows a stronger pharmacological effect than PGE_1 [46-48] and its clinical efficacy has been confirmed in the treatment of peripheral vascular disorders [49, 50], cold hands and feet [51], sensory disturbances, pain, and ulcers resulting from collagen diseases [52]. Lipo-PGE_1 is known to have reduced side effects, such as local irritation near the site of injection following parenteral administration. Regrettably, the pharmaceutical and pharmacokinetic factor, which is responsible for the high efficacy of Lipo-PGE_1, has not been found [53-57]. This problem must be solved if new LMs are to be developed by screening enclosed drugs, which have high targeting efficacy. This review describes, from the pharmaceutical point of view. LM as a DDS pharmaceutical for injection. [1]

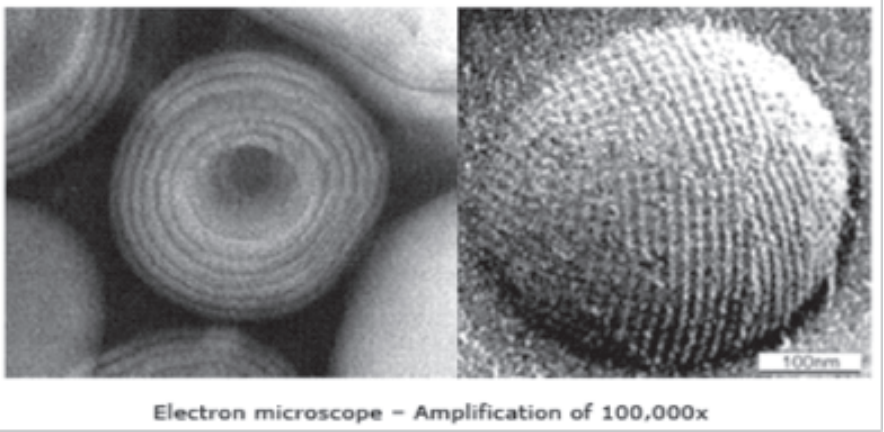

Fig. 1: Morphology of Lipid Microspheres

Advantages of lipid microspheres

- Control and/or target drug release.
- Improve stability of pharmaceuticals.
- High and enhanced drug content (compared to other carriers).
- Feasibilities of carrying both Lipophilic and hydrophilic drugs.
- Most lipids being biodegradable, SLNs have excellent
- Biocompatibility.
- Water based technology (avoid organic solvents).
- Easy to scale-up and sterilize.
- More affordable (less expensive than polymeric/surfactant based carriers).
- Easier to validate and gain regulatory approval.

Liposomes & lipid microspheres

Liposomes have been widely studied as a drug carrier of both water soluble and lipid soluble drugs, since they have both lipid and water layers. Liposomes are reported to be easily taken up by some inflammatory cells, as well as by the reticuloendothelial system (RES). Due to these characteristics, liposome-entrapped anti-inflammatory steroids show stronger activity than an equivalent dose of free steroids, both in humans and in animals. Intra-articular injection of liposomal hydrocortisone was more effective than free hydrocortisone in experimentally induced acute arthritis of rabbits [58]. De Silva et al. [59] reported a similar effect of local liposomal hydrocortisone in the treatment of rheumatoid arthritis.

The problems with liposomal treatment so far may be attributed to the instability of liposomes and a lack of clinical experience. Clinical trials of liposomes have been restricted to local application. However, liposome-entrapped amphotericin B has been developed and was recently marketed in Europe. On the other hand, lipid microspheres are very stable and easily mass-produced, as described above.

To transport a large amount of drugs, suitable carriers are needed. Liposomes are excellent drug carrier vehicles for Drug Delivery Systems (DDS) [60-62]. However, liposomes are relatively unstable and are not easily mass-produced. Lipid microspheres, with an average diameter of 0.2 μm, and consisting of soybean oil and lecithin, however, are widely used in clinical medicine for parenteral nutrition (intralipid, etc.). Lipid microspheres, themselves, are very stable and can be stored for up to two years at room temperature. They have no particular adverse effects, even at dose levels of 500 ml. Regarding their distribution in the body, lipid microspheres, like liposomes, accumulate in inflamed tissues and other lesions [63,64]. Table 1 shows comparision between liposomes and lipid microspheres and Table 2 shows generalised formulation structure.

Table 1: Comparison of lipid microspheres and liposomes3

	Lipid microspheres	Liposomes
Components		Lipid. Water
Lipid membrane	Monolayer single membrane	Mono- or multi-layer double membrane
Emulsion form	O/W	W/O/W
Incorporable drugs	Compounds soluble in soybean oil retainable in lipids.	Water soluble compounds and and compounds retainable in lipids.
Particle diameter	200 - 300 nm	Various sizes
Safety in vivo	Clinically used as intravenous	Toxic
Large-scale Large-scale	Suitable for mass production but a high pressure apparatus is necessary	A special apparatus is not necessary at the research level. An apparatus for mass has recently been developed.
Stability	nutrition in 100 ml doses Stable for 24 months at room Lipo preparations are stored at 4°C	Rather unstable temperature.

Table 2: General Formulation consideration of Lipid microspheres

CATEGORY	EXAMPLES
Oil phase	Soyabean oil, Sunflower oil, sesame oil, cotton seed oil, coconut oil,, fish oil, corn oil, Walnut oil, medium and long chain triglycerides
Emulsifiers	Soy lecithin, Egg lecithin, Phosphatidyl choline, thanolamine
Co-emulsifiers	Tween-80, Span- 60, Span-65, Myrj 52, Pluronic F-68
Stabilizers	Polyetylene glycols, poly propylene glycols, polyglycerol mono oleate.
pH adjusting agents	Oliec acid, Linoleic acid, Stearic acid, palmitic acid and their sodium and potassium salts.
Agents for adjusting isotonicity	Glycerine, sorbitol, Xylitol, Dextrose
Preservative	Benzoic acid,sorbic acid, para amino benzoic acid, methyl paraben, propyl paraben
antioxidants	Ascorbic acid, Alpha tocopherol, Butylated hydroxy anisole.

General method of preparation of Lipid microspheres

The drug to be entrapped in lipid microspheres is first dissolved in soybean oil and then emulsified with lecithin using a Manton-Gaulin homogenizer [65,66]. Since lipid microspheres are delivered preferentially to, and accumulate at, the site of inflammatory lesions as liposomes, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) have been incorporated in them. Figure 2 shows schematic presentation of LM formulation.

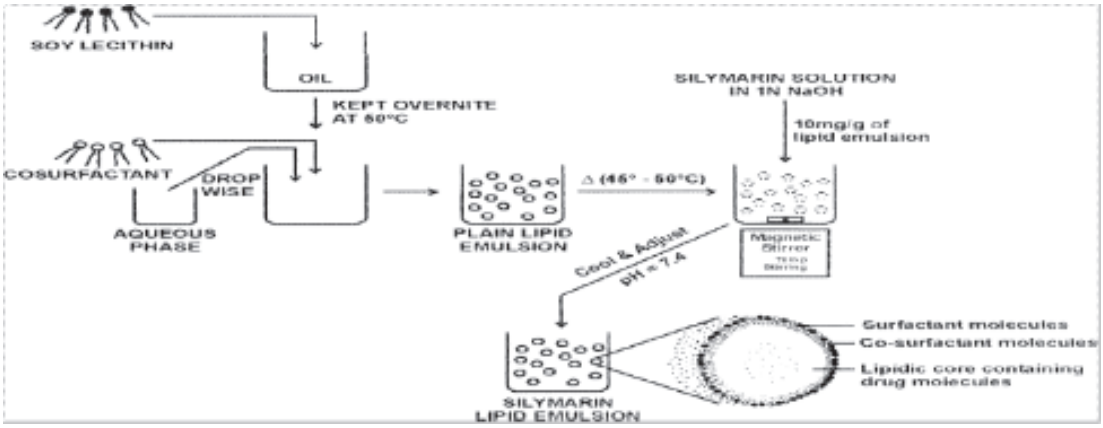

Fig. 2: Schematic presentation of lipid microspheres formulation.

Soyabean lecithin was dispersed well in soyabean oil and allowed to dissolve completely by keeping it overnight at 50^0C. The cosurfactants (hydrophilic/lipophilic) were added to the oily or aqueous phase as per their solubility. The aqueous phase was added to the oily phase dropwise with simple agitation to obtain lipid emulsion. Silymarin solution (10% w/v in 1M sodium hydroxide) was added to the prepared emulsion so as to obtain the final concentration of 10 mg/g of lipid emulsion at a temperature of 50^0C under stirring with a magnetic stirrer. After 10–15 min, the pH was adjusted to 7.4 with 1 N orthophosphoric acid [67].

The phospholipids, or lecithins, used in the preparation of most parenteral emulsions are quite heterogenous materials, being mixtures of phosphatides. A number of different factors affect the physical behaviour of these materials and these have been reviewed by Cevc and Marsh [68]

i) The saturation of the acyl chains influences the transition temperatures and the surface behaviour, both in bilayers and in monolayers. Generally, disaturated lipids have transition temperatures above room temperature (e.g. 42°C for dipalmitoyl phosphatidylcholine, DPPC), and introducing unsaturated bonds causes a reduction in transition temperature (e.g. - 8°C for dioleyl phosphatidylcholine, DOPC). These temperatures apply to the melting of

hydrated bilayers and similar phenomena are seen in lipid monolayers, which undergo solid-liquid type isotherm transitions at ambient temperatures. The extension of these phenomena to the stability of emulsions stabilized by solid- or liquid phase phospholipids is unclear; anecdotal evidence suggests that saturated phospholipids produce very stable emulsions. The majority of phospholipids from egg or soya lecithin, the commonest sources, are unsaturated, and these materials are widely used as emulsifiers for intravenous use. The degree of unsaturation is normally expressed as an iodine number; 80 is typical for egg lecithin. Figure 3 shows various types of phospholipids structures.

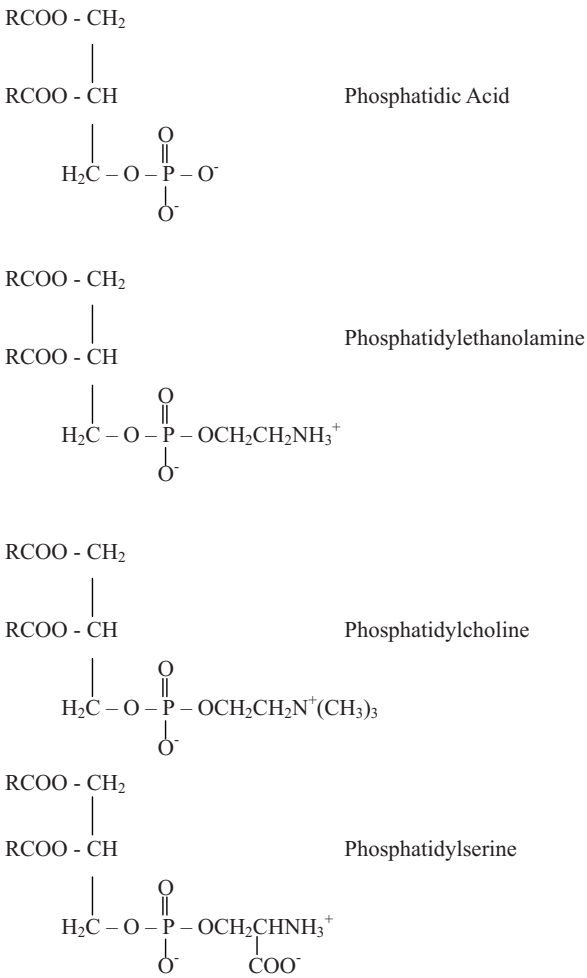

Fig. 3: Phospholipids structures; R is an alkyl chain from 8-24 units long.

ii) The length of the acyl chains influences the transition temperature, with longer chains causing higher melting temperatures (e.g. DPPC, 42°C; Distearoyl, PC 56°C). The majority of natural lecithins have chain lengths from fourteen to twenty carbons, with sixteen to eighteen being predominant.

iii) The nature of the headgroup is important in determining the ionization behaviour of the lipid. The predominant headgroups are choline and ethanolamine, which produce phosphatides (PC and PE) that are neutral at pH 7. Serine and glycerol produce acidic lipids (PS and PG), which are negatively charged at pH 7, as is the unesterified phosphatidic acid, PA. These acidic lipids are present to a much lower extent than PC and PE in natural egg and soy lecithins, and typically comprise l-2% of the total bulk. Despite this, they are of major importance in determining the stability of the emulsions prepared from them. Their concentration is sufficient to confer a surface charge of - 40 to – 60 mV on the emulsion droplets, which results in a long-term stability of several years [69-71].

Because of the extensive interest in phospholipids as emulsifiers, and for use as liposomes for drug delivery, a wide range of lecithins is commercially available. These are produced in a number of ways; crude egg or soy lecithin can be refined chromatographically, removing sterols, lysolipids and a range of other contaminants, to produce a parenteral grade of lecithin, such as Lipoid® E80 (Lipoid® AG) or Ovothin® 180 (Lucas-Meyer). These materials are almost fully unsaturated and contain approximately 80% PC; a small amount of acidic lipid leads to a high surface charge at pH 7, and hence, to excellent emulsion stability. Further chromatographic purification leads to a product which is 95-100% pure PC or PE (e.g. Lipoid® El00 or Ovothin® 200), and has very little acidic impurity; this has a low surface charge at pH 7 and thus is not per se a useful emulsifier.

To produce saturated lipids, these materials can be hydrogenated catalytically, which leads to an iodine number of 2-5, compared to 60-80 for the unsaturated lipid. Thus, Lipoid® El00-3 is a nearly pure hydrogenated PC, with a very low level of charged lipids, and Lipoid® E80-3 is a similarly hydrogenated lipid, with a higher level of acidic lipids.

These materials still have heterogenous chain lengths and some variations in headgroups. Pure individual lipids with well-defined chains cannot easily be produced by further fractionation, due to the large number of separate species in the raw feedstock. There are two possible routes to pure phospholipids; one is total synthesis and the other is the use of phospholipases to selectively transesterify chains. Phospholipase Al and A2 can be used to selectively cleave and replace the

acyl chains, while phospholipase D can modify the phosphate ester group. This process is, however, expensive, and the resulting pure lipids cost £20-80 per gram, making them of limited value for the preparation of large volume parenterals. However, they are commercially viable for the preparation of high added value drug emulsions, which normally have a small volume.

Tissue distribution/ Factors influencing the biodistribution of Lipid microspheres

Earlier studies [63,72] of lipid emulsions demonstrated that lipid microspheres had an affinity to vascular walls (including capillaries), similar to that of chylomicrons. Shaw et al. [73] reported that they had more affinity to vascular walls at inflamed sites. As described by Dr. Igarashi in this issue, we found that lipid microspheres accumulated in damaged vascular walls, such as atherosclerotic vessels and vessels of hypertensive rats.

Stability of emulsion in LM

The stability of colloidal formulations is paramount in their use as drug delivery systems. They must be sufficiently stable to be easily manufactured, sterilized (preferably by terminal autoclaving) and have a shelf life of at least a year, preferably more. Shelf life considerations are particularly important for emulsion systems. Since these are generally stored as liquids, and coalescence or aggregation can occur during storage. In contrast, microparticle colloidal systems are stored as freeze-dried solids for reconstitution, and colloid stability problems do not arise in the same way (although that is not to say that such formulations do not degrade physically during storage). There have been limited attempts to store emulsions in other forms, for example, the perfluorocarbon emulsion Fluosol [12-14] is stored frozen (a process which generally causes extensive emulsion coalescence in other systems), and there have been attempts to freeze dry emulsions.

In addition to long-term stability, it is also necessary to understand the way that colloid stability may be influenced by the various additives that may be needed in the final clinical application. The most important such interaction is that with electrolytes, which may be required to adjust tonicity. Electrolytes interact strongly with charge-stabilized colloids, causing severe stability difficulties; for this reason, the tonicity of emulsions is generally adjusted with glycerol. The interaction of electrolytes with phospholipid- stabilized emulsions is quite well understood, since it has been extensively studied due to its importance in the compounding of parenteral nutrition mixtures [15-19].

The stability of colloids depends on the forces between them; if these are repulsive, approaching droplets repel and form a stable system. If they are attractive, the droplets clump together and are unstable. The forces themselves can arise from a number of sources [22].

i) **Van der Waals forces.** These are attractive forces which exist between all particles. Their magnitude is determined by a factor called the Hamaker constant, which describes the strength of attractive interaction between the disperse and continuous phases.

ii) **Electrostatic forces.** These are repulsive forces (assuming that all the particles have the same surface charge). They can most easily be quantified using the zeta potential, which is the potential surrounding the droplet at the plane of hydrodynamic shear. The repulsive force depends on the square of the zeta potential (i.e. its sign is irrelevant). Electrolytes modify the zeta potential by adsorbing to the droplet surface and screening the droplet charges.

iii) **Solvent forces.** These are short-range repulsive forces caused by solvent-surface interactions, and are normally only important at short droplet separations of a few nanometres (i.e. the droplets are nearly "in contact").

iv) **Steric forces.** These are much less well understood than the previous forces, but are of major importance in many colloidal systems [23]. They arise when long-chain hydrophilic macromolecules are adsorbed or grafted to the colloid surface. They are repulsive in nature, since the overlap of adsorbed macromolecules is energetically unfavourable.

In general, colloids are stabilized either by steric or electrostatic repulsion, depending on the nature of the surfactant. Lecithin-stabilized emulsions are charge-stabilized, and steric forces do not play a significant role [24]. Alternately, emulsions stabilized by block copolymers, such as poloxamers, are sterically stabilized, and charge is of minor importance. Mixed electrosteric systems have also been studied; for example, the perfluorocarbon emulsion, Fluosol, uses a mixture of Pluronic F-68 and lecithin as the emulsifier [25].

Electrolyte stability

Although most lecithin-stabilized emulsions have sufficient surface charge to produce excellent long-term stability, they interact strongly with electrolytes, a phenomenon which has considerable clinical significance. The processes occurring are well-understood and are termed the DLVO theory of colloid stability, after its developers [26,27]. Electrolytes interact with charged colloids by two mechanisms; these are termed nonspecific adsorption and specific adsorption.

Nonspecific adsorption occurs when an ion is attracted to a surface solely due to electrostatic forces. There is no chemical interaction between the ion and the surface. Such an ion is sometimes called an indifferent ion for the surface. The zeta potential falls as the electrolyte concentration is increased, and asymptotes to zero at high electrolyte concentrations. This behaviour is typical of monovalent

cations (e.g. Na^+, K^+) on phospholipid surfaces. As the zeta potential falls, the repulsive force stabilizing the colloid becomes weaker, until at a critical point it is no longer able to overcome the attractive Van der Waals force. At this point the force becomes predominantly attractive, and the colloid flocculates. The concentration of electrolyte required to achieve this is termed the Critical Flocculation Concentration or CFC. Further addition of electrolyte causes the repulsive force to decline further, so the flocculation rate increases to a maximum. The CFC is approximately 0.10 M. This description of the flocculation process is qualitative, but has been put on a quantitative basis [24,28]; The actual interdroplet potentials can be calculated and from them, the flocculation rates. The agreement of the calculated and measured flocculation rates is quite good.

Specific adsorption occurs when an ion interacts with the surface chemically as well as electrostatically. Examples of this process on phospholipid surfaces are Ca^{2+} (which complexes to the lipid phosphate headgroups) and H^+ (which is involved in acid-base equilibria) [29]. Under these conditions, more ion can adsorb to the surface than is required simply to neutralize the droplet surface charge, and so the surface can acquire a charge of the opposite sign to that which it possessed in the absence of the ion. This process is called charge reversal and is characteristic of the specific adsorption process. It was observed that the effect of increasing concentrations of Ca^{2+} on the zeta potential and flocculation rate of Intralipid. Initially the charge is neutralized in a similar manner to that observed for a nonspecfically adsorbed ion, and a CFC is seen at a calcium ion concentration of 2 mM. Further addition of calcium causes all the surface charge to be neutralized at 3-4 mM, and this point is called the point of zero charge, or PZC. At still higher calcium concentrations, the zeta potential becomes positive.

These changes in the surface potential are reflected in the flocculation rate. The CFC is observed in a manner similar to a nonspecifically adsorbing ion; however, the PZC now corresponds to a well-defined maximum in the flocculation rate. As the surface becomes charge-reversed, it regains some repulsive component to the interdroplet force and as a result, the flocculation rate falls. [4]

Physicochemical properties of LM

Table 3 shows the formulae of PC99LM and PC70LM prepared with two kinds of lecithins (PC99, PC70). PC99 and PC70 are lecithins containing 99% and 70% of phosphatidylcholine (PC), respectively. PC70 contains 17% of phosphatidylethanolamine (PE). The pHs, mean particle sizes and ξ potentials for the two LMs are shown in Table 4. The pH and mean particle sizes of PC99LM and PC70LM were the same, but their ξ potentials differed. The absolute ξ potentials of both LMs increased with increasing pH. Since variation in the pH affected the charge on lecithin, it appeared

that the negative charge on the LM particle surface became larger with increasing pH [71,72]. The absolute ξ potential of PC70LM was larger than that of PC99LM. Ishii et al. [73] reported that the absolute ξ potential of LM composed of PE was larger than that of LM composed of PC. It thus appeared to influence PE content of egg yolk lecithin, which comprises the interfacial membrane.

Table 3: Formulas for LMs

Component	PC99LM	PC70LM
PC99	18 g	-
PC70	-	12 g
Soybean oil	100 g	100 g
Glycerol	23 g	23 g
NaOH	-[a]	-[a]
Water for injection[b]	1000 ml	1000 ml

[a] Adjusted to pH 6.
[b] Adjusted to 1000 ml with water for injection.

Table 4: Properties of LMs

	PC99LM	PC70LM
pH	**6.5**	**6.1**
Mean particle size (nm)	**204**	**208**
ξ potential (mV)[a]	**-8**	**-46**

[a] Each value was obtained from measurement of the mean particle electrophoretic mobillity in a 0.5 mM KCl solution at the same pH of LM.

Theoretical analysis of flocculation and coalescence of LM

It is well established that the stability and the behavior of LM in the body are related to the surfactant used and to the condition of emulsification [71-73], but many thermodynamic studies have been carried out on the change in size, flocculation or coalescence of LM particles [79-86]. It appears to be true that the flocculation process can be analyzed with DLVO theory, in a fashion similar to that for flocculation of colloid [87-90]. However, the process of increasing the particle size cannot be understood using this theory alone, since particle destruction also occurs. Thus, flocculation and coalescence of LM must be considered separately. Now, the total energy of the increase in particle size is equal to the sum of the energy of flocculation and coalescence. We analyzed the stabilities of LMs prepared with two kinds of lecithins (PC99, PC70)

taking this into consideration [91]. Both lecithins have been used in drug delivery systems and for nutrients. Only PC99 and PC70 have been used as surfactants in commercial parenteral LMs. Unstable LM particles are the first to flocculate. By the DLVO theory, the total interaction energy V_t of the flocculation of LM is the sum of contributions of the potential energy of electrostatic interaction V_R and that of the van der Waals interaction V_A:

$$V_t(H) = V_R(H) + V_A(H) \quad (1)$$

For bulk solutions containing two kinds of electrolytes, we derived an expression for V_R between two identical spheres immersed in a mixed solution of 1:1 and 2:1 electrolytes using the DLVO theory for colloid stability, as follows [92]

Consider first the electric potential, ψ, produced by a single plate with a surface potential, ψ_o, immersed in a mixed solution of electrolytes. Let n_1 and n_2 be the numberical densities (in units of m^{-3}) of 1:1 and 2:1 electrolytes in the bulk solution phase, respectively. Let the x-axis be perpendicular to the plate, with its origin 0 at the plate surface so that the region $x > 0$ is the solution phase. The Poisson-Boltzmann equation for the electric potential $\psi(x)$ at position x relative to the bulk solution phase, where $\psi(x)$ is set equal to zero, is then given by

$$\frac{d^2\psi}{dx^2} = -\frac{e}{\varepsilon_r\varepsilon_0}\left[n_1\, exp\left(-\frac{e\psi}{kT}\right) + 2n_2\, exp\left(-\frac{2e\psi}{kT}\right) - (n_1 + 2n_2)\, exp\left(\frac{e\psi}{kT}\right)\right] \quad (2)$$

where e is the electric unit charge, ε_r, is the relative permittivity of solution, ε_0 is the permittivity of vacuum, k is the Boltzmann constant, and T is the absolute temperature.

Consider next the potential energy $V_R(H)$ of the electrostatic interaction between two identical spherical particles of radius, a, at separation, H, between their surfaces. With the help of Derjaguin's approximation [93], we can obtain an expression for $V_R(H)$ from the corresponding expression for the interaction between two parallel plates. viz.,

$$V_R(H) = \pi a \int_H^x V_{pl}(h)dh = \frac{64\pi a(n_1 + 3n_2)\gamma^2 kT}{k^2}\exp(-kH) \quad (3)$$

With

$$\gamma = \frac{1}{(1-\eta/3)}\,\frac{[(1-\eta/3)\,\exp(y_0)+\eta/3]^{1/2}-1}{[(1-\eta/3)\,\exp(y_0)+\eta/3]^{1/2}+1} \quad (4)$$

$$\eta = \frac{3n_2}{n_1+3n_2} \quad (5)$$

Where y_0 is the scaled surface potential and x is the Debye-Huckel parameter.

V_A can be calculated as:

$$V_A = -\frac{Aa}{12H} \quad (6)$$

where A is the Hamaker constant.

Thus, from Eq. (3) and Eq. (6), Eq. (1) can be derived. Two LM particles are flocculated when the maximum in the potential curve $V_t = V_R + V_A$, i.e., the potential barrier, disappears.

Next, two LM particles that have undergone flocculation, become one particle by coalescence, and the volume increase. It has been reported that the following equation can be used to predict the rate of increase in LM particle volume [94]:

$$\frac{dv}{dt} = \frac{4kT}{3\eta} \boldsymbol{\phi} \exp(-E/\mathrm{R}T) \quad (7)$$

where v is the mean volume of a particle, η the viscosity of the bulk solution, $\emptyset$ the volume fraction of bulk solution and R is the gas constant. Therefore, the activation energy, E, which includes the energy for destruction of the interfacial membrane, in addition to the maximum total interaction energy (V_t^{max}) as the energy barrier, can be obtained from the plot of the rate of increase in particle volume

Influence of steam under pressure sterilization (SUPS) on mean particle size

Parenteral injections must be sterilized. We tested the sterilization of PC99LM and PC70LM by SUPS. SUPS did not change the pH of PC99LM, but did increase its mean particle size to 320 nm. On the other hand, neither the pH nor the mean particle size of PC70LM was affected by SUPS. The values of V_t^{max} at 121°C were calculated for LM using Eq. (1), by substitution of ξ potentials and mean particle sizes in Table 3 and by the Hamaker constants (PC99LM, 1.4×10^{-22}J; PC70LM, 3.1×10^{-21}J) obtained in a previous study [95]. In order to obtain the relationship between ξ potential and temperature, the ξ potentials of LMs were measured over a range of temperatures. Since the ξ potential of LM was little affected by temperature, the ξ potential at 25°C was used to calculate of V_t^{max} at other temperatures. The values of V_t^{max} for PC99LM and PC70LM at 121°C obtained in this fashion were 4.7 kT and 1.51 kT, respectively. Since the value of V_t^{max} for PC99LM was quite small, PC99LM appeared to undergo flocculation readily.

On the other hand, since the value of V_t^{max} for PC70LM was very large, the energy for flocculation was large and PC70LM did not readily undergo flocculation.

The effect of pH on change in particle size was studied using SUPS. PC99LM and PC70LM were adjusted to various pHs with 0.1 *M* KOH or 0.1 *M* HCl, and the ratios of changes in mean particle sizes, R_p, was obtained as:

$$Rp = \frac{mean\ particle\ size\ after\ SUPS}{mean\ particle\ size\ before\ SUPS} \quad (19)$$

The values of R_p, for PC99LM increased as the pH decreased below pH 8.0, but the mean particle size changed little at values of pH above 8.0. On the other hand, the value of R_p for PC70LM was approximately 1, at values of pH above 4.0, and the mean particle sizes increased very little at pH 4.0 or below. The ξ potentials of these LMs at 121°C were obtained from Fig. 6 by interpolating to pH of the LM, and the values of V_t^{max} at 121°C were calculated from Eq. (12).

Using these values, the relationships between R_p and V_t^{max} for PC99LM and PC70LM were determined. Both R_p values increased as V_t^{max} decreased, when V_t^{max} was less than 15 *kT*. The mean particle sizes of PC99LM and PC70LM increased, since values of

V_t^{max} were below 15 *kT*. These findings indicated that various LMs flocculate easily if their V_t^{max} values are less than 15 *kT*. This is "slow" flocculation, which differs from the "fast" flocculation

that occurred in the absence of the potential barrier. Values of V_t^{max} above 15 *kT* were obtained above pH 8.0 and above pH 4.0 for PC99LM and PC70LM, respectively. These findings demonstrated that the stability of various LMs could be evaluated using this method.

Reviews of lipid microspheres or drug studied for lipid microsphere drug delivery

The presence of an additional component in the emulsion can considerably complicate its behaviour. Fortunately, the effect of the drug can often be predicted (at least in terms of DLVO type emulsion stability) with knowledge of the physicochemical properties of the drug. For the purposes of emulsion formulation, we can classify drugs on the basis of their solubility characteristics and their ionization properties which, of course, are not completely independent.

A) **Class I:** drugs are largely water-soluble. In an emulsion, a significant fraction of the drug would be present in the aqueous phase, and consequently such drugs are not good candidates for emulsion formulations.

B) **Class II:** drugs are predominantly oil-soluble, and in an emulsion would be partitioned

predominantly into the oil phase. Such materials are good candidates for emulsion delivery and could normally be formulated by dissolving the drug in the oil prior to emulsification.

C) Class III: drugs are poorly soluble in both water and oil, and can only be loaded into an

emulsion by adsorbing to the droplet interface. They may require complex formulation methods due to their unusual solubility characteristics, and it is often necessary to post-load emulsions with them, in order to have a large surface area available for loading.

This is naturally an artificial classification, and boundaries between these areas are indistinct, although many drugs do fall clearly into these classes. The classification of a drug can be changed by chemical means; for example, a hydrophobic (class II) base such as chlorpromazine can be converted into its class I hydrochloride salt. Formulation chemists often do this to increase the water solubility of a drug; emulsion chemists normally want to reverse this process! The boundary between classes I and II cannot be assigned to a particular log *P* value, although we would suggest that log $P > 4$ would be a useful starting point. A particular problem can arise if the drug has a very slight water solubility and a high oil solubility, since partition can cause the water solubility to be exceeded and the drug will crystallize out into the aqueous phase. The oil phase will dump its drug load as crystals in the aqueous phase until the aqueous phase solubility is not exceeded.

The class II-III boundary is also often indistinct, since most drugs have some surface activity due to polar or ionized groups, whether strongly oil-soluble or not. Consequently we can usefully subclassify drugs into types a, b and c.

Type a drugs are weak bases and thus are positively charged at the formulation pH.

Type b drugs are weak acids and are negatively charged at the formulation pH.

Type c drugs are uncharged at the formulation PH.

The charge on type a and b drugs leads to surface activity, and so these drugs will normally adsorb, at least partly, to the droplet interface. In doing so, they will contribute some surface charge, which will influence the emulsion stability. Type c drugs may also adsorb to the interface (if, for example, they contain hydroxyl groups) but will not normally influence surface charge. Of course this classification is only valid at a particular or specified pH, which suggests that pH is a major tool to control this aspect of drug behaviour.

Evaluation of Lipid Microspheres:

Various evaluation parameters are done for Lipid Microspheres. Drug loading, % entrapment efficiency, drug content etc., are common evaluations parameters.

1. Structure and Morphology

Morphology and structure of lipid microspheres was determined using Transmission electron microscopy (TEM), and photomicrographs were taken at suitable magnifications.

The morphologies of the lipid microspheres were observed using a FEIQuanta 250 SEM (FEI Corporation, Hillsboro, OR, USA).

2. Size, PDI, and Zeta Potential of Lipid Microsphere

The average particle size, PDI, and zeta potential of the lipid microspheres were measured while using a Malvern laser particle size analyzer (Mal-vern, UK). Samples were diluted appropriately with double-steamed water for the measurements, and zeta potential measurements were detected at 25 °C.

3. Stability Studies

The stability of formulation was tested by exposing them to different storage conditions, i.e., at room temperature (20 ± 5°C), in refrigerator (4°C), and at higher temperature (40 ± 5°C) for 45 days and also subjecting to repeated centrifugation (15, 30, 45, 60, 120, 180, and 240 min) at various rpm. Sustainability of the formulations at different pH (2–12) was also determined.

4. *In Vitro* Release Rate Studies

These studies were carried out through dialysis bag using dissolution apparatus USP 1. The treated dialysis membrane was soaked in diffusion medium up to 48 hr and refrigerated till use. The membrane was washed with distilled water before use. The formulations were filled in different dialysis bags and placed in basket of dissolution apparatus USP 1. The study was run at rpm specified, and the dissolution vessel was maintained at 37 ± 0.5°C. An aliquot of 5 ml of samples was withdrawn at suitable time intervals and replaced with same amount of medium to maintain the volume of dissolution medium as 900 ml. The samples were quantitated by UV spectrophotometer.

5. Drug release mechanism and Statistical Analysis

Drug release mechanism were also studies using software and Pharmacokinetic parameters of lipid microsphere were calculated by Software version 3.3.0 (Shanghai, China).

Table 5 shows various types of drugs are taken under study for lipid microsphere formulation and Table 6 shows some commercially available LM based products.

Table 5: Drugs studied for LM formulation

Drugs	Drugs
Anti tumor drugs	Profesterone
Pregnaolone	Nifedepine
Barbituric acid	Grisofulvin
Indomethacin	Propofol
Cyclandelate and nitro glycerin	Profesterone
Biphenylacetic acid	Ketoprofen
Naproxen	Cyclosporin A and cyclosporins
Tirilazad	Lidocaine

Table 6: Commercially Available LM Drug Delivery Systems

Drug	Company	Brand Name
Dexamethasone Palmitate	Green cross	Limethasone
Flurbiprofen axetil	Green cross	Lipfen
Flurbiprufen axetil	Kaken	Ropion
Prostaglandin E_1	Green cross	Lipfe
Prostaglandin E_1	Taisho	Palux
Parenteral Nutrition	Clintec, Pharmacia, Kabipharmacia	Intralipid
Diazepam	Pharmacia, Dumex	Diazemuls
Propofol	Zeneca, ICI	Dipivan

FUTURE TRENDS:

One of the major problems of LM using as drug delivery system is its rapid uptake by liver, spleen and other RES. For drug delivery purpose, it may necessary to control and modify the uptake of the droplets. Adding block copolymers of ethylene oxide and propylene oxide to stabilize an emulsion prolongs circulation time. Preparation of small particles with negative charge also improves the circulation time of microspheres. Another stratergy for avoiding rapid clearance uses phospholipids modified with PEG or addition of surfactants. Positively charged LM may be used for drug targeting to RES. A continuing challenge is to tailor surface properties of LM to achieve the desired biodistribution. Optimizing certain

characters could endow LM with targeting properties, a line of research that has been prompted with liposomes.

CONCLUSIONS

In the early days of the 20th century, Paul Ehrlich envisioned his magic bullet concept; the idea that drugs reaches the right site in the body, at the right time, at right concentration. It should not exert side effects, neither on its way to the therapeutic target, nor at the target site, nor during the clearance process. The LMs have the potential to achieve, at least partially, these broad objectives. Apart from these, the regular objective of controlled drug delivery is aptly achieved with LMs. They are relatively young drug delivery systems, having received primary attention from the early 1990s and future holds great promise for its systematic investigation and exploitation. We can expect many patented dosage forms in the form of LMs in the future.

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ARTICLE

AN EPITOME ON TUBERCULOSIS: A PHASE OF DRUG DISCOVERY TO NANOTECHNOLOGY

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Abstract

Mycobacterium tuberculosis is a chronic infectious disease. It kills approximately 1.7 million people in the world and also has the highest risk of reactivation in the patients with latent infection. Relapse of the disease and drug resistance (MDR-TB/XDR-TB) are the key parameters of too complex tuberculosis therapy. Due to this varied failure treatment on this globe has asked the researchers to identify novel targets and to intercorrelate its mechanism of action. With an ascending growth of the disease and more specifically drug-resistance has signified its emergence for new anti-tuberculosis drugs. Thus, with the prior knowledge and applying it in the drug discovery has led a convincing opportunity for the modification of current inhibitors or to develop new drugs. With the re-arrangement of recognized scaffolds is applied in its core structure which may help in the improvement of bactericidal, pharmacokinetics and pharmacodynamics activities. Along with the surveys carried out, a large number of compounds are screened against Mycobacterium tuberculosis and can be helpful later in the computer databases. The present drug discovery should include an integrative analysis with computational databases. Nanomedicine also plays an important role in the management of the disease. The nano-sensors which help in the detection of infection rate have provoked its role for the rapid and short term diagnosis. Thus, with the current literature review it can be noted that interconnecting computational chemistry with the nanotechnology diagnosis can be helpful for short term therapy as well as lesser side-effects.

Keywords: Nanosensor; dendrimers; chemoinformatics; mycolic acid; nanotechnology

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