Asian Journal of Chemistry; Vol. 24, No. 5 (2012), 2207-2209

ASIAN JOURNAL OF CHEMISTRY

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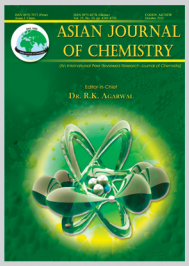

Differential Scanning Calorimetric Analysis of Drug-Polymer Interaction in Glutinous Rice Based Microbeads

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(*Received*: 23 May 2011; *Accepted*: 20 December 2011) AJC-10862

Controlled drug delivery occurs when a polymer, whether natural or synthetic, is judiciously combined with a drug or other active agent in such a way that the active agent is released from the material in a predetermined manner. The differential scanning calorimetry (DSC) offers a rapid convenient and conclusive methodology during preformulation testing, to confirm about the drug-polymer compatibility. It allows and enhances probability of any drug-polymer incompatibility to be established and identified instantaneously. The Assam Bora rice, a variety of glutinous rice cultivated mainly in Assam region was taken as polymer backbone along with sodium alginate in formulation. The fabricated drug delivery systems, formulated so as to provide controlled release of drug were subjected to DSC analysis and a comparative interpretation done by matching the thermograms recorded for drug, polymers and their blend. The results revealed that the matrix micro devices have sufficient stability and there is no indication of chemical interaction between drug and polymer backbone.

Key Words: Differential scanning calorimetry, Thermal analysis, Drug delivery, Drug-polymer compatibility.

INTRODUCTION

Thermal analysis is one of the mainstay families of techniques for the physical and on occasions chemical, characterization of pharmaceutical materials. The long history of using thermal methods within the field and the astonishing variety of applications to which these methods have been put, reflect the necessity of developing reliable and versatile characterization tools for the successful development of pharmaceutical. Indeed, it is interesting to reflect that one of the key focus areas within the industry, next to drug discovery, is analytical development, an area made even more pertinent by the recent Process Analytical Technologies initiative launched by the United States Food and Drug Administration (FDA) whereby the product-to-market process may be accelerated if appropriate validation of each stage of manufacture is provided products[1]. There are examples of thermal methods yielding chemical information such as extent of cross-linking, purity or degradation. The vast majority of applications are associated with the characterization of the physical structure and properties of materials. Classically, this would include the study of melting or crystallization, although other processes such as glass transitions and associated plasticization phenomena are also widely studied. These methods are extremely versatile, allowing useful characterization of almost any sample and may be used to study single or multiple component systems such as finished dosage forms, although care is required in the interpretation of data from the latter. Finally, these methods tend to be simple to use, inexpensive and friendly operation[2]. The thermal analysis methods involve the application or measurement of changes in heat, hence the resulting data tends to relate to temperatures of transitions or heat flow as the samples undergo such a transition. Consequently, the information gained can often only indirectly be related to the feature of interest such as crystal structure, composition, degradation, stability or chemical interaction. This therefore requires the operator to extrapolate this information, inevitably leading to assumptions in interpretation[1]. The most commonly used thermal method is and will almost certainly continue to be differential scanning calorimetry (DSC), in the drug-excipient compatibility study. The basic principle of DSC is that a sample is subjected to a heat signal and the response measured in terms of the energy and temperature of the thermal events that take place over the temperature range or time interval under study[3].

When the sample melts, the rate of temperature increase for the sample will be lower than that of the reference, as the energy imparted by the heating signal will be contributing to the breaking of solid-solid bonds rather than simply the raising of the sample temperature. If there is shift in peak in DSC thermogram, it is logical to suggest that the excipient is

interacting with the drug. The fact that DSC may well be able to detect the presence of slow reactions drug and excipients has caused considerable excitement in the pharmaceutical industry serving the long felt need for a rapid method by which the stability of drugs and the compatibility of drug-excipient mixtures, can be assessed or estimated. It mimics and hastens the harsh conditions and allows polymer incompatibility to be established instantaneously providing fast screening drug-polymer blend during preformulation studies[4].

In present study, the DSC analysis was used to assess any possible chemical interaction between the therapeutic medicament and the polymer backbone in which it is proposed to be matrixed for controlled release. The Assam Bora rice, which is a variety of glutinous rice cultivated mainly in Assam region is proposed as novel mucoadhesive biopolymer in drug delivery and utilized along with sodium alginate as polymer backbone in present study modulating the release of drug substance from fabricated microdevices.

EXPERIMENTAL

Bora rice was procured from the village near to Dibrugarh University and was confirmed by local people. Sodium alginate (Loba Chemi Pvt. Ltd. Mumbai), calcium chloride (Qualigens Mumbai, India), glacial acetic acid (Qualigens Mumbai, India), were procured from the commercial sources. Metformin hydrochloride was kindly gifted by M/s Ranbaxy Laboratories, India. All other reagents were of analytical grade laboratory reagents and were procured from commercial sources.

Preparation of microbeads: The microparticulate drug delivery systems were prepared from the gel blend of pre-gelatinized Bora rice and sodium alginate by a modified ionic gelation technique. The beads were allowed 5-10 min curring time and were washed with a mixture of ethanol and acetone[5]. The beads so prepared dried in vacuum oven at a temperature below 40 ºC and were stored in a desiccator till further use.

Pharmacotechnical characterization: The prepared beads were studied for the drug entrapment, size and size distribution, water vapour uptake, mucoadhesion, swelling, surface and mechanistic properties through phase contrast and electron microscopy; after primary screening for duration and extent of drug release the selected formulations were taken forward for further investigation[6].

Thermal analysis by differential scanning calorimetry: The DSC thermograms of the drug, drug-loaded microbeads, blank microbeads and the two polymers (bora rice and sodium alginate) were obtained using differential scanning calorimeter (Metler Toledo, Switzerland). Samples were prepared according to the procedure of Perdon *et al.*[7]. All the samples were placed in a pre-weighed stainless steel pan and sealed carefully with a sealer supplied by the manufacturer. The sealed pan was weighed to obtain the sample mass. Another sealed empty stainless steel pan was used as the reference. The instrument was calibrated using the melting temperature and enthalpy of indium. The sample was equilibrated to -30 ºC for 5 min and then heated from - 30 ºC to 200-250 ºC at a rate of 10 ºC/min.

RESULTS AND DISCUSSION

The bora rice could be gelatinized successfully by the thermal gelatinization method[8] by heating the aqueous suspension of the finely grinded rice powder above its gelatinization temperature. The gelatinization temperature for the waxy rice is reported to be around 64-71 ºC. The same in case of bora rice was found to be 64 ºC as determined by the DSC (Fig. 1). But the complete gelatinization could not be obtained below the temperature 76-78 ºC for 45 min heating. It seems to be because of the water acts as a plasticizer and mobility enhancer

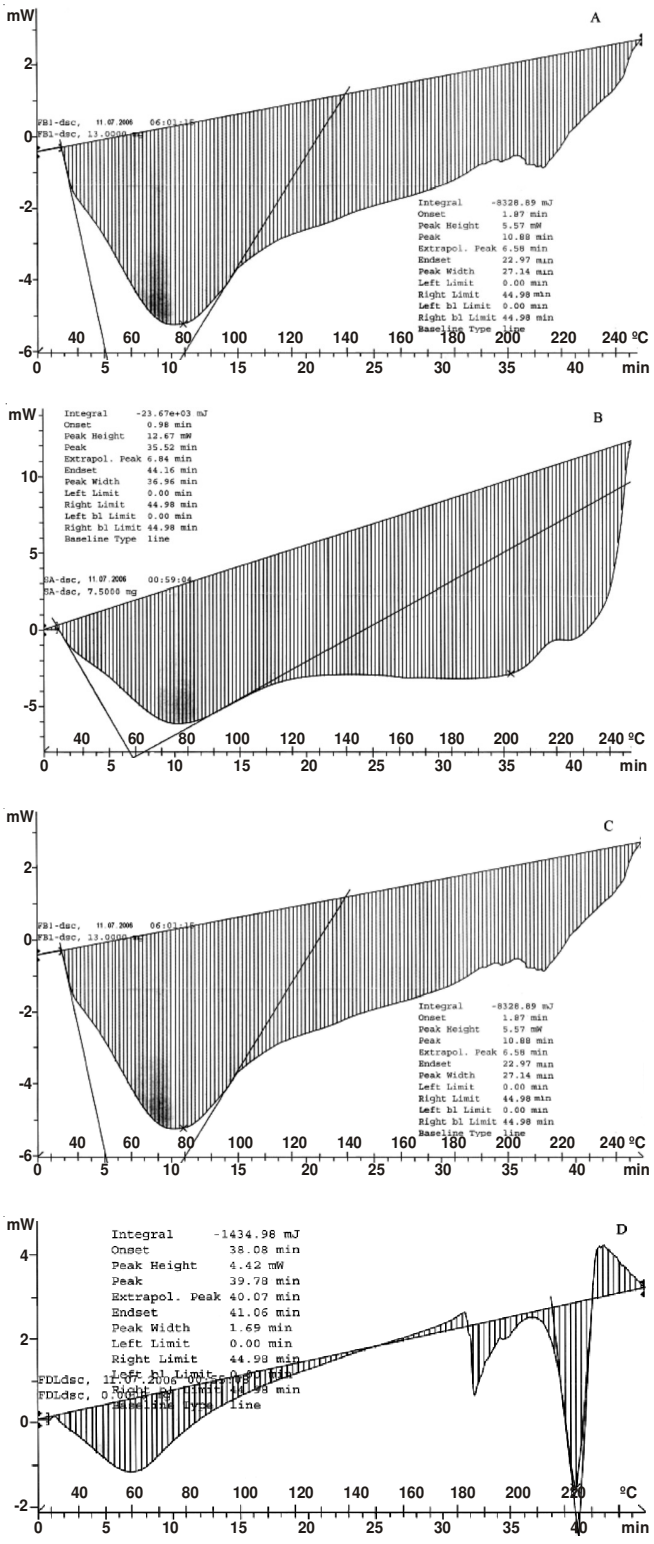

Fig. 1. DSC thermograms of (A) bora rice (B) sodium alginate (C) blank microbeads (D) drug loaded microbeads

in starch/water systems by depressing thermal transitions. This pre-gelatinized rice produced the matrix microcarriers qualifying pharmacotechnical parameters for controlled release of medicament.

Moisture content of the rice is significantly effect on thermal transitions. It is observed that the glass transition temperature (T_g) increases with the decrease in the moisture content. Levine and Slade[9] suggested that an increase in moisture content leads to an increase in free volume and a decrease in local viscosity. Consequently, the segmental mobility of the molecular chain of starch in the amorphous region would rise, resulting in a decrease of T_g. The effects of the moisture content on T_g would be more profound for lower moisture contents[9,10].

The DSC thermal analysis was used, in addition to knowing the thermo-mechanical properties of proposed polysaccharide, to identify any possible chemical interactions between the drug and polymer backbone. DSC offers to be a good thermal analysis method for detecting changes in physical and/or chemical properties of materials as a function of temperature by measuring the heat changes associated with such processes. The sample and an inert reference placed in a temperature-controlled chamber and the heat flow required to maintain the sample and the reference at the same temperature is measured. This results in either absorption of heat (endothermic reaction) or a release of heat (exothermic reaction)[11]. The drug could be either dispersed or dissolved in the polymeric matrix during the process of microfabrication and any abrupt or drastic change in thermal behaviour of either the drug or polymer may indicate a possible drug polymer reaction. The DSC thermograms of drug-loaded microbeads, blank microbeads and the two polymers are presented in Fig. 1. A sharp endotherm at 224 ºC was observed for the drug-loaded beads corresponding to the melting point of metformin hydrochloride[12]. Another broad band was observed at 60-70 ºC that is comparable to the transition temperature of bora rice starch and first endothermic peak of the sodium alginate. The DSC thermograms of the drug and drug loaded beads when compared along with the thermograms of the individual components and of the blank beads; it reflected that the drug-loaded beads are having comparable endothermic peaks to that of drug and the blank beads. There was neither formation of any new peak nor the shifting of any peak significantly in the DSC thermograms indicating that the drug has not undergone any chemical interaction with the polymer backbone during the process of microencapsulation[13]. The endotherm present sodium alginate polymer is not expressed prominently in DSC thermogram of drug loaded microbeads. This may be due to the quantities of excipient used for the analysis. In drug loaded beads the sodium alginate is present only in small fraction when compared to the glutinous rice polysaccharide and the drug substance. The peak shape and enthalpy depend on quantity of material used whilst the peak transition temperature associated with complete fusion is independent. Since the amount of polymer present in the corresponding mixture is less than that in the pure substance, the difference in peak shape was apparent.

Conclusion

The prepared matrix backbone with a combination of glutinous rice polysaccharide and sodium alginate found compatible with the entrapped medicament and the DSC thermograms depicts no interaction between the drug and polymer matrix. It is also observed that the moisture content has significant effects on the thermal and mechanical properties of glutinous rice polysaccharide.

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