Acta Pharm. Sci. Vol 57 No: 1. 2019
DOI: 10.23893/1307-2080.APS.05705

Dexketoprofen trometamol-loaded Eudragit® RL 100 nanoparticle formulation, characterization and release kinetics

A. Alper Öztürk[1*], Evrim Yenilmez[1], Yasemin Yazan[1]

1 Anadolu University, Faculty of Pharmacy, Department of Pharmaceutical Technology, Eskişehir, Turkey.

ABSTRACT

Development and *in vitro* evaluation of dexketoprofen trometamol (DT)-loaded nanosized and controlled release drug delivery system was aimed in this study.

DT-loaded Eudragit® RL 100 polymeric nanoparticles were prepared using nano spray-dryer. Structures of DT-loaded polymeric nanoparticles were elucidated by particle size and zeta potential measurements, shape and surface imaging, thermal analysis, X-ray diffraction and FT-IR and ^{1}H-NMR determinations.

The particle size of the formulations was measured in the range of 475.5-798.7 nm. The droplet size distribution of the formulations was observed in the range of 0.349-0.395. These results showed that nanosized and monodispersed formulations were prepared. The drug content was found to be in the range of 35-38%. DT-loaded particles exhibited nanostructured and spherical shape. In vitro release studies showed extended release of DT. Release was found to fit Korsmeyer-Peppas kinetic model using DDSolver software program.

Depending on the *in vitro* test results obtained, formulations developed in this study seem to extend the release of DT from the nanoparticles prepared which are promising for prolonging analgesic activity.

Keywords: Dexketoprofen trometamol, Eudragit® RL 100, Polymeric nanoparticle, Spray-drying, DDSolver.

INTRODUCTION

DT which is in clinical use since 1996 is the water-soluble salt of dextrorotatory enantiomer of racemic ketoprofen, a non-steroidal anti-inflammatory drug (NSAID). Since dexketoprofen is more lipophilic than ketoprofen, it is rapidly absorbed followed by the activity starting in a short time and reaching

*Corresponding author: A. Alper Öztürk, e-mail: aaozturk@anadolu.edu.tr
(Received 06 November 2018, accepted 19 November 2018)

maximum plasma concentration in a short period.[1]

Polymeric nanoparticles are matrix systems that are prepared with natural or synthetic polymers with sizes in the range of 10 to 1000 nm. Nanoparticles are defined as either nanospheres or nanocapsules depending on their structures where the active substance is solubilized, entrapped and/or adsorbed onto the particle surface. Natural (proteins, polysaccharides) and synthetic polymers (synthesized during production, pre-synthesized) are used in the production of polymeric nanoparticles.[2] Both natural and synthetic particulate drug delivery systems are preferred to obtain controlled drug release for increasing the life quality of patients.[3]

A number of approaches can be used to manufacture polymeric nanoparticles such as salting-out, solvent evaporation, supercritical fluid technology, microemulsion, mini-emulsion, surfactant-free emulsion, and interfacial polymerization.[4] Spray-drying subtitues for a single-step, continuous and scalable procedure devoted to transforming liquid systems

Eudragit® RL, also called Eudragit Retard L, is a copolymer of poly(ethyl acrylate, methyl methacrylate and chloro trimethyl ammonium methyl methacrylate) containing 8.8 %-12 % quaternary ammonium groups. It is insoluble at physiologic pH values with limited swelling thus representing a good candidate for drug dispersions.[8]

Drug release is a significant topic in the context of drug development for years. With intensive progress in drug formulation design with increasing revolution and innovation, drug release is introduced giving it a substantial role in drug formulation development and quality control. It is a relatively rapid and inexpensive technique to predict *in vivo* absorption of a drug formulation. Quantitative evaluation of drug dissolution characteristics is of great interest to the pharmaceutical scientists owing to its outstanding advantages.[9]

DDSolver is a menu-driven add-in program which can be used to facilitate the modeling of dissolution data using nonlinear optimization methods based on a built-in model library containing fourty dissolution models. It offers a number of benefits over the other software packages prepared for dissolution kinetic modeling.[10,11,12] Among the dissolution kinetic models for drug release are zero order, first order, Hixson-Crowell, Higuchi, Korsmeyer-Peppas models, etc. [13,14]

In this study, DT-loaded Eudragit® RL 100 polymeric nanoparticles were prepared using Nano Spray Dryer B-90 and characterized. In vitro dissolution data and kinetic modelling were investigated through DDSolver program aiming sustained release of DT.

METHODOLOGY

DT was a kind gift of Abdi İbrahim (İstanbul, Turkey). Eudragit® RL 100 was obtained from Degussa Röhm Pharma Polymers (Germany). Methanol and deutero chloroform were both purchased from Merck (Germany) while acetonitril, potassium phosphate monobasic and sodium hydroxide were purchased from Sigma-Aldrich (Germany). All other chemicals and reagents were used of pharmaceutical and analytical grade.

Preparation of nanoparticles

For the preparation of the polymeric solution with and without DT, Eudragit® RL 100 was dissolved in methanol under a magnetic stirrer at 250 rpm for 2 hrs to obtain a clear solution. DT was added to this clear solution and stirred further for another 5 minutes. Nano spray-dryer (Nano Spray-Dryer B-90, BÜCHI, Switzerland) was conditioned 30 minutes using methanol to obtain the desired levels of spraying, pump level, inlet temperature, outlet temperature, gas flow and ambient temperature prior to delivering the polymeric soluton. Inlet temperature of 120°C, outlet temperature of 54°C and a needle with 4 μm pore size were used during application (Table 1). Dried nanoparticles were collected in the collecting chamber. Contents of formulations prepared were summarized in Table 2.

Table 1. Spray-drying conditions

Inlet temperature	Outlet temperature	Pump level	Spray level
120°C	54°C	3	100 %

Table 2. Content of polymeric nanoparticles

Code	Eudragit® RL 100 (g)	DT (g)	Methanol (mL)
ERL-blank	1	-	100
ERL-1	1	0.05	100
ERL-2	1	0.1	100
ERL-3	1	0.15	100

**Blank:* *Formulation without active ingredient*

Characterization

Morphology

Particle shape and surface properties of the freshly prepared polymeric nanoparticles (PNP) and pure DT were examined by SEM (Zeiss Ultra Plus Fesem, Germany) after spreading the formulation onto the carbon band and coating with gold.

Particle size, polydispersity index (PDI) and zeta potential

Particle size and distribution of prepared PNPs were measured (Zetasizer Nano ZS, Malvern, UK) by dispersing the formulation in distilled water adjusted to a conductivity of 50 μS with NaCl to avoid measurement deviations. Zeta potential values were determined using the same instrument in a disposable folded capillary zeta cell, at 25°C room temperature and diluted with distilled water.

Thermal analysis (DSC)

Thermal analyses using DSC (Schimadzu DSC-60, Japan) of pure DT, pure polymer and PNPs prepared were performed against an aluminum reference and nitrogen gas at a flow rate of 50 mL. min^{-1} with a temperature increase of 10°C.min^{-1} in the 30-300°C range.

X-ray diffraction (XRD)

XRD analyses of pure DT, pure polymer and PNPs prepared were performed with Rikagu generator (XRD Rikagu Rint 2000, Japan) at a speed of 40 kV, 30 mA current intensity, 2Θ angle and 2°min^{-1} in the range of 2-40°.

Fourier transform infrared spectrophotometry (FT-IR)

FT-IR spectra of pure DT, pure polymer and PNPs prepared were determined at 4000-500 cm^{-1} wavelength using FT-IR (Schimadzu IR Prestige-21, Japan).

Nuclear magnetic resonance (NMR)

NMR analysis (^{1}H-NMR) of pure DT, pure polymer and PNPs prepared were determined (Bruker 500 MHz UltraShield NMR, Germany) by dissolving the samples in deutero chloroform ($CDCl_3$).

HPLC method

HPLC (Shimadzu-20 A, Japan) equipped with reversed- phase NUKLEODUR column (diameter, 4.6 mm; length, 250 mm, C_{18} Gravity, 5 μm pore size) was used. Determination of DT was achieved by a modified HPLC method. 25:75 (v/v) acetonitrile-methanol was selected as the mobile phase following preliminary tests for the best resolution of DT. Flow rate of mobile phase was 1

$mL \cdot min^{-1}$ and constant amount of 25 µL was injected using an automatic injector (Shimadzu, Japan). Fluorescent detector (Shimadzu, Japan) was used at 258 nm and the column temperature was set to 30°C. HPLC method used was validated in reference to previous studies.[15]

Encapsulation efficiency (EE %)

Distilled water was used as a solvent for determining DT amount. 5 mg accurately weighed ERL-1 was put in a 2.5 mL-Eppendorf tube and 2 mL distilled water was added. After ultrasonication for 5 minutes, the upper transparent portion was removed by centrifugation at 11.000 rpm for 5 minutes and the sample was analyzed following dilution and filtration.

To determine DT incorporated into PNPs, 2 mL of the mobile phase where both DT and Eudragit® RL 100 were previously dissolved was added to the remaining particles. Following ultrasonication for 5 minutes, the clear solution obtained was filtered through the polyamide filter after adequate dilutions. Tests were repeated 3 times for each formulation. Loading capacity was calculated using the equation given below.[16]

EE %= [[(Drug concentration in formulation)-(Drug concentration in supernatant)]/ (Drug concentration in formulation)]x100 Eq. 1

In vitro release study

In vitro release of DT from Eudragit® RL 100 PNPs was investigated over 48 hrs using a dialysis membrane. PNP containing 1 mg DT was placed in a cellulose acetate dialysis bag (MW cut off 12-14 kDa, Sigma). After the addition of 1 mL of dissolution medium, the bag was sealed at both ends. Dialysis bag was then placed into an amber glass beaker containing 100 mL PBS (pH 7.4) at 37°C±0.5°C as the dissolution medium under continuous stirring of 100 rpm. The receptor compartment was closed to prevent evaporation of the dissolution medium. Samples were withdrawn at regular time intervals and the same volume was replaced by fresh dissolution medium. DT concentration in the samples was quantified by HPLC method.

Determination of *In vitro* kinetics with DDSolver program

Data obtained in the *in vitro* drug release studies was further investigated for release kinetics using DDSolver software program.[9]

Statistical Analysis

Each experiment was carried out three independent times and the data are presented as mean ± standard error (SE). Microsoft Excel and DDSolver were employed for statistical analysis.

RESULTS AND DISCUSSION

Morphology

SEM images of pure DT and PNPs were given in Figure 1. Figure 1 clearly shows that crystal structure of DT was diminished in the SEM images of PNPs indicating successful loading of DT into the polymer.

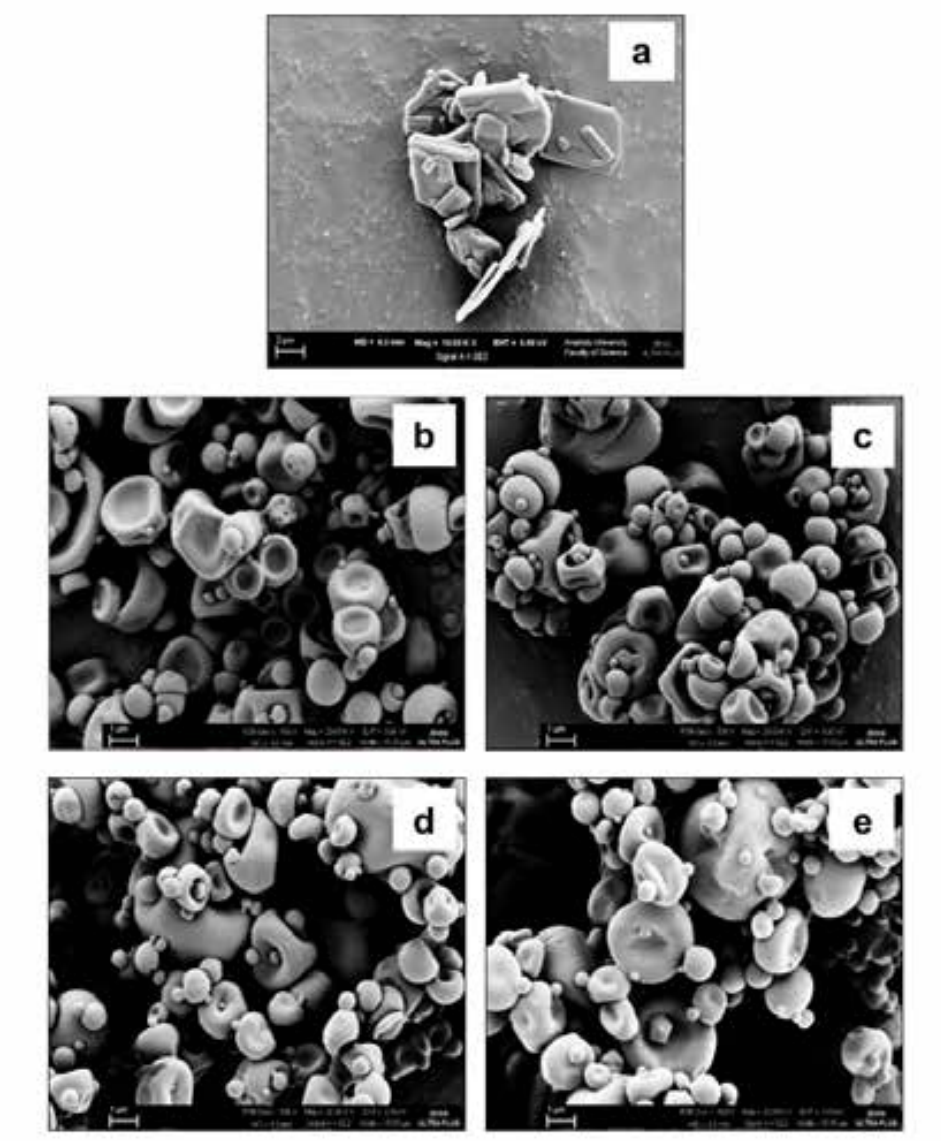


Figure 1. SEM images of pure DT and PNPs, **a:** DT, **b:** ERL-blank, **c:** ERL-1, **d:** ERL-2, **e:** ERL-3

Particle size, PDI and zeta potential

Results of particle size, PDI and zeta potential measurements were given in Table 3. PDI value, used to define particle size distribution, is between 0.01 and 0.5-0.7 for single phase systems. A value higher than 0.7 is indicative of heterogeneous distribution.[17] PDI value of all PNPs prepared in this study was determined to be <0.395±0.015 (mean±SE) meaning uniform particle distributions for all PNPs.

Since Eudragit® RL 100 contains 8.8 %-12 % quaternary ammonium groups, it stands out as a suitable cationic polymer for preparing pharmaceutical dispersions.[18] All PNPs prepared with Eudragit® RL 100 were found to have positive zeta potential value owing to the cationic ammonium groups in its structure. Zeta potential values of all PNPs were in the range of +20.15±0.51 mV and +45.05±0.46 mV. The lowest zeta potential value (+20.15±0.51 mV) was obtained for ERL-3 with the highest DT content when compared to ERL-2, ERL-1 and ERL-blank.

Stability of nanoparticles dispersed in aqueous media is dependent on electrostatic or stearic stability, or both, and high zeta potential value (≥ +/- 30 mV) is correlated with good colloidal dispersion stability.[19] Depending on this knowledge, it can be interpreted that the PNPs prepared were stable.

Table 3. Particle size, PDI and zeta potential values

Code	Particle size (nm) ± SE	Polydispersity index ± SE	Zeta potential ± SE
ERL-blank	475.501±3.852	0.381±0.012	+ 39.11±0.40
ERL-1	540.400±1.715	0.395±0.015	+ 45.05±0.46
ERL-2	571.500±0.615	0.349±0.026	+ 43.81±2.10
ERL-3	798.700±2.312	0.351±0.060	+ 20.15±0.51

*SE: Standard Error

Thermal analysis (DSC)

Thermograms of ERL-blank and all the other freshly prepared formulations were presented in Figure 2 in comparison to DT and Eudragit® RL 100. DSC analyses showed the disappearance of endothermic DT peak observed at 105.1°C in thermograms of all PNPs. Complete disappearance of DT peak is most probably due to homogeneous polymer matrix formation or dilution effect of the polymer.[20] In any case, disappearance of DT peak in all PNPs indicates successful DT loading into nanoparticles, homogenous matrix formation and amorphous DT structure with incorporation significantly reducing its crystal structure.[21]

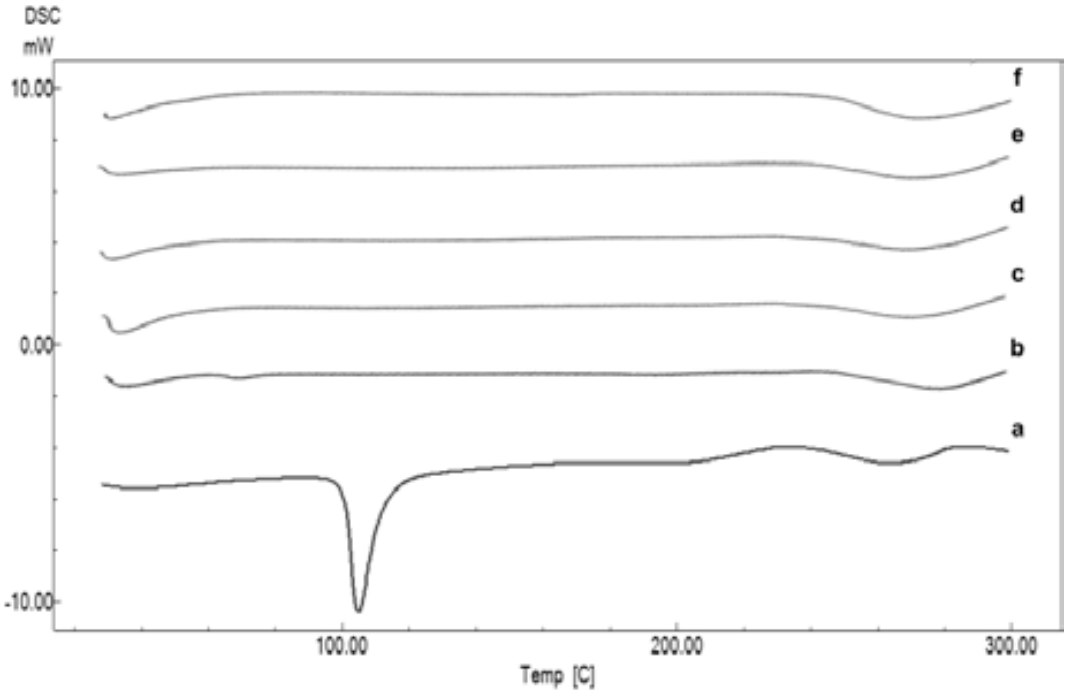


Figure 2. Thermograms of DT, pure polymer and PNPs, **a:** DT, **b:** Eudragit® RL 100, **c:** ERL-blank, **d:** ERL-1, **e:** ERL-2, **f:** ERL-3

X-ray diffraction (XRD)

XRD profiles of ERL-blank and all the other freshly prepared formulations were shown in Figure 3 in comparison to DT and the polymer. XRD analysis is a well-defined analytical method frequently used in research because it reveals the molecular structure of PNPs, examines the crystal state, performs polymorphism studies and also provides information about stability.[22,23] DT dispersion in the polymer matrix at the molecular level and amorphous form of PNPs were determined in this study.[24] The fact that even low intense DT peaks in XRD profiles of PNPs are not seen suggests quite low DT amount adhering to the PNP surface.[16] Disappearance of DT peak for all PNPs may be due to the dilution effect of the polymer network.[18]

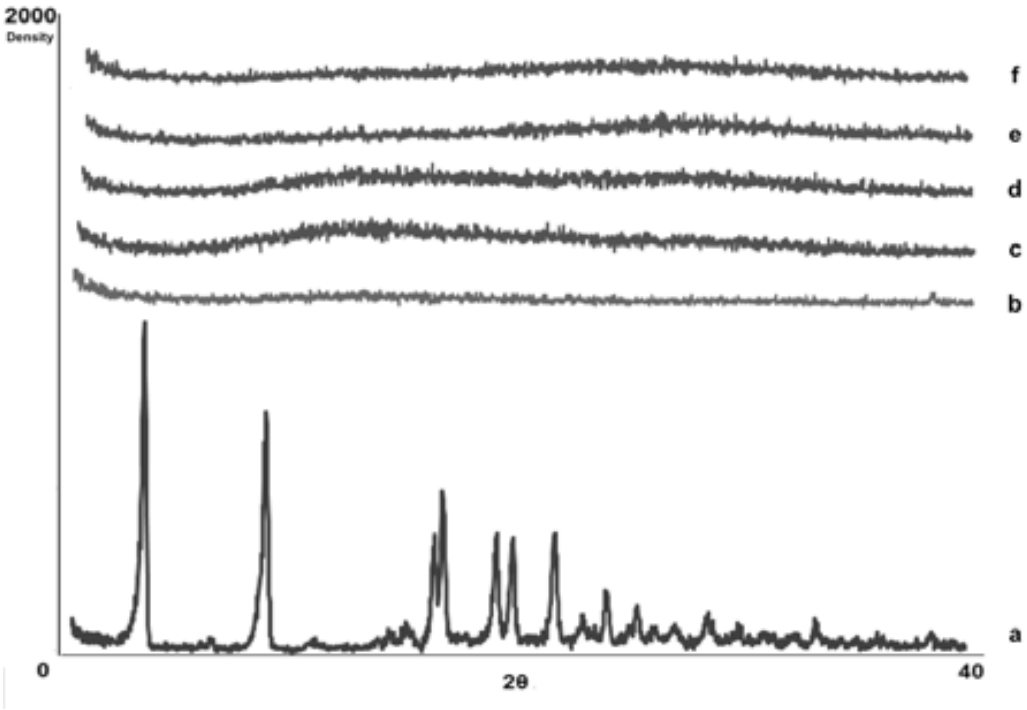


Figure 3. XRD profiles of DT, pure polymer and PNPs, **a:** DT, **b:** Eudragit® RL 100, **c:** ERL-blank, **d:** ERL-1, **e:** ERL-2, **f:** ERL-3

Fourier transform infrared spectrophotometry (FT-IR)

FT-IR spectra of ERL-blank and all freshly prepared PNPs were given in Figure 4 in comparison to DT, Eudragit® RL 100 and the physical mixture. The same spectra of both ERL-blank and pure polymer indicates that production parameters of PNPs had no affect on preparation.[25] No new peak formation of DT in FT-IR specta of PNPs prepared can be evaluated as no existence of chemical interaction between DT and the polymer.[18] It was thought that DT was molecularly dispersed in the polymeric matrix due to the decrease in DT peaks seen in ERL-1, ERL-2 and ERL-3 spectra. This was also supported by thermal and XRD analyses.[26]

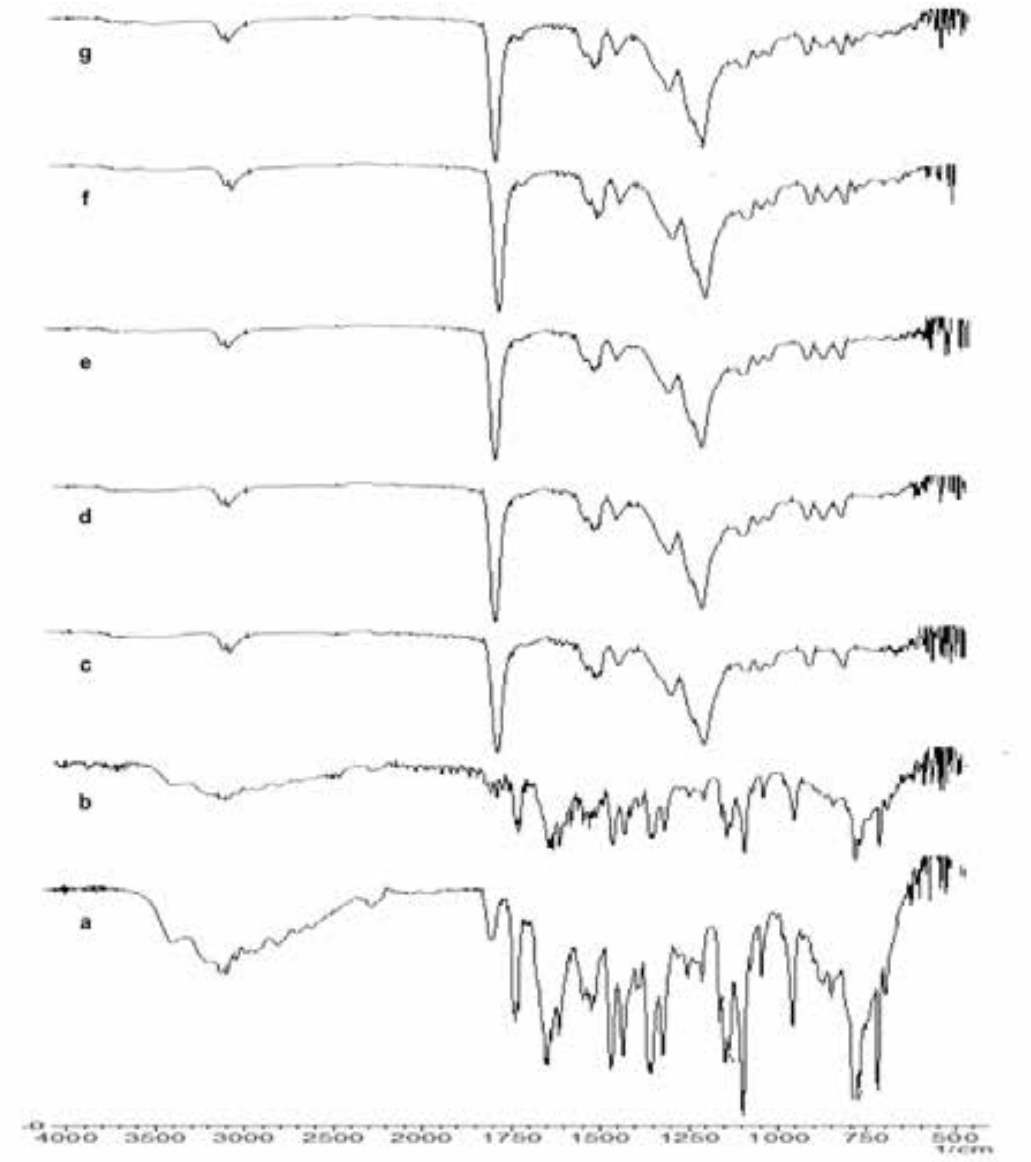


Figure 4. FT-IR spectra of DT, pure polymer, physical mixture and PNPs, **a:** DT **b:** Physical mixture, **c:** Eudragit® RL 100, **d:** ERL-blank, **e:** ERL-1, **f:** ERL-2, **g:** ERL-3

Nuclear magnetic resonance (NMR)

^{1}H-NMR spectra of ERL-blank and all freshly prepared PNPs were presented in Figure 5 in comparison to DT and the pure polymer. ^{1}H-NMR analysis performed in this study is significant for showing the interaction of DT with the polymer and any change in the polymeric structure with addition of DT. Similar spectra of ERL-blank and pure polymer and no peak existence of DT at 7-8 ppm were determined.[16] Presence of characteristic DT peaks was observed in spectra of ERL-1, ERL-2 and ERL-3. Peak intensity which was affected by the

amount of DT added to PNPs was higher in the spectrum of ERL-3 containing the highest DT amount. It was decided that DT was molecularly dispersed in the polymeric structure depending on the correlation between characteristic DT peak and molecular distribution and also DT concentration.[16] This was also interpreted as DT loading into nanoparticles.

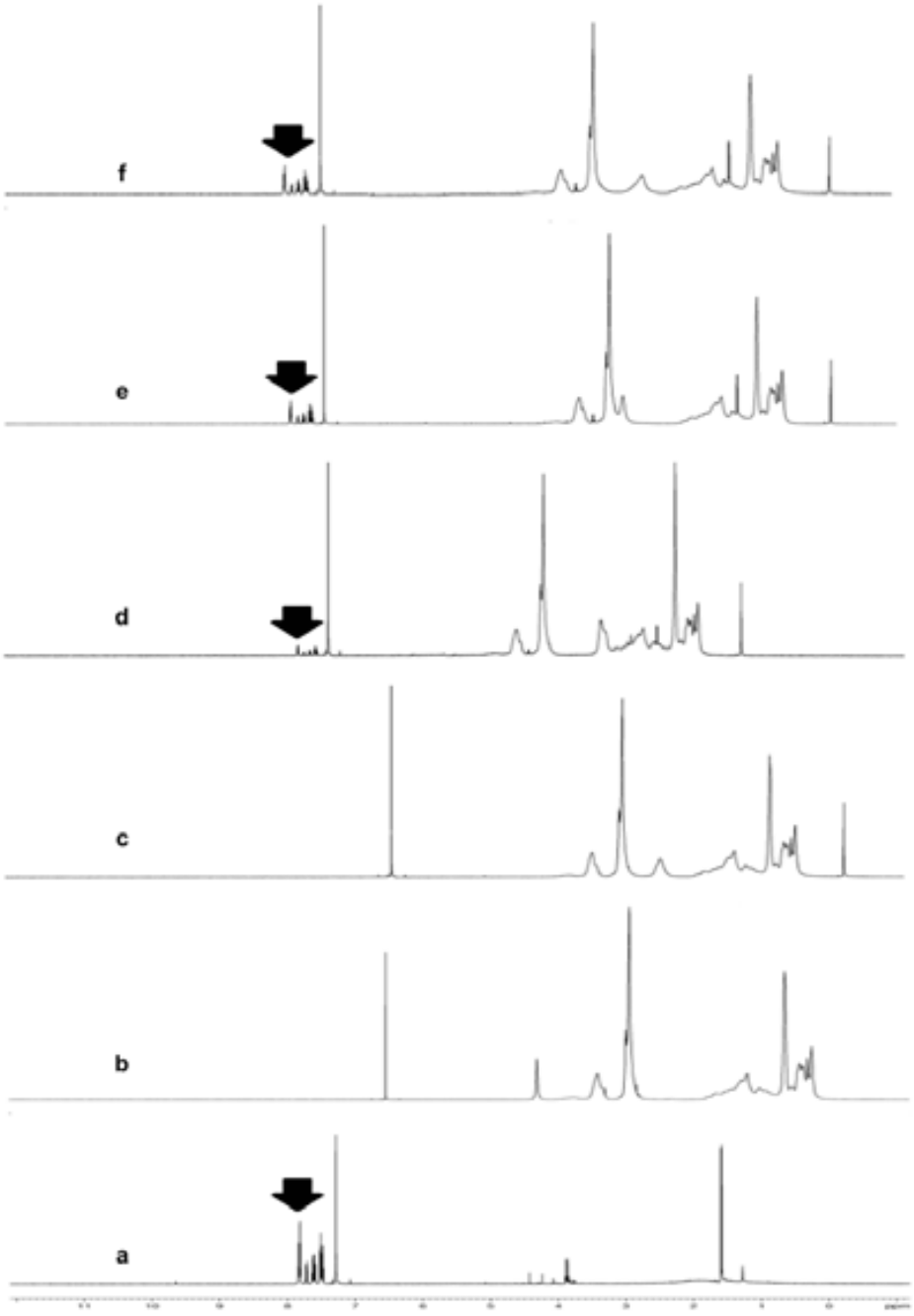


Figure 5. 1H-NMR spectra of DT, pure polymer and PNPs, **a:** DT, **b:** Eudragit® RL 100, **c:** ERL-blank, **d:** ERL-1, **e:** ERL-2, **f:** ERL-3

HPLC method

Modified HPLC method for DT quantification was validated for linearity, specifity, precision and accuracy.[27] Linearity was determined to be at the concentration range of 10-80 μg·mL^{-1} with the regression equation of y = 67363 x - 243811 (r^2=0 9999). The method used was decided to be precise owing to RSD values of < 2 % for repeatability and intermediate precision. Accuracy of the method was determined to be 100.768 % ± 0.3975, 99.964 % ±0.439 and 99.533 % ± 0.312 for the DT concentrations of 20 μg.mL^{-1}, 40 μg.mL^{-1} and 60 μg.mL^{-1}, respectively (n = 6). Recovery of the method was found satisfactory depending on the <2 % RSD value. Limit of detection (LOD) was found to be 0.5613 μg.mL^{-1} while limit of quantitation (LOQ) was 1.7010 μg.mL^{-1}. Conclusively, procedure proposed in this study suggests routine, simultaneous and concurrent use for DT quantification.

Encapsulation efficiency (EE %)

EE % values calculated according to Eq. 1 were given in Table 4. Nanoparticles composed of natural/synthetic polymers or lipids are usually smaller than 1000 μm in size. Active drug ingredient may either be incorporated into the matrix or superficially adsorbed. Therefore, both the amount of encapsulated and the amount of adsorbed to the polymer surface should be determined in analyzing the total amount in the nanoparticulate system.[16] In this study, loading capacity of ERL-2 was found to be the highest among the other formulations. EE% of ERL-3 was lower among the prepared particles. It can be said that the amount of DT loaded on the polymer matrix decreases as the amount of the active ingredient increases.

Table 4. EE % values

Code	ERL-blank	ERL-1	ERL-2	ERL-3
EE % ± SE	-	37.079±1.340	38.873±1.027	35.177±0.458

*SE= standard error

In vitro release

In vitro release and also detailed 2-hr release profiles of pure DT and PNPs prepared were presented in Figure 6. In vitro release test results are frequently used not only for monitoring stability of drugs but also for predicting *in vivo* absorption.[9] Due to the short half-life of DT and rapid release from the conventional tablet formulations marketed, patients need to take the drug at least 3 times a day. Therefore, preparing polymeric nanoparticles to provide initial dose with the superficial DT and maintenance dose with DT entrapped

was aimed in this study. Testing *in vitro* release of pure DT resulted in 92.217 %±0.682 (mean±SE) release within the first 2 hrs while release from all PNPs prepared were sustained. Initial rapid release observed from PNPs was most probably dependent on the rapid dissolution of superficially adsorbed DT and it was found that DT entrapped in PNPs was released in a sustained pattern. ERL-3 demonstrated higher amounts of DT release in 48 hrs with a release of 51.870±1.505 (mean±SE).

In vitro release kinetics

As a result of applying *in vitro* release study data obtained to different kinetic models using DDSolver program, rate constant (k), determination coefficient (r^2) and Akaike information criterion (AIC) found were shown in Table 5. Korsmeyer-Peppas model was determined to be the most appropriate kinetic model for DT release from all PNPs. Release kinetic profiles of all PNPs corresponding to the Korsmeyer-Peppas model were presented in Figure 7.

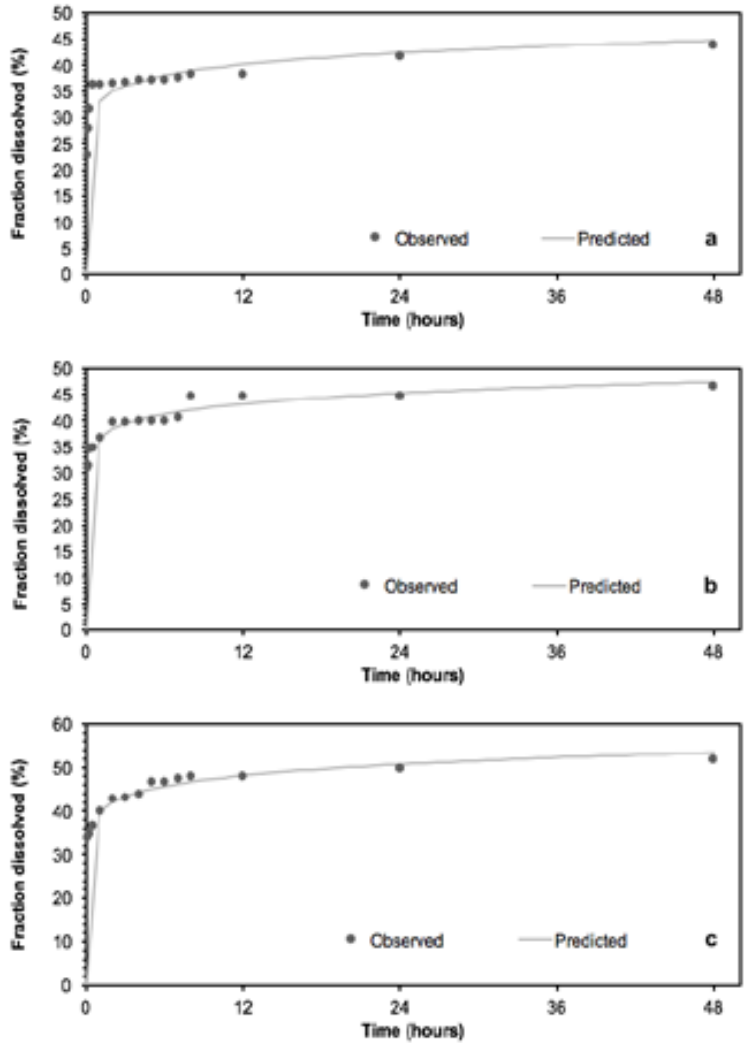


Figure 7. Automated release kinetic profiles of Korsmeyer-Peppas model, **a:** ERL-1, **b:** ERL-2, **c:** ERL-3

Table 5. Release kinetic modeling of PNPs

Kinetic Model	Evaluation Criteria	ERL-1	ERL-2	ERL-3
Korsmeyer- Peppas	k	33.112	36.719	39.984
	r^2	0.815	0.945	0.968
	AIC	67.525	47.284	45.040

Evaluation of drug release data is achieved using many mathematical models and statistical parameters. However, most of those models contain nonlinear equations. In the DDSolver computer program which can evaluate 40 different dissolution parameters, the highest k and r^2 values and the lowest AIC values were used for determining the best fit.[16] Higuchi and Korsmeyer-Peppas models both were determined to give good correspondance. Comparing those two models according to the 3 criteria mentioned above, Korsmeyer-Peppas model was selected to be the best kinetic model which describes controlled release from matrix nano-systems.[16]

CONCLUSIONS

As a result of all particle size, PDI, zeta potential, SEM, DSC, XRD, FT-IR, NMR, EE % and *in vitro* release data obtained, it was decided that sustained release matrix systems could be prepared in this study. Correspondance to Korsmeyer-Peppas model describing controlled release from matrix nano-systems also confirmed the formation of matrix systems in this study. ERL-3 containing the highest amount of active ingredient among the other PNPs prepared was found to be promising for providing sustained analgesic activity. Eudragit® RL polymer containing quaternary ammonium groups represents a good matrix ingredient for further *in vivo* studies due to its cationic character.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

This study was financed by Anadolu University Scientific Research Project Foundation (No: 1502S081). The authors would like to thank Abdi İbrahim (İstanbul, Turkey) for providing a gift sample of DT. Faculty of Engineering is acknowledged for XRD, Faculty of Science for SEM, DOPNALAB Faculty of Pharmacy for FT-IR and AUBIBAM for ^{1}H-NMR analysis facilities.

REFERENCES

1. Eroglu, C.; Durmus, E.; Kiresi D. Effect of low-dose dexketoprofen trometamol and paracetamol on postoperative complications after impacted third molar surgery on healthy volunteers: A pilot study. *Med Oral Patol Oral Cir Bucal.* **2014**, 19 (*6*), 622-627.

2. Derman, S.; Kızılbey, K.; Akdeste, Z. M. Polymeric nanoparticles. *J Eng Natur Sci.* **2013**, *31*, 107-120.

3. Fu, Y.; Kao, W. J. Drug release kinetics and transport mechanisms of non-degradable and degradable polymeric delivery systems. *Expert Opin Drug Deliv*. **2010**, 7 (*4*), 429-444.

4. Rao, J. P.; Geckeler, K. E. Polymer nanoparticles: Preparation techniques and size-control parameters. *Prog Polym Sci*. **2011**, *36*, 887-913.

5. Re, M. Formulating Drug Delivery Systems by Spray Drying. *Dry Technol.* **2006**, 24, 433-446.

6. Li, X.; Anton, N.; Arpagus, C.; Belleteix, F.; Vandamme, T. F. Nanoparticles by spray drying using innovative new technology: the Büchi nano spray dryer B-90. *J Control Rel.* **2010**, *147*, 304-310.

7. Aundhia, C. J.; Raval, J. A., Patel, M. M.; Shah, N. V.; Chauhan, S. P.; Sailor, G. U.; Javia, A. R.; Mahashwari, R. A. Spray Drying in the Pharmaceutical Industry – A Review. *IAJPS*. **2011**, 2 (*1*), 125-138.

8. Das, S.; Suresh, P. K.; Desmukh, R. Design of Eudragit RL 100 nanoparticles by nanoprecipitation method for ocular drug delivery. *Nanomedicine: NBM*. **2010**, *6,* 318-323.

9. Zhang, Y.; Huo, M.; Zhou, J.; Zou, A.; Li, W.; Yao, C.; Xie, S. DDSolver: an add-in program for modeling and comparison of drug dissolution profiles. *The AAPS J*. **2010***, 12*, 263-271.

10. Di Colo, G.; Baggiani, A.; Zambito, Y.; Mollica, G.; Geppi, M.; Serafini, M. F. A new hydrogel for the extended and complete prednisolone release in the GI trac *Int J Pharm*. **2006**, *310*, 154-161.

11. Phaechamud, T. Variables Influencing Drug Release from Layered Matrix System Comprising Hydroxypropyl Methylcellulose. *AAPS PharmSciTech*. **2008**, *9*, 668-674.

12. Korsmeyer, R. W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N. A. Mechanisms of solute release from porous hydrophilic polymers. *Int J Pharm*. **1983**, *15*, 25-35.

13. Singhvi, G.; Singh, M. Revıew: In-Vıtro Drug Release Characterızatıon Models. *IJPSR*. **2011**, 2(*1*), 77-84.

14. Öztürk, A. A.; Yenilmez, E.; Yazan, Y. Development and validation of high performance liquid chromatography (HPLC) modified method for dexketoprofen trometamol. *Eur. Int. J. Sci. Tech.* **2017**, 6(*4*) 33-41

15. Öztürk, A.A.; Yenilmez, E.; Arslan, R.; Şenel, B.; Yazan Y. Dexketoprofen Trometamol-Loaded Kollidon® SR and Eudragit® RS 100 Polymeric Nanoparticles: Formulation and In Vitro-In Vivo Evaluation. *Lat. Am. J. Pharm.* **2017**, 36*(11),* 2153-2165.

16. Lopedota, A.; Trapani, A.; Cutrignelli, A.; Chiarantini, L.; Pantucci, E.; Curci, R.; Manuali, E.; Trapani, G. The use of Eudragit® RS 100/cyclodextrin nanoparticles for the transmucosal administration of glutathione. *Eur J Pharm Biopharm*. **2009**, *72*, 509-520.

17. Pignatello, R.; Ricupero, N.; Bucolo, C.; Maugeri, F.; Maltese, A.; Puglisi, G. Prepara-

tion and characterization of eudragit retard nanosuspensions for the ocular delivery of cloricromene. *AAPS Pharm Sci Tech*. **2006**, 7(*1*), 1-7.

18. Nagarwal, R.C.; Kant, S.; Singh, P. N.; Maiti, P.; Pandit J. K. Polymeric nanoparticulate system: a potential approach for ocular drug delivery. *J Control Release*. **2009**, *136*, 2-13.

19. Pagar, K.; Vavia, P. Rivastigmine-Loaded L-Lactide-Depsipeptide Polymeric Nanoparticles: Decisive Formulation Variable Optimization*Sci Pharm*. **2013**, *81*, 865-885.

20. Mainardes, R. M.; Evangelista, R.C. PLGA nanoparticles containing praziquantel: effect of formulation variables on size distribution. *J Microencapsul*. **2005**, 2(*1*), 13-24.

21. Sapsford, K. E.; Tyner, K. M.; Dair, B. J.; Deschamps, J. R.; Medintz, I. L. Analyzing nanomaterial bioconjugates: a review of current and emerging purification and characterization techniques. *Anal Chem*. **2011**, *83*, 4453-4488.

22. Lin, P. C.; Lin, S.; Wang, P. C.; Sridhar, R. Techniques for physicochemical characterization of nanomaterials. *Biotechnol Adv*. **2014**, *32*, 711-726.

23. Shin, S. B.; Cho, H.Y.; Kim, D. D.; Choi, H. G.; Lee, Y. B. Preparation and evaluation of tacrolimus-loaded nanoparticles for lymphatic delivery. *Eur J Pharm Biopharm*. **2010**, *74*, 164-171.

24. Öztürk, A. A.; Martin Banderas, L.; Cayero Otero, M.D.; Yenilmez, E.; Yazan Y. New Approach to Hypertension Treatment: Carvediol-Loaded PLGA Nanoparticles, Preparation, In Vitro Characterization and Gastrointestinal Stability. *Lat. Am. J. Pharm*. **2018**, 37*(9),* 1730-1741

25. Öztürk A. A., Güven U. M., Yenilmez E, Şenel B. Effects of Different Derivatives of Eudragit Polymer on Entrapment Efficiency, In Vitro Dissolution, Release Kinetics and Cell Viability Results on Extended Release Flurbiprofen Loaded Nanomedicines. *Lat Am J Pharm*. **2018**, 37(*10*), 1981-1992.

26. Öztürk A. A., Güven U. M., Yenilmez E. Flurbiprofen Loaded Gel Based Topical Delivery System: Formulation and In Vitro Characterization with New Developed UPLC Method. Acta Pharm Sci. **2018**, 56(*4*), 81-105.

ACTA PHARMACEUTICA SCIENCIA

International Journal in Pharmaceutical Sciences
is Published Quarterly
ISSN: 2636-8552
e-ISSN: 1307-2080,
Volume: 57, No: 1, 2019
Formerly: Eczacılık Bülteni/Acta Pharmaceutica Turcica
Founded in 1953 by Kasım Cemal Güven

Editor
Şeref Demirayak

Associate Editors
Gülden Zehra Omurtag
Barkın Berk

Coordinators
M. Eşref Tatlıpınar
Metin Uyar

Language Editor
Recep Murat Nurlu
M. Eşref Tatlıpınar
Neda Taner

Biostatistics Editor
Pakize Yiğit

Graphic Design
Sertan Vural
Levent Karabağlı

Editorial Board
Sabahattin Aydın
Ahmet Aydın
Aristidis Tsatsakis
Ayfer Beceren
Dilek Ak
Ebrahim Razzazi-Fazeli
Erçin Erciyas
Erem Memişoğlu Bilensoy
Göknur Aktay
Gülçin Saltan İşcan
Hakan Göker
Hanefi Özbek
Hayati Çelik
İhsan Çalış
Julide Akbuğa
Kenneth A. Jacobson
Leyla Yurttaş
Mesut Sancar
Nesrin Emekli
Nurşen Başaran
Özgen Özer
Roberta Ciccocioppo
Stefano Constanzi
Tuncer Değim
Yıldız Özsoy
Yusuf Öztürk

Address
İstanbul Medipol Üniversitesi
Kavacık Güney Kampüsü
Göztepe Mah. Atatürk Cad.
No: 40 34810 Beykoz/İSTANBUL
Tel: 0216 681 51 00

E-mail
editor@actapharmsci.com
secretary@actapharmsci.com

Web site
http://www.actapharmsci.com

Printing Office
Ege Basım Ltd. Şti.
Esatpaşa Mah. Ziyapaşa Cad. No: 4
Ege Plaza Ataşehir/ İstanbul
Tel: 0216 472 84 01

ISSN: 2636-8552 - e-ISSN: 1307-2080

ACTA PHARMACEUTICA SCIENCIA

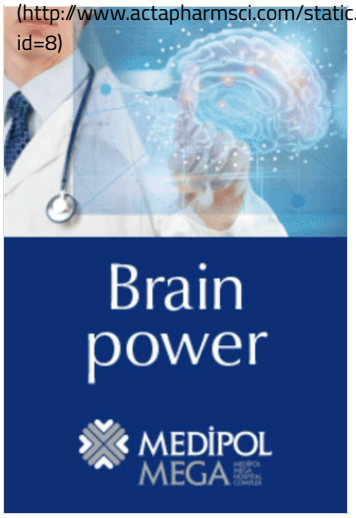


tent.php?

Current Issue: 2019 , Vol 57 , Num 1

Editor-in-Chief: Şeref Demirayak
Associate Editors: Gülden Zehra Omurtag, Barkın Berk
Coordinators: Metin Uyar, M. Eşref Tatlıpınar
Online ISSN: 1307-2080
Frequency: 4 issues / year
Abbreviation: Acta Pharm Sci
Publisher: Behalf of the İstanbul Medipol University Responsible Prof. Sabahattin Aydın, MD

Current Issue
Archive (http://www.actapharmsci.com/content.php?id=67)
Search (http://www.actapharmsci.com/archive.php)
Instructions to Authors (http://www.actapharmsci.com/search.php)
Copyright Form (http://www.actapharmsci.com/static.php?id=4)



(http://www.actapharmsci.com/static.php?id=8)

Submit an Article / Manuscript Review
email
password
login
create account (submit/create-account.php) forgot password (submit/forgot.php)

Most Popular
Download Articles Read Articles
PODIUM PRESENTATIONS WEDNESDAY, SE (abstract.php?id=383)
THE DETERMJNATTON OF PRAZOSIN HYDR (abstract.php?id=349)
Estimation of Abiraterone in Human (abstract.php?id=577)
Turkish Orchids and Salep (abstract.php?id=264)
GUM CORDIA - A NEW TABLET BINDER A (abstract.

ACTA Pharmaceutica Sciencia

Aims and Scope of Acta Pharmaceutica Sciencia. (abstract.php?id=606)
Şeref DEMİRAYAK

Development and Validation of UPLC Method for the Determination of Olopatadine Hydrochloride in Polymeric Nanoparticles. (abstract.php?id=607)
Umay Merve Güven, Murat Sami Berkman, Yasemin Yazan
DOI: 10.23893/1307-2080.APS.05701

Biosynthesis, Characterization and Cytotoxicity of Zinc Nanoparticles Using Panax ginseng Roots, Araliaceae. (abstract.php?id=608)
Mustafa Nadhim Owaid, Tahseen Ali Zaidan, Rasim Farraj Muslim, Mohammed Abdulrahman Hammood
DOI: 10.23893/1307-2080.APS.05702

Enhanced Solubility and Drug Release of Ketoprofen Using Lyophilized Bovine Serum Albumin Solid Dispersion. (abstract.php?id=609)
Meenakshi Bhatia, Rupa Devi
DOI: 10.23893/1307-2080.APS.05703

Microbial Efficacy and Two Step Synthesis of Uridine Derivatives with Spectral Characterization. (abstract.php?id=610)
Sumi R. Devi, Sanjida Jesmin, Mahfuz Rahman, Mohammad A. Manchur, Yuki Fujii, Yasuhiro Ozeki, Sarkar M. A. Kawsar
DOI: 10.23893/1307-2080.APS.05704

Dexketoprofen trometamol-loaded Eudragit® RL 100 nanoparticle formulation, characterization and release kinetics. (abstract.php?id=611)
A. Alper Öztürk, Evrim Yenilmez, Yasemin Yazan
DOI: 10.23893/1307-2080.APS.05705

Determination Amount of Silymarin and Pharmaceutical Products from Milk Thistle Waste Obtained from Cold Press. (abstract.php?id=612)
Derya Duran, Semih Ötleş, Ercüment Karasulu
DOI: 10.23893/1307-2080.APS.05706

Antimicrobial Evaluation of Trisubstituted 2-piperazinyl Thiazoles. (abstract.php?id=613)

(http://creativecommons.org/licenses/ nc-nd/4.0/)
This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (http://creativecommons.org/licenses/ nc-nd/4.0/)

OPEN ACCESS
CAS A DIVISION OF THE AMERICAN CHEMICAL SOCIETY
Scopus®
UDL EDGE

Tarandığı INDEX

Betül Giray, Leyla Yurttaş, Zafer Şahin, Barkın Berk, Şeref Demirayak
DOI: 10.23893/1307-2080.APS.05707

Tarandığı INDEX



Istanbul Medipol University

ACTA PHARMACEUTICA SCIENCIA

International Journal in Pharmaceutical Sciences, Published Quarterly

ISSN: 2636-8552
e-ISSN: 1307-2080,
Volume: 57, No: 1, 2019
Formerly: Eczacılık Bülteni
Acta Pharmaceutica Turcica

Aims and Scope of Acta Pharmaceutica Sciencia
Şeref Demirayak

Development and Validation of UPLC Method for the Determination of Olopatadine Hydrochloride in Polymeric Nanoparticles
Umay Merve Güven, Murat Sami Berkman, Yasemin Yazan

Biosynthesis, Characterization and Cytotoxicity of Zinc Nanoparticles Using Panax ginseng Roots, Araliaceae
Mustafa Nadhim Owaid, Tahseen Ali Zaidan, Rasim Farraj Muslim, Mohammed Abdulrahman Hammood

Enhanced Solubility and Drug Release of Ketoprofen Using Lyophilized Bovine Serum Albumin Solid Dispersion
Meenakshi Bhatia, Rupa Devi

Microbial Efficacy and Two Step Synthesis of Uridine Derivatives with Spectral Characterization
Sarkar M. A. Kawsar, Sumi R. Devi, Sanjida Jesmin, Mahfuz Rahman, Mohammad A. Manchur, Yuki Fujii, Robert A Kanaly, Yasuhiro Ozeki

Dexketoprofen trometamol-loaded Eudragit® RL 100 nanoparticle formulation, characterization and release kinetics
A. Alper Öztürk, Evrim Yenilmez, Yasemin Yazan

Determination Amount of Silymarin and Pharmaceutical Products from Milk Thistle Waste Obtained from Cold Press
Derya Duran, Semih Ötleş, Ercüment Karasulu

Antibacterial Evaluation of Trisubstituted 2-Piperazinyl Thiazoles
Betül Giray, Zafer Şahin, Leyla Yurttaş, Şeref Demirayak

57[1]

Contents

Aims and Scope of Acta Pharmaceutica Sciencia
Şeref Demirayak

Development and Validation of UPLC Method for the Determination of Olopatadine Hydrochloride in Polymeric Nanoparticles
Umay Merve Güven, Murat Sami Berkman, Yasemin Yazan

Biosynthesis, Characterization and Cytotoxicity of Zinc Nanoparticles Using Panax ginseng Roots, Araliaceae
Mustafa Nadhim Owaid, Tahseen Ali Zaidan, Rasim Farraj Muslim, Mohammed Abdulrahman Hammood

Enhanced Solubility and Drug Release of Ketoprofen Using Lyophilized Bovine Serum Albumin Solid Dispersion
Meenakshi Bhatia, Rupa Devi

Microbial Efficacy and Two Step Synthesis of Uridine Derivatives with Spectral Characterization
Sarkar M. A. Kawsar, Sumi R. Devi, Sanjida Jesmin, Mahfuz Rahman, Mohammad A. Manchur, Yuki Fujii, Robert A Kanaly, Yasuhiro Ozeki

Dexketoprofen trometamol-loaded Eudragit® RL 100 nanoparticle formulation, characterization and release kinetics
A. Alper Öztürk, Evrim Yenilmez, Yasemin Yazan

Determination Amount of Silymarin and Pharmaceutical Products from Milk Thistle Waste Obtained from Cold Press
Derya Duran, Semih Ötleş, Ercüment Karasulu

Antibacterial Evaluation of Trisubstituted 2-Piperazinyl Thiazoles
Betül Giray, Zafer Şahin, Leyla Yurttaş, Şeref Demirayak