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Reveiw Article

PHOSPHOLIPIDS AS VERSATILE POLYMER IN DRUG DELIVERY SYSTEMS

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ABSTRACT

Phospholipids become more and more important as pharmaceutical excipients. This review article summarizes meticulous features of phospholipids and their application in various drug delivery systems and elucidates numerous techniques to improve the bioavailability and disposition of drugs administered through various routes. The advantages of phospholipid based drug delivery systems not only enhance the bioavailability of drugs with poor aqueous solubility, membrane penetration, and also enhancement or alteration of uptake and release of drugs, protection of sensitive drugs from degradation in the gastrointestinal tract, reduction of gastrointestinal side effects and even masking of bitter taste of orally administered drugs. Various formulation strategies to achieve these effects are highly diverse and offer various possibilities of liquid, semi-solid and solid lipid-based formulations for drug delivery optimization such as liposomes, lipospheres, lipid nanoparticles, micelles, nanoemulsions, solid dispersion etc.,

Keywords: Phospholipid, Lecithin, Emulsifier, Permeation enhancer, Drug release, Carrier.

INTRODUCTION

Phospholipids are amphiphilic molecules, consists of hydrophobic tails and a hydrophilic head. The hydrophilic head contains the negatively charged phosphate group, and may contain other polar groups. The hydrophobic tail usually consists of long fatty acid hydrocarbon chains. When placed in water, phospholipids form a variety of structures depending on the specific properties of the phospholipid. These specific properties allow phospholipids to play an important role in the formation of phospholipid bilayer. Phospholipids have attracted much attention in drug delivery development, polymer science, food and cosmetics formulations, and biomedical engineering, etc., [1].

The gastrointestinal (GI) tract is a physiological and chemical barrier and thus poses complex demands on oral therapy. The fact that about 50% of recently developed drugs are either poorly soluble or practically insoluble in aqueous medium, leads to formulation challenges because of their poor absorption and low bioavailability. Phospholipid-based formulations can positively impact the absorption of active ingredients through the following mechanisms (a) modification of drug release (b) enhance the bioavailability (c) modification of the composition and hence the character of the intestinal location (d) motivation of the lymphatic transport (e) reduction of drug induced side effects (f) modification of transdermal permeation. And also used as solubilizers, surfactants, antioxidants, permeation enhancer, release modifiers, coating agent, and act as carrier material for various drug delivery systems like liposphere, liposomes, solid lipid nanoparticles, phytosomes, nanoparticles, solid dispersion and etc,. In this review, we demonstrated the effect of phospholipid molecules in various drug delivery systems [1].

Classification of phospholipids

The common sources of industrially manufactured phospholipids are soya, rapeseed, sunflower, chicken eggs, bovine milk, fish and eggs etc. Each source has unique properties of individual phospholipid species and consequently differing applications in food, pharmaceuticals and cosmetic industry (table 1) [1, 2].

Table 1: Classification of Phospholipids

Phospholipids	Phosphatidic acids	1,2-Dimyristoyl-sn-glycero-3-phosphate (DMPA)
		1,2-Dipalmitoyl-sn-glycero-3-phosphate (DPPA)
		1,2-Distearoyl-sn-glycero-3-phosphate (DSPA)
	Phosphatidyl glycerols	,2-Dimyristoyl-sn-glycero-3-phosphoglycerol (DMPG)
		1,2-Dipalmitoyl-sn-glycero-3-phosphoglycerol (DPPG)
		1,2-Distearoyl-sn-glycero-3-phosphoglycerol (DSPG)
		1,Palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol (POPG)
	Phosphatidyl ethanolamines	1,2-Dimyristoyl-sn-glycero-3-phosphoethanolamine (DMPE)
		1,2-Dipalmitoyl-sn-glycero-3-phosphoethanolamine (DPPE)
		1,2-Distearoyl-sn-glycero-3-phosphoethanolamine (DSPE)
		1,2-Dioleoyl-sn-glycero-3-phosphoethanolamine(DOPE)
	Phosphatidyl cholines	1,2-Dilauroyl-sn-glycero-3-phosphocholine (DLPC)
		1,2-Dimyristoyl-sn-glycero-3-phosphocholine (DMPC)
		1,2-Dipalmitoyl-sn-glycero-3-phosphocholine (DPPC)
		1,2-Distearoyl-sn-glycero-3-phosphocholine (DSPC)
		1,2-Dioleoyl-sn-glycero-3-phosphocholine (DOPC)

Applications of phospholipids in drug delivery systems

Permeation enhancer

Unsaturated phospholipids are essential part of the cell membranes in the epidermis. Because the unsaturated phospholipids are in liquid-crystalline state at body temperature, they modify and fluidize the structure of the barrier layer, resulting in an increased permeability of bioactives. The authors Claudia Valenta et al., investigated the permeation of cyproterone acetate (CPA) from Derma Membrane Structure (DMS) creams and liposomal

formulations performed by Standard diffusion experiments with dermatomed porcine skin. The cumulative amount of permeated CPA (DMS creams) was between 2.9 and 6.8 µg/cm^2 within 48 h. By the addition of a phospholipid concentrate, the CPA permeation further increased to 2.6 fold compared to the control DMS [3].

Solubility enhancer

The amphiphilic nature of phospholipid has ability to improve the solubility of poorly aqueous soluble bioactives. The phospholipid concentrates in a water miscible solvent were explored as injectable formulations for the poorly aqueous- soluble drugs, using the anti-infective PHA 244. The formulations containing phospholipid (70%w/v) could dissolve 15% PHA 244. These formulations showed excellent syringe-ability and no precipitation of the drug after dilution in an excess quantity of water. The local tolerability and pharmacokinetics of the formulations were explored after subcutaneous injection into cattle. A sustain release pattern over a 2-week period and excellent local tolerability at the site of injection were observed [4].

Emulsion stabilizer

Phospholipids have the ability to emulsify oils and lipophilic drugs to form water-in-oil or oil-in-water emulsions. The author Chuan-Chuan Lin, et al., formulated curcumin loaded microemulsion system using lecithin and Tween 80 and studied the stability of the formulations. These findings indicated that the encapsulation of curcumin in microemulsion was not only prevented from degradation but also increased the concentration of curcumin in aqueous solution. This microemulsion possesses an ability to be diluted without destroying its structure [5].

Lipospheres

Lipospheres were first reported by Domb, who described them as water-dispersible lipid microparticles (0.2 -100µm in diameter), composed of a solid lipid matrix stabilized by a monolayer of phospholipids embedded in the microparticles surface. The authors Morel, Gasco, and Cavalli applied warm multiple microemulsion technique for the production of lipospheres, in which the peptide was dissolved in an aqueous solution and added to a Mixture of melted stearic acid, egg lecithin, and butyric acid at 70°C. This primary microemulsion was then transferred to an aqueous solution of egg lecithin, butyric acid, and taurodeoxycholate sodium salt at 70°C. Addition of warm multiple microemulsions to water at 2°C leads to precipitation of the lipid phase, forming solid lipospheres. This encapsulation efficiency of peptide loaded lipospheres was achieved upto 90% and the controlled particle sizes. [6].

Solid lipid nanoparticles (SLN)

The authors Vijayan V et al., prepared Repaglanide loaded solid lipid nanoparticles (SLN) by hot homogenization technique using cephalin and lecithin as lipid carriers and Tween 80 as a stabilizer. The entrapment efficiency of Repaglanide loaded SLN was increased from 82 to 92% as when concentration of lecithin increased from 5 to 10g. They concluded that, the concentration of lipid increased the entrapment efficiency of Repaglanide also increased proportionally [7].

The author Doijad et al. have developed Cisplatin loaded SLN by micro-emulsification technique by using stearic acid, soy lecithin and sodium glycolate as surfactant and co-surfactant respectively. And they investigated the entrapment efficiency of Cisplatin- SLN. The formulated SLN were oval shape with size range 250- 500nm. The *in vitro* drug release was achieved upto 78% at 16h and the *in vivo* study of Cisplatin-SLN revealed that the drug was preferentially targeting to liver followed by brain and lungs [8].

Nanogel

Flubiprofen Nano-structured lipid carriers (FP-NLC) based topical gel were developed by using lecithin. In this Nano-structured lipid carriers based topical Gel of Flubiprofen was successfully formulated and size were remained within the colloidal range and it was uniformly dispersed after suitably gelled by carbopol. It was indicated that the *in vitro* permeation studies of FP-NLC-gel had a more pronounced permeation profile compared with that of FP-loaded conventional gel. From these results the authors concluded that the permeation rate of Flubiprofen was appreciably influenced by the presence of lecithin molecule [9].

Vesicular phospholipid gels

Vesicular Phospholipid Gels (VPG) were exhibit that vesicular structures are formed as well if the hydration of phospholipid (Phosphatidylcholine ~500mM) with minimal amounts of water is performed under high-pressure homogenization [10].

VPG was formulated with hydrogenated egg PC using high-pressure homogenization technique. The various bioactive ingredients such as Gemcitabine [11], Vincristine [12], Cefrorelix [13], and 5-Fluorouracil [14] were successfully formulated as VPG topical delivery system using phospholipids as carrier materials and the entrapment efficiency were achieved at range of 30-70%. The entrapment efficiency of theses bioactives in VPG system were influenced by concentration of phospholipids.

Liposomes

Giovanni Puglisi et al., studied the formulation parameters of pefloxacin and ofloxacin loaded liposomes and *in vitro* antimicrobial activity. Multi-lamellar vesicles (MLVs) were able to entrap greater amount of two drugs, especially when the drugs were co-dissolved with the lipid mixture in the organic phase. The encapsulation efficiency was influenced by the presence of negatively charged lipid in the lipid composition: the greater the concentration of charged lipid mixture, the larger is the amount of drug entrapped. Among the charged systems, a dipalmitoylphosphadiylcholine-cholesterol-dihexadecyl phosphate mixture exhibited the highest encapsulation capacity. In fact, the increase in encapsulation capacity for the lecithin-cholesterol-dihexadecyl phosphate conformed to the following order: Dipalmitoylphosphadiylcholine > Dimyristoylphosphadiylcholine > Egg phosphatidylcholine [15].

Ethosomes

Ethosomes are noninvasive delivery systems that facilitate drugs to reach the deep skin layers and/or systemic circulation. Ethosomes are formulated with derivatives of phospholipids, alcohol (ethanol and isopropyl alcohol) and water. Unlike traditional liposomes, ethosomes were shown to permeate through the stratum corneum layer and were reported to possess significantly higher transdermal flux in comparison to liposomes. The synergistic effects of combination of phospholipids and ethanol in vesicular systems have been suggested to be responsible for deeper distribution and penetration in the skin [16].

Phytosomes

Phytosomes are novel complex structures which are formulated by using natural or synthetic phospholipids, such as phosphatidylcholine, phosphatidylethanolamine or phosphatidylserine. Phytosomes are formulated by binding of herbal extract to phosphatidylcholine molecule and has achieved excellent absorption and bioavailability. Phytosomes results from the reaction of a stoichiometric amount of the phospholipid with the standardized extract or polyphenolic constituents (like flavonoids, terpenoids, tannins, xanthones) in a non-polar solvent. In this phytosomes, the water-soluble phytoconstituents are incorporated into lipid compatible molecules to cross the lipid biomembranes and enters into systemic circulation, which exhibit greater absorption. Some herbal extracts to which the phytosome technology has been applied including marsupsin, olive fruits and leaves, hawthorn, grape seed, milk thistle, green tea, ginseng, kushenin, Ginkgo biloba and curcumin extracts. Phosphatidylcholine used in the formulation of phytosomes, besides acting as a carrier and hepatoprotective, hence giving the synergistic effect when hepatoprotective substances are employed. Chemical bonds are formed between phosphatidylcholine molecule and phyto-constituent, so the phytosomes demonstrate better stability and added nutritional benefit [17].

Pharmacosomes

The well documented problem of aspirin is poorly soluble in water and causes gastrointestinal irritation. To overcome these problems

aspirin was entrapped into pharmacosomes using phospholipid-80 were prepared in an organic solvent and investigated for its solubility. The physico-chemical investigations showed that aspirin formed a complex with phospholipids with improved solubility and dissolution rate. As the phospholipid complexes have also been reported to reduce the gastrointestinal toxicity of the drugs, which may be validated further through *in vivo* studies [18].

Liposomal gel

Livia Budai, et al., developed ciprofloxacin (CPFX) loaded liposomal gel to minimize tear-driven dilution in the conjunctival sac. In this liposomal gel carrier system, multilamellar vesicles from lecithin (LEC) and α-L- dipalmithoyl-phosphatidylcholine (DPPC) provided the encapsulating agent. A comparison of the release half-time values for LEC- and DPPC-liposomes, shows that DPPC prolongs the CPFX-release to a greater extent than LEC. Optimized combination of viscosity modifier and phospholipid carrier can result in the desired rheological characteristics and prolonged drug release. By increasing the concentration of the viscosity modifiers and by use of liposomal formulation with appropriate lipid composition, higher drug concentration can be achieved at the site of action. Concomitantly the time of contact can prolonged thus ocular bioavailability can be improved [19].

DNAsomes

DNAsomes as a vesicular carrier system can carry multiple drugs as well as RNA molecules designed to block the expression of genes, an improvement over other drug-delivery systems such as liposomes (tiny wrappers of the phospholipid molecules that make up cell membranes) or polymer nanoparticles. About the size of a virus, the DNAsomes engulfed by the cell membrane and taken into a cell in a similar way as a virus, he explained. The DNAsome can be tagged with molecules that target a specific site, such as a cancer cell [20].

Nanosuspensions

The *In vivo* behavior of nanosuspension strongly depends on three factors: (a) particle size; (b) dissolution rates; and (c) nature and density of coatings materials. The phospholipid-based nanosuspension of flurbiprofen had the same pharmacokinetic behavior and *in vivo* distribution as a high-pH solution formulation of the drug after intravenous injection in rats [21].

Lipid Nano-capsules (LNC)

Various LNC formulations were prepared by a phase inversion technique. Briefly, The oil phase was mixed with the appropriate concentration of surfactant (PEG–HS), lecithin, sodium chloride, and distilled water and heated under magnetic stirring up to 85^0C. The cooling step was performed until the temperature of was attained at 55^0C. This cycle was repeated another two times before adding 5 ml of distilled cold water at 2^0C. The formulation was stirred for another 10 min [22].

Nanostructured lipid carriers (NLC)

The NLC was formulated by hot high-pressure homogenization technique, and investigated the effect of surfactants on the formation and characterization of NLC. Lecithin, Poloxamer 188 and Tween-80, and their mixtures were chosen as emulsifier. Effects of different surfactants on properties of NLC such as particle size distribution, zeta potential and crystal structure were investigated. The formulation comprised various types of surfactants including SDC, Poloxamer 188, Tween-80 and lecithin were with the smallest mean particle size, and it could stabilize for more than 1 year, revealing considerably favorable physio-chemical properties [23].

Nanocomplex

The simplistic synthesis of biocompatible and nontoxic gene delivery vectors has been the attention of research in recent years due to the high potential in treating genetic diseases. 2-Methacryloxyethyl phosphorylcholine (MPC) copolymers were recently studied for their ability to produce nontoxic and biocompatible character. The synthesis of well-defined and water-soluble MPC polymer based cationic vectors for gene delivery purposes was therefore attractive, due to excellent biocompatibility of the resulting copolymers. Herein, cationic MPC copolymers of varying architectures were formulated by the reversible addition-fragmentation chain transfer (RAFT) polymerization technique. The copolymers were characterized for their gene delivery efficiency in the presence and absence of serum. It was found that copolymer architectures and molecular weights do affect their gene delivery efficiency [24].

Micelles

The formulation of drug-loaded Polyethylene glycol-Phosphatidyl ethanolamine (PEG-PE) micelles was prepared by evaporation of an organic solvent solution of the mixture, and hydration of the dry firm with an aqueous solution/buffer by intensive shaking to form drug-loaded micelles. The insoluble drug is precipitated in a crystalline form and removed by filtration. In order to improve drug solubilization, additional micelle-forming compounds such as egg phosphatidylcholine are added to PEG-PE micelles. A numerous poor aqueous soluble drugs were successfully solubilized in PEG-PE micelles with higher encapsulation efficiencies [21].

Micelle like nanoparticles (MNP)

Micelle-like nanoparticle (MNP) were engineered by condensing plasmid DNA with a chemical conjugate of phospholipid with polyethylenimine and then coated the complexes with an envelope of lipid monolayer additionally containing polyethylene glycol-phosphatidyl ethanolamine (PEG-PE), resulting in spherical 'hard-core' nanoparticles encapsulated with DNA. MNP were allowed for complete protection of the entrapped DNA from enzymatic degradation, resistance to salt-induced aggregation, and reduced cytotoxicity. MNP also exhibited prolonged systemic circulation and little RES accumulation. Intravenous injection of MNP loaded with plasmid DNA encoding for the Green Fluorescence Protein (GFP) resulted in an effective transfection of a distal tumor. Thus, MNP offered a promising carrier for systemic gene therapy [25].

Nanoparticles

The nanoparticles loaded insulin–phospholipid complex were formulated by reverse micelle–solvent evaporation technique, in which soybean phosphatidylcholine was utilized to enhance the solubility of insulin, and biodegradable polymers as carrier materials to control the drug release. The effects of formulation parameters such as polymer/ soybean phosphatidylcholine weight ratio, organic phase and polymer type on the properties of the nanoparticles were investigated. Spherical particles of 200 nm mean diameter and a narrow size distribution were obtained under optimal formulation condition. The insulin entrapment efficiency was achieved upto 90%. The *in vitro* drug release was characterized by an initial burst and subsequent delayed release in both pH 6.8 and pH 1.2 dissolution medium. The influence of polymer type on the drug release was also investigated. Intra-gastric administration of the 20 IU/kg nanoparticles reduced fasting plasma glucose levels to 57.4% within the first 8 h of administration and this continued for 12 h. PK/PD analysis indicated that 7.7% of oral bioavailability relative to subcutaneous injection was obtained [26].

Zykova MG., investigated antitumor effect of Nanophospholipid (NPh) doxorubicin in mice with two cancer models with various sensitivity to chemotherapy -lymphoid malignancy P-388 and Lewis lung carcinoma (LLC). Inclusion of drugs into different transport systems based on polymers or lipids is the modern approach to increase their bioavailability. The treatment with doxorubicin in nanoformulation of phospholipids, obtained as the ultra-fine emulsion with a particle size less than 30 nm, has demonstrated in mice with LLC substantially higher antitumor efficiency as compared with free doxorubicin, despite of absence of such effect in more sensitive tumor model, lymphoid malignancy P-388. Preferential effect of NPh doxorubicin as compared with free drug in LLC tumor was especially notable at low drug doses and particularly at the regimen of repeated weekly administrations [27].

Polysaccharide Nanoparticles

Nanoparticles constituted of a modified polysaccharide core coated with phospholipids (SMBV for Supra Molecular BioVect) were

developed by Biovector Therapeutics Company. They were designed as therapeutic a vector, that is to protect active drugs from degradation, and to carry them to a target site. Actually, these nanosystems combine the ability to transport hydrophilic and lipophilic drugs. According to the authors, they are artificial analogues of virus (as regards their size and structure), preferably without being infectious, toxic or immunogenic. The SMBV were evaluated as protein and/or peptide carriers in vaccinal applications. They also exhibited a high efficiency for drug delivery either by intravenous or intranasal route [28].

Solid dispersion

Phosphatidylcholine (PC), palmitoylphosphatidylcholine (DPPC) and dimyristoylphosphatidylcholine (DMPC) have been used to enhance the dissolution rate and bioavailability of poorly aqueous soluble drugs. Several phospholipids were used as potential carriers for rapidly dissolving solid formulations of piroxicam. The solid dispersions of varying piroxicam/ dimyristoyl phosphatidylglycerol (DMPG) ratios were formulated and characterized. On the basis of *in vitro* studies, DMPG was ranked as the potent dissolution rate enhancer. Hence, DMPG was regarded as the most promising phospholipid carrier for enhancing oral bioavailability of piroxicam and other BCS Class II drugs too [29].

CONCLUSIONS

Broad ranges of phospholipids are worldwide being used as registered pharmaceutical excipient, because of their physiological occurrence, well tolerated, toxicologically harmless and suitable for various administration route. The nature of the polar head group and fatty acid composition, determines the physico-chemical properties of phospholipids. In pharmaceutical technology, phospholipids are used as, emulsifiers, wetting agents, coating agents, carriers, permeation enhancers and solubilizers. Selection of right phospholipid excipient with drug substances, to accommodate the intended use and properties of the drugs, requires a sufficient understanding of the properties of the phospholipids.

REFERENCE

1. Mashaghi S, Jadidi T, Koenderink G, Mashaghi A. Lipid Nanotechnology. Int J Mol Sci 2013; 14: 4242-82.
2. Fahy E, Subramaniam S, Murphy R, Nishijima M, Raetz C, Shimizu T, et al. Update of the LIPID MAPS comprehensive classification system for lipids. *J. Lipid Res* 2009; 50: S9-S14.
3. Claudia Valenta, Michaela Janisch Permeation of cyproterone acetate through pig from different vehicles with phospholipids. International Journal of Pharmaceutics 2003; 258: 133-39.
4. Harry Tiemessen, Peter van Hoogevest, Mathew LS Characteristics of a novel phospholipid- based depot injectable technology for poorly water-soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics 2004; 58: 587-93.
5. Chuan-Chuan Lin, Hung-Yin Lin, Hsu-Chih Chen, Ming-Wen Yu, Mei-Hwa Lee Stability and characterization of phospholipid-based curcumin-encapsulated microemulsions. Food Chemistry 2009; 116: 923-28.
6. Elisabetta Esposito, Rita Cortesi, and Claudio Nastruzzi production of lipospheres for bioactive compound delivery editor. Claudio Nastruzzi Lipospheresis in drug targets and delivery approaches, methods and applications. New York: CRC press; 2005.
7. Vijayan V, Srinivasa Rao D, Jayachandran E, Anburaj J Preparation and characterization of anti diabetic drug loaded solid lipid nanoparticles, JITPS 2010; 1 Suppl 8: 320.
8. Doijad RC, Manvi FV, Godhwani DM, Joseph R, Deshmukh NV Formulation and targeting efficiency of cisplatin engineered solid lipid nanoparticles. Indian journal of pharmaceutical sciences 2008; 70 Suppl 2: 203-07.
9. FeiHan, RanYin, XinChe, JingYuan, YananCui, HeYin, Sanming Li Nanostructured lipid carriers (NLC) based topical gel of flubiprofen Design, characterization and in vivo evaluation, International Journal of Pharmaceutics 2012; 439: 349–357.
10. Brandl M, Drechsler M, Bachmann D, Bauer KH Morphology of semisolid aqueous phosphatidylcholine dispersions, a freeze fracture electron microscopy study. Chem Phys Lipids 1997; 87 Suppl 1:65–72.
11. Moog R, Burger AM, Brandl M Change in pharmacokinetic and Pharmacodynamic behavior of gemcitabine in human tumor xenografts upon entrapment in vesicular phospholipid gels. Cancer Chemother Pharmacol 2002; 49 Suppl 5: 356-66.
12. Guethlein F, Burger AM, Brandl M Pharmacokinetics and antitumor activity of vincristine entrapped in vesicular phospholipid gels. Anti-Cancer Drugs 2002; 13 Suppl 8: 797-805.
13. Grohganz H, Tho I, Brandl M Development and in vitro evaluation of a liposome based implant formulation for the decapeptide cetrorelix. Eur J Pharm Biopharm 2005; 59 Suppl 3: 439-48.
14. Kaiser N, Kimpfler A, Massing U 5-Fluorouracil in vesicular phospholipid gels for anticancer treatment: entrapment and release properties. Int J Pharm 2003; 256 (1 Suppl 2):123-31.
15. Giovanni Puglisi, Massimo Fresta, Gioacchino Mazzone, Pio M Furneri, Gianna Tempera Formulation parameters of fluoroquinolone loaded liposomes and in vitro antimicrobial activity. International journal of pharmaceutics 1995; 118: 65-76.
16. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. AAPS PharmSciTech 2007; 8 Suppl 4: 111.
17. Roy Chowdhury Santanu, Bhandari Neeraj, Verma Pooja Phytosomes as emerging technology in phtomedicine: a Review. International journal of pharmacy 2012; 3 Suppl 10: 61-65.
18. Semalty A, Semalty M, Singh D, Rawat MSM Development and Characterization of Aspirin -Phospholipid Complex for Improved Drug Delivery. International Journal of Pharmaceutical Sciences and Nanotechnology 2010; 3 Suppl 2: 940-47.
19. Livia Budai, Maria Hajdu, Marianna Budai, Pal Grof, Szabolcs Beni, Bela Noszal, et al. Gels and liposomes in optimized ocular drug delivery: Studies on ciprofloxacin formulations. International Journal of Pharmaceutics 2007; 343: 34-40.
20. Bill Steele DNAsomes' can deliver multiple drugs or genetic therapy. Cornell chronicle 2011; Accessed from http://news.cornell.edu/stories/2011/04/dna-nanoparticles-carry-drugs-and-gene-therapy.
21. Panayiotis P Constantinides, Mahesh V Chaubal, Robert Shorr Advances in lipid Nanodispersions for parenteral drug delivery and targeting. Advanced Drug Delivery Reviews 2008; 60: 757-67.
22. Betul Arica Yegin, Alf Lamprecht. Lipid nanocapsule size analysis by hydrodynamic chromatography and photon correlation spectroscopy. International Journal of Pharmaceutics 320 (2006) 165–170.
23. Fei Han, Sanming Li, Ran Yin, Hongzhuo Liu, Lu Xu Effect of surfactants on the formation and characterization of a new type of colloidal drug delivery system: Nanostructured lipid carriers. Colloids and Surfaces A: Physicochem. Eng. Aspects 2008; 315: 210-16.
24. Ahmed M, Bhuchar N, Ishihara K, Narain R Well-controlled cationic water-soluble phospholipid polymer-DNA nanocomplexes for gene delivery. Bioconjug Chem 2011; 15 (22 Suppl 6): 1228-238.
25. Young Tag Ko, Amit Kale, William C Hartner, Brigitte Papahadjopoulos-Sternberg, Vladimir P Torchilin Self-Assembling Micelle-like Nanoparticles Based on Phospholipid-Polyethyleneimine Conjugates for Systemic Gene Delivery. J Control Release 2009; 19 (133 Suppl 2): 132-38.
26. Cui FD, Tao AJ, Cun DM, Zhang LQ, Shi K. Preparation of insulin loaded PLGA-Hp55 nanoparticles for oral delivery. J Pharm Sci 2007; 96 Suppl 2: 421-27.
27. Zykova MG, Medvedeva NV, Torkhovskaya TI, Tikhonova EG, Prozorovskii VN, Zakharova TS, et al. Influence of doxorubicin inclusion into phospholipid nanoformulation on its antitumor activity in mice: increased efficiency for resistant tumor model. Experimental oncology 2012; 12-24.
28. Anne-Lise Troutier, Catherine Ladavière An overview of lipid membrane supported by colloidal particles. Advances in Colloid and Interface Science 2007; 133: 1-21.
29. Sabiruddin Mirza, Inna Miroshnyk, Muhammad J Habib, James F Brausch, Muhammad D Hussain Enhanced Dissolution and Oral Bioavailability of Piroxicam Formulations: Modulating Effect of Phospholipids. Pharmaceutics 2010; 2: 339-50.