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Short Communications

In vitro and in vivo suppository studies with perturbed angular correlation and external scintigraphy

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Recently, there has been an increased interest in the rectal delivery of drugs as an alternative to parenteral administration (Nishihata et al., 1980, 1981). Because of their complexity, little is known about the release behavior of drugs from suppositories in vivo, and the universal applicability of most in vitro tests developed to date awaits broad acceptance. A novel technique has recently been utilized for the measurement of both in vitro and in vivo dissolution profiles of solid oral dosage forms (Beihn and Digenis, 1982). This technique, known as perturbed angular correlation (PAC), utilizes the property of cascading decay exhibited by Indium-111 (^{111}In), a radionuclide commonly employed in diagnostic nuclear medicine (Goodwin et al., 1971). We now wish to report on the application of this technique for in vitro studies measuring the dissolution of an [^{111}In]salicylate coprecipitate incorporated in a suppository base. The PAC technique was also used in combination with external scintigraphic techniques for the in vivo measurement of the deformation and liquefaction of a suppository containing ^{111}In in humans in a totally non-invasive manner.

Suppositories were formulated using a suppository base consisting of glycerol esters of mixtures of saturated vegetable fatty acids (Witepsol H 15). To 2 g of the base was added 200 μCi of [^{111}In]diethylenetriaminepenta-acetic acid ([^{111}In]DTPA) [1] either as an aqueous solution (0.1 ml) or as a coprecipitate with 50 mg of sodium salicylate (80 mesh). The apparatus for the in vitro measurements was a standard jacketed dissolution beaker at 37°C. The suppository was immobilized in a surgical gauze bag and was suspended in 350 ml of water in the dissolution beaker.

[1] Medi-Physics, Emoryville, CA.

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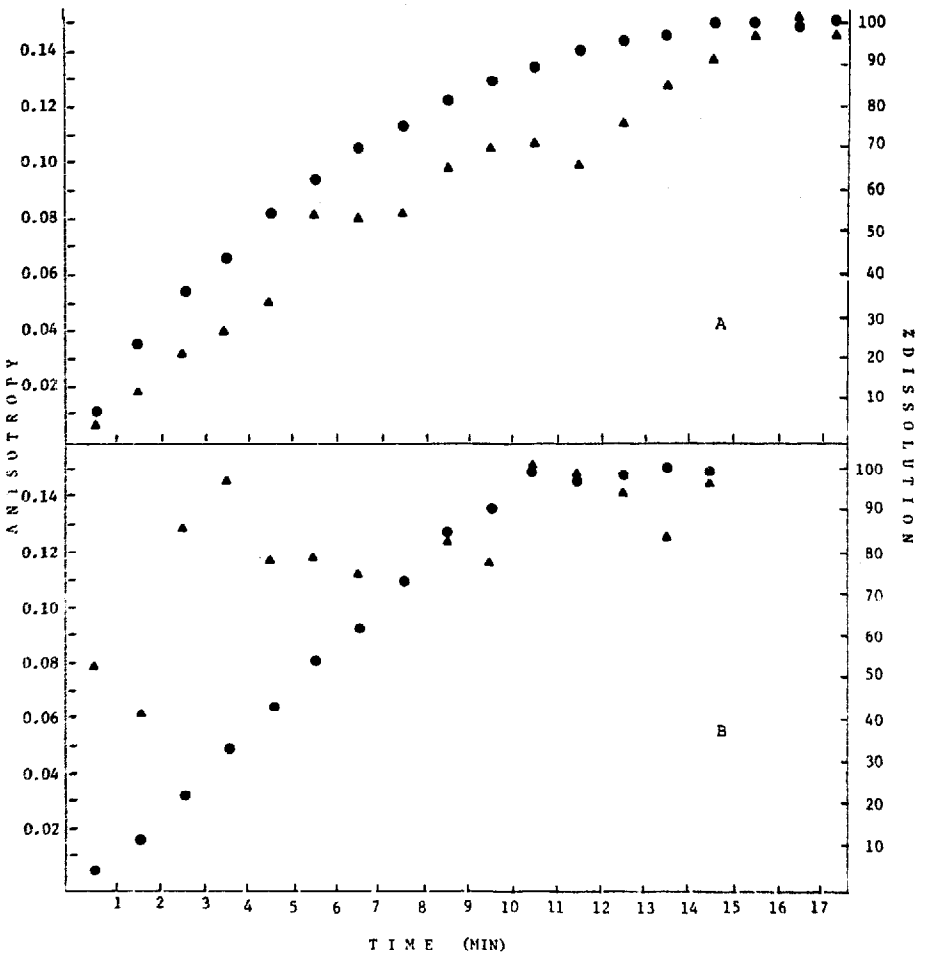

Fig. 1. In vitro dissolution of [^{111}In]DTPA in a Witepsol H15 suppository. The anisotropy–time curve as measured by PAC is represented by (▲) while the % dissolution–time curve determined by serial sampling is represented by (●). A: [^{111}In]DTPA incorporated into the suppository as a coprecipitate with salicylate. B: [^{111}In]DTPA incorporated as an aqueous solution.

Dissolution of [^{111}In]DTPA was determined by the anisotropy values generated using the PAC method, and confirmed by radio-analysis of serial samples withdrawn from the jacketed beaker using a gamma-scintillation counter [2]. The anisotropy values are a measure of the rotational freedom of the ^{111}In nucleus and are affected by the physical state of the dosage form. [^{111}In]DTPA in complete solution exhibits a relatively high anisotropy value while relatively low anisotropy values are observed for [^{111}In]DTPA in a highly ordered (solid) environment (Beihn and Digenis, 1980). Thus, suppositories containing [^{111}In]DTPA coprecipitated with sodium salicylate in a solid form exhibit an initial low degree of anisotropy compared to the relatively high values observed for suppositories containing [^{111}In]DTPA in solution. The

[2] Packard Instruments, Downer's Grove, IL.

results of the dissolution study for the suppository in which the [^{111}In]DTPA had been coprecipitated with sodium salicylate are illustrated in Fig. 1A. The plot of anisotropy as a function of time parallels the dissolution curve obtained by serial sampling. However, for the suppository in which the [^{111}In]DTPA was incorporated as an aqueous solution (Fig. 1B), no correlation was observed between anisotropy values obtained by PAC and dissolution as measured by serial sampling. The relatively high anisotropy values observed for the initial period in Fig. 1B resulted from the fact that the [^{111}In]DTPA existed as an aqueous solution dispersed throughout the intact suppository. Thus, the [^{111}In]DTPA remained in solution in the solid suppository, resulting in no change in anisotropy of the ^{111}In nucleus as the suppository melted. Therefore, in order to conduct a meaningful PAC in vitro suppository dissolution study, the [^{111}In]DTPA must exist in a highly ordered (low anisotropic) state in the intact dosage form as observed for the suppository containing [^{111}In]DTPA coprecipitated with salicylate. The PAC anisotropy data obtained from an appropriately prepared ^{111}In-label provided an accurate profile of drug release from a suppository in vitro.

The PAC technique was further evaluated for its utility in characterizing preabsorptive suppository behavior in vivo in human volunteers. Concomitant external scintigraphic studies were performed using a gamma-scintillation camera with a pinhole collimator (Casey et al., 1976). Following insertion of a suppository containing an [^{111}In]DTPA–salicylate coprecipitate, the anisotropy values unexpectedly decreased as a function of time. Since anisotropy should have risen due to dissolution of the [^{111}In]DTPA–salicylate, the observation was believed to be due to the binding of the ^{111}In-label to some component of the rectal compartment resulting in the formation of a very low anisotropic state. Evacuation of the rectum indicated that the ^{111}In-label was primarily associated with some component of the mucous and not associated with the melted suppository base or fecal matter. In a subsequent experiment, a rectal tube containing an aqueous solution of [^{111}In]DTPA was inserted in a subject, and as expected, high anisotropy values were observed. When the contents of the rectal tube were released and allowed to come in contact with the rectal mucosa, the anisotropy immediately fell to low values.

Based on this information, a second suppository containing [^{111}In]DTPA incorporated as an aqueous solution was administered in another experiment and anisotropy was observed as a function of time (Fig. 2). Since the binding of the ^{111}In to a mucosal component was virtually instantaneous as previously demonstrated by the rectal tube experiment, the prolonged decrease in anisotropy values after suppository administration was reflective of the rate of release of the ^{111}In-label from the suppository base.

The curve in Fig. 2 was obtained in a completely non-invasive manner and readily identifies the suppository liquefaction time and release rate of the radiolabel from the suppository base. The external scintigraphic studies revealed that the rate of release of the ^{111}In-label from the suppository correlated well with the spreading behavior of the suppository base. Furthermore, only limited upward mobility of the radioactivity originating from the dosage form was observable and little absorption of the ^{111}In from the rectal vault occurred.

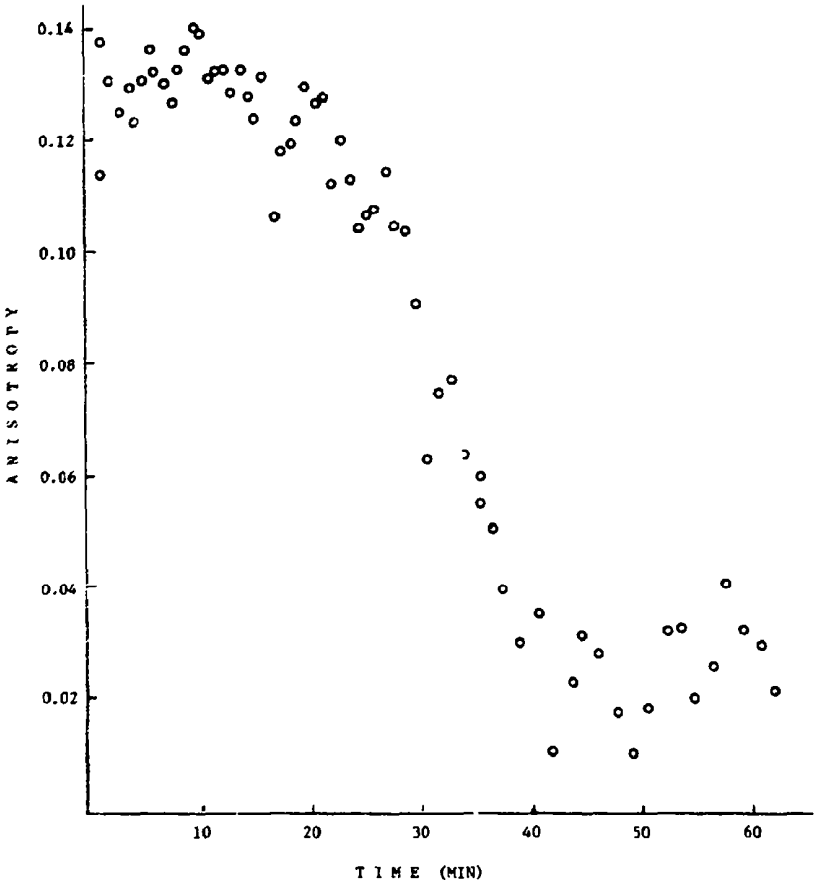

Fig. 2. Anisotropy as a function of time in a human subject for a Witepsol H15 suppository containing [^{111}In]DTPA incorporated as an aqueous solution.

The present communication illustrates that the use of external scintigraphy and PAC techniques used in combination holds great promise in monitoring the in vivo deformation and liquefaction of suppositories. The above information, when coupled with drug plasma level monitoring, will provide a more complete picture as to the nature of the release of drugs from suppositories. Work is in progress to further evaluate the use of these techniques as tools for the in vivo measurement of suppository behavior and to the nature of the low anisotropic ^{111}In-complex formed within the rectal vault. Details of further experiments will be published in a subsequent publication.

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