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SYNTHESIS OF DRUG MICROPARTICLE WITH HYDROPHILIC CARRIER AND ITS CHARACTERIZATION

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Abstract – In the present study, a model drug, with its low permeable and low aqueous soluble properties, was selected to produce microparticles using an anti-solvent precipitation technique with two different drugs: polymer (0.5, 1.0, w/v %) ratios. The characterization tests were performed using SEM, EDAX, FTIR, and TGA analyses. SEM results showed that a second drug: polymer ratio obtained homogenous surface morphology and the spherical microparticles with 2µm particle size. According to the TGA results, the hydrophilic carrier, bulk drug, and physical mixture were stable up to 200 ∘C, and then the decomposition started. The decomposition behavior of bulk drug and physical mixture showed a similar tendency, whereas the solid dispersion system, a chemical process, showed differences during its decomposition. FTIR results of solid dispersion of model drug had a broadened peak at 3250 cm^{-1}, and the peak intensity at 1750 cm^{-1} decreased to compare the FTIR spectrum of hydrophilic carrier. FTIR spectra of bulk drug and physical mixture, a physical process, showed similar peaks except for the peak at 1250 cm^{-1} being in the physical mixture.
Keywords – Danazol, Solid dispersion, anti-solvent precipitation, SEM, TGA, FTIR.

I. INTRODUCTION

Oral drug absorption encounters multiple restraints commonly originating from the physicochemical properties of the active pharmaceutical ingredients. Most active pharmaceutical ingredients have poor aqueous solubility and dissolution rates throughout the gastrointestinal tract, resulting in poor drug permeability and low bioavailability after oral administration[1,2].

Several hydrophilic carriers, known for their biocompatible, aqueous soluble and non-toxic properties, combined with the low aqueous soluble active pharmaceutical ingredients (APIs) to tackle this complex issue. This strategy holds great promise in enhancing drug permeability and bioavailability[3,4]. The poorly water-soluble drugs are molecularly dispersed into these hydrophilic carriers to reduce particle size, increase surface area, and improve wettability and solubility[5,6] to prepare solid dispersion systems, which is one of the most widely used, simple, and effective solubility enhancement techniques in pharmaceutical research[7].

Danazol (DNZ, $C_{22}H_{27}NO_2$, Figure 1.) is an isoxazole derivative of a 17-alpha-ethinyl testosterone-type drug[8], which belongs to Class II in the biopharmaceutical classification system. DNZ is a neutral, low aqueous soluble (C_w: 0.42g/ml, 37°C)[9], and it has a lipophilic (log P: 4.53) structure in its nature. It is widely used in the treatment of endometriosis[10] and in the treatment of fibrocystic breast disease, breast cancer, and hemophilia[11].

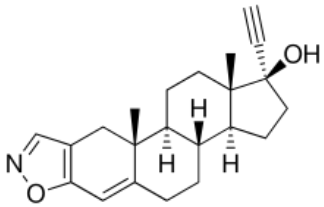


Fig.1. The chemical structure of the DNZ[12]

This study aims to prepare solid dispersions of DNZ with two different drug: polymer (0.5, 1.0, w/v %) ratios to obtain homogeneous surface morphology. The characterization tests of solid dispersions, bulk DNZ, and physical mixture were carried out with SEM, TGA, and FTIR analyses.

II. MATERIALS AND METHOD

2.1. Materials

DNZ was purchased from Cayman Chemical Company, USA. Distilled water was bought from Polifarma (Tekirdağ, Türkiye).

2.2. Preparation of the DNZ solid dispersions

The DNZ solid dispersions were prepared by the anti-solvent precipitation method with minor modifications of the reported paper[13]. A precisely weighed quantity of 100 mg of DNZ was dissolved in 50 ml of appropriate organic solvent. After that, by using a syringe, the DNZ was dropped into distilled water containing the polyvinyl alcohol (0.5, 1.0, w/v %) under a magnetic stirrer at 1000 rpm for four hours until the organic solvent was evaporated entirely, thereby resulting in supersaturation of the DNZ in solution and solid dispersion formation. The prepared DNZ solid dispersions were kept at ambient temperature for characterization tests.

2.3. *Material characterization*

The surface morphology of DNZ and the solid dispersions were examined using a Scanning Electron Microscope (SEM) (FEI QUANTA FEG 250, USA) with a high resolution and magnification ranging from 30x to 300Kx (SDU, YETEM, Türkiye).

The thermal properties of the samples were rigorously investigated using a simultaneous TGA analyzer (LABSYS evo, SDT650, Setaram Ins., USA) in a controlled temperature range of 25 ∘C to 750 ∘C at a heating rate of 10 ∘C/min under a nitrogen atmosphere.

The FTIR analyses were performed by Shimadzu IRTracerTM-100 with the resolution of 4.0 cm^{-1}. The IR spectra were acquired in the wavenumber range of 4500 cm^{-1} to 500 cm^{-1}. The TGA and FTIR analyses were conducted at the R&D Training and Measurement Center, KORL and TAL laboratories Türkiye, respectively.

III. Results and Discussion

The preparation of the successful dispersion of the active pharmaceutical ingredient (API) in the hydrophilic carrier, at a molecular level, overcomes the intermolecular force between API molecules and leads to the formation of the homogeneous phase[14,15] of the solid dispersion, which can help increase the solubility and dissolution rate of poorly water-soluble drugs with consequent improvement in bioavailability[16].

The synthesis of solid dispersions of DNZ was carried out with two different drug: polymer ratios and SEM images of two solid dispersions were given in Figure 2A-B.

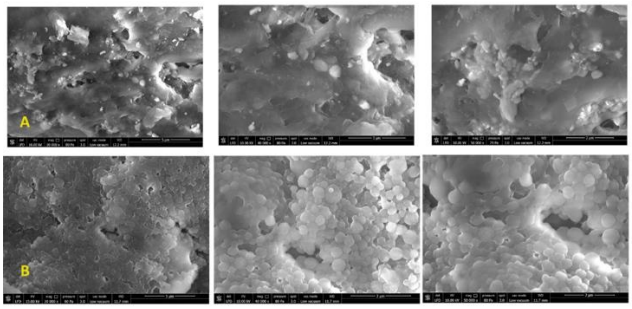
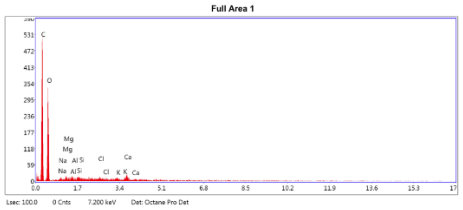


Fig. 2A-B. The SEM images of solid dispersions of DNZ, with three different magnifications (scale bar =5µm (20000X), 3µm(40000X) and 2µm(50000X) (⇨)).

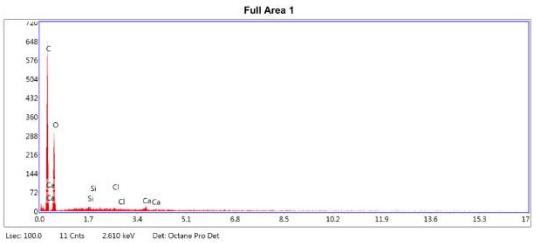
The cavity and channel formation occurred on the surface of the solid dispersion with a heterogeneous surface appearance (Figure 2A). The white particles belong to hydrophilic carriers and could not be mixed very well with active pharmaceutical ingredients. Figure 2B revealed apparent changes in the morphology of powder particles with evident formation of spherical shapes and better homogeneity of the surface. The obtained particles with the size of 2µm, were smaller than the reported paper in the literature[17].

The EDAX results of the solid dispersions are given in Figure 3. The weight percentages of carbon and oxygen were 51.52 and 46.20 for 0.5 % (w/v) and 55.78 and 42.98 for 1.0 % (w/v) for the synthesized dispersions (Figure 3). It was assumed that the other trace metals come from impurities in solvents used in the synthesis procedure.



eZAF Smart Quant Results

Element	Weight %	Atomic %	Net Int.	Error %	Kratio	Z	R	A	F
C K	51.52	59.20	25.55	7.88	0.3032	1.0239	0.9888	0.5750	1.0000
O K	46.20	39.86	17.11	11.65	0.0870	0.9784	1.0076	0.1924	1.0000
NaK	0.22	0.13	0.21	88.47	0.0007	0.8874	1.0302	0.3741	1.0018
MgK	0.19	0.11	0.33	78.77	0.0009	0.9022	1.0367	0.5475	1.0030
AlK	0.16	0.08	0.35	75.57	0.0010	0.8685	1.0427	0.7040	1.0049
SiK	0.14	0.07	0.37	70.37	0.0011	0.8872	1.0483	0.8233	1.0075
ClK	0.18	0.07	0.40	64.77	0.0015	0.8260	1.0632	0.9939	1.0261
K K	0.31	0.11	0.59	64.75	0.0028	0.8216	1.0715	1.0237	1.0488
CaK	1.07	0.37	1.70	22.50	0.0096	0.8365	1.0753	1.0280	1.0460



eZAF Smart Quant Results

Element	Weight %	Atomic %	Net Int.	Error %	Kratio	Z	R	A	F
C K	55.78	63.06	29.66	7.51	0.3403	1.0209	0.9903	0.5977	1.0000
O K	42.98	36.48	15.51	11.92	0.0762	0.9754	1.0090	0.1818	1.0000
SiK	0.22	0.10	0.58	67.03	0.0016	0.8844	1.0494	0.8372	1.0074
ClK	0.27	0.11	0.62	62.14	0.0023	0.8232	1.0642	0.9993	1.0247
CaK	0.75	0.25	1.24	33.14	0.0068	0.8337	1.0761	1.0313	1.0511

Fig. 3. The EDAX spectra of solid dispersions of DNZ

The thermogravimetric analysis (TGA) technique determined the stability of DNZ, and solid dispersions and physical mixtures were developed in a temperature range between 25 ∘C and 750 ∘C. The results are given in Figure 4.

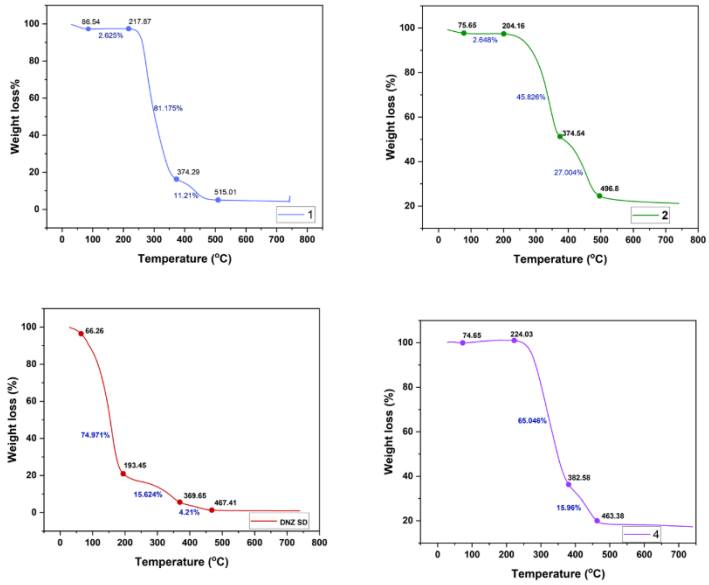


Fig. 4. TGA curves of samples
1-Hydrophilic carrier, 2-Bulk DNZ, 3-Solid dispersion, 4-Physical mixture.

The water absorbed on the surface of the molecules evaporates between the initial temperature of 25 ∘C to 100 ∘C for the given TGA curves[18]. These temperatures were 86.54 ∘C,75.65 ∘C, ~50 ∘C and, and 74.65 ∘C for 1, 2, 3, and 4, respectively. Hydrophilic carriers showed two decomposition stages: a continuous weight loss between 200-400 ∘C and a weight loss that continues between 400-500 ∘C[19]. The hydrophilic carrier, bulk DNZ, and physical mixture were stable up to 200 ∘C, and then decomposition started. The solid dispersion of DNZ started to decompose at 66.26 ∘C. The other decomposition temperatures were given in the figures, and the decomposition percentages were also shown in blue colors. The TGA curve mass loss percentage becomes constant, starting from 500∘C to 750 ∘C, due to carbonaceous mass forming a layer on the polymer surface due to the degradation of the polymer chains[20].

The FTIR spectra of the studied samples are given in Figure 5. The characteristic peaks of bulk DNZ were as follows[21]: stretching vibration of acetylene group at 2099 cm^{-1}, stretching vibration of isoxazole ring at 1631 cm^{-1}, and stretching vibration at 1600 cm^{-1}. The bulk DNZ and physical mixture showed almost similar IR peaks at the spectrum except for the peaks at 3000 cm^{-1}, which are weaker than the bulk DNZ in the physical mixture. The sharp C-O-C peak was obtained at 1250 cm^{-1} in the physical mixture.

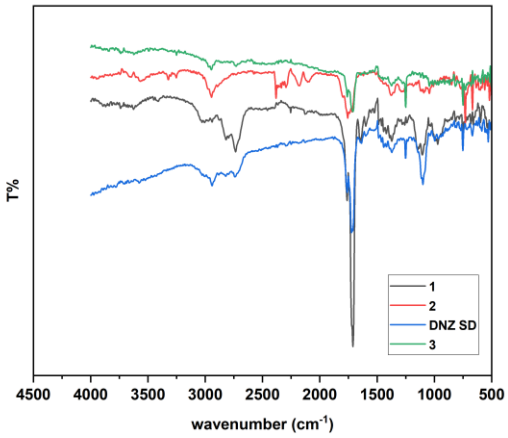


Fig. 5. FTIR spectra of samples

(1-Hydrophilic carrier, 2-Bulk DNZ, 3-Physical mixture)

IR peaks of hydrophilic carrier as follows: The O-H from the intermolecular and intramolecular H bonds[22] was at 3550-3200 cm^{-1}, C-H from alkyl groups[23] was at 2840-3000 cm^{-1}, C=O stretching vibration[23] was at 1750-1735 cm^{-1}, -CH2[24] was at 1461-1417 cm^{-1}, C-O-C[22] was at 1150-1085 cm^{-1} and C-O crystallinity[23] was 1141 cm^{-1}. When we compare IR spectra of solid dispersion of DNZ with hydrophilic carrier, the broadened peak was observed at 3550-3200 cm^{-1}. The peak intensity decreased at 1750-1735 cm^{-1} and the sharper peak than hydrophilic carrier was seen in solid dispersion at 1150-1085 cm^{-1}.

IV. CONCLUSION

In conclusion, synthesized solid dispersions of DNZ with two different drug: polymer (0.5, 1.0, w/v %) ratios, were performed. A physical mixture containing a hydrophilic drug carrier was also prepared. According to the SEM images, homogenous surface morphology and spherical particle shape with 2µm particle size were obtained with the second drug-polymer ratio. According to the TGA results, the hydrophilic carrier, bulk drug, and physical mixture were stable up to 200 ∘C, and then the decomposition started. The decomposition behaviour of bulk drug and physical mixture showed a similar tendency, whereas the solid dispersion system, a chemical process, showed differences during its decomposition. The comparison of IR spectra of solid dispersion of DNZ with hydrophilic carrier showed that the broadened peak was observed at 3550-3200 cm^{-1}, the peak intensity decreased at 1750-1735 cm^{-1}, and the sharper peak was seen at 1150-1085 cm^{-1} in synthesized solid dispersion.

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