Turkish Pharmaceutical Technology Scientists' Association
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8th BBBB

EUFEPS
EUROPEAN FEDERATION FOR PHARMACEUTICAL SCIENCES

International Conference on Pharmaceutical Sciences

"Innovations and Challenges in Drug Research and Development"

14 - 16 October 2019

Radisson Blu Hotel, Çeşme, İzmir · Turkey



ABSTRACT BOOK

OP-03
DEVELOPMENT OF PROLONGED RELEASE KETOROLAC TROMETHAMINE LOADED *IN SITU* GELLING SYSTEM AND NANOPARTICLES BY NANO SPRAY DRYING METHOD: FORMULATION AND *IN VITRO* CHARACTERIZATION

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1. INTRODUCTION

Ketorolac Tromethamine (KT) is a non-steroidal anti-inflammatory drug (NSAID), acting as a non-selective COX inhibitor, from the class of heteroaryl acetic acid derivatives. KT has short plasma half-life ($t_{1/2}$ » 5.5 h) [1]. Colloidal drug delivery systems, including nanoparticles (NPs), are good drug delivery candidates as they can enhance safety and efficiency of local or systemic drug delivery [2]. Methods used for formulating NPs may vary; in this study a mechanical method, spray drying was applied. Spray drying is a rapid, reproducible, continuous method for generating NPs by transforming liquid substances into solid powders. Depending on characteristics of NPs and polymer which is used, they can control the release of the drug they carry. Controlled release of a drug may provide many advantages for therapeutic control by reducing dosing frequency and decreasing side effects. Eudragit RS 100 (ERS) is a copolymer of ethyl acrylate, methyl methacrylate and low content of methacrylic acid ester with quaternary ammonium groups. The ammonium groups are present as salts and make the polymers permeable [3].

In this study, KT loaded *in situ* gelling system with Pluronic F-127 and ERS NPs are produced by nano spray drying method and *in vitro* characteristics are evaluated.

2. MATERIALS AND METHODS

2.1. Materials

KT is kind gift from Deva İlaç (Istanbul, Turkey). All other chemicals used were of analytical grade.

2.2. Preparation of nanoparticles and *in situ* gelling system

NPs were prepared using Nano Spray-Dryer (B-90, Büchi Labortechnik AG, Switzerland). For the preparation of NPs, ERS was dissolved in methanol prior to the addition of KT. Spray-drying conditions and NPs ingredients are summarized in Table 1 and Table 2, respectively. Polymeric solutions were prepared using the cold method for in situ gelling system. Pluronic F-127 was dispersed in cold water with continuous magnetic stirring at 4°C for at least 24 hours. Formulation studies were started by determining constituent ratios. Pluronic F-127 aqueous solution with a concentration of 20% has a gelling temperature at 37°C.

Table 1. Spray-drying conditions

Inlet Temperature	Outlet Temperature	Pump Level	Spray Level
100°C	54°C	4	100 %

Table 2. Nanoparticle ingredients

Code	ERS	KT	Methanol
NP-Blank	1 g	-	100 mL
NP-1	1 g	0.5 g	100 mL

2.3. Characterization of nanoparticles

Particle size (PS), polydispersity index (PDI) and zeta potential (ZP) of NPs analyzed by a Zetasizer Nano ZS (Malvern Instruments, UK).

Morphological and structural characteristics of the NPs prepared were investigated using SEM (FEI Quanta FEG 650, US). The entrapment efficiency (EE%) and release study of NP was performed with UPLC. UPLC conditions are shown in Table 3.

In vitro release study of the formulations was investigated over 48 hours and performed in simulated intestinal fluid (SIF, pH 6.8).

Table 3. UPLC conditions

Device	Agilent Technology 1290 Infinity
Stationary Phase	Zorbax Eclipse Plus C18 (2.1x50 mm, 1.8 µm)
Mobile phase	Water : Acetonitrile (50:50, v/v)
Oven temperature	40°C
Flow rate	0.25 mL.min-^{1}
Injection volume	0.5 µL
Detection Wavelength	315 nm

3. RESULTS AND DISCUSSION

3.1. Characterization of nanoparticles

PS, PDI, ZP and EE % values of NPs are shown in Table 4. SEM images of pure KT and NPs are shown in Fig. 1. *In vitro* release profile of KT and formulations are shown in Fig. 2.

Table 4. PS, PDI, ZP and EE % results

Code	PS	PDI	ZP	EE %
NP-Blank	376.1±7.3	0.36±0.01	+41.7±1.3	-
NP-1	401.8±9.4	0.37±0.12	+40.6±2.4	%72.8±3.2

PS's are appropriate for oral application. All NPs presented PDI values lower than 0.5 and therefore particle size distribution was decided to be monodisperse. Positive/Cationic ZP values of NPs highlighted the presence of cationic ammonium group of ERS [3].

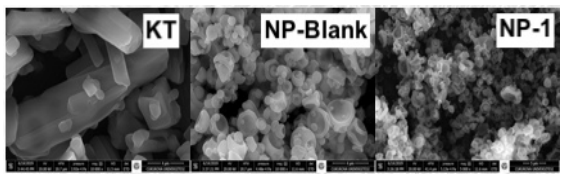

Figure 1. SEM images of KT and NPs

Fig. 1 clearly shows that crystal structure of KT was diminished in the SEM image of NP-1 indicating successful loading of KT into the polymer. Fig. 1 indicated a mostly spherical smooth shape for all NPs [4]. The release of KT from NP-1 and NP-1-gel continued over 24 hours while pure KT exhibited a rapid release of 94.6%±3.3 (Mean± SD) in 3 hour. Gel containing only KT reached 96.7%±0.2 release at 9th hour. The release rates observed from NP-1 and NP-1-gel coded formulations after 24 hours were 78.4%±2.9 and 44.5%±3.6, respectively, demonstrating extended release from all formulations, relative to pure KT.

4. CONCLUSION

Eudragit RS 100 nanoparticles were prepared for analgesic delivery of Ketorolac Tromethamine by nano spray-drying method. And, *in situ* gelling system was prepared using cold method. The particle size, zeta potential and polydispersity index, Scanning electron microscopy, entrapment efficiency and release analysis of formulations justified that ketorolac tromethamine was incorporated into nanoparticles and/or gel system successfully. All formulations is promising to be for extended release of ketorolac Tromethamine with successfully loaded.

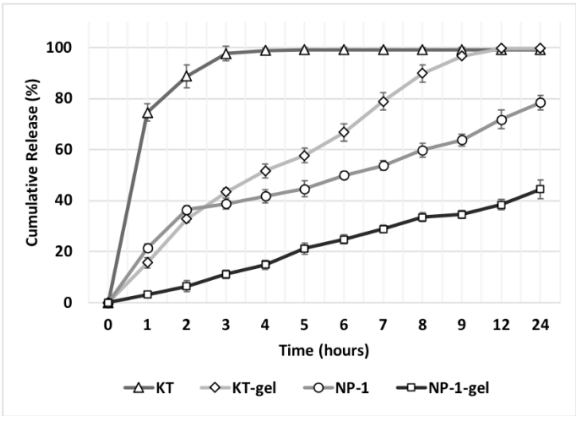

Figure 2. Release profile of KT and formulations

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surements. Thermochimica acta, 2013, 552, p. 5-9.

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AUTHOR INDEX

I

IBRAHIM, YOUSIF H-E. Y. 109
IBRIĆ, SVETLANA 230, 253

İ

İLBASMIŞ TAMER, SIBEL 140, 293
İLEM ÖZDEMIR, DERYA 58
İMAMOĞLU ŞİRVANLI, NALAN 60
İNAL, OZGE 125
İNCECAYIR, TUBA 365
İZAT, NIHAN 332, 371

J

JIWA, NAILLA 260, 263
JÓZSA, LIZA 70
JR., GÉZA REGDON 109
JUHÁSZ, BÉLA 70
JUKIČ, MARKO 35

K

KABAN, KÜBRA 363
KAHRAMAN, EMINE 143, 302
KAIRANE, CESLAVA 354
KALAMI, ELMIRA 302
KALAYI, MOHAMMED 312
KANDILLI, BÜŞRA 166, 247
KANTARCI, GÜLTEN 363
KÁNTÁS, BOGLÁRKA 287, 352
KAPLAN, OZAN 332
KARA, ADNAN ALTUĞ 87, 273
KARA, ASLI 116, 221
KARABULUT, ERDEM 192
KARASULU, ERCÜMENT 134, 136, 216, 283, 358
KARASULU, HATİCE YEŞİM 373
KARASULU, H. YEŞIM 276, 280, 334, 358
KARATAŞ, AYŞEGÜL 237, 361
KARAVANA, SINEM YAPRAK 218
KARPUZ, MERVE 90
KÁSA, PÉTER 367
KAVAS, AYCAN 216
KAZANCI, ATILLA 20
KÉRI, GYÖRGY 352
KHALIL, RUQAIYA 66
KHAMIS, HALA 260
KIR, FATMA 332
KIRSIMÄE, KALLE 79
KISAND, VAMBOLA 289
KISA, ÖZGÜL 317
KOCBEK, PETRA 131
KOGERMANN, KARIN 27, 64, 79, 159, 289
KONDIC, JELENA 230
KORCZYK, PIOTR 64
KORHONEN, OSSI 30
KÕRKJAS, ARLE 159
KOSE OZKAN, CANSEL 114
KRISTL, JULIJANA 131, 155, 157
KRISTÓ, KATALIN 109
KRONSTRÖM, KAI 159
KUNT, SERIF TUGRUL 216
KÜÇÜKGÜZEL, Ş. GÜNIZ 60, 358
KÜÇÜKTÜRKMEN, BERRIN 171
KURALAY, FILIZ 20
KURT, NIHAT 348

L

LAIDMÄE, IVO 79, 159, 289
LALIĆ-POPOVIĆ, MLADENA 212
LANNO, GEORG-MARTEN 64
LAVRIČ, ZORAN 224
LEDNECZKI, ISTVÁN 31
LEHTO, VESA-PEKKA 32
LEPETRE-MOUELHI, SINDA 20
LÓPEZ-MACÍAS, CONSTANTINO 356
LORYAN, I. 26
LUDÁNYI, ZSÓFIA 328

M

MADŽAREVIĆ, MARIJANA 253
MÄEORG, UNO 289
MAHLAPUU, RIINA 354
MALEKGHASEMI, SOHEIL 195
MATJAŽ, MIRJAM GOSENCA 199, 268
MEDAREVIC, DJORDJE 230
MEHMETOGLU, AYCA 283
MEOS, ANDRES 289
MESUT, BURCU 72, 138, 285, 312
MIHELČIČ, ANJA 35
MIKOV, MOMIR 212
MIRTIČ, JANJA 131, 155, 157
MUT AŞKUN, MELIKE 197
MUTLU-AGARDAN, N. BASARAN 128

N

NAGY, SÁNDOR 153
NAJIB, NAJI M. 34
NAMLI, İREM 168, 175, 178, 226
NAZLI, HAKAN 138
NEMUTLU, EMIRHAN 20
NIEMCZYK-SOCZYNSK, BEATA 64
NIEMINEN, HEIKKI. J. 159

O

OBREZA, ALEŠ 35
OKTAY, AYSE NUR 140
OLGAÇ, SEVAL 74, 100
OMASA, TAKESHI 136
ONAYO, M. MAYOWA 325
ONGUN, MELIKE 270, 273
ONTIVEROS-PADILLA, LOUIS 356
ONUK GÖREN, FIGEN 337
ORAK, DUYGU 309

Ö

ÖLGEN, SUREYYA 350
ÖNER, LEVENT 20, 189, 192, 348
ÖZALP, YILDIZ 260, 263, 285, 322, 325
ÖZCAN BÜLBÜL, ECE 77
ÖZÇELIKAY, ARIF TANJU 92
ÖZDEMIR, ERTAN 371
ÖZDEM, SADI S. 37
ÖZER, A. YEKTA 62, 90, 102
ÖZER, ÖZGEN 214, 309
ÖZER, SINAN 148
ÖZGENÇ, EMRE 58
ÖZGÜNEY, IŞIK 210
ÖZKAN, YALCIN 107, 114
ÖZKÖSE, UMUT UGUR 221
ÖZKUL, AYKUT 356
ÖZLISELI, EZGI 235
ÖZMEN, GÜLÇE 134
ÖZPOLAT, LEYLA 216
ÖZSOY, YILDIZ 72, 77, 138, 143, 228, 285, 302, 312
ÖZTÜRK, A. ALPER 55, 168, 175, 226
ÖZTÜRK-ATAR, KIVILCIM 80, 173
ÖZTÜRK, NAILE 116, 221
ÖZTÜRK, ŞÜKRÜ 20
ÖZTÜRK, SÜLEYMAN CAN 90
ÖZ, UMUT CAN 171

P

PAAVER, URVE 289
PAKSOY, BAŞAK 182
PALA KARA, ZELIHA 112
PALCSÓ, BARNABÁS 297
PÁL, SZILÁRD 153, 367
PAVLOVIĆ, NEBOJŠA 212
PAYRITS, MAJA 287
PEKCAN, MERT 356
PESEN OKVUR, DEVRIM 38
PEZIK, ESRA 256, 258, 341, 343, 345, 369
PINTÉR, ERIKA 352
PINTYE-HÓDI, KLÁRA 153
PIRINÇCI, YAĞMUR 72
PIRNAT, SAŠA 155
POBIRK, ALENKA ZVONAR 199
POLAT, KEREM HEYBET 202, 205
POROSK, RANDO 354
POTOČNIK, ŠPELA 35
POTPARA, ZORICA 253
PREŠERN, ANJA 268
PURALI, NUHAN 356
PUTRINŠ, MARTA 64

R

RAJABALAYA, RAJAN 51
RAŠČAN, IRENA MLINARIČ 35
RENÇBER, SEDA 210
RIVERO-ARREDONDO, VANESSA 356
ROSENHOLM, JESSICA 235

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Dear *Tilbe Çevikelli*

Thank you for your abstract submission to 8th BBBB International Conference on Pharmaceutical Sciences, which will be realized in Radisson Blu Otel, Çeşme-Turkey between October 14-16, 2019.

I would like to inform you that your abstract entitled ***Development of Prolonged Release Ketorolac Tromethamine Loaded In Situ Gelling System and Nanoparticles by Nano Spray Drying Method: Formulation and In Vitro Characterization*** has been accepted by the scientific committee for oral presentation. You can find the details of your presentation below.

We look forward to seeing you at the symposium in Çeşme.

With best regards,

Prof. Nevin Çelebi
Chair of 8th BBBB

Oral presentation date	: 15 October 2019
Oral presentation time	: 14:15 – 14:30
Hall	: Hall A