Top Ten Publications with brief description of important contributions with Illustrations

S No.	Publication Details	I.F
1	Sandeep Urandur, Venkatesh TejaBanala, Ravi Prakash Shukla, Naresh Mittapelly, Gitu Pandey, NavodayamKalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, Pratibha Ramarao, **Prabhat Ranjan Mishra** Anisamide Anchored Lyotropic Nano Liquid Crystalline Particles with AIE Effect-A Smart Optical Beacon for Tumor Imaging and Therapy ***ACS Appl. Mater. Interfaces*** 10(15) 12960-12974 (2018) ***(Corresponding author)***	**9.23**
2	Venkatesh Teja Banala, Shweta Sharma, Puja Barnwal, Sandeep Urandur, Ravi P Shukla, Naseer Ahmad, Naresh Mittapalley, Gitu Pandey, Monika Dwivedi, Navodayam Kalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, **Prabhat Ranjan Mishra** Synchronized Ratiometric Co-Delivery of Metformin and Topotecan Through Engineered Nanocarrier Facilitate In-Vivo Synergistic Precision Levels at Tumor Site ***Adv. Healthcare Mater.*** 7(19):e1800300 (2018). ***(Corresponding author)***	**9.93**
3	Shweta Sharma, Ashwni Kumar Verma, Jyotsana Singh, B Venkatesh Teja, Naresh Mittapelly, Gitu Pandey, Sandeep Urandur, Ravi Shukla, Rituraj Konwar, **Prabhat Ranjan Mishra*** Vitamin B6 Tethered Endosomal pH Responsive Lipid Nanoparticles for Triggered Intracellular Release of Doxorubicin ***ACS Appl. Mater. Interfaces*** 8 (44), 30407–30421 (2016) ***(Corresponding author)***	**9.23**
4	Sandeep Urandur, Venkatesh Teja Banala, Ravi Prakash Shukla, Shalini Gautam, Disha Marwah, Nikhil Rai, Madhu sharma, Shweta Sharma, Pratibha Ramarao, **Prabhat Ranjan Mishra** Theranostic lyotropic liquid crystalline nanostructures for selective breast cancer imaging and therapy ***Acta Biomater.*** 113, 522-540 (2020) **(Corresponding author)**	**8.95**
5	Gitu Pandey, Naresh Mittapelly, Venkatesh Teja Banala, and **Prabhat Ranjan Mishra*** Multifunctional Glycoconjugate Assisted Nanocrystalline Drug Delivery for Tumor Targeting and Permeabilization of Lysosomal Mitochondrial Membrane ***ACS Appl. Mater. Interfaces*** *10* (20), 16964–16976 (2018) ***(Corresponding author)***	**9.23**
6	S Sharma, A Verma, G Pandey, N Mittapelly, **and PR Mishra*** Investigating the role of Pluronic-g-Cationic polyelectrolyte as functional stabilizer for nanocrystals: Impact on Paclitaxel oral bioavailability and tumor growth ***Acta Biomater.*** 26, 169-183 (2015). ***(Corresponding author)***	**8.95**
7	Venkatesh Teja Banala, Sandeep Urandur, Shweta Sharma, Madhu Sharma, Ravi P. Shukla, Disha Marwaha, Shalini Gautam, Monika Dwivedi and **Prabhat Ranjan Mishra*** Targeted co-delivery of the aldose reductase inhibitor epalrestat and chemotherapeutic doxorubicin via a redox-sensitive prodrug approach promotes synergistic tumor suppression ***Biomater. Sci.***, 7, 2889-2906 (2019) ***(Corresponding author)***	**6.84**
8	Ravi Prakash Shukla, Sandeep Urandur, Venkatesh Teja Banala, Disha Marwaha, Shalini Gautam, Nikhil Rai, Neha Singh, Pratiksha Tiwari, Prashant Shukla, Prabhat Ranjan Mishra* Development of Putrescine anchored nano-crystalsomes bearing Doxorubicin and Oleanolic acid- Deciphering its role in inhibiting metastatic breast cancer ***Biomater. Sci***., 9, 1779-1794 (2021) ***(Corresponding author)***	**6.84**
9	Ashwni Verma,Shweta Sharma, Pramod Kumar Gupta, Awadhesh Singh, B Venkatesh Teja, Pankaj Dwivedi, Girish Kumar Gupta, Ritu Trivedi, **Prabhat Ranjan Mishra*** Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH responsive carrier for improved oral delivery of insulin ***Acta Biomater.*** 31:288-300. doi: 10.1016/j.actbio (2016). ***(Corresponding author)***	**8.95**
10	S Kansal, R Tandon, A Verma, P Misra, AK Choudhary, R Verma, PRP Verma, A Dube, **PR Mishra*** Coating doxorubicin loaded nanocapsule with alginate enhances therapeutic efficacy against *Leishmania* in hamsters by inducing Th1 type immune responses ***Br. J. Pharmacol.*** 171(17):4038-50. (2014)***. (Corresponding author)***	**8.74**

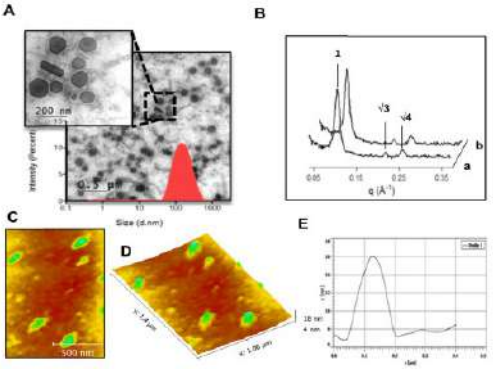
ACS APPLIED MATERIALS & INTERFACES
Research Article
Cite This: ACS Appl. Mater. Interfaces 2018, 10, 12960−12974
www.acsami.org

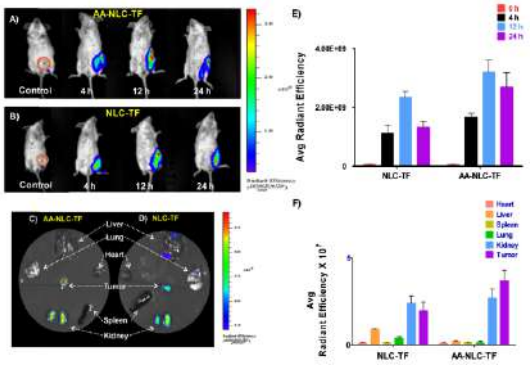
Anisamide-Anchored Lyotropic Nano-Liquid Crystalline Particles with AIE Effect: A Smart Optical Beacon for Tumor Imaging and Therapy

Sandeep Urandur,[†] Venkatesh Teja Banala,[†] Ravi Prakash Shukla,[†] Naresh Mittapelly,[†] Gitu Pandey,[†] Navodayam Kalleti,[‡] Kalyan Mitra,[§] Srikanta Kumar Rath,[‡] Ritu Trivedi,[∥] Pratibha Ramarao,[⊥] and Prabhat Ranjan Mishra*[,†]

10(15) 12960-12974 (2018) **(Corresponding author)** **(I.F. 9.23)**

Highlights: To overcome exposure to harmful ionizing radiation and poor diagnostic accuracy, multifunctional nanoparticles (as theranostics) was developed for synchronized imaging and tumor-targeted non-invasive therapy through optical imaging. A novel optical beacons with distinct aggregation-induced emission (AIE) property in combination with therapeutic functions into one theranostic systems has been exploited as all-in-one approach. We have developed inverse hexagonal nano-liquid crystalline (NLC) particles that are able to host formononetin (FMN), a phytoestrogen with known anticancer activity, and tetraphenylethene (TPE), an iconic optical beacon with aggregation-induced emission (AIE) signature, simultaneously. The developed nanoparticles having three-dimensional mesoporous structure was covalently anchored with anisamide (AA), a novel sigma receptor targeting ligand. The existence of AIE effect in the nanoparticles was evidenced through the photophysical studies that advocate the application of NLC NPs in fluorescence-based bio imaging. Moreover, confocal microscopy illustrated the single living cell imaging ability endowed by the NLC NPs. *In vitro* and *in vivo* studies supported the enhanced efficacy of targeted nanoparticles (AA-NLC-TF) in comparison to non-targeted nanoparticles (NLC-TF) and free drug. The data provide the evidence that this critically designed multimodal NLC NPs may establish a promising platform for targeted and image-guided chemotherapy for breast cancer.





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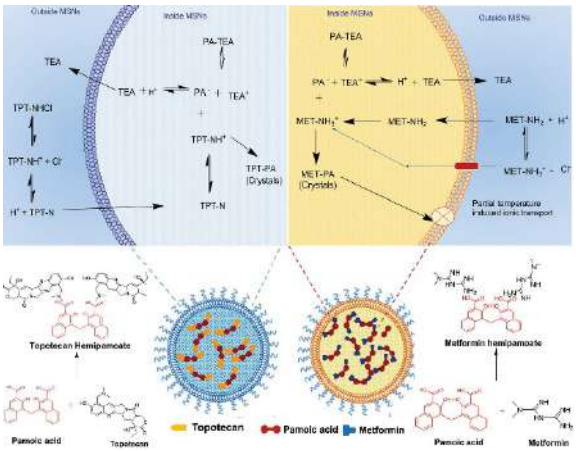
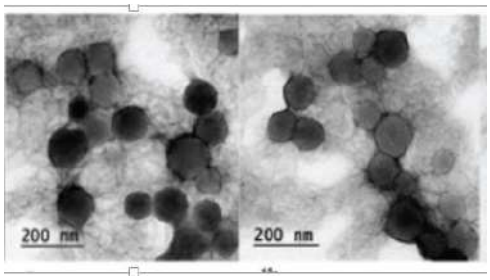
Synchronized Ratiometric Codelivery of Metformin and Topotecan through Engineered Nanocarrier Facilitates In Vivo Synergistic Precision Levels at Tumor Site

*Venkatesh Teja Banala, Shweta Sharma, Puja Barnwal, Sandeep Urandur, Ravi P. Shukla, Naseer Ahmad, Naresh Mittapelly, Gitu Pandey, Monika Dwivedi, Navodayam Kalleti, Kalyan Mitra, Srikanta Kumar Rath, Ritu Trivedi, and Prabhat Ranjan Mishra**

7(19):e1800300 (2018). ***(Corresponding author)*** **(I.F. 9.93)**

Highlights: The combination of metabolic modulators with chemotherapy holds vast promise for effective inhibition of tumor progression and invasion. Herein, a ratiometric co-delivery platform is developed for metformin (MET), a known metabolic modulator and topotecan (TPT), a chemotherapeutic drug, by engineering lipid bilayer–camouflaged mesoporous silica nanoparticles (LB-MSNs). In an attempt to deliver and maintain high tumor site concentrations of MET and TPT, a novel ion pairing–assisted loading procedure was developed using pamoic acid (PA) as an in situ trapping agent. PA, a hydrophobic counterion, increases the hydrophobicity of MET and TPT and facilitates MSNs with exceptionally high payload capacity (>40 and 32 wt%, respectively) and controlled release profile. Further, the synergy between MET and TPT determined by a modeling approach helps to afford synchronized delivery of both the drugs. Co-loaded MET and TPT LB-MSNs present synergistic cytotoxicity against MDA-MB-231/4T1 cells and effectively promote apoptosis via mitochondrial membrane depolarization and cell cycle arrest. Extended pharmacokinetic profiles in preclinical models with fourfold to sevenfold longer circulation half-life and 7.5–100 times higher tumor site concentrations correspond to a significant increase in pharmacodynamics efficacy. Taken together, the developed co-delivery approach effectively addresses the challenges in the chemotherapeutic efficacy of MET and TPT collectively.





ACS APPLIED MATERIALS & INTERFACES
Research Article
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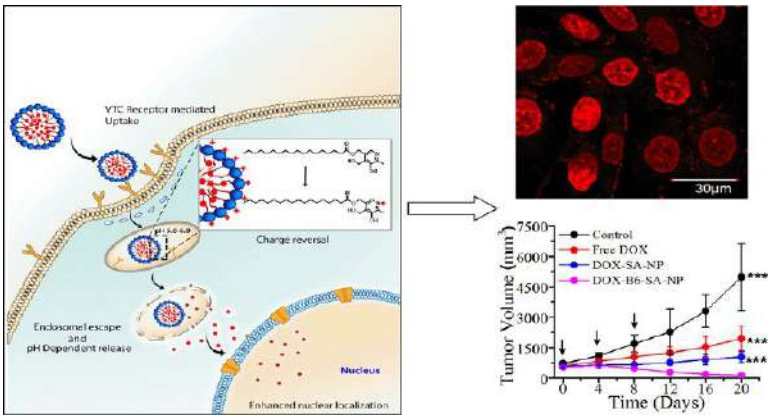
Vitamin B6 Tethered Endosomal pH Responsive Lipid Nanoparticles for Triggered Intracellular Release of Doxorubicin

Shweta Sharma,[†,§] Ashwni Verma,[†] Jyotsana Singh,[‡,§] B. Venkatesh Teja,[†] Naresh Mittapelly,[†,§] Gitu Pandey,[†,§] Sandeep Urandur,[†] Ravi P. Shukla,[†] Rituraj Konwar,[‡] and Prabhat Ranjan Mishra*[†,§]

8 (44), 30407–30421 (2016) ***(Corresponding author)*** **(I.F. 9.23)**

Highlights: This study reports the development of Vitamin B6 (VitB6) modified pH sensitive charge reversal nanoparticles for efficient intracellular delivery of Doxorubicin (DOX). Herein, VitB6 was conjugated to stearic acid, and the nanoparticles of the lipid were formulated by solvent injection method (DOX-B6-SA-NP). Because of the pKa (5.6) of VitB6, DOX-B6-SA-NP showed positive charge and enhanced release of DOX at pH 5. Confocal microscopy illustrated that DOXB6- SA-NP treatment kept higher DOX accumulation inside the cells than conventional pH insensitive lipid nanoparticles (DOX-SA-NP). The cationic charge of nanoparticles subsequently facilitated the endosomal escape and promoted the nuclear accumulation of DOX. Furthermore, in vitro cytotoxicity, apoptosis, cell cycle arrest, and mitochondrial membrane depolarization studies supported the enhanced efficacy of DOX-B6-SA-NP in comparison to free DOX and DOX-SA-NP. Intravenous pharmacokinetics and bio-distribution investigations indicated that pH sensitive nanoparticles can significantly prolong the blood circulation time of DOX in biological system and increase the drug accumulation to tumor site. Consequent to this, DOX-B6-SA-NP also exhibited much enhanced therapeutic efficacy and lower toxicity in tumor-bearing rats compared to free DOX. The reduction in toxicity was confirmed by histological and survival analysis. In conclusion, these results suggest that the VitB6 modified charge reversal nanoparticles can be a novel platform for the successful delivery of anticancer drugs.



Acta Biomaterialia 113 (2020) 522–540

Contents lists available at ScienceDirect

Acta Biomaterialia

journal homepage: www.elsevier.com/locate/actbio

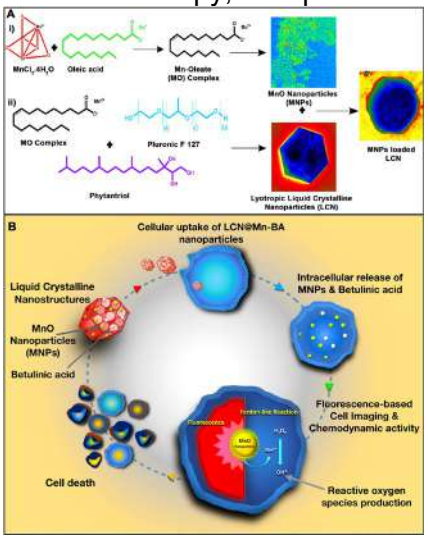
Full length article

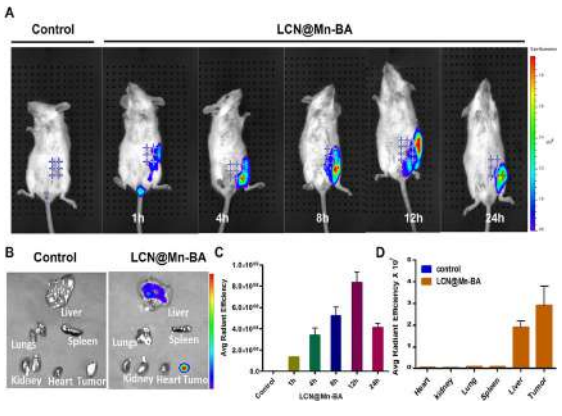
Theranostic lyotropic liquid crystalline nanostructures for selective breast cancer imaging and therapy

Sandeep Urandur[a], Venkatesh Teja Banala[a], Ravi Prakash Shukla[a], Shalini Gautam[a], Disha Marwaha[a], Nikhil Rai[a], Madhu Sharma[a], Shweta Sharma[a], Pratibha Ramarao[b], Prabhat Ranjan Mishra[a,*]

113, 522–540 (2020) **(Corresponding author)** **(I.F. 8.95)**

Highlights: Compared to radiation, photodynamic and photothermal therapy, the specific and selective activation of tumor microenvironmental endogenous stimuli for the logical generation of cytotoxic OH ·free radicals serves as an efficient therapeutic strategy for chemodynamic-cancer treatment. Herein, we report the development of theranostic lyotropic liquid crystalline nanostructures (LCN's) loaded with unique MnO nanoparticles (MNPs) for selective cancer imaging and therapy. MNPs serves as a fluorescent agent as well as a source of manganese (Mn^{2+}) and enables localized oxidative stress under the hallmarks of cancer (acidosis, high H_2O_2 level). In pursuit of synergistic amplification of Mn^{2+} antitumor activity, betulinic acid (BA) is loaded in LCN's. In this investigation, nano-architecture of LCN's phase interface is established via SAXS, Cryo-TEM and Cryo-FESEM. Intriguing *in vitro* studies showed that the LCN's triggered hydroxyl radical production and exhibited greater selective cytotoxicity in cancer cells, ensuring the safety of normal cells. Significant tumor ablation is realized by the 96.5 % of tumor growth inhibition index of LCN's as compared to control group. Key insights into on-site drug release, local anti-cancer response, and tumor location are gained through precise guidance of fluorescent MNPs. In addition, comprehensive assessment of the safety, pharmacokinetics and tumor distribution behavior of LCN's is performed *in vivo* or *ex vivo*. This work emphasizes the promise of modulating tumor microen- vironment with smart endogenous stimuli sensitive nano systems to achieve advanced comprehensive cancer nano-theranostics without any external stimulus. In this investigation, MnO nanoparticles fulfill two needs (fluorescence- based optical imaging and a source of Mn^{2+} based chemodynamic therapy) in one unit. This approach also ensures the safety of normal cells, as the toxic OH ·free radical activity is substantially suppressed under the mild alkaline/H_2O_2 conditions in normal cell microenvironment.





ACS APPLIED MATERIALS & INTERFACES

Research Article

Cite This: ACS Appl. Mater. Interfaces 2018, 10, 16964−16976

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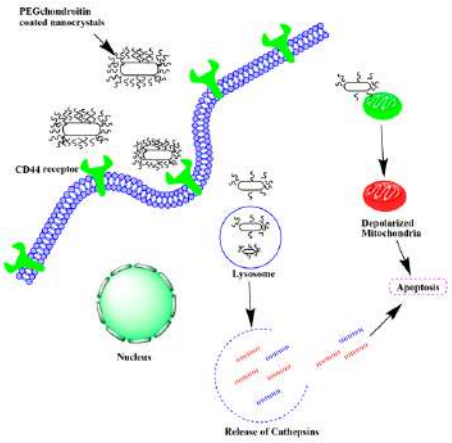
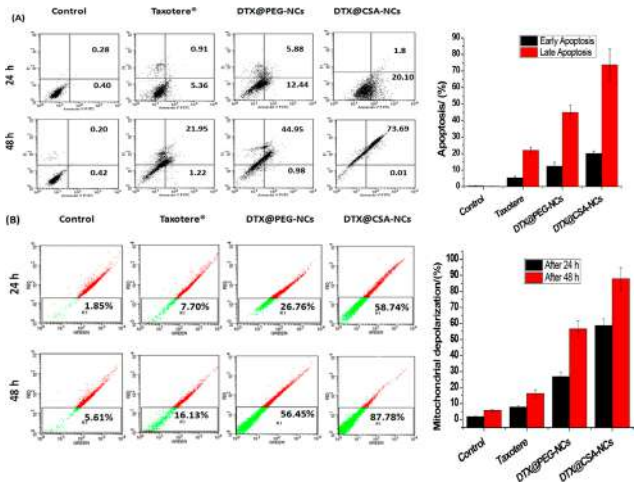
Multifunctional Glycoconjugate Assisted Nanocrystalline Drug Delivery for Tumor Targeting and Permeabilization of Lysosomal-Mitochondrial Membrane

Gitu Pandey,[†,‡] Naresh Mittapelly,[†,‡] Venkatesh Teja Banala,[†] and Prabhat Ranjan Mishra*[,†,‡]

10 (20), 16964–16976 (2018) ***(Corresponding author)*** **(I.F. 9.23)**

Highlights: Nanotechnology has emerged as the most successful strategy for targeting drug payloads to tumors with the potential to overcome the problems of low concentration at the target site, nonspecific distribution, and untoward toxicities. Here, we synthesized a novel polymeric conjugate comprising chondroitin sulfate A and polyethylene glycol using carbodiimide chemistry. We further employed this glycoconjugate possessing the propensity to provide stability, stealth effects, and tumor targeting via CD44 receptors, all in one, to develop a nano-crystalline system of docetaxel (DTX@CSA-NCs) with size < 200 nm, negative zeta potential, and 98% drug content. Taking advantage of the enhanced permeability and retention effect coupled with receptor mediated endocytosis, the DTX@CSA-NCs cross the peripheral tumor barrier and penetrate deeper into the cells of tumor mass. In MDA-MB-231 cells, this enhanced cellular uptake was observed to exhibit a higher degree of cytotoxicity and arrest in the G2 phase in a time dependent fashion. Acting via a mitochondrial-lysosomotropic pathway, DTX@CSA-NCs disrupted the membrane potential and integrity and outperformed the clinically used formulation. Upon intravenous administration, the DTX@CSA-NCs showed better pharmacokinetic profile and excellent 4T1 induced tumor inhibition with significantly less off target toxicity. Thus, this glycoconjugate stabilized nanocrystalline formulation has the potential to take nano-oncology a step forward.





Acta Biomaterialia 26 (2015) 169–183

Contents lists available at ScienceDirect

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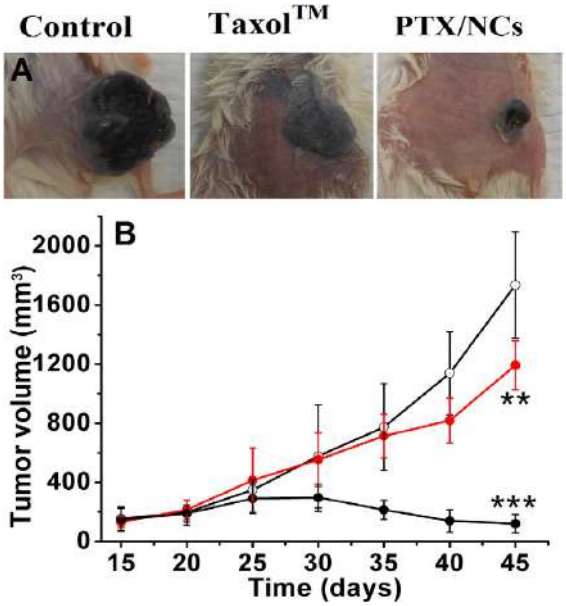
Investigating the role of Pluronic-g-Cationic polyelectrolyte as functional stabilizer for nanocrystals: Impact on Paclitaxel oral bioavailability and tumor growth

Shweta Sharma, Ashwni Verma, Gitu Pandey, Naresh Mittapelly, Prabhat Ranjan Mishra *

26, 169-183 (2015). ***(Corresponding author)*** **(I.F. 8.95)**

Highlights: Paclitaxel (PTX) is a potent anticancer drug which suffers limitations of extremely low oral bioavailability due to low solubility, rapid metabolism and efflux by P-gp transporters. The main objective of this study was to overcome the limitation of PTX by designing delivery systems that can enhance the absorption using multiple pathways. A novel Pluronic-grafted chitosan (Pl-g-CH) copolymer was developed and employed as a functional stabilizer for nanocrystals (NCs) and hypothesized that it would improve PTX absorption by several mechanisms and pathways. Pl-g-CH was synthesized and characterized using 1H NMR and then used as a stabilizer during nanocrystal development. To establish our proof of concept the optimized formulation having a particle size 192.7 ± 9.2 nm and zeta potential (+) 38.8 ± 3.12 mV was studied extensively on in vitro Caco-2 model. It was observed that nanocrystals rendered higher PTX accumulation inside the cell than TaxolTM. P-gp inhibitory potential of Pl-g-CH was proved by flow cytometry and fluorescence microscopy where the much enhanced fluorescence intensity of Rhodamine 123 (Rho-123, P-gp substrate) was observed in the presence of Pl-g-CH. In addition, a significant decrease in Trans Epithelial Electrical Resistance (TEER) of Caco-2 cell monolayers was observed with nanocrystals as well as with TaxolTM (in the presence of free Pl-g-CH compared to only TaxolTM). This supports the role of the stabilizer in reversible opening of tight junctions between cells which can allow paracellular transport of drug. The in vivo results were in complete corroboration with in vitro results. Nanocrystals resulted in much enhanced absorption with 12.6-fold improvement in relative bioavailability to that of TaxolTM. Concomitantly efficacy data in B16 F10 murine melanoma model also showed a significant reduction in tumor growth with nanocrystals compared to TaxolTM and control. Based on the results it can be suggested that nanocrystals with functional stabilizers can be a promising approach for the oral delivery of anticancer drugs which are P-gp substrates.



Biomaterials Science

PAPER

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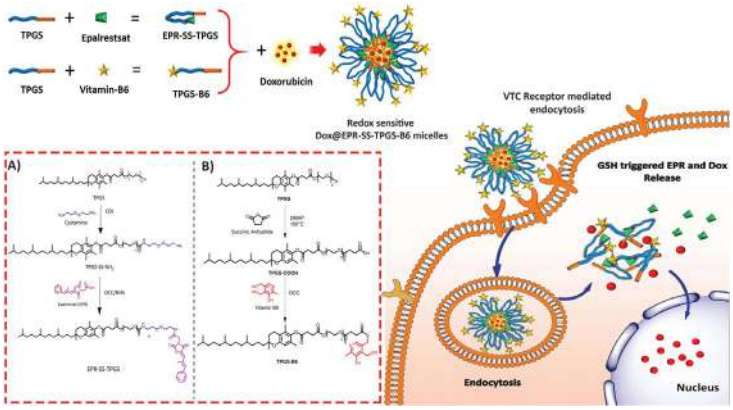
Cite this: *Biomater. Sci.*, 2019, **7**, 2889

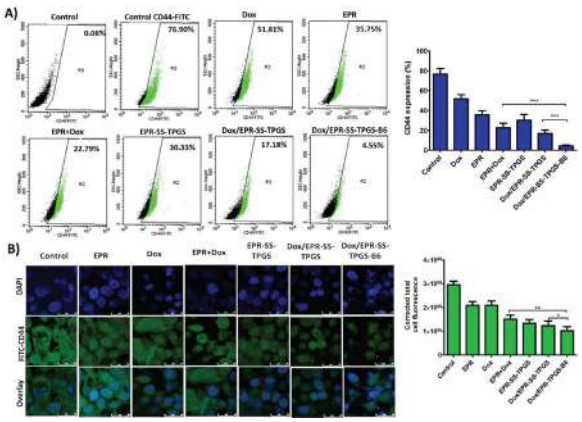
Targeted co-delivery of the aldose reductase inhibitor epalrestat and chemotherapeutic doxorubicin *via* a redox-sensitive prodrug approach promotes synergistic tumor suppression†

Venkatesh Teja Banala, Sandeep Urandur, Shweta Sharma, Madhu Sharma, Ravi P. Shukla, Disha Marwaha, Shalini Gautam, Monika Dwivedi and Prabhat Ranjan Mishra *

7, 2889-2906 (2019) *(**Corresponding author)*** **(I.F. 6.84).**

Highlights: Rapidly growing evidence suggests a strong dependence of a polyol pathway enzyme Aldose Reductase (AR) in cancer progression and invasion. Thus, inhibiting the AR through therapeutic inhibitors has a potential application in cancer treatment. Epalrestat (EPR) is the only marketed AR inhibitor with proven safety and efficacy in the management of complications like diabetic neuropathy. However, its short half-life and highly hydrophobic nature restrict its use as an anticancer agent. In the present study, we first developed a redox-sensitive prodrug of EPR by conjugating Tocopherol Polyethylene Glycol Succinate (TPGS) which can form a self-assembled micellar prodrug (EPR-SS-TPPGS). Subsequently, to achieve synergistic chemotherapeutic efficacy Doxorubicin (Dox) was co-loaded into the EPR-SS-TPGS micelles where the system is disrupted in a tumor redox environment and co-delivers Dox and EPR in a ratiometric manner. We then employed TPGS conjugated vitamin-B6 as a targeting moiety and prepared the mixed micelles to facilitate VTC receptor-mediated uptake. The encapsulation of Dox and EPR with the developed prodrug approach showed significant synergies with increased intracellular accumulation and redox triggered release in MDA-MB-231 and 4T1 cell lines leading to superior cell cycle arrest, mitochondrial membrane potential, and apoptosis. Prolonged circulation half-life and tumor site bioavailability were achieved for both the drugs with the developed approach. Surprisingly, EPR and Dox combination significantly down-regulated the CD44 receptor expression which is the main contributing factor of tumor metastasis. Furthermore, in vivo evaluation demonstrated a significant reduction in Dox-induced cardiotoxicity. In summary, this nanoencapsulation paradigm of AR inhibitors with chemotherapeutic agents lays the foundation of new opportunities in combination chemotherapy.





Biomaterials Science

ROYAL SOCIETY OF CHEMISTRY

PAPER

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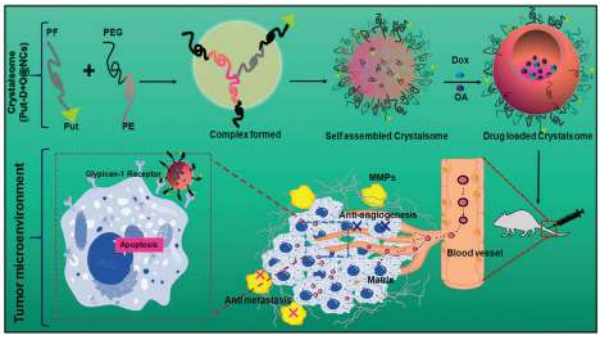
Cite this: *Biomater. Sci.*, 2021, **9**, 1779

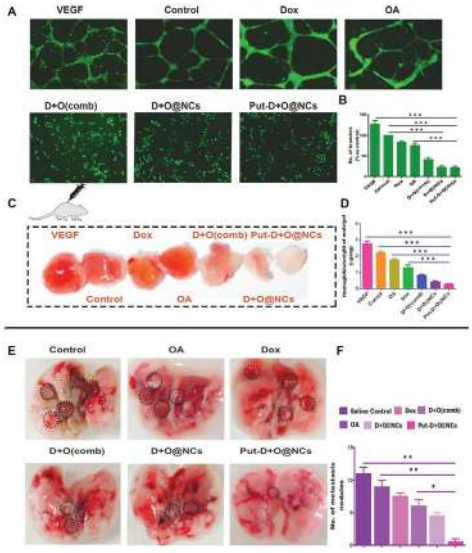
Development of putrescine anchored nano-crystalsomes bearing doxorubicin and oleanolic acid: deciphering their role in inhibiting metastatic breast cancer†

Ravi Prakash Shukla, Sandeep Urandur, Venkatesh Teja Banala, Disha Marwaha, Shalini Gautam, Nikhil Rai, Neha Singh, Pratiksha Tiwari, Prashant Shukla and Prabhat Ranjan Mishra *

9, 1779-1794 (2021) *(**Corresponding author**)* **(I.F. 6.84).**

Angiogenesis driven tumor initiation and progression calls for a targeted therapy. Moreover, combined chemotherapy supplements the therapy to act on the cause of concern. In this study, we aimed to develop a targeted crystalsomes approach to delineate tumor cells against normal cells. Self-assembled crystalline monodispersed nanosized polyethylene-polyethylene glycol (PE-PEG)-based hollow crystalsomes were modified with pluronylated putrescine (Put-PF) and loaded with doxorubicin (Dox), synergistically in combination with oleanolic acid (OA) to target the glypican-1 (gp-1) receptor on tumor cells. The developed crystalsomes (Put-D + O@NCs) showed increased intracellular accumulation of Dox and OA in a synergistic combination inside the MDA-MB-231 cell lines. The developed crystalsomes marked an enhanced depolarization of the mitochondrial membrane potential and cell cycle arrest leading to apoptosis. Furthermore, the proposed therapy has a greater anti-angiogenesis activity with vascular endothelial growth factor (VEGF) dependent modulation in the proliferation, invasion, migration and tube formation of human endothelial umbilical vein cells (HUVECs) in vitro and in vivo in a BALB/c mouse model. Interestingly, the perseverance of the tumor boundary, inhibiting the expression and activity of the matrix metalloproteinase (MMPs) (>5.2-fold) with suppressed degradation of the extracellular matrix paves the way for significant inhibition of metastases. However, an intravenously administered Put-D + O@NCs showed an improved pharmacokinetic profile and exquisite inhibition of the 4T1 induced tumor with a significantly lower toxicity. In a nutshell, these findings highlight the important role of Put in the gp-1 receptor for specific targeting and synergistic delivery of Dox and OA through crystalsomes as a potential approach for the treatment of metastatic breast cancer using combined chemotherapy. This work provides a platform for preparing multifunctional crystalsomes and offers a proof of concept that nanosized Putrescine grafted Doxorubicin and OA encapsulated PE-PEG crystalsomes could be used to reduce cancer growth via gp-1 receptor-targeted inhibition of angiogenesis, as well as metastasis via the MMP-9 driven TME protection.





Acta Biomaterialia 31 (2016) 288–300

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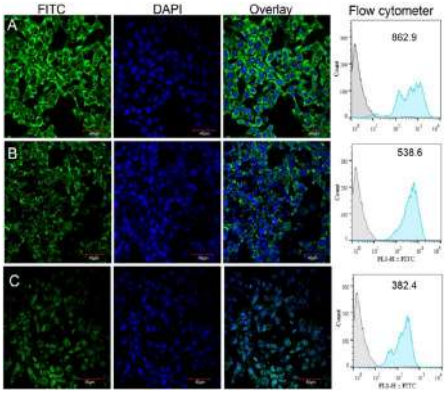
Full length article

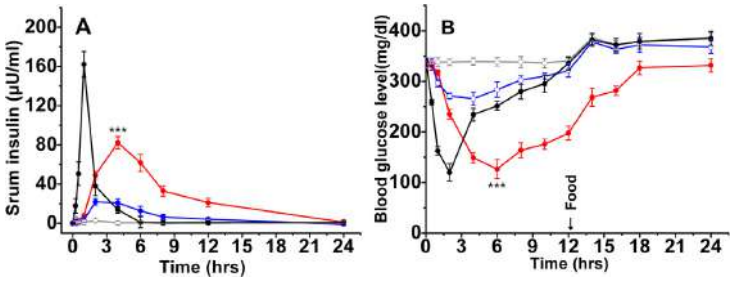
Vitamin B12 functionalized layer by layer calcium phosphate nanoparticles: A mucoadhesive and pH responsive carrier for improved oral delivery of insulin

Ashwni Verma [a], Shweta Sharma [a], Pramod Kumar Gupta [a], Awadhesh Singh [c], B. Venkatesh Teja [a], Pankaj Dwivedi [a], Girish Kumar Gupta [a], Ritu Trivedi [b], Prabhat Ranjan Mishra [a,*]

31:288-300 (2016). ***(Corresponding author)*** **(I.F. 8.95)**

Highlights: The present study investigates the potential of layer by layer coated calcium phosphate nanoparticles-for oral delivery of insulin where Vitamin B12 grafted chitosan and sodium alginate have been used as cationic and anionic polyelectrolyte respectively. The major emphasis has been given on the role Vitamin B12 conjugated chitosan as cationic polyelectrolyte (VitB12-Chi) in the delivery system. VitB12-Chi conjugate was prepared by carbodiimide reaction. The formulated VirB12-Chi-CPNPs were tested for in vitro and in vivo efficacy studies carried out in Caco-2 monolayers and diabetic rats. VitB12-Chi-CPNPs with particle size <250 nm and zeta potential + 32.56(±2.34) exhibited pH responsive insulin release at simulated gastric fluid and simulated intestinal fluid. Fluorescence microscopy and flow cytometry studies revealed higher uptake of VitB12-Chi-CPNPs in Caco-2 monolayer in comparison to Chi-CPNPs. Further reduction in TEER supported paracellular transport of insulin because of opening of tight epithelial junctions. In vivo intestinal uptake of FITC tagged Vit-B12-Chi-CPNPs from different intestinal segments supported paracellular and receptor mediated uptake of VitB12-Chi-CPNPs. Plasma insulin and blood glucose levels were measured in diabetic rats and showed about four fold increases in insulin bioavailability and sustained hypoglycemic effects up to 12 h of administration with VitB12-Chi-CPNPs in comparison to Chi-CPNPs. Results of the study revealed the potential of layer by layer nanoparticles for oral insulin delivery. The study also specifically highlighted the role of VitB12 as a pH sensitive and targeting ligand which significantly participated in enhancing insulin oral bioavailability.





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RESEARCH PAPER

Coating doxorubicin-loaded nanocapsules with alginate enhances therapeutic efficacy against *Leishmania* in hamsters by inducing Th1-type immune responses

S Kansal[1]*, R Tandon[2]*, A Verma[1], P Misra[2], A K Choudhary[2], R Verma[1], P R P Verma[3], A Dube[2] and P R Mishra[1]

Correspondence
Prabhat Ranjan Mishra, PCS-002/011-Preclinical south, CSIR-Central Drug Research Institute, BS-10/1 sector-10 Jankipuram Extension, Lucknow 226001, India. E-mail: mishrapr@hotmail.com; prabhat_mishra@cdri.res.in

*Both authors contributed equally.

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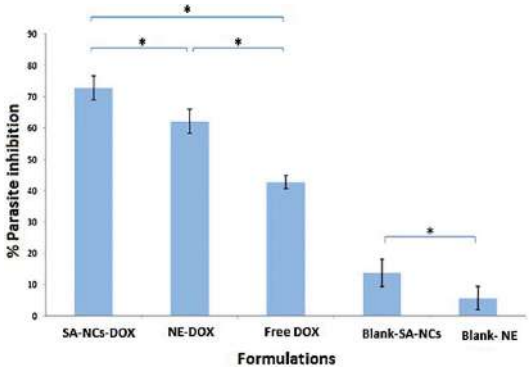
The aim of the present study was to evaluate the immunomodulatory and chemotherapeutic potential of alginate-(SA) coated nanocapsule (NCs) loaded with doxorubicin (SA-NCs-DOX) against visceral leishmaniasis in comparison with nano-emulsions containing doxorubicin (NE-DOX). NE-DOX was prepared using low-energy emulsification methods. Stepwise addition of protamine sulphate and SA in a layer-by-layer manner was used to form SA-NCs-DOX. SA-NCs-DOX, NE-DOX and Free DOX were compared for their cytotoxicity against



Leishmania donovani-infected macrophages *in vitro* and generation of T-cell responses in infected hamsters *in vivo*. Size and ζ potential of the NE-DOX and SA-NCs-DOX formulations were 310 ± 2.1 nm and (−)32.6 ± 2.1 mV, 342 ± 4.1 nm and (−)29.3 ± 1.2 mV respectively. SA-NCs-DOX was better (1.5 times) taken up by J774A.1 macrophages compared with NE-DOX. SA-NCs -DOX showed greater efficacy than NE-DOX against intramacrophagic amastigotes. SA-NCs-DOX treatment exhibited enhanced apoptotic efficiency than NE-DOX and free DOX as evident by cell cycle analysis, decrease in mitochondrial membrane potential, ROS and NO production. T-cell responses, when assessed through lymphoproliferative responses, NO production along with enhanced levels of iNOS, TNF-α, IFN-γ and IL-12 were found to be up-regulated after SA-NCs-DOX, compared with responses to NE-DOX *in vivo*. Parasitic burden was decreased in *Leishmania*-infected hamsters treated with SA-NCs-DOX, compared with NE-DOX. Our results provide insights into the development of an alternative approach to improved management of leishmaniasis through a combination of chemotherapy with stimulation of the innate immune system.