Publications Template

#	Research Title	Field	Abstract	Year of Publication	Publishing Link "URL"
1	Lecithin-based nanostructured gels for skin delivery: an update on state of art and recent applications		Conventional carriers for skin delivery encounter obstacles of drug leakage, scanty permeation and low entrapment efficiency. Phospholipid nanogels have recently been recognized as prominent delivery systems to circumvent such obstacles and impart easier application. The current review provides an overview on different types of lecithin nanostructured gels, with particular emphasis on liposomal versus microemulsion gelled systems. Liposomal gels investigated encompassed classic liposomal hydrogel, modified liposomal gels (e.g. Transferosomal, Ethosomal, Pro-liposomal and Phytosomal gels), Microgel in liposomes (M-i-L) and Vesicular phospholipid gel (VPG). Microemulsion gelled systems encompassed Lecithin microemulsion-based organogels (LMBGs), Pluronic lecithin organogels (PLOs) and Lecithin-stabilized microemulsion-based hydrogels. All systems were reviewed regarding matrix composition, state of art, characterization and updated applications. Different classes of lecithin nanogels exhibited crucial impact on transdermal delivery regarding drug permeation, drug loading and stability aspects. Future perspectives of this theme issue are discussed based on current laboratory studies.	2014	https://www.sciencedirect.com/science/article/abs/pii/S0168365914000704
2	Nanotechnology-based drug delivery systems for Alzheimer's disease management: Technical, industrial, and clinical challenges		Alzheimer's disease (AD) is a neurodegenerative disease with high prevalence in the rapidly growing elderly population in the developing world. The currently FDA approved drugs for the management of symptomatology of AD are marketed mainly as conventional oral medications. Due to their gastrointestinal side effects and lack of brain targeting, these drugs and dosage regiments hinder patient compliance and lead to treatment discontinuation. Nanotechnology-based drug delivery systems (NTDDS) administered by different routes can be considered as promising tools to improve patient compliance	2017	https://www.sciencedirect.com/science/article/abs/pii/S0168365916308367

			and achieve better therapeutic outcomes. Despite extensive research, literature screening revealed that clinical activities involving NTDDS application in research for AD are lagging compared to NTDDS for other diseases such as cancers. The industrial perspectives, processability, and cost/benefit ratio of using NTDDS for AD treatment are usually overlooked. Moreover, active and passive immunization against AD are by far the mostly studied alternative AD therapies because conventional oral drug therapy is not yielding satisfactorily results. NTDDS of approved drugs appear promising to transform this research from 'paper to clinic' and raise hope for AD sufferers and their caretakers. This review summarizes the recent studies conducted on NTDDS for AD treatment, with a primary focus on the industrial perspectives and processability. Additionally, it highlights the ongoing clinical trials for AD management.		
3	Novel curcumin-loaded gel-core hyaluosomes with promising burn-wound healing potential: development, in-vitro appraisal and in-vivo studies		Despite its effectiveness, curcumin (Curc) dermal delivery is handicapped by hydrophobicity, high metabolism and poor skin permeation. In this work, the potential of novel self-assembled nanogels, namely gel-core hyaluosome (GC-HS) to enhance Curc delivery to wound sites, enhance healing rate and decrease scar formation was evaluated. Curc–GC-HS were prepared using film hydration technique and evaluated regarding size, zeta potential (ZP), entrapment efficiency (% EE), and in vitro release. Structure elucidation was performed using light, polarizing and transmission electron microscopy (TEM). In-vivo burn-wound healing potential, skin deposition ability and histological study were evaluated using female Sprague Dawley rats. Curc–GC-HS were compared to conventional transfersomal gel (Curc–T-Pl gel), and other conventional gels. Curc–GC-HS showed nanosize (202.7 ± 0.66 nm), negative ZP (−33 ± 2.6 mV) and % EE (96.44 ± 1.29%). TEM revealed discrete vesicles with characteristic bilayer structure. Polarizing microscopy proposed liquid crystalline consistency. Burn-wound healing study showed that Curc–GC-HS was the only system exhibiting marked improvement at day 7 of treatment. At 11th day, Curc–GC-HS treated wounds showed almost normal skin with no scar confirmed by histological analysis. Curc–GC-HS showed five folds higher skin	2015	https://www.sciencedirect.com/science/article/abs/pii/S0378517315002689

			deposition compared to conventional Curc–T-Pl gel. To conclude, novel gel-core hyaluosomes elaborated are promising nanogels able to increase Curc skin penetration and dermal localization while protecting it against degradation. Future perspective encompasses assessing potential of novel nanocarrier for skin cancer therapy.		
4	Hyalugel-integrated liposomes as a novel ocular nanosized delivery system of fluconazole with promising prolonged effect		Fungal infections need long-term therapy with the proper antifungal agent. Despite effectiveness, Fluconazole (FLZ) ocular delivery is constrained by limited penetration, short residence time, in addition to the common barriers of the eye. Hyalugel-integrated liposomes were designed as novel ocular delivery systems integrating hyaluronic acid (HA) inside and surrounding vesicles by a simple preparation technique. The impact of combining HA hydrogel and liposomes was investigated in a series of different formulations. Full in-vitro optimization was performed regarding; HA and FLZ concentration, entrapment efficiency, particle size and stability to select the formula with the best characteristics. Structure elucidation of gel integration was done using polarizing and transmission electron microscopes before and after Triton-X100 addition. Corneal deposition and permeation were examined ex-vivo and in-vivo on male albino rabbits. Selected formulation (HYS7) showed gel-integrated structure, nanosize (218.50 ± 4.50 nm) and % EE 42.81% ± 1.66. Ex-vivo cumulative corneal permeation of FLZ after 6 h from HYS7, was 2.99 and 4.18 folds higher than conventional liposomes and FLZ suspension, respectively. In-vivo corneal permeation of HYS7 showed unprecedented sustained effect of FLZ reaching 24 h. In conclusion, novel hyalugel-integrated liposomes significantly enhanced corneal permeability compared to conventional liposomes and FLZ suspension. They would be promising alternates for eye drops; decreasing frequency of administration and increasing patients' compliance.	2017	https://www.sciencedirect.com/science/article/abs/pii/S0378517317309572
5	Novel self-assembled, gel-core hyaluosomes for non-invasive management of		Purpose Hyaluronic acid (HA) is an imperative biomaterial with desirable rheological properties to alleviate symptoms of osteoarthritis. Nevertheless, scantly percutaeous permeation of this macromolecule handicaps its effective use for orthopedics and triggers intra-articular injection as the only surrogate. This study presents novel self-	2015	https://link.springer.com/article/10.1007/s11095-015-1672-8

	osteoarthritis: in-vitro optimization, ex-vivo and in-vivo permeation		assembeld HA-based gel core elastic nanovesicles, (hyaluosomes; GC-HS), for non-invasive transdermal delivery of HA. Methods GC-HS were prepared with 1% HA using simple film hydration technique. Their size, zeta potential, percentage entrapment efficiency (% EE), elasticity, and ex-vivo transdermal permeation were evaluated compared to conventional liposomes CL. Structure elucidation of the formed novel system was performed using light, polarizing and transmission electron microscopy. In-vivo permeation of GC-HS through knee joints of female Sprague Dawley rats was compared to CL and HA alone. Results GC-HS showed nanosize (232.8 ± 7.2), high negative zeta potential (−45.1 ± 8.3) and higher elasticity (size alteration 5.43%) compared to CL. This novel system has self-penetration enhancing properties compared to CL and plain gel. GC-HS showed self-assembled properties and high physically stable for at least 6 months at 4°C. Ex-vivo permeation of HS was significantly higher than CL and plain HA gel alone. In-vivo study exhibited significant six folds increase in transdermal permeation of HA to knee joints from GC-HS compared to plain HA gel. Conclusion Novel GC-HS are promising nanogels for topical management of osteoarthritis surrogating the need for intra-articular injection.		
6	Bioadhesive chitosan-coated cationic nanoliposomes with improved insulin encapsulation and		Oral administration of insulin is hampered by the lack of carriers that can efficiently achieve high encapsulation, avoid gastric degradation, overcome mucosal barriers, and prolong the hypoglycemic effect. Chitosan (CS)-coated insulin-loaded cationic liposomes have been developed and optimized for improved oral delivery. Liposomes were prepared cationic to improve insulin encapsulation. CS was selected as a mucoadhesive coat to prolong the system's residence and absorption. The performance of CS-coated liposomes compared with	2018	https://www.sciencedirect.com/science/article/abs/pii/S0022354918302144

	prolonged oral hypoglycemic effect in diabetic mice		uncoated liposomes was examined in vitro, ex vivo, and in vivo in streptozotocin-induced diabetic mice. Free uncoated liposomes showed high positive zeta potential of +58.8 ± 2.2 mV that reduced (+29.9 ± 1.4 mV) after insulin encapsulation, confirming the obtained high entrapment efficiency of 87.5 ± 0.6%. CS-coated liposomes showed nanosize of 439.0 ± 12.3 nm and zeta potential of +60.5 ± 1.9 mV. In vitro insulin release was limited to 18.9 ± 0.35% in simulated gastric fluid, whereas in simulated intestinal fluid, 73.33 ± 0.68% was released after 48 h from CS-coated liposomes. Ex vivo intestinal mucoadhesion showed increased tissue residence of CS-coated liposomes compared with uncoated liposomes. A striking reduction in the glucose level was observed 1 h after oral administration of CS-coated liposomes and maintained up to 8 h ($p < 0.01$ vs. insulin solution or uncoated liposomes) within the normal value 129.29 ± 3.15 mg/dL. In conclusion, CS-coated insulin-loaded cationic liposomes improved loading efficiency with promising prolonged pharmacological effect.		
7	Hepatic stellate cell-targeted imatinib nanomedicine versus conventional imatinib: a novel strategy with potent efficacy in experimental liver fibrosis		Liver fibrosis is a global health problem without approved treatment. Imatinib inhibits two key profibrotic pathways; platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) and thus can be used to treat liver fibrosis. However, conventional imatinib therapy is hampered by low concentration at target tissue and increased toxicity to other tissues especially heart, lung and liver. Since hepatic stellate cells (HSCs) are the main contributors to liver fibrosis pathogenesis and sole hepatic vitamin A (VA) storage cells, they can be actively targeted by coupling liposomes to VA. In this study, novel VA-coupled imatinib-loaded liposomes (ILC) were prepared and optimized regarding VA-coupling efficiency, imatinib entrapment efficiency, and particle size. Preferential accumulation of the selected formula in liver was proved by tracing intraperitoneally (i.p.)-injected VA-coupled liposomes loaded with Nile Red (LCNR) to rats with CCl4-induced liver fibrosis using live animal imaging. Co-localization of LCNR with immunofluorescently-labeled PDGFR-β in frozen liver tissue sections confirmed HSCs targeting. ILC bio-distribution, following single i.p. injection, revealed 13.5 folds higher hepatic accumulation than conventional imatinib in addition to limited bio-	2017	https://www.sciencedirect.com/science/article/abs/pii/S0168365917308696

			distribution to other organs including heart and lung reflecting diminished adverse effects. ILC therapy resulted in a potent inhibition of phosphorylated PDGFR-β expression when compared to conventional imatinib. Subsequently, there was a statistically significant improvement in liver function tests and reversal of hepatotoxicity along with liver fibrosis. Anti-fibrotic effect was evident from histopathologic Ishak score reduction as well as normalization of the level of profibrotic mediators (hydroxyproline, TGF-B and matrix metalloproteinase-2). Thus, HSC-targeted imatinib therapy shows outstanding anti-fibrotic effects with reduced cytotoxicity compared to conventional imatinib. It can represent a promising novel approach for liver fibrosis treatment.		
8	Gel in core carbosomes as novel ophthalmic vehicles with enhanced corneal permeation and residence		Carbopol is a good bio-adhesive polymer that increases the residence time in the eye. However, the effect of blinking and lacrimation still reduce the amount of polymer and the incorporated drug available for bioadhesion. Gel-core liposomes are advanced systems offering benefits making it a good tool for improved ocular drug delivery and residence time. Incorporation of carbopol in gel-core liposomes and their potential in ocular delivery have not so far been investigated. Fluconazole (FLZ) was selected as a challenging important ocular antifungal suffering from poor corneal permeation and short residence time. In this study, gel-core carbosomes have been elaborated as novel carbopol-based ophthalmic vehicles to solve ocular delivery obstacles of FLZ and to sustain its effect. Full in vitro appraisal was performed considering gel-core structure, entrapment efficiency, particle size and stability of the vesicles as quality attributes. Structure elucidation of the nanocarrier was performed using optical, polarizing and transmission electron microscopy before and after Triton-X100 addition. Ex-vivo ocular permeation and in vivo performance were investigated on male albino rabbits. Optimized formulation (CBS5) showed gel-core structure, nanosize (339.00 ± 5.50 nm) and not defined before (62.00% ± 1.73) entrapment efficiency. Cumulative amount of CBS5 permeated ex-vivo after 6 h, was 2.43 and 3.43 folds higher than that of conventional liposomes and FLZ suspension, respectively. In-vivo corneal permeation of CBS5 showed significantly higher AUC0-24 h (487.12 ± 74.80) compared to that of FLZ	2018	https://www.sciencedirect.com/science/article/abs/pii/S0378517318303491

			suspension (204.34 ± 7.46) with longer residence time in the eye lasts for more than 18 h. In conclusion, novel gel-core carbosomes could successfully be used as a promising delivery system for chronic ocular diseases.		
9	Oral vitamin-A-coupled valsartan nanomedicine: High hepatic stellate cell receptors accessibility and prolonged enterohepatic residence		So far, liver fibrosis still has no clinically-approved treatment. The loss of stored vitamin-A (VA) in hepatic stellate cells (HSCs), the main regulators to hepatic fibrosis, can be applied as a mechanism for their targeting. Valsartan is a good candidate for this approach; it is a marketed oral-therapy with inverse- and partial-agonistic activity to the over-expressed angiotensin-II type1 receptor (AT1R) and depleted nuclear peroxisome proliferator-activated receptor-gamma (PPAR-γ), respectively, in activated HSCs. However, efficacy on AT1R and PPAR-γ necessitates high drug permeability which is lacking in valsartan. In the current study, liposomes were used as nanocarriers for valsartan to improve its permeability and hence efficacy. They were coupled to VA and characterized for HSCs-targeting. Tracing of orally-administered fluorescently-labeled VA-coupled liposomes in normal rats and their fluorescence intensity quantification in different organs convincingly demonstrated their intestinal entrapment. On the other hands, their administration to rats with induced fibrosis revealed preferential hepatic, and less intestinal, accumulation which lasted up to six days. This indicated their uptake by intestinal stellate cells that acted as a depot for their release over time. Confocal microscopical examination of immunofluorescently-stained HSCs in liver sections, with considerable formula accumulation, confirmed HSCs-targeting and nuclear uptake. Consequently, VA-coupled valsartan-loaded liposomes (VLC)-therapy resulted in profound re-expression of hepatic Mas-receptor and PPAR-γ, potent reduction of fibrogenic mediators' level and nearly normal liver function tests. Therefore, VLC epitomizes a promising antifibrotic therapy with exceptional extended action and additional PPAR-γ agonistic activity.	2018	https://www.sciencedirect.com/science/article/abs/pii/S0168365918302864
10	Formulation and evaluation of taste-masked		The use of lipids as taste-masking excipients in paracetamol sachets and chewable tablets without compromising drug release was investigated. Twelve paracetamol granule formulations were prepared by melt granulation, using Precirol® (glyceryl palmitostearate), cetyl	2014	https://link.springer.com/article/10.1007/s40005-014-0137-0

	paracetamol-lipid sachets and chewable tablets		alcohol and stearic acid, at different paracetamol-lipid ratios. Based on efficient taste-masking results coupled with minimum retardation of drug release, paracetamol-Precirol (1:1), paracetamol-cetyl alcohol (1:2) and paracetamol-stearic acid (1:2) granules were selected for preparation of chewable tablets and sachets. Formulations were evaluated for the effect of storage, at 40 °C and 75 % RH for 6 months, on their performance. Results inferred that paracetamol sachets, after reconstitution in 100 ml water, showed efficient taste-masking compared to control sachets (without lipids). The sachets released more than 90 % of their drug content in 30 min, when tested in 900 ml of phosphate buffered saline, pH 5.8. Chewable tablets exhibited comparable taste-masking effect to a reference product, Tylenol® 80 mg chewable tablets, and yielded similar drug dissolution profiles (similarity factor f 2 > 50). Differential scanning calorimetry indicated the absence of interaction between paracetamol and lipids. Scanning electron micrographs supported the obtained results. Upon storage at 40 °C and 75 % RH for 6 months, all the prepared sachets and chewable tablets were found to be stable except cetyl alcohol-based tablets that showed decrease in the efficiency of taste masking with increase in release rate. In conclusion, selected lipids, Precirol®, cetyl alcohol and stearic acid, could be efficiently used in formulation of taste masked paracetamol sachets and chewable tablets without adversely delaying drug release.		
11	Smart ultrasound-triggered doxorubicin-loaded nanoliposomes with improved therapeutic response: a comparative study		Doxorubicin (DOX) effectiveness in cancer treatment is hampered by its nonspecific accumulation in organs. Ultrasound (US) is a promising noninvasive targeting approach. Currently, studies focus on developing more DOX-loaded US-triggered formulations with different composition, DOX doses, and US intensities. No studies were emerged to compare and select the most effective approach to endure. The aim of this study is to prepare and comparatively address the therapeutic potential of 2 different US-tunable nanosized liposomes while minimizing DOX dose and US intensity. One of the liposomes is tailored to be responsive for US non-thermal effects (DOX-USLs) and the other is designed to be thermoresponsive (DOX-TSLs). Both systems were compared in terms of cellular uptake, cell viability and	2020	https://www.sciencedirect.com/science/article/abs/pii/S0022354920302574

			apoptosis using HeLa cells as a cancer model. The IC50 of DOX-USLs and DOX-TSLs was 2.5–5 times lower than that of free DOX. IC50 reflected the significant superior cytotoxicity of DOX-TSLs (0.1 μg/mL) over DOX-USLs (0.2 μg/mL). Cellular uptake indicated that DOX-TSLs were inside the nucleus while DOX-USLs were accumulated everywhere in the intracellular space with lower fluorescent intensity inside the nucleus. However, both showed enhanced apoptosis in terms of enhanced caspase-3 activity, reduced glutathione levels and DNA fragmentation when compared to free DOX treatment.		
12	Oral genistein-loaded phytosomes with enhanced hepatic uptake, residence and improved therapeutic efficacy against hepatocellular carcinoma		Genistein (Gen) is one of the most potent soy isoflavones used for hepatocellular carcinoma (HCC) treatment. Low aqueous solubility and first-pass metabolism are the main obstacles resulting in low Gen oral bioavailability. The current study aims to introduce phytosomes as an approach to improve Gen solubility, protect it from metabolism by complexation with phospholipids (PL), and get used to PL in Gen lymphatic delivery. Different forms of PL namely: Lipiod® S100, Phosal® 53 MCT, and Phosal®75 SA were used in phytosomes preparation GP, GPM, and GPL respectively. The effect of formulation components on Gen absorption, metabolism, and liver accumulation was evaluated following oral administration to rats. Cytotoxicity and cellular uptake studies were applied on HepG2 cells and in-vivo anti-tumor studies were applied to the DEN-mice model. Results revealed that GP and GPL remarkably accumulated Gen aglycone in hepatic cells and minimized the metabolic effect on Gen. They significantly increased the intracellular accumulation of Gen in its complex form in HepG2 cells. Their cytotoxicity is time-dependent according to the complex stability. The enhanced in-vivo anti-tumor effect was observed for GP and GPL compared to Gen suspension on DEN-induced HCC in mice. In conclusion, Gen-phytosomes can represent a promising approach for liver cancer treatment.	2021	https://www.sciencedirect.com/science/article/abs/pii/S0378517321003690
13	Improving the Efficacy of Cyclooxegenase-2 Inhibitors in the		Oral carcinoma is a worldwide health threat with high rate of recurrence and metastasis. Cyclooxygenase-2 (COX-2) enzyme is over expressed in oral cancer cells and affects certain crucial processes in carcinogenesis. The inhibition of COX-2 enzyme could be an intriguing remedial target. Selective COX-2 inhibitors were recently	2020	https://www.sciencedirect.com/science/article/abs/pii/S177322472031529X

	Management of Oral Cancer: Insights into the Implementation of Nanotechnology and Mucoadhesion		considered as effective chemopreventive therapeutics in head/neck and oral carcinoma. Unfortunately, their clinical efficacies are vulnerable because of the poor aqueous solubility and hence, scanty absorption and bioavailability. Furthermore, the adverse effects of COX-2 inhibitors would further limit their potential. The recent advances in nano-drug delivery systems could offer a promising hope to circumvent these drawbacks. Herein, the possible role of COX-2 in the progression of oral cancer as well as the potential of COX-2 inhibitors in the management of this threat were highlighted. The factors limiting the application of COX-2 inhibitors were discussed. The state-of-the-art implementation of nanocarriers like nanocrystals, polymeric micelles, nanoemulsions and lipid-based carriers (liposomes, solid lipid nanoparticles & nanostructured lipid carriers) for improving the efficacy of COX-2 inhibitors were summarized. Finally, the possible contribution of mucoadhesive nanocarriers in the management of oral cancer was pointed out.		