

CURRENT RESEARCH TOPICS IN PHARMACY: *Drug Delivery*

February 28th, 2023 12.00 PM ISTANBUL

FOR REGISTRATION:



First Session- Moderator: Gülşah GEDİK 12.00-13.30 PM

Welcome- Prof. Oya Kerimoğlu
Marmara University, Istanbul, Türkiye

Core-shell type lipid-polymer hybrid nanocarriers as novel-generation drug delivery platform – Assoc. Prof. Ceyda Tuğba Şengel Türk
Ankara University, Ankara, Türkiye

Drug delivery systems used for biological products- Assist. Prof. Ongun Mehmet Saka
Ankara University, Ankara Türkiye

Viral delivery systems within the gene therapy landscape- Dr.Ceyda Ekentok Atıcı
Marmara University, Istanbul, Türkiye

Second Session – Moderator: Ongun Mehmet SAKA 14:00-15.30 PM

Nanobiomaterials for drug delivery- Assist. Prof.Gülşah Gedik
Trakya University, Edirne, Türkiye

Microneedles : A smart approach for intradermal and transdermal drug delivery systems-Assist.Prof.Ebru Altuntaş
Istanbul University, Istanbul, Türkiye

Nose-to-brain drug delivery of nanoformulations:Preparation and in vitro evaluation– Dr.Özge Gün Eşim
Ankara University, Ankara, Türkiye

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Third Session- Moderator: Ceyda EKENTOK ATICI 16.00-18.30 PM

Microemulsion utility in pharmaceuticals: An overview and pharmaceutical applications- Assist.Prof.Emre Şefik Çağlar
University of Health Sciences, Istanbul, Türkiye

Journey of the saponin from the plant to the formulation for the blocking tumor activities – Dr.Burcu Üner
The University of Health Science and Pharmacy in St. Louis, MO, USA

Development of injectable ROS responsive nanoparticles with identified protein for improvement of the cardiac repair following myocardial infarction- Dr. Renuka Khatnik
Washington University in St.Louis, MO, USA

Groundbreaking delivery systems: Liposomes-microbubbles complexes - Dr. Pankaj Dwivedi
University of Health Sciences and Pharmacy in St. Louis, MO, USA

Breaking the barriers with cutting edge intradermal delivery towards pain-free skin therapy: Dissolvable microneedle devices for localized therapy – Dr.Monica Dwivedi
Birla Institute of Technology, Mesra, India

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NOSE-TO-BRAIN DRUG DELIVERY OF NANOFORMULATIONS: PREPARATION AND *IN VITRO* EVALUATION

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Central nervous system (CNS)-related diseases constitute 6.3% of all diseases globally. Because of the increased prevalence of CNS-diseases, the requirement for novel strategies for delivering therapeutics across the blood-brain barrier (BBB) has arisen [1]. The management of CNS diseases is challenging. BBB is the main obstacle preventing traditional therapeutics from reaching the CNS.

Researchers have developed strategies that can deliver therapeutics to the CNS, such as (1) bypassing BBB by using other administration routes, (2) transient disrupting BBB by physical or biochemical approaches, (3) enabling penetration into BBB by administration of endogenous transporters and receptors, (4) inhibition of efflux transporters, (5) using drug carriers [2].

Nose-to-brain route has been considered a viable alternative to deliver therapeutics to the brain. Intranasal delivery to the CNS has some advantages including non-invasiveness, minimized systemic exposure, rapid transport from the nasal mucosa to the brain and prompt efficiency, elimination of the first-pass effect, lower side effects [3]. Although it has many advantages, mucociliary clearance, and limited absorption from the nasal epithelium are also disadvantages [4]. Due to the disadvantages of intranasal administration, various approaches are needed to increase drug penetration. Nanotechnology-based drug delivery systems including nanoparticles, in situ gels and liposomes have been designed to make use of the superiorities nanocarriers, such as extended retention at the nasal mucosa, nano-ranged size, and ability to open the tight junctions [2, 3].

In this study, migraine, a chronic neurological disease, was chosen as a model, and dexketoprofen trometamol (DXT) loaded chitosan- and chitosan/alginate nanoparticles were developed and characterized for treatment of migraine. Chitosan has been chosen as an ideal polymer for targeting the brain via intranasal therapy due to its capacity to generate inter-/intramolecular bonding and polycationic surface as a result of its amino groups. The developed nanoparticle formulations were formulated into a chitosan-based hydrogel formulation and the mucoadhesive properties of the formulations were investigated.

In this research two types of chitosan-based nanoformulations were prepared by the ionic gelation method. Chitosan-TPP nanoparticles were prepared using TPP

solution as a crosslinking agent at different concentrations (0.25-0.75%) and pH values (7-10) and chitosan at 0.2% (w/v) concentration. The resulting nanoparticles had particle size of 390.71-974.15 nm, with positive zeta potential and encapsulation efficiency in range between 2.33-22.18%. When the TPP concentration increased, the particle size of the nanoparticles increased while the encapsulation efficiency decreased due to the increased hydrophobicity of the carrier. Moreover, the increased TPP concentration has slowed down drug release for the same reason. However, no improvement in particle characteristics was observed with different pH values.

To improve the encapsulation efficiency and particle size, chitosan-alginate nanoparticles were prepared with different drug-to-alginate ratios and calcium chloride concentrations. The developed nanoparticles showed 223.60-480.42 nm of particle size, 9.65-14.23 mV of zeta potential and 9.04-31.31% of encapsulation efficiency. The increased drug-to-alginate ratio increased the encapsulation efficiency of DXT. However, the particle size was not affected by the drug-to-alginate ratio. On the other hand, the varying calcium chloride concentrations caused no statistically significant effect on the nanoparticles. When drug release profiles were investigated it was seen that the greater drug release was obtained from 368.45 nm sized optimum formulation with the highest encapsulation efficiency (31.31%) and surface charge (14.23 mv). Hence, further experiments were performed using this formulation.

The morphological structure of both type of nanoparticles was investigated using SEM images. The all nanoparticles revealed a homogeneous morphology.

The chitosan-alginate based optimum DXT-loaded nanoparticle was embedded into a mucoadhesive gel based on chitosan to prolong the mucosal retention of nanoparticles. The gel formulations were prepared by adding three different concentrations of ammonium sodium phosphate solution until pH 7 which is suitable for non-irritating nasal administration. Besides, the viscosity of all formulations was appropriate for nasal application and about 900 cPs. The gel formulation containing nanoparticles was subjected to *in vitro* dissolution study and slowed down the drug release compared to the nanoparticles. The results were also evaluated to determine the drug release mechanism. According to the determination coefficients, while drug release from nanoparticle formulation fits first-order kinetics, nanoparticle-containing gel showed Higuchi kinetics.

It was anticipated that prolonging the retention of formulation at the nasal mucosa through its mucoadhesive capabilities could improve its efficiency [5]. The mucoadhesive performance of the formulations were evaluated by penetrometer by using mucin dispersion instead of natural mucosal membrane. Both the nanoparticles and the gel formulations showed acceptable adhesive force and work of adhesion for nasal mucosa. The mucoadhesion values of chitosan-TPP nanoparticles were higher than chitosan-alginate nanoparticles due to the higher chitosan concentration of chitosan-TPP nanoparticles. Moreover, all the gel formulations demonstrated

mucoadhesion values than all nanoparticles and the mucoadhesion was positively correlated with the concentration of alkalizing agent because of the increased gelling properties. The mucoadhesive properties of the formulations were based on the use of positively charged chitosan and the formation of electrostatic interactions between the oppositely charged chitosan and mucin, resulting in superior mucosal retention [6].

Keywords: Chitosan, dexketoprofen trometamol, nanoparticle, nose-to-brain.

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