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A Formulation Study for Enteric Microspheres of Tenoxicam Using Cellulose Acetate Phthalate Part-I: DTA/TG Analysis

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Tenoxicam is an antiinflammatory drug causing irritation on stomach mucosa upon per oral administration in the form of tablets or hard gelatin capsules. Preparation of cellulose acetate phthalate microspheres of tenoxicam with solvent evaporation technique was suggested to overcome gastric irritancy of the pure drug. At first, it was determine to conduct preformulation studies. Thermal behaviour of pure drug (tenoxicam), polymer (cellulose acetate phthalate) and their physical mixtures was investigated as part of preformulation studies. Differential thermal analysis and thermogravimetry techniques were used for this purpose. The thermal analysis data obtained in this study revealed that there is no interaction between the polymer and the pure drug, indicating the appropriateness of the polymer of choice for preparation of enteric micropsheres.

Key Words: Tenoxicam, Cellulose acetate phthalate, DTA/TG, Microspheres, Enteric microspheres, Preformulation studies.

INTRODUCTION

It is well-known fact that non-steroidal antiinflammatory drugs (NSAIDs) possess gastric ulcers upon oral administration of conventional dosage forms[1]. The mechanism of their pharmacological activity is the inhibition of prostaglandin synthesis[2]. Tenoxicam, 4-(hydroxy-pyridine-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2u{6},7-dithia-3-azabicyclo-[4.3.0]nona-8,10-dien-5-one (Fig. 1) is an analgesic and antiinflammatory drug used orally in the treatment of rheumatic disorders[3]. It causes gastric mucosal damage[3]. The best approach to overcome this problem may be to prepare enteric dosage forms of the drug[4,5]. Enteric-coated oral dosage forms are soluble in intestinal fluid rather than gastric fluid and hence, avoid gastric mucosal damage[4,5]. Enteric dosage forms may be prepared by means of enteric-coated tablets or microparticulate systems[4-7].

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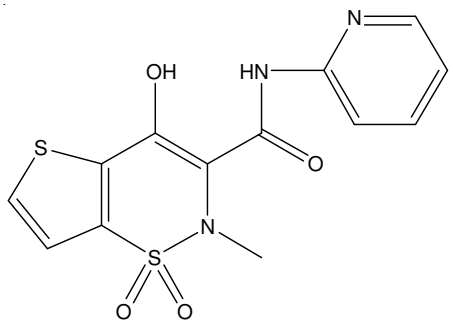

Fig. 1. Chemical structure of tenoxicam, 4-(hydroxy-pyridin-2-ylamino-methylidene)-3-methyl-2,2-dioxo-2u{6},7-dithia-3-azabicyclo[4.3.0]-nona-8,10-dien-5-one

Microparticulate dosage forms spread out more uniformly in the gastrointestinal tract and lower the gastro-irritant effect of single unit dosage forms, such as conventional tablets. Microspheres are a class of microparticulate systems in which drug is distributed in a polymeric matrix. Enteric microspheres are more advantageous than enteric coated tablets as these microparticulate systems possess better formulation properties and absorption[7-9]. The physical state of the drug in microspheres influences the kinetics of drug release and is dependent on the solubility of the drug in the polymer matrix.

Cellulosic derivatives are some of the most widely used polymers for the preparation of enteric dosage forms[3,6,8,10]. Cellulose acetate phthalate (CAP) is the most widely used polymer[11]. It has been used as enteric coating polymer for preparation of enteric tablets and also utilized in microsphere formulation studies[7,12-17].

Preformulation studies are of great importance for developing new dosage forms, especially for the ones with modified release profiles. The most important criteria for choosing the appropriate polymer are to be inert in nature (*i.e.*, the polymer shouldn't chemically interact with the drug, causing instability)[6]. Possibility of a chemical interaction can be investigated by means of FT-IR, DTA/TG, DSC and X-ray analysis of polymer, pure drug and their physical mixture[6].

No evidence was found in literature investigating thermal behaviour of tenoxicam, CAP and their physical mixture as part of preformulation studies to form microspheres. The goal of our study is to determine whether any interaction occurs between the cellulose acetate phthalate (CAP) and the drug (tenoxicam) during the formation of microspheres. In this study, DTA/TG techniques were utilized for this purpose. DTA/TG analysis was performed for tenoxicam, cellulose acetate phthalate and their physical mixture.

EXPERIMENTAL

Materials and preparation of physical mixture: Tenoxicam was gift from Roche, Istanbul, Turkey. Cellulose acetate phthalate was donated by Eastman Kodak, UK. All other reagents and chemical substances were of analytical grade. It was planned to prepare the enteric microspheres of tenoxicam employing solvent evaporation technique as described elsewhere[7,14]. In the procedure in question, 1:1 drug to polymer (CAP) ratio was utilized to prepare microspheres. Taking that into account, the physical mixture of tenoxicam with cellulose acetate phthalate was prepared in the ratio of 1:1. Accurately weighed amount of tenoxicam was uniformly mixed with CAP using a dynamic mixer for 0.5 h. The obtained mixture (PM) was then stored in a scintillation vial in a desicator for further experiments.

Differential thermal analysis and thermal gravimetry studies: The thermal studies were carried out on a Shimadzu DT-40 thermal analyzer with simultaneous DTA-TG module. The thermal analysis system was used over the temperature range 298-1250 K. The samples were placed in Pt crucibles and α-Al_2O_3 was used as the reference material. The measurement was performed using a dynamic nitrogen furnace atmosphere at a flow rate of 60 cm^3/min. The heating rate was 10 K/min and the sample sizes ranged in mass from 8 to 10 mg.

RESULTS AND DISCUSSION

Tenoxicam is available in amorphous powder and its physicochemical properties have been described elsewhere. The DTA/TG profiles of the Tenoxicam are shown in Fig. 2. It melts at 495 K (496 K)[18] with simultaneous decomposition. The first mass loss was observed at 494 K in the TG

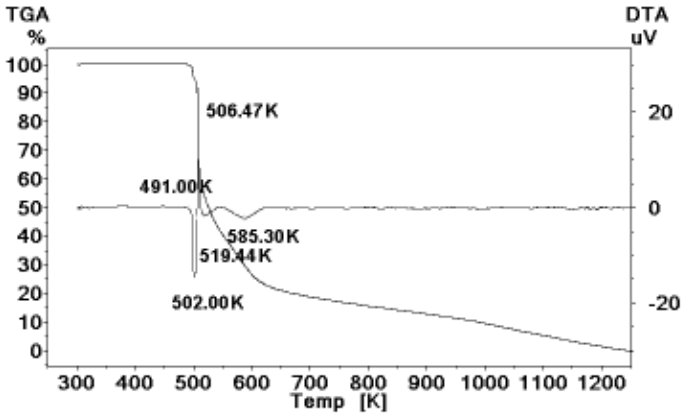

Fig. 2. DTA/TG diagram of tenoxicam

profile. From the TG curve, it appeared that the sample decomposes in two stages over the temperature range 298-1250 K. The first decomposition occurs between 491 and 550 K with a mass loss of 59.3 %. The second decomposition takes place between 550 and 1250 K with a mass loss of 40.6 %. From the corresponding DTA profile, three endothermic and one exothermic peaks are noted, the first endothermic peak between 491 and 505 K with a maximum at 502 K, the second endothermic peak between 508 and 547 K with a maximum at 519 K, the third endothermic peak between 547 and 624 K with a maximum at 585 K and the exothermic peak between 505 and 508 K with a maximum at 506 K.

It is apparent from the TG analysis data that the CAP looses 99.9 % of its original mass between 298 and 1250 K. The DTA/TG data for CAP is shown in Fig. 3. The sample decomposes in three stages. The first decomposition occurs between 426 and 496 K with 16.6 % mass loss. The second decomposition takes place between 496 and 578 K with 45.5 % mass loss. The third decomposition occurs between 578 and 1250 K with 37.7% mass loss. Two endothermic and one exothermic peak were observed in the DTA analysis. The first peak is obtained between 426 and 495 K with a maximum at 467 K. The second peak occurs between 495 and 578 K with a maximum at 528 K and the third one between 578 and 639 K with a maximum at 611 K.

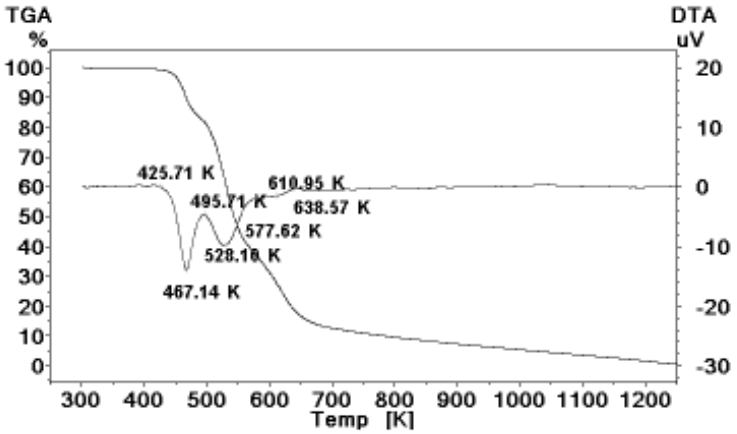

Fig. 3. DTA/TG diagram of CAP

In the last part of our study, physical mixture of tenoxicam (PM) was prepared with CAP in the drug:polymer ratio of 1:1. The TG studies on the PM of tenoxicam indicated that the initial mass loss occurs at 426 K. Decomposition ends with a total of 99.9 % mass loss at 1250 K. DTA/TG diagrams of the PM are shown in Fig. 4. It was observed from the TG curve that the sample decomposes in three stages and it looses 14.3, 37.4 and

48.2 % of its mass in each stage, respectively. The temperature ranges of these decompositions are found to be 426-482, 482-544 and 544-1250 K, respectively. The DTA curves show three endothermic and one exothermic peak. The first endothermic peak occurs between 426 and 483 K with a maximum at 462 K. The second one is obtained between 483 and 498 K with a maximum at 493 K. The third one occurs between 498 and 625 K with a maximum at 585 K. The exothermic peak occurs between 498 and 519 K with a maximum at 502 K.

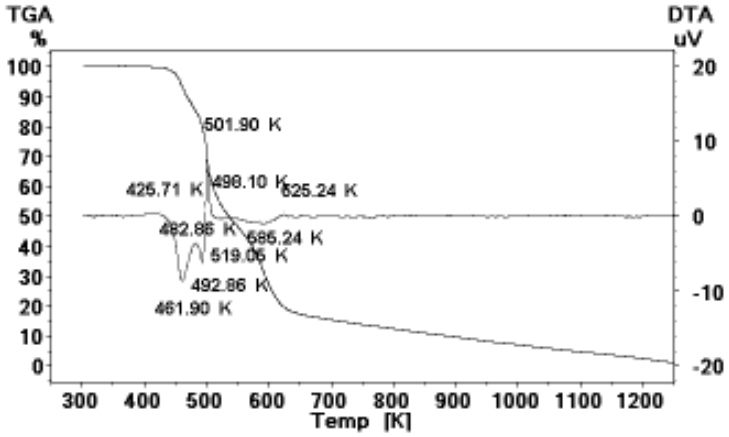

Fig. 4. DTA/TG diagram for the enteric microspheres of CAP and tenoxicam

DTA/TG data for tenoxicam indicated the presence of a typical sharp endothermic melting peak at 502 K and a sharp, exothermic, decomposition peak at 507 K. On DTA/TG curves of CAP, it was observed that there exist two endothermic peaks at 467 and 528 K as well as one exothermic decomposition peak at 611 K. In case of a chemical interaction between the pure drug and the polymer during microparticulate formulation, the specific peaks for the drug and the polymer show significant shift or disappear on the curve of their physical mixture. All endothermic and exothermic effects obtained from individual thermal analysis of tenoxicam and CAP was also observed on the DTA/TG curves of physical mixture. However, the maximum peak values were lower than those obtained for pure tenoxicam and CAP (5-6 K reduction). This reduction is usually obtained for the physical mixture of pure substances. Based on these data, it can be concluded that tenoxicam and CAP shouldn't chemically interact upon formation of enteric microspheres, which is the desired property for formulating such microparticulate systems.

Conclusion

In this study, preparation of enteric microspheres of tenoxicam with CAP was suggested to overcome gastric irritancy problem of the drug. Before carrying out the formulation studies further, we determined to perform preformulation studies using DTA/TG analysis. In the first part of our study, which is presented here, thermal behaviour of pure drug (tenoxicam), enteric polymer (CAP) and their physical mixture was investigated. Specific endothermic and exothermic peaks of tenoxicam and CAP were obtained on the DTA/TG curves of physical mixture. Thus, comparison of DTA/TG diagrams indicates that no chemical interaction should take place between pure drug and polymer while forming the microspheres. Based on this finding, it can be concluded that CAP can be used to prepare enteric microspheres of tenoxicam as it doesn't influence the drug's stability during formulation.

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