Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(10):559-563

Review Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Recent excavations on cationic solid lipid nano particles

Sankha Bhattacharya[1] and Bhupendra G. Prajapati[2]

[1]School of Pharmacy, RK University and B. Pharmacy College-Rampura, Godhra, Gujarat, India
[2]Dept. of Pharmaceutical Technology, Ganpat University, Kherva, Mehsana, Gujarat, India

---

ABSTRACT

Cationic solid lipid nano particles is a new trend in nano medicine family .Due to its cationic nature genes, proteins, enzymes, hormonal delivery is possible along with selective drug in targeted cells. This review discuss about mechanism involving cationic nano drugs to reach in target cells, it also speaks about various cationic surfactant used in forming cationic solid lipid nano particles. In modern time so many excavation and achievements took place on cationic solid lipid nano particles, we discussed recent formulation approaches in short .This review helps to understand significantly the challenges of cationic solid lipid nano particles in recent time.

Key words: Cationic solid lipid nano particles (cSLNs), 5-HT, Lipoplexes, CETAB, BBB.

INTRODUCTION

The alteration of surface modification of nano particles using changing of polymer, co-polymer& surfactant with reforming hydrophilic and lipophilic properties causes evaluation of new varieties of nano particles. In recent time nano particular drug delivery system become more effective and target specific that more surface specific research is going on extensively , on this context cationic polymers have shown a new light because of its significant property to form aggregates with protein, forming a narrow size ranged nano particles[1]. On the other hand cationic lipid also forms aggregates but in large size. But as far as therapeutic value is concern cationic solid lipid nano particles is much more effective as compare to cationic polymeric nano particles .It helps the active ingredient to pass Blood Brain Barrier (BBB) efficiently and increase intercellular uptake which helps to inhibit intercellular parasitic infection. Recent scientific experiment signifies gene, protein, hormone & enzymatic drug delivery is possible to any infected cells by using cationic solid lipid nano particles (cSLNs)

2. Advantages:

1. Cationic SLNs can mainly use for poorly soluble drugs and gene delivery purpose.
2. Cationic SLNs can acts as a carrier and upon conjugation with bovine serum albumin, 5-HT[2] alongside with some suitable chemotherapeutic drugs, acts as an excellent medicament to circumvent BBB and destroy site specific cancerous cells in brain. Recent research shows less cytotoxicity and enhance bio availability for Cationic SLNs.
3. Cationic nano particles are more physically and chemically stable and wide alteration in routes variation is possible. Cationic SLNs also avoids proteolytic degradation in proteins by which it sustained the release of incorporated molecules. New research is going on to graft cationic SLNs with cyclosporine A, insulin, calcitonin, and somatostatin[3].
4. Using hydrophilic drugs and protein cationic SLNs shows good results in ocular drug delivery system[4].
5. Lyophilisation and spray drying is possible.

3. Disadvantages:

1. Cationic surfactant are very costly.
2. Drug loading and entrapment efficacy is difficult.
3. Due to cationic nature, in basic condition cationic nano particles activity is questionable.

4. Still date stability of the cSLNs formulations remain key concern.
5. Uncertain gelation tendency and particles growth in storage is a key concern.

4. Cationic mediated transfer:

In modern era Lipofectamine™ 2000 transfection reagents enhance DNA and siRNA delivery into targeted cells[5] Actually positive surface charge of cationic polymers tried to conceal the anionic DNA by which it originate entrance into target cells .Most cationic lipid nano particles facilitate formation of nano sized complexes with DNA ,siRND . It was observed, encapsulation of genes, DNA, Chemo therapeutic agents in form of cationic nano scale medicines helps increasing cytotoxicity and transfection of target cell.Functionally cationic lipids consisting of positively charged head group and some hydrocarbon chains which accelerate DNA condensation in targeted cells. By using extrusion or micro fluidization technique cationic lipid were formed .Cationic lipids carries some helper lipids also .In water, cationic lipids shows liposomal morphology.Cationic lipids causes fusion to negatively charged cell membrane by endocytosis technique .In endocytosis process DNA:Cationic Lipid complex engulfed in cellular membrane by forming intracellular vesicles .After entering intracellular fluid DNA: Cationic Lipid complex at first should resist endosomal path way, second should pass by through active cytoplasm using active diffusion, and finally it should reach nucleus for gene expression[1].

Usually in presence of cationic lipid reagents, DNA(negatively charged) deliberately encapsulated with positively charged lipid nano particles. Sometimeselectroporation, low efficacy of DNA delivery, poorreproducibility, less selectivity and degradation due to endosomal path way causes less stability to cationic lipid nano particles, however using cationic lipid reagent increased efficiencies in a vast verities of eukaryotic cells. Figure1 depicts the possible mechanism of DNA entry to targeted cell by using cationic solid lipid nano particles[6, 7, 8].

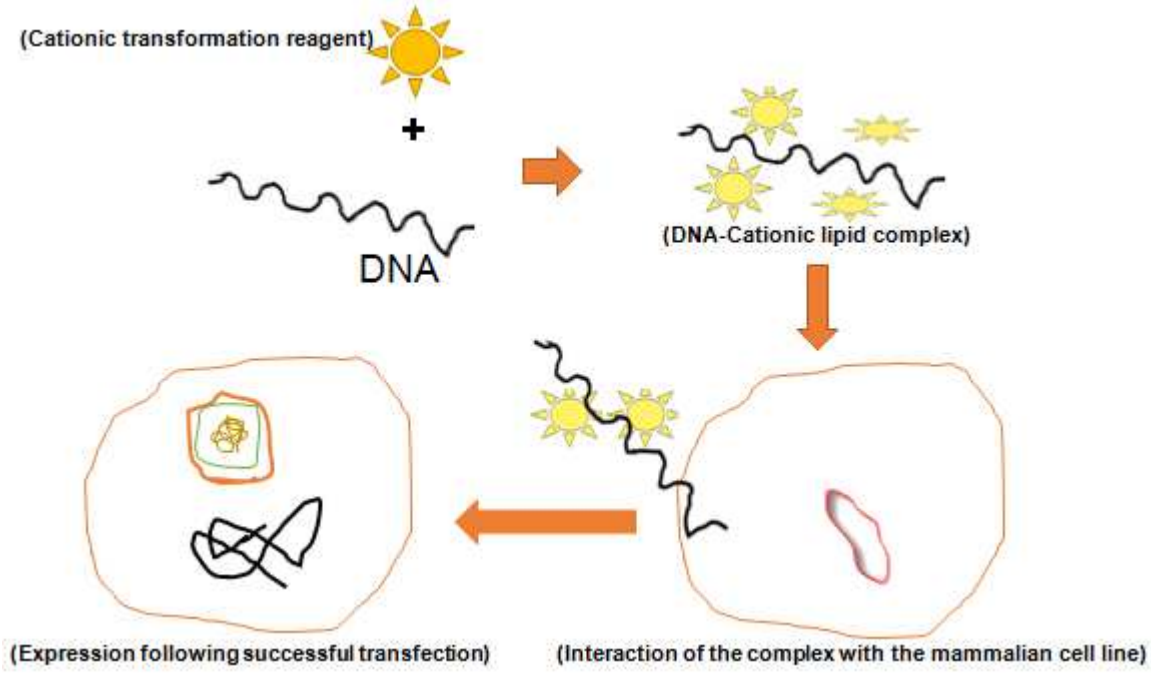


Figure 1: General lipid design and expected mechanism for DNA entry into targeted cells

5. Cationic lipid complex (Lipoplexes): Fegner *et al;* had introduced Lipoplexes for gens transfer for clinical application. The main function of Lipoplexes is to absorb into anionic plasma membrane of mammalian cell via electrostatic interaction.Lipoplexes is a huge potential to target brain, as it facilitate endocytosis in Blood Brain Barrier (BBB). During endocytosis process Lipoplexes forms tubular shape which actually mimic perinuclear structure of endosomes, further it converts into bi layered inverted micellar vesicles .During the time of mutation endosomal wall might raptured and it releases DNA with help of lysosome and further attached with targeted nucleus .Thus cationic Lipoplexes helps in targeting cancerous cells as well. The cationic Lipoplexes shown great selectivity for vascular endothelial cells of tumour.

6. Cationic surfactants:

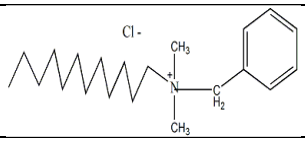
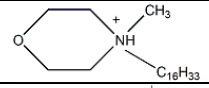
Cationic surfactants are expensive but has good germicidal, cytotoxic property .Cationic surfactant plays a key role in preparing cationic lipid nanoparticles. Most of the cationic surfactants are fatty amines, mostly the amines labelled as primary, secondary, and tertiary. The nitrogen is attached with alkyl group[9]. Table 1 enlisting some cationic surfactant used recently to prepare cationic solid lipid nano particles.

7. Formulation approach on cationic lipid drug complexes:

Abhinav Agarwal *et al* (2011)[11] Formulated cationic conjugated solid lipid nano particles, where Methotrexate were used as a drug. This process talks about forming a stable solid lipid nano particles using ethylene diamine .Conjugation of Bovine Serum Albumin (BSA) in nano particle formations provides positive zeta potentials. Further TEM studies reviles, addition of 1-ethyl-3-(3- dimethylaminopropyl) carbodiimide[EDAC] helps in proper conjugation of proteins with previously prepared SLNs, but particle size would emerges littlehigher. To make this solid lipid nano particle more stable, addition of N-Hydroxy succinimid (NHS) and Dicyclohexyl carbodimide (DCC) were added with constant stirring.

Recently Yung-Chih Kuo *et al* (2014)[2] developed cationic solid lipid nano particles for etopside delivery into braine using surface 5-HT –moduline .In this preparation Decyltrimethylammonium bromide (DTMAB) and Sodium dodecyl sulfate (SDS) mixed together in varying concentration in ultrapure water to form aqueous phase. The lipid phase were prepared by adding Dynasan-114 , cocao butter , steric acid and etopside in methanol .Upon addition of cationic surfactant in aqueous phase and constant stirring with lipid phase forms a good quality cationic solid lipid nano particles . Further research is needed to curtail the preparative cost of cationic solid lipid nano particles and improving stability profile of the formulations.

Table 1: List of cationic surfactant and their molecular structure

S.No	Molecular structure of cationic surfactant	Name of the cationic surfactant
1	$R\text{-}NH_3^+ CL^-$	Alkyl-ammonium salt
2	$C_{12}H_{25}NH_2$	Dodecyl amine or Lauryl amine
3	$C_{14}H_{29}NHCH_3$	Tetradecyl methyl amine
4	$C_{16}H_{33}\text{--}N^+(CH_3)_3Br^-$	Cetyl Trimethyl Ammonium Bromide (CETAB) or Hexadecyl Trimethyl Ammonium Bromide (HTAB)
5		Bezaalkonium or alkyl dimethyl benzyl-ammonium chloride
6	$C_{12}H_{25}\text{-}O\text{-}SO_3^-$	Dodecyl sulphate anion
7		N,N,-Cetylmethyl morpholinium cation
8	$CH_3(CH_2)_{11}NH_3^+Cl^-$	Dodecyl amine hydrochloride

8. Recent advancement in cationic solid lipid nano particles:

In recent time extensive research took place on cationic solid lipid nano particles because of high drug entrapment efficacy and high selectivity of cationic groups. Eventually decade old formulations were polymeric nano particles but at present time cationic lipid nano particles are the best alternatives. Wei Lu *et al*. (2005) formulated cationic albumin –conjugated pegylated nano particles as a novel drug carrier for brain delivery[10], where poly(ethyleneglycol)-poly(lactide) used as a principle polymer and methyl-PEG-PLA and Maleimide-PEG-PLA were used after polymerization technique .The nano formulations was prepared by double emulsion and solvent evaporation technique. The thiol group conjugated cationic bovine serum albumin used to form bonding with poly ethylene glycol. In fluorescence probe 6-coumarin conjugated cationic nano particles shows promising capillary cellular uptake on rat brain compare to normal nano particles. Further *in vitro* and *in vivo* studies showed that cationic bovine serum albumin conjugated nano particles results low toxicity and high selectivity on brain cells. On the other hand Abhinav Agarwal *et al.* (2011)on the bases of former study prepared cationized albumin conjugated solid lipid nano particles as vectors for brain delivery of an anti-cancer drug[12]. This study reviles that, in capillary endothelial of brain, cationic bovine serum albumin conjugated nano particles undergo transcytosis .Further comparative studies with plain Methotrexate(MTX) and Cationic bovine albumin serum conjugated nano particles of Methotrexate(CBSA-MTX) in Human neuroglia culture (HNGC)-1 tumour cell shows great cytotoxicity effect on HHGC1 cells by CBSA-MTX compare with plain MTX. The study also concluded that CBSA conjugated SLNs loaded with MTX has tremendous capability to bypass blood brain barrier. Now a day's gene delivery using cationic solid lipid nano particles is a burning question in between nano scientists. Maria Luisa Bodi *et al.* (2007) prepared novel cationic nano particles by micro emulsion technique using Compritol ATO 888 as matrix lipid, dimethyldioctadecyalammonium bromide charge carrier and finally Pluronic F68 as surfactant[12]. The particles size was found to be 120nm with zeta potential value of +45Mv in double distilled water. It was observed cationic SLN forms stable complexes with DNA, as far toxicological studies are concern SLN and SLN-DNA complexes shows very mere range of toxicity and indicate a good promotion of transfection in liver cells. This study concluded with new direction of using cationic SLN for gene therapy extensively. In recent time adding value to previous excavation,Won Ho Kong *et al.* (2013) prepared cationic solid lipid nano particles using apolipoprotein free low

density lipo protein (LDLs) for the treatment of liver fibrosis. The cationic solid lipid nano particles (CSLNs) were prepared by modified emulsification and solvent evaporation methods[13]. The main components were used such as, Cholesteryl oleate(45%w/w) , Triolean(3%w/w) as a core component .In outer surface to make it more cationic, Cholesterol(9.9%w/w) ,Cationic DC-Chol(28%) ,Fusogenic 1-α-dioleoyl phosphatidylethanolamine(DOPE-14% w/w),DSPE-PEG 2k (0.1%) were used .Chloroform used as an organic solvent and de-ionised water used as an aqueous solvent. After performing ultra-sonication, solid lipid nano particles were formed .The main advantages of this formulation was more stability, because of using cholesteryl oleate , which has high melting point of 52ºC which is above normal body temperature. This cationic nano particles then conjugated with siRNA .The bio distribution study using fluorescence bio-imaging and single–photon emission compound tomography (SPECT) reviled good target specificity and build-up of CSLNs/siCTGF conjugate in liver cells . Improving bioavailability was a challenging task for any nano pharmaceutical scientist, biased upon this changes Sumeet sood *et al*. (2013) prepared olanzapine loaded cationic solid lipid nano particles by micro emulsion technique using steric acid and glycerol monostearate as a lipid substance, soya lecithin, as co-surfactant , poloxamer 188 as astabiliser and stearyl amine as charge modifier[14]. For bio availability studies wistar rats were used .The cSLNs were administered by oral routs. It was observed Area under the curve was increased up to 4 fold and clearance was decreased when olanzapine cSLNs was administered as compared to normal olanzapine suspension. Result indicates cationic solid lipid nano particles of olanzapine could be a good alternative for improving drug bio availability.Ahmet Alper Ozturk *et al*. (2014) prepared paclitaxel loaded cationic solid lipid nano particles where prepared formulation was evaluated by colorimetric MTT studies , cell cytotoxicity and MDA studies[15] .MCF-7 cells were used in this studies . It was found that paclitaxel loaded cationic nano particles has good bio degradation property and have good cytotoxicity. Stability of SLNs was all ways been a great concern for scientists, on this direction Anna Fabregas *et al*. (2010) did extensive studies on thermal stability of a cationic solid lipid nano particles (cSLN),which is prepared by using stearic acid, octadecylamide & Poloxamer 188using micro emulsification method. The thermal accelerated temperature maintained at 4ºC, 25ºC, and 37ºC. It was observed that at 37ºC temperature the products were more stable irrespective to unknown behaviour after nucleic acid binding .The main advantages of this cSLN is good bio compatibility in physiological condition. As far as the brain drug delivery is concerned, cationic lipid nano particles enhance endocytosis and easily cross Blood Brain Barrier (BBB) .Yung-Chih Kuo *et al*. (2011) developed cationic solid lipid nano particle of carmustine which inhibits Human brain malignant glioblastoma when grafted with anti-epithelial growth factor[16]. He found the minimal average diameter of BCNU-CASLNs and maximal entrapment efficiency of BCNU emerged when the concentration of catanionic surfactants was 1 mm. An increase in the weight percentage of cacao butter (CB) reduced the zeta potential, enhanced the viability of human brain microvascular endothelial cells (HBMECs), and decreased the expression of tumour necrosis factor-a by HBMECs. The dissolution rate of BCNU and inhibition against the multiplication of U87MG cells using anti-EGFR/BCNU-CASLNs followed the order: 100% CB > 0% CB > 50% CB. Anti-EGFR/BCNU-CASLNs demonstrated the properties including an effective delivery to U87MG cells and ant proliferative efficacy against the growth of malignant brain tumours. It very difficult to circumvent within BBB to target cancerous cells, but recent surface modification and grafting of essential elements in outer surface of solid lipid nano particles not only increased cellular uptake but effects more target specific action .Recently Yung-Chih Kuo *et al.* (2014) prepared etoposide(ETP) loaded cationic solid lipid nano particles grafted with 5-hydroxytryptamine-moduline(ETP-CASLNs). Cationic micro emulsion technique was used to prepare ETP-CASLNs. The prepared formulation shows maximum entrapment efficacy enhance permeability of ETP across BBB[2]. This study gives us a new direction of using 5-HT moduline with ETP loaded cationic solid lipid nano particles as a promising drug delivery for brain tumour targeting. All though Cationic nano particles has long way to go, recently Joana F. Fangueiro *et al.* (2014) designed cationic lipid nano particles using multi emulsion technique for ocular delivery. Cetyltrimethylammonium bromide (CTAB) is used to prepare cationic surface modified lipid nano particles[4]. The lipid matrix of cationic nano particles obtained after factorial design .Varying concentration of 0.25%, 0.5%, 0.75%, or 1% wt of CTAB were used. Formulated nano particles were tested with physical, chemical parameters, lipid crystallization and polymorphism and stability .This prepared cationic nano particles then exposed to human retinoblastoma cell line Y-79.The optimised concentration of CTAB which shows encouraging results was found to be 0.5wt %.Recently Tsong-Long-Hwang *et al.* (2015) studied the impact on human neutrophil activation and formation of new type of neutrophil extracellular traps (NETs) by using cationic solid lipid nano particles .Human polymorph nuclear neutrophil is the potential target for prepared cationic solid lipid nano particles .Mainly in this study human polymorph nuclear neutrophil cell (PMNs) stimulation were examined by testing cytotoxicity ,pro-inflammatory mediator neutrophil extracellular traps (NETs) , mitogen–activated protein kinases(MAPKs), Ca^{+} influx, and oxidative stress and degradation .In conclusion it was concluded that cSLNs helps to govern human neutrophils .

CONCLUSION

The main objectives shall remain open to all nano scientist to develop more stable more precise and less cytotoxic cationic solid lipid nano particles, in recent advancement we have come across hormonal drug delivery to enzymatic

drug delivery by using cSLNs complexes. As far as Lipoplexes and gene delivery were concern, so many new research is needed in limited time frame. The general constrains of reticule endothelium systems phagocytic cell towards cSLNs is a big challenge to overcome .After all constrains, still very little marketed product emerges .We must be confident about cSLNs will prove its place and serve all typical BCS class drugs along with excellent bio availability, less toxicity, higher selectivity. Still long way to go.

Acknowledgement
We would like to acknowledge our colleagues cordial supports and enormous wishes for this article.

REFERENCES

[1] Erem Bilensoy. Cationic nanoparticles for cancer Therapy. PubMed. http://www.researchgate.net/publication/44577370**. 2010.**485983.
[2] Yung-Chih Kuo; Tsu-Yu Hong. International Journal of Pharmaceutics., 2014,Volume 465, Issues 1–2, 25,132–142.
[3] António J. Almeida a; Eliana Souto b. *Advanced Drug Delivery Reviews.*, **2007**,59, 478–490.
[4] Joana F. Fangueiro; Tatiana Andreania; Maria A. Egea; Maria L. Garcia;Selma B. Souto; Amélia M. Silva; Eliana B. Soutoa. *International Journal of Pharmaceutics*.,**2014**,461, 64– 73.
[5] Robert MacDonald. Cationic phospholipid derivatives. North-western University.
[6] Hu-Lieskovan S; Heidel JD;Bartlett DW.*Cancer Res.*,**2005**, 65(19), 8984-92.
[7] Schiffelers RM; Ansari A; Xu J.*Nucleic Acids Res.*,**2004**, 32(19):e149.
[8] Urban-Klein B; Werth S. *Gene Ther.*,**2005,** 12(5),461-6.
[9] Jean-Louis SALAGER.Surfactants Types and Uses.*Universidad de los andesFacultad de ingenieria escuela de ingenieria quimica.Firp booklet* # e300-a.,**2002**,Versión # 2.
[10] Wei Lu; Yan Zhang; Yu-Zhen Tan; Kai-Li Hu; Xin-Guo Jianga, Shou-Kuan Fu.*Journal of Controlled Release.*,**2005,** 107, 428– 448.
[11] Abhinav Agarwal; Saikat Majumder; Himanshu Agrawal; Subrata Majumdar; Govind P. Agrawal.*Current Nanoscience.*,**2011**,7,71-80.
[12] Maria Luisa Bondi; Antonina Azzolina; Emanuela Fabiola Craparo; Nadia Lampiasi; Giulia Capuano; Gaetano Giammona; Melchiorre Cervello.*Journal of Drug Targeting.*,**2007**,15(4),295–301.
[13] Won Ho Kong; Kitae Park; Min-Young Lee; Hwiwon Lee; Dong Kyung Sung; Sei Kwang Hahn.*Biomaterials.*,**2013**,34,542e551.
[14] Sumeet Sooda; Natarajan Jawahara; Kunal Jaina; Kuppusamy Gowthamarajana; Subramania Nainar Meyyanathanb.*Current Nanoscience.*,**2013,** 9, 26-34
[15] Ahmet Alper Ozturk; Behiye Senel; Evrim Yenilmez; Ebru Basaran; Gulay Buyukkoroglu.*J Nanomed Nanotechnol.*,**2014**, 5:5.
[16] Yung-Chih Kuo; Cheng Te Liang.*Biomaterials.*,**2011**,32, 3340-3350.