Peertechz

Chemistry Group

Peertechz Journal of Medicinal Chemistry and Research

DOI CC By

Naman Krishna Kasera*, Pramod Kumar Sharma and Rahul Gupta

Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Greater Noida, UP, India

Dates: Received: 15 December, 2016; **Accepted:** 29 December, 2016; **Published:** 30 December, 2016

***Corresponding author:** Naman Krishna Kasera, Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Plot No. 17A, Yamuna Expressway, Greater Noida, UP, India, Tel: +919451327322; E-mail: namankk@gmail.com

Keywords: Lipid polymer hybrid nanoparticles; Core shell structure; Tumor targeting; Liposomes; Supramolecular

https://www.peertechz.com

Research Article

Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles

Abstract

In recent years, robustness and surface engineering of dosage form made improvement in pharmacokinetics with decrease in dose of drug. Specificity with adherence of ligands has now become the reality as surface modification can easily deceive phagocytic system. Lipid molecules ensures the release of drug at lymphatic system, entrapment of polymeric nanoparticles in lipoidal core led to the avoidance of disadvantage of low entrapment efficiency if use of hydrophobic drug with hydrophobic polymer becomes essential. Various studies have been published and the best formulations with optimal *In vitro and In vivo* results are highlighted in this paper. In this review most advanced researches and accepted patents were discussed so to act as a medium for getting everything regarding lipid polymer hybrid particles under one umbrella.

Abbreviations

EPR: Enhanced Permeability and Retention; MPS: Mononuclear Phagocyte System; PLGA: Poly D,L-Lactic-Co-Glycolic Acid; PEG: Polyethylene Glycol; Nps: Nanoparticles; RES: Reticuloendothelial System; DOTAP: 1,2-Di-(9Z-Octadecenoyl)3-Trimethyl Ammonium Propane; DMAB: Dimethyldidoceylammonium Bromide; DPPC: 1,2-Dipalmitoyl-Sn-Glycero-3-Phosphocholine; DSPE: 1,2-Distearoyl-Sn-Glycero-3-Phosphoethanolamine-N-[Methoxy(Polyethylene Glycol)-2000; HSPC: Hydrogenated Soy Phosphatidylcholine; DNA: Deoxyribo Nucleic Acid; RNA: Ribonucleic Acid

Introduction

In the past century, there has been much research analysis towards achieving a better concept of cancer causing agent, diagnosis treatment and cure [1]. The main focus relies towards understanding the peculiar microenvironment of tumor which acts as one of the barrier of drug targeting often results into systemic toxicity as well as various undesirable side effects [2]. The unusual tumor vasculature and its unregulated growth comprises of heterogeneous blood flow and vascular resistance often leads to poor therapeutic response of drug administered with multiple drug resistance mechanism shown by the tumor cells [3,4]. During such conditions tumor vasculature can also be characterized by distorted vascular permeability, elevated interstitial pressure, extracellular acidosis and hypoxia [5]. From long time back all such factors were studied by pool of eminent scientists for tumor targeting of chemotherapeutic agents. One such targeting mechanism based upon tumor vasculature was called as enhanced permeability and retention (EPR) effect in which tumor vasculature shows enhanced permeability allowing large molecules and lipids to easily enter the extravascular space in tumors and finally retains there due to poor development in lymphatic drainage [6], [7,8]. The circulation of colloidal carriers in systemic circulation so that to reach its target site is also one of the deciding factor affecting tumor targeting as mononuclear phagocyte system (MPS) rapidly use to uptake colloidal particles via process of opsonization [9,10]. Surface engineering of colloidal carriers for increasing the circulation time of carriers was the development made to deceive reticuloendothelial system to avoid opsonization [11]. Thus, it can be inferred that the development of lipoidal colloidal carriers with stealth nature can be used as drug delivery approach for achieving better tumor targeting. This is done through PEGylation of the surface ensuring the "stealth" property. While various natural polymer such as dextans, pullalans, gangliosides have also been used for such stealth property [12,13]. In one research work, salidroside entrapped lipid polymer nanoparticles were formulated using PLGA-PEG-PLGA sequences of the polymer and lecithin and cholesterol as lipid and the evaluation result obtained for the formulated nanoparticles showed (65%) entrapment efficiency, 150nm size, and surface was negatively charged (-23mV). It could efficiently release salidroside from the nanoparticles and the drug act against the tumour cells. It

Citation: Kasera NK, Sharma PK, Gupta R (2016) Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles. Peertechz J Med Chem Res 2(1): 009-013.

selectively showed antitumour activity against PANC-1 and 4T1 cancer cell lines [14]. So, the main focus of this article was to illuminate the effectiveness of newly developed lipid polymer hybrid nanoparticles for its use in tumor targeting through recent research publications as well as various patents.

The concept of prod rug for its unrecognization for opsonization as well as cleavage mechanism at target site is the only approach which can be used for tumor targeting of chemotherapeutic agents [2]. The development of such delivery system requires the conjugation of chemotherapeutic agent with tumor recognition moiety to which suitable linkers are attached and having an outer layer of stealth polymer [15]. Hybrid lipid-polymer nanoparticles acting as one of the conjugate system can be used for tumor targeting [16]. The patented technique was published in 2008. The invention was related to the development of nanoparticulate colloidal delivery vehicle comprising a hydrophobic biodegradable polymer in blend with a hydrophobic lipid component which is either PEGylated phospholipid or simple phospholipid with attached targeting / recognizing compounds [17]. The development of lipid polymer hybrid nanoparticles was mainly related to mitigate the limitations associated with liposomes as well as nanoparticles [18]. Polymeric NPs which are suitable for systemic administration may be produced by self-assembly of biodegradable copolymers consisting of two or more polymer blocks with different hydrophobicities. NPs were mixed with liposomes to form lipid-polymer complexes such as lipoparticles where the lipid bilayer fuses on the surface of polymeric NPs. In one research, the authors had relied upon the use of two preparation techniques, one being, two-step process in which polymer core and lipid shell are produced individually and then mixed whereas the second method is a single step process by nanoprecipitation and self-assembly process [19].

In a study, it was found that macromolecules with molecular weight ranging from 15000 to 70000 g/mol could easily segregate at the solid tumour site with an ease. Although, the size of the nanoparticles is an important property for the accumulation at tumour site. This was further elaborated by comparing the smaller and larger sized particles wherein the smaller molecules accumulated at the target site much faster but larger molecules remain accumulated for a much longer period of time. Hence, size is an important parameter to be taken into consideration [20]. The size of the nanoparticles reported to be less than 200nm can efficiently had a longer circulation time because of low uptake by Reticuloendothelial system (RES). While the nanoparticles having size of 400nm were capable to reach the tumour extravasculature. The nanoparticles of 500nm were defined to be the maximum size to move across the cell membrane [21].

Several studies have been focusing on the lipid uptake and its metabolism. One study discussed about the methods eg. Adsorption, flip flop, acidification of micelles, uptake accompanied through hepatocytes etc [22].

In one research work, lipid polymer hybrid nanoparticles were produced by a pattern tunnable microvortex ensuring increase in production with proper efficiency in size. Solution of PLGA dissolved in acetonitrile from central outlet and lecithin and DSPE-PEG (lipid PEG) in 4% ethanol aqueous solution in outer outlet were passed through microfluidic channels and mixed rapidly. It was observed that by differing the flow rates, the size of the nanoparticles could be controlled and high productivity could be maintained [23]. In another work, author had demonstrated the in-situ polymerization of soyabean oil. In this, soyabean oil of different concentration was interacted with mineral medium comprising 1%w/vNH_4NO_3, 2.55%w/v NaH_2PO_4, 0.5%w/v $MgSO_4.7H_2O$, 0.1%w/v $CaCl_2$.H2O, 0.02 %w/v $MnSO_4$.H2O, 1%w/v Peptone and 0.5%w/v Glucose was incubated with agitation (200rpm) at 37°C for 240 hours. The self-assembled multilayered nanoparticles was characterized and was suitable for both hydrophilic and hydrophobic drugs because use of a mineral medium eased entrapment of hydrophilic and soyabean oil being the entrapment site for hydrophobic drugs. The size of the particles obtained was approximately 2 cm in diameter [24]. One such effort used double emulsion technique for the formulation of solid lipid nanoparticles (SLNs). It made use of Methocel as the polymer. These hybrid nanoparticles were used for the oral drug delivery of insulin because methocel lipid nanoparticles prevent the degradation of insulin which was done by chymotrypsin, an intestinal enzyme, at the gastrointestinal pH. These demonstrated with enhanced or doubled entrapment efficiency of the insulin. The methocel hybrid nanocarrier ensured overcome of other drawbacks of the oral drug delivery such as cytotoxicity [25]. The other work was to establish influence of the cationic lipid on the properties of Lipid polymer hybrid nanoparticles. The work includes the preparation of nanoparticles using PLGA (poly D,L-lactic-co-glycolic acid) core and 1,2-di-(9Z-octadecenoyl)3-trimethyl ammonium propane (DOTAP) as cationic lipid by emulsion solvent evaporation method using different concentration of lipid. It had better plasmid DNA binding capacity [26]. Another work was ensured bypassing of multidrug resistance in cancer cells. The nanoparticles was prepared using dimethyldidoceylammonium bromide (DMAB), modified poly lactic-co-glycolic acid (PLGA) surrounded by 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) shell and Doxorubicin as a P-glycoprotein substrate. The nanoparticles have increased accumulation in drug resistant cells with its size approximately 200nm and loading content was 0.71%+- 0.06% [27]. In other research, gelatin (Type a , cationic below its isoelectric point (7.0-9.0) as polymer , lecithin as lipid was cored with Amphotericin B by two step desolvation method for the improved oral bioavailability. The particle was of size range 253+- 8nm and 50.61+- 2.20% entrapment efficiency and 0.274 +- 0.008 polydispersity index was obtained [28]. The research was done for the dual targeting of the nanoparticles. It was prepared to target solid gastric tumour having Her2 and CD44 wit loaded SN38. The nanoparticles was prepared using biodegradable polymer PLGA and lipid shell of AHNP peptide and n-hexadecylamine (HAD) to the carboxyl group of Hyaluronic acid (HA). The particle was of size range 353.6- 532.9 nm and specifically blocking CD44 and Her2 [29].

In a work by researchers, the core shell lipid polymer hybrid nanoparticles was prepared and loaded with Erlotinib. It was

Citation: Kasera NK, Sharma PK, Gupta R (2016) Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles. Peertechz J Med Chem Res 2(1): 009-013.

prepared by single step sonication method using polycaprolactone (PCL) as polymeric core and phospholipid shell composed of 1,2-distearoyl-sn- glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000 (DSPE-PEG2000) and hydrogenated soy phosphatidylcholine (HSPC). It was characterized with mean size of 170nm and 66% entrapment efficiency [30]. Further, the work moved towards the use of natural polymer, Chitosan was used for oral drug delivery of insulin using hybrid nanoparticles. The lipid nanoparticles (LNPs) were of size 265.3+-34 nm to 387.4+- 35.6 nm and 85% entrapment efficiency [31]. In a recent contribution towards the advancement of hybrid nanoparticles, the core shell nanoparticles were achieved for the delivery of small interfering RNA. The hybrid nanoparticles was prepared by using PLGA as inner polymer layer, PEG as outer layer, while in between these two layer a lecithin layer was present. The hollow core entrapped and reported targeted gene delivery of the small interfering RNA [32].

Patents associated with lipid polymer hybrid nanoparticles

1. **Hybrid lipid polymer nanoparticulate delivery composition:** The innovators provides with a biocompatible, stable polymer lipid hybrid nanoparticle. The formulation had no such characteristic of phase separation, drug leaking and precipitation. It was also observed that combination of biodegradable polymer with solid lipids have showed good drug loading, stability and possibility of regulating release patterns and degradation parameters. Hybrid polymer-lipid nanoparticles (HPLNP) comprised a biodegradable polymer, e.g., polycaprolactone (PCL), polylactic-polyglycolic copolymer (PLGA) and a solid lipid, e.g., tripalmitin, glycerin stearate, tristearin, cholesterol, tocopherol palmitate, tocopheryl succinate, stearyl stearate, tribehenin, cetostearyl alcohol, benzoyl behenate, stearic acid, camauba or cande lilla wax, cocoa butter, SuppocireTM CM/DM, WecobeeTM M and other lipids, having a melting point past 20° C i.e., solid at room temperature. In one such formulation, PLGA , as polymer, Tristerin , as lipid, ethylacetate , as solvent was used and obtained nanoparticles of 185 nm with 95% yield while in other cases they used PCL , Cholesterol , and ethylacetate and resulted into 100% yield with size of 101nm [33].

2. **Adjuvant incorporation of immunotherapeutics:** This invention ensures composition and system for delivery of nanoparticle towards the stimulation of cells of immune system as the nanoparticles was used to entrap various immunostimulatory moieties. The patent ensures designing, manufacturing, pharmaceutical compositions [34].

3. **Lipid polymer hybrid particles:** The patent by inventor includes an aqueous core enclosed by an amphiphilic layer which is further surrounded by a polymeric matrix. The inner core entrap hydrophilic drug eg. Nucleic acids proteins, peptides. The polymer layer is also used to entrap hydrophobic drugs and could be surrounded by conjugated lipoidal molecules. The major step is of formulating both polymer and lipid based nanoparticles with a size range of less than 400 micrometers. An example of formulation is an aqueous core optionally containing a nucleic acid (e.g., siRNA) is surrounded by an inner lipid (e.g., EPCl4: 1) layer. The hydrophobic portions of the inner lipids interact with a polymeric shell (e. g., PLGA), which encapsulates a drug (e.g., docetaxel). The polymeric shell is surrounded by an outer lipid layer that includes one or more lipids (e.g., lecithin) and a PEGylated lipid [35].

4. **Porous nanoparticle supported lipid bilayer nanostructures:** Another patent, provides the description and formulation of the protocells. These are nanostructures which contains porous particle core and enclosed by a lipid bilayer. It was capable to entrapping more than one component, further, unloading of those components at the particular target site. These were found to capable to deliver peptides, antibodies. The polymer allowed better stability of the protocells. The protocells including porous nanoparticles had 110nm in atleast one dimension [36].

5. **Nanoparticles with lipid core and polymer shell structures for protein drug delivery prepared by nanoencapsulation:** The invention relates to the stabilized nanoparticles involving lecithin playing role as a component of core structure and enclosed covering by poloxamer. It referred to the freeze dried nanoparticles with lecithin, aqueous drug solution and polaxamer in the presence of a cryoprotectant. These were also added with some additives for the stabilization such as emulsifier. Both the lecithin and the polaxamer with the protein drug were prepared individually. The polaxamer or a block copolymer is a poly(oxyethylene)-poly(oxypropylene)-poly(oxyethylene) triblock copolymer, which is usually called poloxamer [37].

6. **Carbohydrate based lipid compositions and supramolecular structures comprising same:** In this patent, it refer to the exceptional class of the nanoparticles wherein the glycerol substrate is replaced with carbohydrate. Zwitter ion, cationic, anionic carbohydrate based phospholipid was synthesized and evaluated. The hybrid lipid nanoparticles were generated with different ingredient of carbohydrate based phospholipid such as dimyristyl phosphocholine (DPMC), nucleic acid etc leading to the supramolecular structures. It was also replaced by polyether, polyester, polyamine, polyacrylic acid, polysaccharide [38].

7. **Targeted and triggered Chitosan lipid core shell nanoparticles for combination chemotherapy:** The patent is aimed to ensure chitosan lipid polymer hybrid nanoparticles for the action of two or more anticancer drugs. It was such designed to evoke drug release at the target site under the influence of enzyme with a size of less than 200nm. It was also interacted with transferrin

Citation: Kasera NK, Sharma PK, Gupta R (2016) Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles. Peertechz J Med Chem Res 2(1): 009-013.

peptide to counter the transferrin receptors on cancerous cells. These ultimately under fire the cancer cells with two or more cancer treating drugs [39].

8. **Supramolecular structure biodegradable polymeric assembly for drug delivery:** This invention introduces a novel drug carrier into a living body consisting of a highly water-soluble polymer that can carry and release a drug at a desired rate. It is a supramolecular-structured biodegradable polymeric assembly that can release the drug as a purpose of the specific actions of biodegradation of a diseased body. Characterized in that the linear polymeric chain compound threading through the structural cavity of the cyclic compounds is poly (ethylene glycol), poly (propylene glycol), polyisobutylene or a block copolymer. A supramolecular-structured biodegradable polymeric assembly characterized in that the drug to be combined with cyclodextrins is a peptide drug [40].

9. **Core shell nanoparticles including nucleic acid hydrogel and method of producing the same:** This invention embodies a functional complex particle prepared by filling a nucleic acid hydrogel inside a liposome and a method of producing the core shell nanoparticles. The invention may have an effect of increasing an expression of protein factors included in the particle by incorporating an X-shaped nucleic acid monomer in the nucleic acid hydrogel. Accordingly, when the core-shell particle is prepared using the method according to an embodiment of the invention, an effect of facilitating an introduction of a genome into the nucleic acid hydrogel may be obtained, and thereby the core-shell particle may be used as a protein production platform copying a cell nucleus, wherein the lipid includes one or more selected from the group consisting of 1,2-dihexadecanoyl-sn-glycero-3-phosphoethanolamine, triethylammonium salt (Texas Red DHPE), cholesterol, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC), 1-palmitoyl-2-oleoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (POPG), and mixtures thereof [41].

Conclusion

Lipid polymer hybrid nanoparticles constituting lipids is carried in the blood plasma in the form of chylomicrons or micelles. Although, lymphatic system is the route of the lipid metabolism. From the various studies, it can be extracted that insertion of cholesterol into the formulation, increases the half- life of the lipid and decreasing the lipid clearance and these could further result into the extension of the drug release. Lipid polymer hybrid nanoparticles on further advancement can also be used for the therapy of other diseases apart from the cancer therapy such as diabetes. It can also be used in the delivery of immunostimulatory agents, genes, hormones etc. These nanoparticles can be administered by intravenous route as well as by oral administration by preventing it from enzymal degradation representing its stealth property.

References

1. Hoffman AS (2008) The origins and evolution of "controlled" drug delivery systems. J Control Release 132: 153–163. Link: https://goo.gl/HM2PgF
2. Choi SW, Kim JH (2007) Design of surface-modified poly(d,l-lactide-co-glycolide) nanoparticles for targeted drug delivery to bone. J Control Release 122: 24–30. Link: https://goo.gl/wLURyy
3. Maeda H, Fang J, Inutsuka T, Kitamoto Y (2003) Vascular permeability enhancement in solid tumor: various factors, mechanisms involved and its implications. Int Immunopharmacol. 3: 319–328. Link: https://goo.gl/1CVhOo
4. Gillies RJ, Schornack PA, Secomb TW, Raghunand N (1999) Causes and effects of heterogeneous perfusion in tumors. Neoplasia. 1: 197–207. Link: https://goo.gl/ZdGc2u
5. Siemann DW (2011) The Unique Characteristics of Tumor Vasculature and Preclinical Evidence for its Selective Disruption by Tumor-Vascular Disrupting Agents. Cancer Treat Rev 3: 63–74. Link: https://goo.gl/2fs63c
6. Dabbas S, Kaushik RR, Dandamudi S, Kuesters GM, Campbell RB (2008) Importance of the liposomal cationic lipid content and type in tumor vascular targeting: physicochemical characterization and in vitro studies using human primary and transformed endothelial cells. Endothelium 15: 189–201. Link: https://goo.gl/IMcTVH
7. Owens DE, Peppas NA (2006) Opsonization, biodistribution, and pharmacokinetics of polymeric nanoparticles. Int J Pharm 30: 93–102. Link: https://goo.gl/zbiV7W
8. Nag OK, Awasthi V. (2013) Surface Engineering of Liposomes for Stealth Behavior. Pharmaceutics 5: 542–569. Link: https://goo.gl/CJmthL
9. Jung SW, Jeong Y, Kim Y-H, Kim S-H (2004) Self-assembled polymeric nanoparticles of poly(ethylene glycol) grafted pullulan acetate as a novel drug carrier. Archives of Pharmacal Research 27: 562–569. Link: https://goo.gl/zv9GA5
10. Alexis F, Pridgen E, Molnar LK, Farokhzad OC (2008) Factors Affecting the Clearance and Biodistribution of Polymeric Nanoparticles. Mol Pharm 5: 505–515. Link: https://goo.gl/ITxGG4
11. Kakde D, Jain D, Shrivastava V, Kakde R, Patil AT (2011). Cancer therapeutics-opportunities, challenges and advances in drug delivery. Journal of Applied Pharmaceutical Science 1: 1–10. Link: https://goo.gl/RndQul
12. Ameller T, Marsaud V, Legrand P, Gref R, Barratt G, et al. (2003) Polyester-poly(ethylene glycol) nanoparticles loaded with the pure antiestrogen RU 58668: physicochemical and opsonization properties. Pharm Res 20: 1063–1070. Link: https://goo.gl/RLSHkj
13. Zhang N, Wardwell PR, Bader RA (2013) Polysaccharide-Based Micelles for Drug Delivery. Pharmaceutics 5: 329–352. Link: https://goo.gl/Z95KGO
14. Madhusudhan A, Reddy GB, Venkatesham M, Veerabhadram G, Kumar DA, et.al. (2014) Efficient pH dependent drug delivery to target cancer cells by gold nanoparticles capped with carboxymethyl chitosan. Int J Mol Sci 15: 8216–8234. Link: https://goo.gl/uLqC2r
15. Jaracz S, Chen J, Kuznetsova L V., Ojima I (2005) Recent advances in tumor-targeting anticancer drug conjugates. Bioorg Med Chem 13: 5043–5054. Link: https://goo.gl/ElXdw9
16. Yi Y, Li Y, Wu H, Jia M, Yang X, et al. (2014) Single-step assembly of polymer-lipid hybrid nanoparticles for mitomycin C delivery. Nanoscale Res Lett 9: 560. Link: https://goo.gl/eQePtW
17. Shi J, Xiao Z, Vilos C, Votruba A, Langer RS, et al. (2013) Lipid-polymer hybrid particles. Link: https://goo.gl/bSZXhZ

Citation: Kasera NK, Sharma PK, Gupta R (2016) Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles. Peertechz J Med Chem Res 2(1): 009-013.

18. Zhang L, Zhang L (2010) Lipid–Polymer Hybrid Nanoparticles: Synthesis, Characterization and Applications. Nano Life 01: 163–173. Link: https://goo.gl/EjjPo9

19. Mandal B, Bhattacharjee H, Mittal N, Sah H, Balabathula P, et al. (2013) Core-shell-type lipid-polymer hybrid nanoparticles as a drug delivery platform. Nanomedicine 9: 474–491. Link: https://goo.gl/OpqvXu

20. Matsumura Y, Maeda H (1986) A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs .Cancer Res 46: 6387–6392. Link: https://goo.gl/sf5U5N

21. Bae YH, Park K (2011) Targeted drug delivery to tumors: Myths, reality and possibility. J Control Release 153: 198–205. Link: https://goo.gl/VjnyHr

22. Bernlohr DA, Jenkins AE, Bennaars AA (2002) Adipose tissue and lipid metabolism. Biochem lipids, lipoprotein. 4th ed, Vence JE, Vence D, Elsevier Sci Amsterdam 263–289. Link: https://goo.gl/6PUmhh

23. Kim Y, Lee Chung B, Ma M, Mulder WJ, Fayad ZA, et al. (2012) Mass production and size control of lipid-polymer hybrid nanoparticles through Controlled Microvortices. Nano Lett. 12: 3587–3591. Link: https://goo.gl/h6R3FA

24. Kavitha V, Gnanamani A (2013) A multilayered supramolecular self-assembled structure from soybean oil by in situ polymerization and its applications. Indian J Exp Biol. 51: 400–405. Link: https://goo.gl/qizssq

25. Boushra M, Tous S, Fetih G, Xue H-Y, Tran NT, et al. (2016) Methocel-Lipid Hybrid Nanocarrier for Efficient Oral Insulin Delivery. J Pharm Sci. 105: 1733–1740. Link: https://goo.gl/JnEPnU

26. Bose J, Arai Y, Chan Ahn J, Park H, Lee SH (2015) Influence of cationic lipid concentration on properties of lipid–polymer hybrid nanospheres for gene delivery. Int J Nanomedicine. 10: 5367–5382. Link: https://goo.gl/UYCFqd

27. Li B, Xu H, Li Z, Yao M, Xie M, et al. (2012) Bypassing multidrug resistance in human breast cancer cells with lipid/polymer particle assemblies. Int J Nanomedicine. 7: 187–197. Link: https://goo.gl/rBqRvQ

28. Jain S, Valvi PU, Swarnakar NK, Thanki K (2012) Gelatin coated hybrid lipid nanoparticles for oral delivery of amphotericin B. Mol Pharm 9: 2542–2553. Link: https://goo.gl/H0701a

29. Yang Z, Luo H, Cao Z, Chen Y, Gao J, et al. (2016) Dual-targeting hybrid nanoparticles for the delivery of SN38 to Her2 and CD44 overexpressed human gastric cancer. Nanoscale 8: 11543-11558. Link: https://goo.gl/ui77m7

30. Mandal B, Mittal NK, Balabathula P, Thoma LA, Wood GC, (2016) Development and in vitro evaluation of core-shell type lipid-polymer hybrid nanoparticles for the delivery of erlotinib in non-small cell lung cancer. Eur J Pharm Sci. 81: 162–171. Link: https://goo.gl/QyJDtb

31. Shi J, Xiao Z, Votruba AR, Vilos C, Farokhzad OC, (2011) Differentially charged hollow core/shell lipid-polymer-lipid hybrid nanoparticles for small interfering RNA delivery. Angew Chem Int Ed Engl 50: 7027–7031. Link: https://goo.gl/rJf5B3

32. Mukhopadhyay P, Mishra R, Rana D, Kundu PP (2012) Strategies for effective oral insulin delivery with modified chitosan nanoparticles: A review. Progress in Polymer Science 3: 1457–1475. Link: https://goo.gl/YIlmjc

33. Gao HY, Schwarz J, Weisspapir M (2008) Hybrid Lipid Polymer Nanoparticulate delivery composition. Link: https://goo.gl/9uHyvs

34. Alexis F, Iannacone M, Shi J, Basto P, Moseman EA, et al. (2014) Adjuvant Incorporation in Immunonanotherapeutics. Link: https://goo.gl/ulRrUC

35. Shi J, Xiao Z, Vilos C, Votruba A, Langer RS, et al. (2013) Lipid Polymer Hybrid Paricles. Link:

36. Liu J, Brinker JC, Ashley (2011) Porous Nanoparticle supported Lipid Bilayer Nanostructures. Link: https://goo.gl/OXdE0h

37. Yuk SH, Oh KS (2009) Nanoparticles with Lipid core and polymer shell structure for protein drug delivery prepared by nanoencapsulation. Link: https://goo.gl/RTRkZk

38. Grinstaff MW, Hird GS (2004) Carbohydrate based Lipid composition and supramolecular structure comprising same Link: https://goo.gl/r9qGqj

39. Banerjee R, Ketan T, Joshi N (2013) Targeted and Triggered Chitosan lipid core shell nanoparticles for combination chemotherapy.

40. Yui N (1996) Supramolecular-structured biodegradable polymeric assembly for drug delivery. Link: https://goo.gl/jULQ2L

41. **Um SH, Shin SW (2015**) Core Shell nanoparticles including nucleic acid hydrogel and method of producing the same. Link: https://goo.gl/BaaesJ

Citation: Kasera NK, Sharma PK, Gupta R (2016) Recent Advancement and Patents of the Lipid Polymer Hybrid Nanoparticles. Peertechz J Med Chem Res 2(1): 009-013.