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Design and Development of Lipid Polymer Hybrid Nanoparticles for Combinatorial Drug Delivery

Mrs Disha Chouhan[1*], Dr Rajesh Mujariya[2]

[1]Research Scholar & Associate Professor, [2]Professor & Director
Institute of Pharmaceutical Science & Research
Sardar Patel University Balaghat (M.P.), India
Corresponding Author:-Mrs Disha Chouhan[1*]
Email - dishapatleqa@gmail.com

Abstract:
In Cancer Therapy there are many problems like multi drugs therapy, short circulation half-life and nonspecific systemic distribution. Important Process to deal with these concerns is to style a drug delivery vehicle that has versatile functionality, good serum stability, circulates within the body long enough to succeed in the targeting tissues and is biocompatible. These features are overcome by formulating the lipid-polymer hybrid nanoparticles. The surface characteristics of these nanoparticles such as charge, lipid density and targeting ligand can be modified to allow for specific cellular uptake, controlled vincristine sulfate and a lomustine releases kinetics, and enhanced pharmacokinetics. Present study show that the hybrid nanoparticles could easily be formulated with negatively and positively charged lipids in order to change the overall surface charge. The particle size remained in the distribution was narrow and desirable range. The present Formulation has the capacity to co-encapsulate vincristine sulfate and a lomustine. To investigate, vincristine sulfate and a lomustine were dually loaded within the hybrid nanoparticle system. This combination formulation was characterized by dynamic light scattering for zeta potential, particle size and poly-dispersity index, in-vitro vincristine sulfate and a lomustine release and cytotoxicity. The release studies showed that addition of the vincristine sulfate and a lomustine within the lipid-polymer hybrid nanoparticle system didn't affect the vincristine sulfate and a lomustine release profiles of the each vincristine sulfate and a lomustine.

Index Terms **-** lipid-polymer hybrid Nanoparticles, vincristine sulfate, lomustine, dynamic light scattering, zeta potential, particle size and poly-dispersity index.

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I. INTRODUCTION

In recent years, the application of nanotechnology has been translated to medicine. Nanotechnology encompasses the design, synthesis, and characterization of materials and or devices, which are functionally organized in at least one dimension on the nano-scale (Ahirwar CS, 2017). The use of these nanoscale or nanostructured materials in medicine, termed as Nanomedicine, has unique medical properties and effects owing to the small size (1 –1000 nm) and structure. The ability to engineer and control materials in this size rage results in new medical efforts, innovative chemistry techniques, and novel manufacturing approaches (Ahirwar CS, 2017)

In the recent years, the potential of LPHNPs for gene delivery has been widely investigated by the researchers. Due to the same features of LPHNPs for drug delivery (high stability, extended circulation time, high biocompatibility and ability to get escaped from immune recognition), it has also been employed for gene delivery. (Badwaik HR, 2019). Different methods have been employed for the fabrication of hybrid nano-carriers depending upon their chemical composition and applications. The lipid-polymer hybrid, polymer inorganic hybrid, metal (gold, silver or iron) polymer, silica (SiO2) based hybrid nano-systems and hybrid polymeric nano-carriers have been most widely investigated. Most of these hybrid carriers utilized two distinctive fabrication approaches. First, a two-step conventional approach process, in which the inner core and outer shell are prepared separately and then are co incubated for the formation of hybrid nanoparticle. The second approach is the single step, in which various state-of-the art techniques of the self-assembling are being incorporated. These processes are further modified with different chemical moieties to obtain versatile hybrid nanoparticles meeting specific need of therapy. (Asadullah M, 2017)

In Cancer Therapy there are many problems like multi drugs therapy, short circulation half-life and nonspecific systemic distribution. Important Process to deal with these concerns is to style a drug delivery vehicle that has versatile functionality, good serum stability, circulates within the body long enough to succeed in the targeting tissues and is biocompatible. These features are overcome by formulating the lipid-polymer hybrid nanoparticles. The surface characteristics of these nanoparticles such as charge, lipid density and targeting ligand can be modified to allow for specific cellular uptake, controlled vincristine sulfate and a lomustine releases kinetics, and enhanced pharmacokinetics.

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The current treatment of cancer falls short because of various problems associated with drug distribution leading to cytotoxicity of healthy cells, poor circulation half-life, instability in the blood-stream causing decreases in efficacy, insufficient drug concentrations at the specified sites, and multi drug resistance.

1. Drug & Excipients :-

Lomustine Sulphate, Vincristine obtained gift Sample from Concept Pharmaceuticals, Aurangabad, Ester-terminated poly(DL-lactic-co-glycolic acid) (PLGA), 1,2- Distearoyl-sn-glycero-3-phosphoethanolamine-N-carboxy(poly(ethylene glycol)) 2000 (DSPE-PEG-COOH), L-α-phosphatidylcholine (Egg Chicken, EGG PC) and 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) also obtained from Concept Pharmaceuticals, Aurangabad

2. Method :-

3.1 Hybrid Nanoparticle Synthesis

Hybrid nanoparticles were prepared using the sonication method. The surface zeta potential of these nanoparticles was done on the nature of the lipids. The stock solutions of all the materials prepared as shown in Table 1 and kept under 4^0C for the synthesis. These stock solutions used only for the period of 21 days and there after the solutions were replaced by freshly prepared solutions. In a hybrid nanoparticle synthesis, 25 µg of EGG- PC and 250 µg of DSPE-PEG dissolved in 275 µL of 4 % Ethyl Alcohol were diluted to three mL with water. In Formulation, 1 mg of PLGA dissolved in 400 µL of acetonitrile (ACN) was added with sonication. The calculated amount of deionized water was added to adjust the final volume to 4 mL and the volume ratio of aqueous to organic solution was 8:2. The mixture was sonicated during a capped glass vial for five min employing a Fisher Scientific bath sonicator at a frequency of 42 kHz at 100 W powers. The solutions washed 3 times with deionized water using a Millipore centrifuge filter with a molecular weight cutoff of 10 kDa. The samples were concentrated upto 1 mg of PLGA polymer with 1 mL of particle solution. Remaining formulations were prepared as per shown in Table 1 by changing the lipid accordingly to obtain hybrid nanoparticles with various surface zeta-potential. Control lipid vesicle solutions were prepared for the surface charge of lipid. 200 µg of lipid was added to 800 µL of water and was vortexed.

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Table 1. Hybrid nanoparticle formulation compositions.

Formulation	Amount lipid (1 mg/mL)	Amount DSPE- PEG-COOH (1 mg/mL)	Amount PLGA (2.5 mg/mL)	Amount Water
1	0 µL	350 µL	300 µL	3350 µL
2	25 µL	350 µL	300 µL	3325 µL
3	50 µL	350 µL	300 µL	3300 µL
4	100 µL	350 µL	300 µL	3250 µL

Hybrid Nanoparticle Synthesis

Hybrid nanoparticles were prepared using the **Sonication Method**

↓

25 µg of EGG- PC and 350 µg of DSPE-PEG dissolved in 275 µL of 4 % EtOH were diluted to 3.3 mL with water.

↓

To this solution, 1 mg of PLGA dissolved in 300 µL of acetonitrile (ACN) was added under sonication.

↓

The calculated amount of deionized water was added to adjust the final volume to 4 mL and the volume ratio of aqueous to organic solution was 9:1.

↓

The mixture was sonicated in a capped glass vial for 5 min using a Fisher Scientific (FS30D) bath sonicator at a frequency of 42 kHz and power of 100 W.

↓

The solutions were washed 3 times with deionized water using a Millipore (Amicon Ultra) centrifuge filter with a molecular weight cutoff of 10 kDa.

↓

The samples were concentrated down to 1 mg of PLGA polymer to 1 mL of particle solution.

↓

All other formulations were prepared similarly as shown in Table 1 by changing the lipid accordingly to obtain hybrid nanoparticles with various surface zeta-potential.

↓

Control lipid vesicle solutions were prepared to confirm the surface charge of each lipid. Briefly, 100 µg of lipid was added to 900 µL of water and was vortexed.

Fig 1:- Hybrid Nanoparticle Synthesis

Table 2: Formulation for Hybrid Nanoparticle Synthesis

Formulation	Amount lipid (1 mg/mL)	Amount DSPE-PEG-COOH (1 mg/mL)	Amount PLGA (2.5 mg/mL)	Amount Water
1	0 µL	350 µL	300 µL	3350 µL
2	25 µL	350 µL	300 µL	3300 µL
3	50 µL	350 µL	300 µL	3250 µL
4	100 µL	350 µL	300 µL	3150 µL

Lipid-Polymer Hybrid Nanoparticle Synthesis

In a typical preparation, **200 µg of a platinum-lipid (Pt-lipid)** solution in **tetrahydrofuran** (THF) was placed in a glass vial and the THF was evaporated using nitrogen gas.

↓

After the solvent has been dried off, **260 µL of a 1 mg/mL DSPE-PEG solution in 4% ethanol was added** to the vial and the volume was adjusted to 2 mL with 4% ethanol.

↓

The sample was mixed while **stirring at 80^0C**.

↓

In a separate glass vial, **100 µg of Vincristine Sulphate & Lomustine in 100 uL of THF and 1 mg of PLGA in ACN** was mixed and diluted to 1 mL with ACN.

↓

For the nanoprecipitation process, this **1 mg/mL polymer solution with 100 µg Vincristine Sulphate & Lomustine** was added **dropwise to the Pt-lipid**, DSPE-PEG sample on the heat plate.

↓

After that, 1 mL of water was added dropwise to the sample. The sample was then removed from the heat and placed on a stir plate at room temperature to **stir for two hours** in order to evaporate any leftover organic solvent.

↓

The **solutions were washed 3 times** with deionized water using a Millipore (Amicon Ultra) centrifuge filter with a molecular weight cutoff of 10 kDa.

↓

The samples were concentrated down to **1 mg of PLGA polymer to 1 mL of particle solution**.

↓

Control samples were also prepared according to the procedure using **EGG PC instead of Pt-lipid.**

Fig 2 :- Lipid-Polymer Hybrid Nanoparticle Synthesis

2.2 Lipid-Polymer Hybrid Nanoparticle Synthesis

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In a formulation, 200 µg of a platinum-lipid solution in tetrahydrofuran (THF) was placed in a glass vial and the THF was evaporated using nitrogen gas. After the solvent has been dried off, 5% ethanol and 260 µL of a 1 mg/mL DSPE-PEG solution was added to the vial and the volume was adjusted to 2 mL with 5% ethanol. The sample was mixed while stirring at 80^0C. In a glass vial, 100 µg of Vincristine Sulfate and a lomustine in 100 uL of tetrahydrofuran and 1 mg of PLGA in acetonitrile was mixed and diluted to 1 mL with acetonitrile. For the nano-precipitation process, this 1 mg/mL polymer solution with 100 µg vincristine sulfates and a lomustine was added drop wise to the Pt-lipid, DSPE-PEG sample on the heat plate. 1 mL of water was added drop wise to the sample. The sample was removed from the heat and placed on a stir plate at room temperature to stir for Two hours in order to evaporate any left organic solvent. The solutions were washed three times with deionized water using a Millipore centrifuge filter with a molecular weight cutoff of 10 kDa. The samples were concentrated upto 1 mg of PLGA polymer to One mL of particle solution. In the present formulation, various lipids depending on their cationic, anionic, and neutral charge have been employed in order to synthesize nanoparticles that show promise as vincristine sulfate and lomustine delivery vehicles. As shown in Figures 2.1, 2.2, and 2.3, the hydrodynamic size of these hybrid nanoparticles exhibit an average size of ~100 nm. All the nanoparticles prepared are uniform and uni-model in size distribution with a narrow polydispersity index. The formation of uniform nanoparticles was further characterized using electron microscopy. Surface and internal structures suggested the formation of well-defined spherical nanoparticles. The SEM image (Figure 2.4) shows that the hybrid nanoparticles posses spherical morphology. The shape of the particle will play a key role in pharmacokinetics, vincristine sulfate and a lomustine release, and cell uptake. It also confirms that there is a narrow particle size distribution within the formulation with particles having ~100 nm size. TEM micrographs confirm the formation of lipid coated polymeric nanoparticles. The TEM micrograph (Figure 2.5) showed the spherical units that were sealed with thin lipid monolayer. The negative staining clearly indicates the higher contrast on the circumference of the nanospheres that confirms the presence of lipid monolayer. It is evident from TEM image that during the nanoprecipitation process the hydrophobic PLGA polymer amassed to contribute the core of the nanoparticles whereas lipid are assembled onto the surface of the nanoparticles. In Figure 2.7, the surface potential of the hybrid nanoparticles are shielded with cationic lipid i.e., shows the decrease in negative zeta-potential whereas that of the anionic lipid EGG PA (Figure 2.8) shows an increase in negative zeta-potential. Although the overall charge of hybrid nanoparticles was negative due to the presence of –COOH group in DSPE-PEG-COOH, the tuning the amount of the second lipid component tunes the overall charge. As shown in Figure 2.9, EGG PC, which is a neutral lipid didn’t contribute significantly to tune the surface zeta-

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potential due to DSPE-PEG-COOH. This further confirms the capacity to modify the zeta-potential by changing the nature and the concentration of the lipids.

Pt-lipid was characterized by ^{195}Pt-NMR to determine chemical identity. Thin layer chromatography (TLC) was used to purify the product and electro-spray ionization mass spectrometry (ESI-MS) used to confirm the molecular weight of the product. Particle size, polydispersity index (PDI), and zeta potential were measured to characterize the effect of dual vincristine sulfate and a lomustine encapsulation of drug and Pt-lipid on lipid-polymer hybrid nanoparticle. Scanning electron microscopy (SEM) was employed to determine particle morphology and surface structure.

4. Evaluation :-

4.1 Pt-lipid

195Pt-NMR

195Pt NMR spectra recorded in deuterated chloroform ($CDCl_3$). For ^{195}Pt NMR measurement, the shift in Pt-lipid resonance was measured with respect to the standard saturated solution of potassium tetrachloro palatinate (II) in 0.05 M HCl containing 10% of D_2O. Samples were measured at the spectral width of 21615.8 Hz with spectral frequency of 107.22 MHz within a 200 ppm offset. ^{195}Pt NMR δ ppm; -1578.0 (standard), -1377.2 (product).

4.2 TLC (Rf)

The product was purified by column chromatography (5% methanol in chloroform) and by thin layer chromatography (3 % methanol in chloroform) with the product Rf= 0.44.

4.3ESI-MS

Electrospray ionization mass spectrometry was used to determine the mass of the compound. ESI-MS (negative): m/z: 861.08 $[M-H]^-$, 896.94 $[M+Cl]^-$, 825.33 $[M-HCl-H]^-$.

4.4 Lipid-Polymer Hybrid Nanoparticles

4.4.1 Particle Size and Polydispersity Index (PDI)

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Particle size measurements were performed by using dynamic light scattering (DLS) technique. Three sub runs were carried out per measurement and the average values were taken.

4.4.2 Zeta Potential

Zeta potential measurements were the electrophoretic mobility on the surface of the nanostructures was measured. The measurements were carried out at room temperature with the backscatter angle of 173^0. Three sub runs carried out per measurement, and average values were taken.

4.4.3 Microscopic Analysis by SEM

Samples for SEM were prepared by dropping 5 mL of a nanoparticle solution onto a polished silicon wafer. Drying the droplet at room temperature overnight, the sample was coated with chromium and then imaged.

4.4.4 Vincristine sulfate and a lomustine Loading

The initial amounts of both vincristine sulfate and a lomustine contained within the lipid-polymer hybrid nanoparticles were assessed in order to determine encapsulation efficiency and a starting point for in vitro release studies. The initial vincristine sulfate and lomustine content was analyzed by UV-Vis spectroscopy while the initial Pt-lipid content was measured by inductively coupled plasma analysis.

4.4.5 UV-Vis Spectroscopy

Lipid-polymer hybrid nanoparticle samples containing Vincristine sulfate and a lomustine were lyophilized and the remaining solids were dissolved in tetrahydrofuran (THF). Samples were analyzed with the UV-Vis spectrophotometer using an absorbance wavelength of 310 nm.

4.4.6 Inductively Coupled Plasma Optical Emission Spectroscopy (ICP- OES)

Samples with Pt-lipid were measured using the ICP-OES technique. Ytrium was used as an internal standard.

4.4.7 Reversed-Phase High-Performance Liquid Chromatography (RP- HPLC)

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Vincristine sulfate and a lomustine loading for the samples used for the cytotoxicity study was determined using a C18 column with an Agilent Series 1100 system. The mobile phase was 65:35 (v/v) acetonitrile:water and the column temperature was set to 40^0C.

4.4.8 In Vitro Vincristine sulfate and a lomustine Release

To measure the release profile of vincristine sulfate and a lomustine from the lipid-polymer hybrid nanoparticles, the dialysis technique was used (10 kDa molecular weight cut off). Samples were dialyzed against 2L of pH 7.4 phosphate buffered saline (PBS) at 37^0C. At each time point, samples from three mini dialysis units were collected separately for vincristine sulfate and a lomustine quantitation by UV-Vis spectroscopy.

To measure the release profile of Pt-lipid from the lipid-polymer hybrid nanoparticles, the dialysis technique was used (12-14 kDa molecular weight cut off). Each formulation was dialyzed against 25 mL of pH 7.4 PBS at 37^0C. At each timepoint, 3 mL of dialysis media was removed and collected, and 3 mL of fresh PBS was added. The samples were analyzed by ICP-OES.

5. Results and Discussion

Synthetic approach was taken due to the ease of the coordination reaction with the potassium salt of the platinum chloride, potassium tetrachloroplatinate (II). In a biphasic solvent, Pt (II) is attached to the acyl chains and extracted into the organic solvent. During this extraction step, the inorganic salt of Pt (II) is converted to the organo platinum (II) complex (bis(2-stearoylhydraziny)platinum (II) chloride) (Pt-lipid). This formed Pt-lipid complex has decent solubility in organic solvent with a quantitative yield, ~ 75%. For the Pt-lipid, characterization was done by nuclear magnetic resonance to determine the chemical identity of the molecule after synthesis. Figure 3.2 shows a single signal for the standard at -1578.0 ppm. When coordinated with stearic hydrazide the chemical shift moves upfield at δ -1377.2 ppm. The *cis* configuration was confirmed by using the Kurnakov's test. The sample was treated with thiourea, which resulted in the formation of a yellow precipitate followed by crystallization. Yellow colored crystals shaped like needles were formed. The Pt-lipid complex was further confirmed by ESI-MS by determining the mass of the compound. The mass spectral data, shown in Figure 3.3, are in agreement with the calculated values and display the proper isotopic mass distribution patterns.

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Vincristine sulfate and a lomustine are S-phase chemoagents that disrupt DNA synthesis, which ultimately leads to cell apoptosis. A convenient and elegant way to combine both modes of action from each vincristine sulfate and a lomustine is to formulate them together in a single lipid- polymer hybrid nanoparticle delivery vehicle. By delivering them together an increase in the therapeutic effect could be translated to further reduce cancer cell viability. The lipid-polymer hybrid nanoparticle platform is robust system in which the hydrophobic Vincristine sulfate and a lomustine can be encapsulated inside the PLGA polymeric core and the lipophilic Pt-lipid complex can comprise the lipid shell with the Platinum as the head group. Three sets of formulations were fabricated: control nanoparticles containing only Vincristine sulfate and a lomustine, control nanoparticles containing only the Pt-lipid complex, and a combination nanoparticle formulation that contains both vincristine sulfate and a lomustine. Physical characterization was done on these nanoparticles to determine particle size, zeta potential, polydispersity index, and morphology. As seen in Figure 3.4 and Table 3.1, particle size for the vincristine sulfate and a lomustine formulation was 65 nm and the Platinum loaded one was 80 nm. When the two vincristine sulfate and a lomustine s are dually loaded in the system, the particle size was 61 nm. The combination particle size reflects closely with the vincristine sulfate and a lomustine control nanoparticles. The polydispersity index values are indicative of homogeneous distribution of particles. Table 3.1 shows the surface charge values for each of the formulations, with the vincristine sulfate and a lomustine control nanoparticles having the most negative charge (- 72 mV). The combination nanoparticles have a similar surface charge to that of the Pt-lipid control nanoparticles, both having a zeta potential ~ - 60 mV. Vincristine sulfate and a lomustine loading percentage was determined for each vincristine sulfate and a lomustine from the combination nanoparticles. As seen in Figure 3.6, the control vincristine sulfate and a lomustine nanoparticles had a 1.7% percent loading and control Pt-lipid nanoparticles had 0.6% Platinum loading, while the combination particles had 1.2% vincristine sulfate and a lomustine and 0.9% Platinum vincristine sulfate and a lomustine loading. The combination formulation has a decrease in the vincristine sulfate and lomustine loaded content, but shows an increase in the Platinum loading. One possible explanation could be that the lipid portion of the Platinum complex is also incorporated into the polymeric core, which would decrease available space for vincristine sulfate and a lomustine to reside in the core.

In vitro release studies results show that there is minimal difference on release profiles when comparing the system loaded with one vincristine sulfate and a lomustine as opposed to dually loaded. Adding another vincristine sulfate and a lomustine does not significantly affect the release profile. This information suggests that the core does not affect hydrolysis of the shell.

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Within 72 hours, 100% of the vincristine sulfate and a lomustine were released while only 55% of the Platinum was released. This could be an indication that Platinum release may last longer from the hybrid nanoparticles than 72 hours, but future studies would need to be conducted to confirm that. In vitro cytotoxicity was also examined with the lipid- polymer hybrid combination formulations. In Figure 3.10, the combination formulation shows that it can reduce ovarian cancer cell viability. Future studies need to be conducted where the relative cell viability is tested and compared against the free vincristine sulfate and a lomustine , a mixture of both free vincristine sulfate and a lomustine s, the single vincristine sulfate and a lomustine loaded hybrid nanoparticles, a cocktail mixture of the single vincristine sulfate and a lomustine loaded hybrid nanoparticles, and the combination nanoparticle formulation in order to determine if there is synergism in the dual loaded system.

Table 3 Table shows the average particle size, zeta potentials, and PDI for each of the nanoparticle formulations.

Formulation	**Particle Size (nm)**	**Zeta Potential (mV)**	**PDI**
Pt-lipid nanoparticles	89.5 ± 0.6	-52.7 ± 0.5	0.315 ± 0.006
vincristine sulfate and a lomustine nanoparticles	76.7 ± 0.5	-74.1 ± 2.2	0.239 ± 0.007
Pt-lipid vincristine sulfate and a lomustine combination nanoparticles	68.3± 0.3	-69.6 ± 0.5	0.314 ± 0.003

6. Conclusion

The hybrid nanoparticle system is a robust platform for drug delivery because the **particle size can be maintained at ~100 nm**, and the surface charge can be modified with lipid concentration in an addition step of the fabrication process. Without lipids, the nanoparticle has a highly negative surface charge due to the carboxy group of the DSPE- PEG. Surface charge can be easily tuned by choosing the appropriate lipid type and by changing the lipid concentration. Depending on where the drug needs to be delivered, nanoparticles with a **positive surface charge can enter cells through clathrin-mediated endocytosis**, which is relatively quick while negatively charged nanoparticles internalize slower due to the negatively charged cell membranes. The **particle size** is an important component because **nanoformulations can provide more improved drug release profiles** and pharmacokinetic properties. With the **sonication method** of nanoparticle fabrication, the **particles have a low polydispersity index, which is indicative of a narrow size distribution**. The **particles produced** from this method have a **spherical morphology according to the SEM data**. This particle shape may have an impact on release kinetics as well as biodistribution.

These results show that the **hybrid nanoparticle** platform can be tuned to have **different surface charge**. The versatility and the ease to apply surface charge modifications for this drug delivery system can be **useful for targeting specific tissues and cells in different disease states.** The **fabrication process is reliable** and produces particles with a polymer core and a lipid shell, which was confirmed by the TEM results. Hydrophobic drugs can be encapsulated in the polymeric core while lipophilic drugs can be encapsulated in the lipid shell. This hybrid nanoparticle system proves useful as a way to deliver multiple drugs for combination therapy, which can reduce drug resistance with chemotherapeutic agents for example.

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