

Overview of The Targeted Treatment Through Nano-Drug Delivery Systems and Controlled-Drug Release Systems

BEYZA NUR CAM¹, MUCIP GENİŞEL²,

¹Agri Ibrahim Cecen University, Faculty of Pharmacy, Agri, Turkey

²Agri Ibrahim Cecen University, Faculty of Pharmacy, Department of Pharmaceutical Botany, Agri, Turkey

Abstract

Controlled-drug release systems simplify dosing regimen and minimize drug side effects. These systems increase patient compliance as well as treatment efficacy and safety. Spansules, contain drug capsules surrounded by slowly soluble substances, have been emerged as the first controlled release product. Unlike desired pathological region, influence on all parts of the body of drug active substances is one of the biggest problems in treatments. This problem has been tried to be minimizing through target-specific drug carrier systems. These systems are head role players in targeted treatment. They can release the desired amount of active substance to the desired area, and thus provide important therapeutic benefits for patients. In addition, due to their high economic value, the production of these systems attracts pharmaceutical manufacturers and many countries.

Keywords: : Controlled-drug release, spansules, nanocarrier, drug targeted, drug delivery system

Introduction

The influences except for the target section in the human body of drug active substances is one of the main problems in the treatment process. Recently, it has been designed target-specific drug release systems to providing convenience and efficacy to the patient in treatment by overcoming this problem. These systems, provide release of the substance with the therapeutic effect in the desired amount and in the required amount to the pathological region, are called as the drug delivery systems. Thanks to this system, access speed of drug to the desired area can be determined previously. In other words, the drug release systems have been designed to carry drug within a certain speed and time to the desired region (VASIR and LABHASETWAR 2005; TUYLEK 2017).

Targeted Treatments

Thanks to recent developments in biotechnology and pharmaceutical technology, it has been developed new drug formulations with effective in a specific area. Therapy through these drugs is called as the targeted treatment. The main purpose of drug targeting is storage in the target part of tissues or organs of the drug active substances. In other word, it is possible to transport to the target body parts of the conventional and biotechnological drugs by using drug release systems. Therefore, drug release systems, an indispensable element of targeted treatment, have turned into a field of considerable interest for researchers and drug sectors. Conventional drug formulations require usage with frequent intervals by patients. In treatment with these formulations, it may occur problems such as botulism or drop below the therapeutic dose of an active substance in the systemic circulation in the day. It is targeted to overcome these problems with targeted drug release systems (TUYLEK 2017).

Drug release systems can only be designed with nanoscale structures and through nanotechnology applications. Nanotechnology term is usually used for size 10-100 nm. However, for definition as nano of an item, it should be questioned not only its size but also

Received: 11.06.2019

Revised: 17.06.2019

Accepted: 18.06.2019

Corresponding author: Mucip GENİŞEL, PhD

Agri Ibrahim Cecen University, Faculty of Pharmacy,
Department of Pharmaceutical Botany, Agri, Turkey

E-mail: m.genisel@hotmail.com

Corresponding author: Beyza Nur Cam

Agri Ibrahim Cecen University, Faculty of Pharmacy, Agri,
Turkey

E-mail: cambezanur191@gmail.com

Cite this article as: B. N. Cam and M. Genisel, Overview of Targeted Treatment Through Nano-Drug Delivery Systems and Controlled-Drug Release Systems, Eastern Anatolian Journal of Science, Vol. 5, Issue 1, 43-49, 2019

its other properties. Developments in nanotechnology field have led to an increase in the number of researches on nanoparticles such as carbon nanotubes, nanoemulsions, and brought about a great innovation process for medicine and pharmacy the field. Nano-size powder drug and drug-carrier nanoparticles are called nanopharmaceutical (SAYINER and COMOGLU 2016).

Nanopharmaceutical products increase the absorption and dissolution of the drugs and thus maximize the bioavailability of drugs (SAYINER and COMOGLU 2016). Nanoparticles may prolonged duration of action by adding substances such as polyethylene glycol (PEG), polyoxyethylene (POE). Besides, the contrast agents, targeting groups, temperature and pH sensitive substances can be added to active substances. Nanocarriers, contain contrast agents as well as active substance, are called theranostics at the same time (CELEBI and GURSOY 2014).

Nanostructured systems are quite successful in terms of target specificity and imaging in treatment. Due to changes in the surface, the nanostructures have high stability. Therefore, they can increase the blood residence time of active therapeutical substance. Also, it can be enhanced the effectiveness of the treatment in the desired body or tissue part by utilizing from the difference in their pH and temperature sensitivity (SENGEL-TURK and HASCICEK 2009; SAYINER and COMOGLU 2016).

The pegylation, modification of the drug by binding one or more PEG molecules to a drug molecule, is one of the examples of modifications to nano-carrier systems. Kolate et al. (2014) have informed that pegylation makes to hydrophilic the surface of the drug carriers, and thus the inactivation and absorption of the proteins and these carriers by the reticuloendothelial system can be prevented.

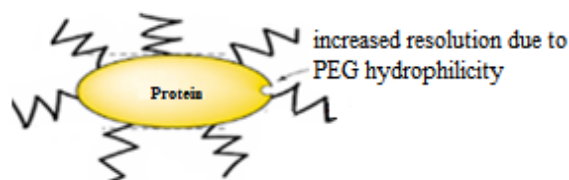


Figure 1. Pegylation (BAYINDIR 2007)

The targeted treatment applications divide into two parts as active and passive targeting. Passive targeting is the transport of drugs to the desired region through natural physiological events and passive factors. In this targeting, nanopharmaceuticals is canalized to the

tumour cell via passive diffusion or convection which called the movement of substances in the liquid (ONYUKSEL and COMOGLU 2014). On the other hand, active targeting is known as specific delivery of an active substance-carrying structure to the desired cell, tissue or organs. In this targeting method, to direct into the specific cells the nanoparticles, it is utilized from the physical factors such as heat, magnetic field, ultrasound as well as chemical factors such as pH, reactive oxygen species, proteases (ONYUKSEL and COMOGLU 2014).

Drug Carrier Systems Used in Targeted Treatment

Niosomes are formed of active substance ion-free in aqueous media and are divided into two as single-layer, multi-layer depending on their formation strategies. They increase drug solubility due to containing both amphiphilic and lipophilic structures,. Therefore, they can be used to transport drugs with low solubility. Niosomes, acting as a reservoir for drugs, can determine the rate of drug release and also prevent the inactivation of the drugs by interacting with biological fluids (MAKESHWAR and WASANKAR 2013).

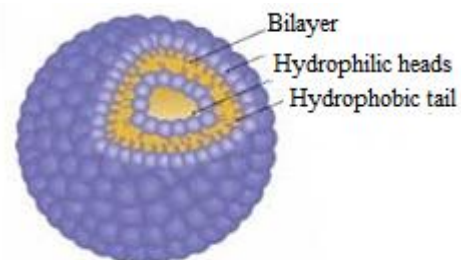


Figure 2. Structure of niosome (FATIMA et al. 2017)

Nanogels, formed by crosslinking of positively charged polymers, are reticulate structures with the ability to swell with water. Nanogels can absorb water up to 10-20% of own weight and can form a hydrogel in the presence of crosslinker. Nanogels used in treatment increase bioavailability especially in oral intake by protecting drugs from adverse environmental conditions, biological fluids. In addition this, they can provide drug release to some specific barrier such as blood-brain barrier in the body (CELEBI and GURSOY 2014).

Nanoemulsions are formulations containing nm-sized particles in the dispersed phase produced with the surfactants, water and oil. Dilution, pH, temperature do not cause any changes on nanoemulsion formulations. These formulations may also contain auxiliary emulsifying agents (free fatty acids), preservatives (EDTA), antioxidants (tocopherol) (SAYINER and COMOGLU 2016). They increase the water solubility

of the drugs due to their good wetting and dispersing properties. On the other hand, nanoemulsion formulations don't remain stable for a long time since phase separation in these systems disrupts after a while (TIRNAKSIZ and GURSOY 2014).

Nanocrystals are nanometer-sized crystal structures and their most striking feature is the transport of just active substances. Nanocrystals offer a number of advantages such as the reduction of dose due to the increase of oral bioavailability of drugs, ease to preparation with organic solvents and simple use procedures (ONER et al. 2014).

Carbon nanotubes, 2-100 nm in diameter and 5-550 nm in length, occur by rounding of carbon layers. These nanotubes are quite stable and non-cytotoxic. Also, drug loading and transport operations can take place in a simple way by using them. Moreover, it has therapeutically important that the outer part of the carbon nanotubes can be modified with the desired chemical for targeting. Because of the large surface areas, their adsorption properties are good (YANG et al. 2008). Carbon nanotubes are used in antigen identification via DNA and protein sensors (DEGIM and GURSOY 2014).

Liposomes, surrounded by a phospholipid layer in the range of nm and mm in size, are in biocompatible vesicle form, not forming an immune response (SILINDIR et al. 2013). Treatment problems such as the low resolution, serious side effects, low bioavailability and short half-life for drugs could be minimized by using liposomes. Liposomes are also used in cancer treatment since they affect the blood permeability positively in cancerous tissues (WANG et al. 2008).

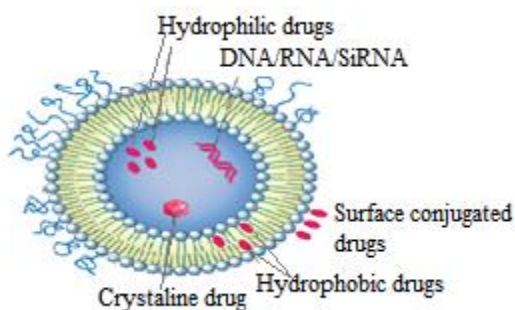


Figure 3. Structure of liposome (RAFE and AHMET 2017)

Nanoparticles are prepared with natural or artificial polymers in the range of 10-100 nm and defined as nanospheres or nanocapsules depending on the

technique of production. They make possible the delivering to specific tissue of genes and enable long-term drug release. Also, nanoparticles increase the stability of the active substances. Moreover, the sterilization process of the nanoparticles is very easy and the drug loading potential is high. Therefore, effective drug release and bioavailability may be increased by using nanoparticles (DERMAN et al. 2013).

Nanocapsule is a system consisting of vesicle structures. In this system, after the active substance is placed in any cavity in the body, it is coated by a membrane. Nanocapsules are easily able to access to the bloodstream bypassing vascular structures. Their surface areas and active substance solubility are proportional (SINGH and LILLARD 2009). Nanocapsules allow reaches the target of the active substance. Due to their stability and long shelf life, in the preparation of new pharmaceutical products, they are also used.

Micelles are spherical shaped particles strengthened with hydrophilic polymer extensions with a core formed by hydrophobic blocks. They increase the solubility of drugs and thus bioavailability. They allow the accumulation of the active substance in places where the vascular structure is weak. Micelles are connected to the only specific ligand and protect the drug from the external environment and biological interactions. Therefore, they can minimize drug side effects (CANEFE and DUMAN 1994; SEZGIN et al. 2003).

Dendrimers are of large molecule groups that repeat each other with symmetrical branching. They have functional groups showing branching around the nuclei and different active molecules can be added to these groups. Dendrimers are used as drug carrier systems controlled through encapsulation of active substances (TUYLEK 2017).

Controlled Release Systems

The main objective of drug design studies is the elimination of side effects of drugs, minimization the amount of active substance, simplification of the dosing regime and improvement of the patient's living standards with changes in all these parameters. The systems, provide all this together, is called controlled release systems (BASAR 2006). The controlled release systems release a fixed dose of the therapeutic substance. In other words, they release locally or systematically the active substance at an equivalent amount to the drug eliminated from the body within a

certain period of time (SUMEDH et al. 2017). They have some advantages such as a decrease in side effects and increase in tolerability, high therapeutic effectiveness, patient compliance, decrease in health expenditures. On the other hand, difficulty in dosing and an increase in the first-pass effect are among the disadvantages of these systems (SUMEDH et al. 2017).

Example of first controlled drug release system

The first controlled release formulation produced by Smith Kline in a French laboratory was named Spansule forming from time (span) and capsule (capsule) words (BASAR 2006). The basis of this system is based on the placement of drugs in capsules produced with slow dissolving materials. This drug release system has been used effectively in treatment the past to the present day. Multiple drugs can be administered in combination with spansules and these release systems provide release of the active substance with different amounts and time intervals (HAUNG and KAO 2000).

Spansules compared to conventional drugs have numbers of therapeutic advantages such as maximum patient compliance, simple dosing regimen, increase the reliability level of highly effective drugs, minimal systemic and localized side effects, prevention sudden change in drug concentration in the blood and thus increase the degree of bioavailability, and staying of the active substance in a stable form for a long time in the gastrointestinal tract (SUMEDH et al. 2017). On the other hand, spansules include disadvantages such as the low usage capacity as systemic, high cost, treatment difficulties of the toxic reactions caused by this kind of long-acting pharmaceutical products (SUMEDH et al. 2017).

Microencapsulation method

Microencapsulation is defined as the coating with a coating material of active substances such as liquid, solid or gas (NEDOVIC et al. 2011; DINC et al. 2012; BULDUR 2012) (Table 1.). The inner part of the microcapsule is referred to as the core, inner phase, or fill and its outer part is defined by names such as shell, shield, coating or membrane. The substances used in the microencapsulation method should be biodegradable and should be able to isolate the internal phase from environmental factors such as temperature, microorganism and humidity (YANG et al. 2009; SANLIDERE- ALOGLU and ONER 2010; BULDUR 2012). Microcapsules can be produced in different forms such as simple, irregular, multi-core, multi-walled, and matrix depending on the

physicochemical properties of the shell composition as well as the structure and number of the core (GHARSALLAOUI et al. 2007; BULDUR 2012) (Fig. 4.).

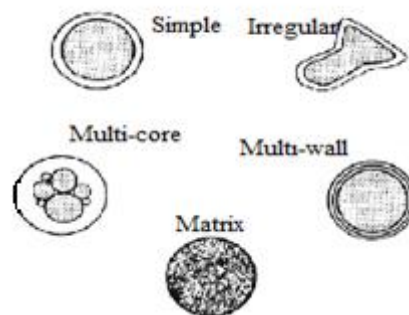


Figure 4. Microcapsule types (GHARSALLAOUI et al. 2007).

The size of particles obtained in the microencapsulation is vary between a few nm to a few mm (NEDOVIC et al. 2011; BULDUR 2012). By using the microencapsulation technique, some vitamins, drugs, unsaturated fatty acids, probiotics, biocatalysts such as enzymes can be preserved from the external environment differences like pH changes (SANLIDRE- ALOGLU and ONER 2010).

Natural Polymers	Synthetic Polymers
Agar	Acrylic polymers
Albumin	Aliphatic polymers
Alginate	Polyethylene glycol
Gelatine	Polyamide
Acacia	Polyvinyl alcohol
Cellulose	Polystyrene
Pectin	Silicones
Casein	Cellulose derivatives
Dextran	Polylysine

Table 1. Polymers used in microcapsule production (KAS 2002).

The stability of analgesic, antibiotics, antihistamines, sedatives, antibodies, hormones, vitamins, cardiovascular drugs and enzymes can be increased by using microcapsule technology. Besides these drug groups, it is utilized from the microencapsulation in cosmetic applications such as perfumery, aromatherapy as well as the production of phase changing materials, liposome, colour changing substances, insect repellents (DAS et al. 2011).

Transdermal Applications

Transdermal systems contain small needles and the drug passes through these small needles to the subcutaneous. Example, nicotine bands. When taken orally, the use of drugs that are completely eliminated by the liver has become possible with transdermal applications. They offer advantages such as bypassing the gastrointestinal tract, pain-free use, and a constant dose release (BASAR 2006).

Implants

The implant applications are based on the placement of the concentrated active substance under the skin. In the 1990s, two implant systems are produced, one of which was silicon and the other was the lactic / glycolide copolymer (DANCWERTS and FASSIHI 1991; YAPAR 2012). Prior to the development of implant systems, almost all drugs had been administered orally in liquid and powdered forms. Just after these therapeutic agents intake from oral, they cannot maintain their effective doses due to interaction with the gastrointestinal system. In order to eliminate these negations, it has become obligatory to produce new dosage forms and this status has triggered the production of drug carrier systems such as implants long stably affecting the specific areas of the body (ZAKI et al. 2012). Recently, implant drug systems have been widely used as a pacemaker, joint prosthesis and pain pump in cardiology, neurology and orthopaedics areas. Also, the subcutaneous implant systems containing goserelin acetate produced with polylactic glycolic acid are used to treat prostate cancer. Additionally, narcotic analgesic effective naltrexone zinc tannate complexes and subcutaneous implants of human growth hormone could be produced (YAPAR 2012). Implant Controlled Release Systems can be divided into two groups as diffusion and activation controlled systems depending on the release mechanism of the active substance.

Diffusion Controlled Systems

Membrane Controlled Systems

In these systems, the therapeutic agent is imprisoned by the polymer membrane and its release rate is controlled with diffusion velocity of the membrane. The membranes used in this system may be homogeneous, heterogeneous, porous, non-porous and semi-permeable. To prevent the non-biodegradable membrane-induced toxification, biodegradable membranes containing polymer fibres should be preferred in the production of the membrane controlled systems (EENINK et al. 1987). The most important point in this system is the maintenance of system

integrity while therapeutic agent releases via the dissolve of the polymer membrane (YAPAR 2012).

Matrix Diffusion Controlled Systems

In these systems, active substances are dispersed in the lipophilic or hydrophilic polymer matrix. The rate of release of the active substance is determined by its diffusion rate from the polymer matrix. The formation of this system is based on cross-link and dispersion of the active substance thorough viscous and semi-solid polymers at 25° C. These systems can also be prepared by solvent evaporation technique. In swell controlled systems, the polymer matrix system absorbs body fluids and thus the expanding system release the active substance in short. The rate of drug release in these systems can be controlled by the diffusion rate of body fluids to the polymer matrix system (REMINGTON et al. 2005; YAPAR 2012).

Microreservoir Dissolution Control Systems

These systems are small structures prepared by homogeneously suspending of the crystal therapeutic agents in the matrix. The systems can be coated with different polymers and thus the drug release rate can be modified (REMINGTON et al. 2005).

Osmotic Pressure Activation Systems

In these systems, the release rate of the therapeutic agent in the reservoir is controlled by the osmotic pressure difference (YAPAR 2012).

Vapour pressure activated systems

These systems contain moving chambers and the therapeutic agent is in these chambers. Vapour pressure generated in the human body by substances such as fluorocarbon leads to the release of the active substance from these chambers. The release rate of active substances is controlled with the pressure level at the body temperature (MORAIS et al. 2010).

Activation controlled system

Systems with magnetic activation

The release of therapeutic agents containing large molecules are slow. Therefore, to increase the release rate of these active ingredients, it has been developed implants prepared with magnetic particles. In these systems, the therapeutic agent and iron powders (magnetic beads) are homogeneously mixed and are dispersed in the polymer (YAPAR 2012).

Ultrasonic wave the activation systems

These systems are prepared with biodegradable polymeric matrices such as poly [bis (p-carboxyphenoxy) alkane anhydride]. When this material used for matrix, it can be increased the rate of drug release by ultrasonic waves (YAPAR 2012).

Hydrolysis activated systems

These systems are prepared by dispersing the therapeutic agent in the biodegradable polymer and the dissolution time of this polymer determines the rate of drug release. The pH changing substances such as calcium lactate can be added to these implant systems to control the erosion speed of the polymers (DANCWERTS and FASSIHI 1991; CHIEN and LIN 2006).

Conclusion

The classical dosage forms used for the therapeutical agents are insufficient in effective and reliable treatment. When drugs are used in these classical form, they affect not only the pathological regions of the body but also healthy parts of the body. This problem is tried to be overcome with the target-specific drug carrier systems. One of the most important problems in the use of classic drugs is the frequent dosing interval; therefore, patients who use continuous medication have to carry their medication with them. In case of a dose of the drug is omitted, serious problems and life hazards for patients may occur. However, when controlled release products are taken one dose in a day or are adhered to the skin, they release the therapeutic agent at certain intervals without the need for further process. Besides therapeutic advantages, the economic value of controlled release products is quite high. Therefore, their production will contribute significantly to the economy of the countries.

References

BASAR, H.M. (2006), Yüksek Lisans Tezi, Organik kokulu doğal adsorbanlarla kontrollü ilaç salımı. İstanbul Teknik Üniversitesi/ Fen Bilimleri Enstitüsü, İstanbul

BAYINDIR, Z., YUKSEL, N. (2007), Pegilasyon, PEG konjugantlarının hazırlanması ve uygulamaları, Ankara Ecz. Fak. Derg., 36 (4), 249 – 266.

BULDUR, P.M. (2012), Yüksek Lisans Tezi, Encapsulation of Food Flavors Via

Coacervation Method. Molecular Biology–Genetics & Biotechnology Programme, İSTANBUL TECHNICAL UNIVERSITY, İstanbul.

- CANEFE, K., DUMAN, G. (1994), İlaçların seçici taşınması ve hedeflendirilmesi, Ankara Ecz. Fak. Derg., 23: 1-2.
- CHIEN Y.W., LIN S. (2006), Drug delivery: controlled release. Encyclopedia of Pharmaceutical Technology, 1(1), 1082-103.
- ÇELEBİ, N., GURSOY, A. (2014), Nanojeller zırh içinde, nanofarmasötikler ve uygulamaları, İstanbul: Kontrollü Salım Sistemleri Derneği, 89-100.
- DANCWERTS, M., FASSIHI A. (1991), Implantable controlled release drug delivery systems: A review, Drug Dev Ind Pharm, 17(11), 1465-502.
- DAS, S.K., DAVID, S.R.N., RAJABALAYA, R., MUKHOPADHYAY, H. K., HALDER, T., PALANISAMY, M., KHANAM, J. (2011), Microencapsulation techniques and its practices, Int J Pharma Sci Tech; 6(2), 1-23.
- DEGİM, L.T., GURSOY, A. (2014), Fulleren, karbon nanotüp, nanolif, zırh nanokafesler içinde, Nanofarmasötikler ve uygulamaları, İstanbul: Kontrollü Salım Sistemleri Derneği, 139-150.
- DERMAN, S., KIZILBEY, K., AKDESTE, Z. (2013), Polymeric Nanoparticles, Journal of Engineering and Natural Sciences Mühendislik ve Fen Bilimleri Dergisi Sigma, 31, 109-122.
- DINC, M., ASLAN, D., ICYER, N.C. , CAM, M. (2012), Gıda Teknolojileri Elektronik Dergisi, Mühendislik Fakültesi, Erciyes Üniversitesi, Kayseri , 7(2), 1-11.
- EENINK, M.J.D., FEIJEN, J., OLIJSLAGERI, J., ALBERS, J.H.M., RIEKE, J.C., GREIDANUS, P.J. (1987), Biodegradable hollow fibres for the controlled release of hormones., J Control Release , 6(1), 225-47.
- FATIMA, S.S., BEGUM, S., FATIMA, T. (2007), Madiha Jabeen, 1B-Pharmacy, Deccan School of Pharmacy, Hyderabad. Telangana. India, 2Assistant Professor, Department of pharmaceuticals, Deccan school of Pharmacy, Hyderabad. Telangana, India.
- GHARSALLAOUI, A., ROUDAUT, G., CHAMBİN, O., VOİLLEY, A., SAUREL, R. (2007), Applications of spray-drying in microencapsulation of food ingredients: An overview. *Food Research International*, 40(9), 1107-1121.
- HAUNG, J., KAO, H., WV XY. (2000), The pH-dependent biphasic release of azitromyidine from a layered composition of PVP disks and

- P (MMA/MAA) spheres. *Journal of Controlled Release*, 67(1), 45-54.
- KAS, S.H. (2002), İlaç taşıyıcı partikülersistemler, *Kontrollü salım sistemleri* içinde, İstanbul; Kontrollü Salım Sistemleri Derneği Yayınları, 1,65-99.
- KOLATE, A., BARADIA, D., PATİL, S., VHORA, L., KORE, G., MISRA, A. (2014), PEG-A versatile conjugating ligand for drugs and drug delivery system, *Journal of Controlled Release*, 67-81.
- MAKESHWAR, K. B., WASANKAR, S.R. (2013), Niosome: a Novel Drug Delivery System. *Asian. J.Pharm. Res.*, 16-20.
- MORAIS, J.M., PAPANITRAKOPOULOS, F., Burgess, D.J. (2010), *Biomaterials/tissue*
- NEDOVIC, V., KALUSEVIC, A., MANOJLOVIC, V., LEVIC, S., BUGARSKI, B., et al . (2011), An overview of encapsulation technologies for food applications. *Procedia Food Science*,(1), 1806-1815.
- ONER, L., GURSOY, R.N., GURSOY, A. (2014), Nanokristaller. zırh içinde, nanofarmasötikler ve uygulamaları, İstanbul: Kontrollü Salım Sistemleri Derneği, 125-137.
- ONYUKSEL, H., COMOGLU, T. (2014), Nanotaşıyıcılarda hedeflendirme, nanofarmasötikler ve uygulamaları, *Kontrollü Salım Sistemleri Derneği*, 211-225, İstanbul.
- RAFE, R., AHMED, Z. (2017), Liposomal drug delivery systems, Have Opened a New Window in Pharmaceutical Sciences, Department of Pharmacy, Southeast University, Dhaka, 11(4), 250.
- REMINGTON, J.P., WILLIAMS, L., WILKINS, 2005. Diffusion controlled systems, University of the Sciences in Philadelphia, Remington: The science and practice of pharmacy, USA, 947-8.
- SANLIDERE- ALOGLU, H., ONER, Z. (2010), Peyniraltı Suyu Proteinlerinin Mikroenkapsülasyon Teknolojisinde Kaplama Materyali Olarak Kullanım Olanakları, Süleyman Demirel Üniversitesi, Mühendislik-Mimarlık Fakültesi, Gıda Mühendisliği Bölümü, Isparta, Akademik Gıda 8(3), 38-42.
- SAYINER, Ö., COMOGLU, T. (2016), Nanotaşıyıcı sistemlerde hedeflendirme, Ankara Üniversitesi, Eczacılık Fakültesi Dergisi, Farmasötik Teknoloji AD., 40(3), 62-79.
- SENGEL-TURK C.T., HASCICEK C. (2009), Polimerik nanopartiküller ilaç taşıyıcı sistemlerde yüzey modifikasyonu, Ankara Eczacılık Fakültesi Dergisi, 137-154.
- SEZGIN, Z., YUKSEL, N., BAYKARA, T.,(2003), İlaç taşıyıcı sistemler olarak polimerik misellerin hazırlanması ve karakterizasyonu, Ankara Ecz. Fak. Derg., 32(2) 125-142.
- SILINDIR, M., ERDOGAN, S., OZER A.Y. (2013), Nanosized multifunctional liposomes for tumor diagnosis and molecular imaging by SPECT/CT. *J Liposome Res* , 23, 20-27.
- SINGH, R., LILLARD, J.W. (2009), Nanoparticle-based targeted drug delivery, *Experimental and Molecular Pathology*, 86, 215-223.
- SUMEDH, N.M., Dr. SHIVSHANKAR, D., MHASKE and MAHESH, B. N. (2017), Assessment of controlled release formulation for different drug in spansules , *WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES*, 6(11), 908-916.
- TIRNAKSIZ, F., GURSOY, A. (2014), Nanoemülsiyonlar zırh. içinde, nanofarmasötikler ve uygulamaları, İstanbul:Kontrollü Salım Sistemleri Derneği, 101-110.
- TUYLEK, Z. (2017), İlaç taşıyıcı sistemler ve nanoteknolojik etkileşim, elektronik ve otomasyon bölümü, biyomedikal cihaz teknolojisi, *Bozok Tıp Dergisi* , 89-98.
- VASIR, J.K.; LABHASETWAR V. (2005), Targeted drug delivery in cancer therapy, *Technology in Cancer Research and Treatment*, 4(4), 363-374.
- WANG, X., ZHANG, L., LEE, S., DAI, H. (2008), Application of nanotechnology in cancer therapy and imaging, *A Cancer Journal For Clinicals*; 58 (2), 97-110.
- YANG, F., Fu, D.L., LONG, J., Ni, Q.X . (2008), Magnetic lymphatic targeting drug delivery system using carbon Nanotubes, *Medical Hypotheses*,765-767.
- YANG, J., Xiao, J.-X., DING, L.-Z. (2009), An investigation into the application of konjac glucomannan as a flavor encapsulant. *European Food Research and Technology*, 229(3), 467-474.
- YAPAR, E.A. (2012), İmplant edilebilen polimerik ilaç salım sistemlerine genel bakış, *Türkiye Klinikleri J Pharm Sci* ; 1(2), 73-82.
- ZAKI, M. A.J., SATISH, K.P., DHEERAJ, T.B., DINESH, K.J. (2012), Implantable drug delivery system, *International Journal of PharmTech Research*; 4,280-292.