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ABSTRACT BOOK

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DESIGN OF LAMIVUDINE LOADED NANOPARTICLES BY NANO SPRAY DRYING METHOD FOR ORAL APPLICATION

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1. INTRODUCTION

Lamivudine (LAM), known as 3TC, is an antiviral drug in the class of nucleoside analogue reverse transcriptase inhibitors (NRTIs). LAM is widely used for treatment of human immunodeficiency virus (HIV) and proven effective against hepatitis B virus (HBV). It is commercially available in tablet and oral solution dosage forms and used both in children and adult patients. Even though oral bioavailability is high as 60-80%, the problem with treatment is that it requires frequent administration due to its short half-life of 4 to 6 hours. Considering that chronic use with constant exposure causes accumulation and dose dependent side effects, it is necessary to develop new systems to improve therapy with LAM [1]. Modified release kinetics can be achieved by nanoparticles (NPs) prepared with various materials including polymers. One of the most common polymer groups used is Eudragit; which has many variations that can be used alone or in combinations. Eudragit RS 100 (ERS) is a copolymer of poly (ethylacrylate, methyl-methacrylate and chlorotrimethyl-ammonioethylmethacrylate) containing quaternary ammonium groups [2].

In this study, LAM loaded NPs are prepared by nano spray drying method and their *in vitro* characteristic properties are evaluated.

2. MATERIALS AND METHODS

2.1. Materials

Lamivudine is a kind gift from Sanovel İlaç (Istanbul, Turkey). Evonik Nutrition & Care GmbH (Darmstadt, Germany) provided the Eudragit RS 100. All other chemicals used were of analytical grade.

2.2. Preparation of nanoparticles

Nano Spray-Dryer (B-90, Büchi Labortechnik AG, Switzerland) was used to produce NPs. For the preparation of NPs, ERS was dissolved in ethanol and LAM was added. Spray-drying conditions and NPs ingredients are summarized in Table 1 and Table 2, respectively.

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	LAM	Ethanol
NP-Blank	1 g	-	50 mL
NP-1	1 g	0.1 g	50 mL
NP-2	1 g	0.15 g	50 mL
NP-3	1 g	0.2 g	50 mL

2.3. Characterization of nanoparticles

Zetasizer Nano ZS (Malvern Instruments, UK) was used to analyze particle size (PS), polydispersity index (PDI) and zeta potential (ZP) of NPs.

The entrapment efficiency (EE%) and release study of NPs were performed with UV-vis spectrophotometer (Shimadzu UV-160A, Japan) and the detection wavelength is 272 nm. For EE%, accurately weighed NPs (2 mg) were dispersed in water (10 mL), vortexed for 1 min and centrifuged at 13 000 rpm for 15 min for the determination of LAM remaining on NP's surface (LAMs).

As the difference between the initially added (LAM_t) and the LAM_s. EE (%) was calculated by following Equation 1 (Eq. 1).

$$EE\% = [\frac{\text{LAMt} - \text{LAMs}}{\text{LAMt}}] \times 100 \qquad \text{Eq.1.}$$

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

3. RESULTS AND DISCUSSION

3.1. Characterization of nanoparticles

PS, PDI, ZP and EE % values of NPs are shown in Table 3. *In vitro* release profile of DS and formulations are shown in Fig. 1.

Table 3. PS, PDI, ZP and EE % results

Code	PS	PDI	ZP	EE %
Blank	262.1±15.0	0.535±0.042	61.7±0.6	-
NP-1	373.3±10.9	0.541±0.027	60.0±0.6	79.18±3.56
NP-2	460.6±7.5	0.597±0.005	62.2±0.9	64.26±1.96
NP-3	486.0±27.3	0.517±0.006	60.7±3.0	61.84±1.60

Particle size of NPs prepared using ERS was determined to increase as the amount of LAM increased. NPs were prepared in sub-micron size in accordance with the literature [3]. PDI is used to estimate the average uniformity of particles, and larger PDI values correspond to a larger size distribution in the particle sample. PDI ranges from 0.01 to 0.5-0.7 for single phase systems where values higher than 0.7 are indicative of a very large particle size distribution [2, 4]. All NP formulations prepared in this study presented PDI values lower than 0.7 and therefore particle size distribution was decided to be uniform. Positive ZP values of NP formulations highlighted the presence of cationic ammonium group of ERS [2].

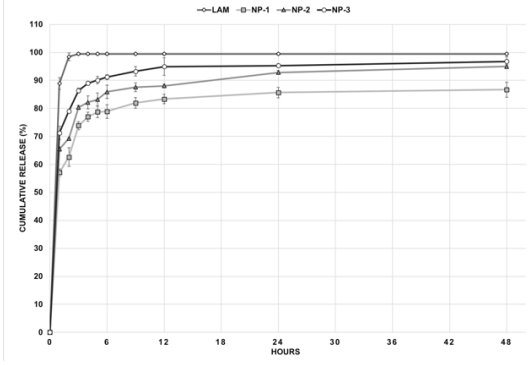

Figure 1. Release profile of LAM and LAM from NP formulations.

EE % of NP-3 containing 0.2 g LAM was the lowest meaning the amount of LAM encapsulated in the polymer decreased as the amount of active ingredient increased in ERS. As a result, as the amount of active ingredient added during formulation preparation increased, EE% decreased [5]. *In vitro* release of pure LAM resulted in 98.4 % ± 1.4 (mean±SD) release within the first 2 h while release from NPs was prolonged. Initial rapid release observed from NPs was most probably dependent on the rapid dissolution of superficially adsorbed LAM and it was found that LAM encapsulated in NPs was released in a prolonged pattern.

4. CONCLUSION

This study shows that LAM loaded ERS NPs can be prepared successfully by nano spray drying method. The formulations are nanoscale, the size distribution is uniform and have a positive zeta potential value that is important for cellular uptake and, has high entrapment efficiency, ideal for oral administration. As a conclusion, the LAM-loaded ERS NPs represent a promising system with prolonged delivery of LAM for oral application.

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