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Thermal analysis on phase sensitive granisetron *in situ* forming implants

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ABSTRACT

In this study effect of gamma irradiation sterilization and storage conditions on thermal properties of phase sensitive granisetron *in situ* forming implant (ISFI) was investigated. ISFI was prepared by mixing Poly (DL-lactide-co-glycolide) (PLGA) with dimethylsulfoxide (DMSO) : propylene carbonate (PC) (1:1) solvent combination then granisetron HCl was added and homogenized. Following application of gamma irradiation, ISFI was stored at 25 °C for 4 months. Differential Scanning Calorimeter (DSC) measurements and Thermogravimetric Analysis-Differential Thermal Analysis (TGA-DTA) were carried out on fresh, irradiated and aged forms of granisetron ISFI. According to DSC, TGA and TGA-DTA thermograms and mass loss results application of gamma irradiation and storage of irradiated ISFI at 25 °C for 4 months have not significant effect on thermal stability of ISFI.

INTRODUCTION

A novel biodegradable injectable polymeric system namely ISFI has been developed and looks very promising in drug delivery due to advantages in manufacturing process and patient compliance. The term ISFI has been used to describe a variety of polymer based systems that can be classified into four categories, namely: (i) thermoplastic pastes, (ii) *in situ* cross-linked systems, (iii) *in situ* precipitation systems and (iv) solidifying organogels are initially comprised of a liquid solution that undergoes a process of solidification after placement in a site of interest (Hatefi and Amsden, 2002; Packhaueser *et al.*, 2004; Patel *et al.*, 2010). One such ISFI product defined as *in situ* precipitation (phase sensitive) system was first developed by Dunn *et al.* (1990), which consist of a biodegradable polymer dissolved in water miscible organic solvent that undergoes phase inversion when injected into a water rich phase and formed solid *in situ* implant. Mostly used polymers and solvents in this system are polyesters such as poly(d,l-lactide) or PLGA and N-methyl-2-pyrrolidone or DMSO respectively (Dunn and Tipton, 1997; Hatefi and Amsden, 2002; Packhaueser *et al.*, 2004). Because of desorption in the body, it is necessary to sterilize this systems before application. However sterilization of such polymeric systems has great importance and has some disadvantages dependent on preferred sterilization method. For PLGA implants most preferable sterilization method is gamma irradiation which characteristically highly penetrating with a low dose rate (kGy/hour) (Bernkopf, 2007). Nevertheless, it is well known that gamma irradiation sterilization may cause radiolytic degradation with variable quantities on polymers which induces a dose dependent chain scission leading to M_w reduction which is effective on viscosity. Viscosity changes which are raised from solvent loss may be effective on solidifying properties and thus injectability and drug release of *in situ* forming implants could be investigated by thermal analysis. Compatibility of drug and polymer could be investigated by DSC measurements (Eliaz and Kost, 2000; Hatefi, 2002; Dong *et al.*, 2006) while effect of gamma irradiation sterilization and storage conditions on formulations could be investigated thermally by simultaneous TGA-DTA (Hausberger *et al.*, 1995; Penco *et al.*, 2000; Bakhshi *et al.*, 2006; Rafienia *et al.*, 2007). In our previous study ISFI composed from granisetron HCl, PLGA and DMSO:PC solvent system was evaluated by rheological and polymer degradation analysis, *in vitro*

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release, *in vivo* release and biocompatibility studies which gave successful results (Algın Yapar *et al.*, 2014), and in this study the same formulation was investigated for thermal stability in terms of gamma irradiation and storage conditions effects performed with DSC and TGA-DTA measurements.

MATERIALS AND METHODS

Materials

The materials used include granisetron HCl (Cipla Limited, India), PLGA (Plga 50:50, Resomer RG 504H, M_w 48 kDa, Boehringer Ingelheim GmbH, Ingelheim, Germany), dimethylsulfoxide (Merck, Darmstadt, Germany), propylene carbonate (Sigma-Aldrich, Steinheim, Germany) and all other chemicals were analytical grade.

Methods

Preparation of in situ forming implant system

In situ forming implant formulation was prepared by mixing PLGA with mixture of two solvents (DMSO:PC 1:1) in glass vial until the formation of a clear solution and granisetron HCl was homogenized (Bandelin Sanoplus HD 2070, Germany) in polymer solution. Percentage of polymer, solvent and drug was 32%, 64% and 4% respectively in formulation and formulation was coded as FDP. Liquid implant formulation was then sealed and heated to 65 °C to remove trapped air bubbles (Bakhshi *et al*., 2006; Algın Yapar *et al.*, 2014).

Sterilization process

Liquid implant formulations (FDP) were placed in glass aluminum sealed vial, then irradiated with a ^{60}Co source (Tenex Issledovatel, TAEK, Ankara, Turkey) and irradiated form was coded as RDP. A 25 kGy dose was applied following the European Pharmacopoeia recommendations for an effective sterilization (European Pharmacopeia).

Thermal analysis

Thermal analysis of granisetron HCl and polymer was carried out by DSC (DSC-60, TA Instruments, New Castle, DE). Samples approximately 5 mg for drug and 10 mg either for polymer or drug- polymer mixture (which were prepared as same as *in situ* liquid formulation then injected into dissolution medium and after solidification they were prepared for thermal analysis) were encapsulated in hermetically sealed aluminum pans. Experiments for polymer were performed under 1.5 bar nitrogen flow at heating rate of 10 °C min^{-1} from 20 to 250 °C while experiments for drug and drug-polymer mixture were performed under 1.5 bar nitrogen flow at heating rate of 10 °C min^{-1} from 20 to 400 °C (Eliaz and Kost, 2000; Late and Banga, 2005).

Effects of irradiation and storage conditions on *in situ* implant formulation were investigated by DSC (DSC-60, TA Instruments, New Castle, DE), TGA and TGA-DTA (DTG-60H, TA Instruments, New Castle, DE). Approximately 15 mg samples were encapsulated in hermetically sealed aluminum pans. Experiments were performed under 1.5 bar nitrogen flow at heating rate of 10 °C min^{-1} from 20 to 400 °C (Penco *et al.*, 2000; Rafienia *et al.*, 2007).

RESULTS AND DISCUSSION

Obtained DSC thermograms for granisetron HCl and Resomer RG 504H are presented in Figure 1 (a, b) and determined Tg values are 304.03 ºC for drug and 53.85 ºC for polymer which are in accordance with the literature (Hatefi, 2002; Lata and Banga, 2005). DSC analysis of drug and polymer mixture (Figure 1 c) show that crystal form changes of drug resulted as splay peak which has a maximum of 298.63 °C and peak for polymer as 56.31 °C which were proximate for Tg values of pure drug and polymer. Thus, it was inferred that there was not an interaction exist between drug and polymer.

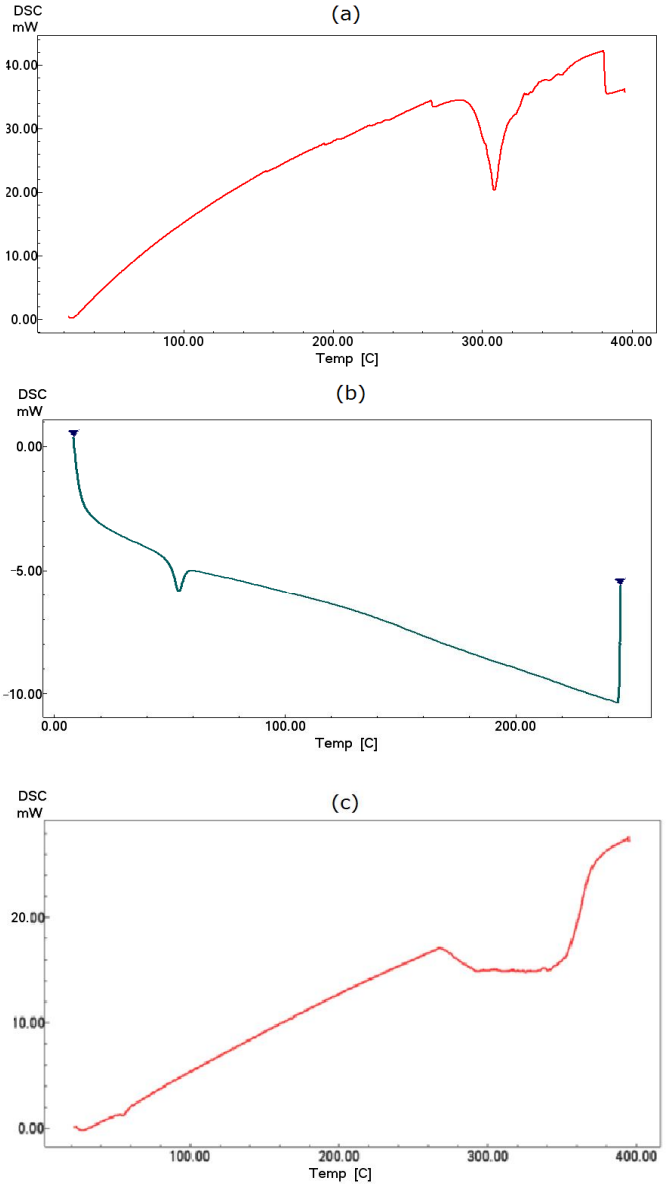

Fig. 1: DCS thermograms; a) granisetron HCl, b) Resomer RG504H, c) drug and polymer mixture.

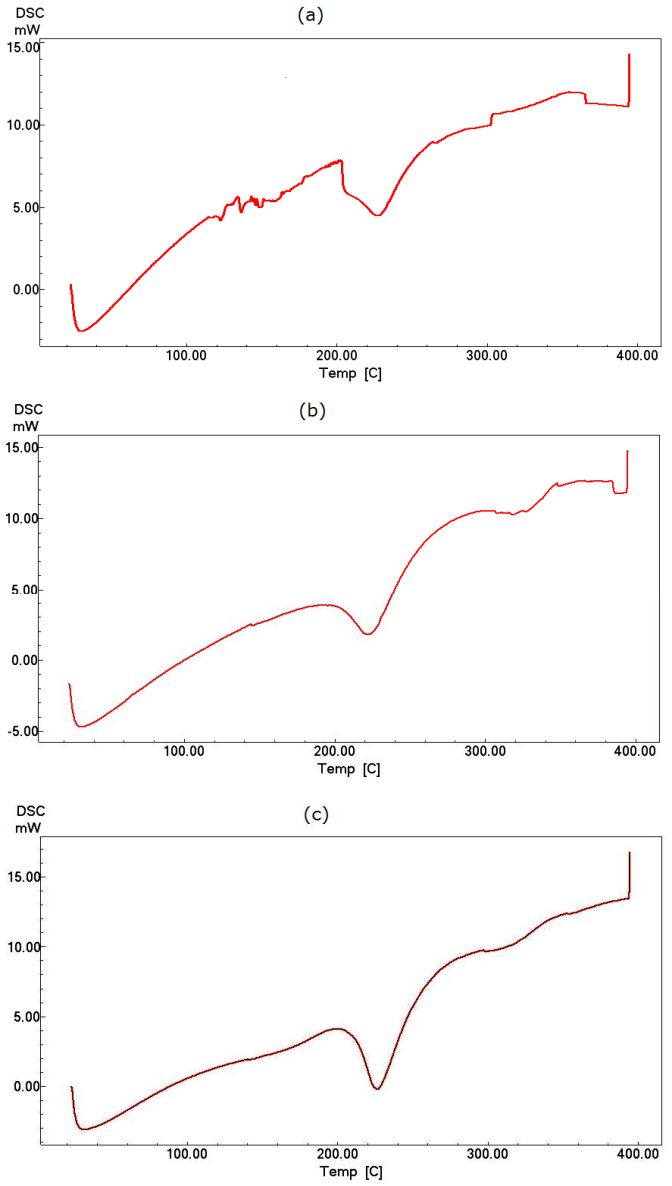

Fig. 2: DSC thermograms of formulations; a) FDP, b) RDP and c) RDP stored in 25±2 ℃ for 4 months.

DSC thermograms for FDP, RDP and RDP formulation stored in 25±2 °C for 4 months are given in Figure 2. Because of drug and polymer solved in solvent system or dispersed as amorphous form in implant system their characteristic endothermic peaks were not observed, endothermic peak of solvent system was observed between boiling points of PC and DMSO of 189 °C and 240 °C respectively in the thermograms. Therefore, it was inferred that either gamma irradiation or storage conditions were not cause to crystallization of drug or polymer which could be proved with the thermograms that have not any endothermic peak belong to drug or polymer.

TGA and TGA-DTA thermograms of FDP, RDP and RDP stored in 25±2 °C for 4 months are presented in Figure 3, 4 and 5 respectively. When the TGA results for formulations mass loss curves compared to FDP, RDP and RDP (stored at 25 °C for 4 months) the initial temperature for the mass loss was (inflection point: inflection point) average 56 °C and were close to each other, the mass loss average of the temperature in the second stage was begin at 226 °C and has been identified as being close to each other and the total mass loss was completed in two stages (Fig. 3a-5a).

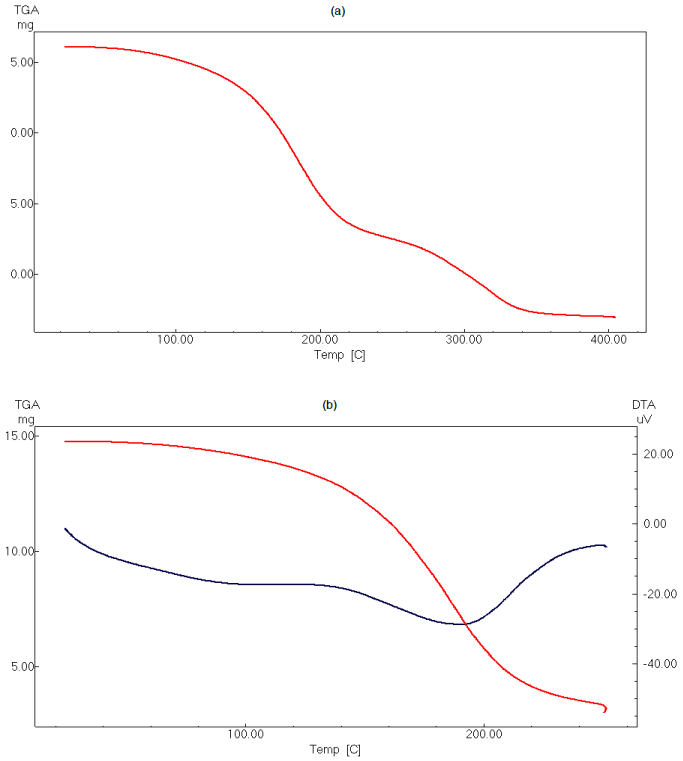

Fig. 3: TGA (a) and TGA-DTA (b) thermograms of FDP.

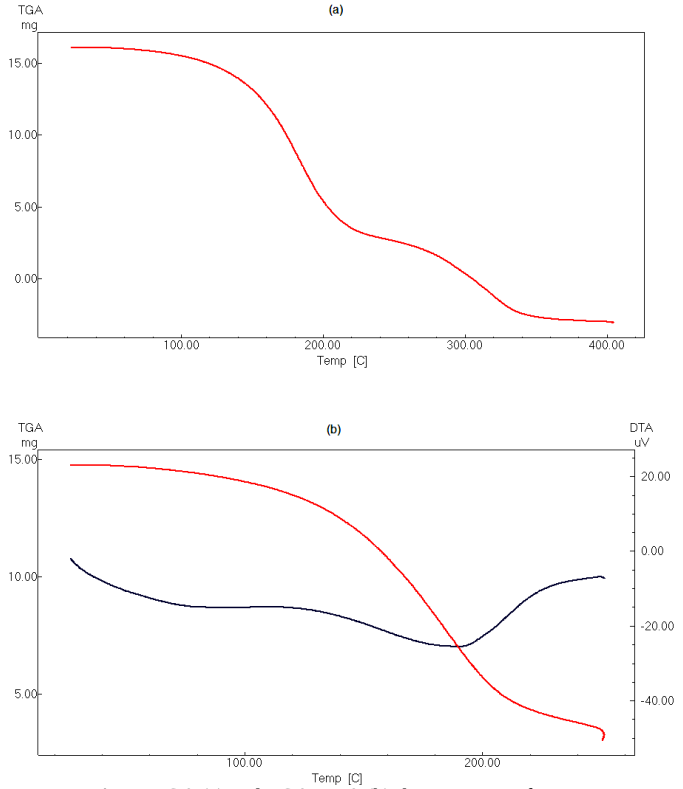

Fig. 4: TGA (a) and TGA-DTA (b) thermograms of RDP.

Simultaneous TGA-DTA results showed that FDP, RDP and RDP (stored at 25 °C for 4 months) loss of mass are quite similar according to obtained thermograms (Fig. 3b-5b). At the intersection of TGA and DTA thermograms endothermic shoulder of DTA was observed between the boiling points of solvents of the formulation (boiling points of PC and DMSO are 189 °C and 240 °C respectively) (Figure 3-5). Comparison of mass loss curves of FDP, RDP and RDP (stored at 25 °C for 4 months) showed that the inflection point average of 56 °C was too close to one another, mass loss was begin in the second phase about an average of 226 °C and completed in this phase (Fig. 3-5).

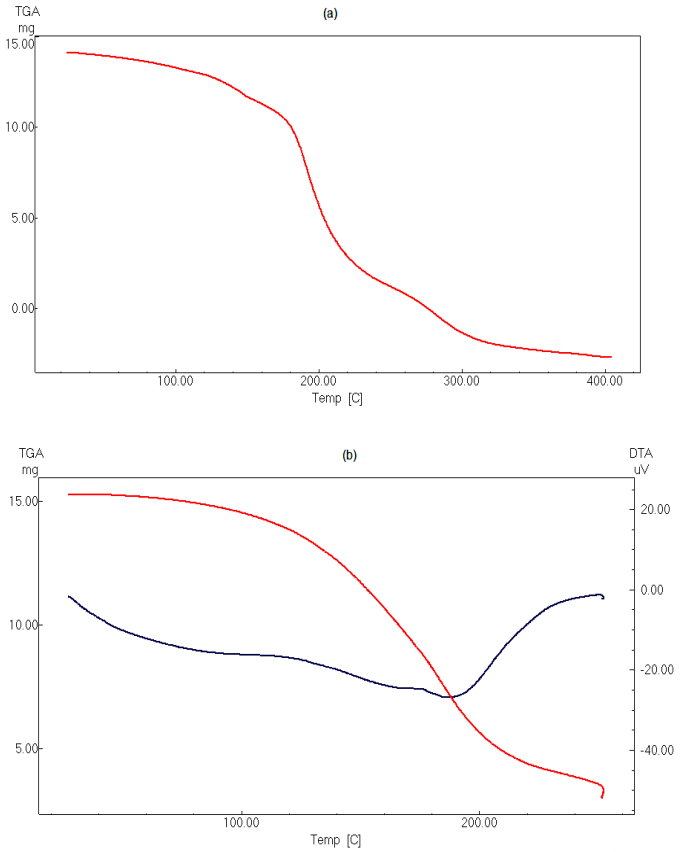

Fig. 5: TGA (a) and TGA-DTA (b) thermograms of RDP stored in 25 °C for 4 months.

In first stage the polymer and in second stage the solvent system was exposed to mass losses which were in accordance the data obtained and the thermograms. In the light of the results of previous researchers investigated the effects of irradiation process or storage conditions on PLGA thermal stability (Penco *et al*., 2000) and solvents loss for ISFI systems (Bakhshi *et al*., 2006) our results are acceptable as our formulation have an acceptable thermal stability.

CONCLUSION

As a conclusion application of gamma irradiation and storage at room temperature for 4 months have not a significant change in the thermal stability of ISFI systems.

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