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Preparation, Characterization, and Stability of New Prostaglandin E_2 Gel for Local Administration

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Abstract □ A new gel delivery system for the local application of prostaglandin E_2 consists of drug incorporated in the matrix of a cross-linked starch polymer. The properties of the starch powder provide a stabilizing milieu for the labile prostaglandin E_2 and, by addition of saline, a ready-to-use gel for immediate local administration. The gel offers advantages over existing preparations in terms of chemical and microbiological stability, homogeneity, and dosage safety. This report outlines the pharmaceutical aspects involved in the development of the delivery system.

Keyphrases □ Prostaglandin E_2—preparation, characterization, and stability of gel delivery system □ Drug delivery systems—prostaglandin E_2 gel, preparation, characterization, and stability

The discovery, isolation, and characterization of the various prostaglandins have created substantial interest in their physiological role and therapeutic applications (1). Their use in human reproduction (2) clearly demonstrates their clinical value. However, the broad spectrum of pharmacological responses and the general instability of the prostaglandins have made it difficult to achieve specific therapeutic aims without significant side effects.

BACKGROUND

In the E series, for example, the cervical ripening effect of prostaglandin E_2 first was observed in early studies using intravenous infusion prior to therapeutic abortion or induction of labor in patients at term (3). The large dose required to achieve these effects was associated with frequent systemic side effects such as vomiting and diarrhea (4). The most recent phase in such use of prostaglandin E_2 has been a low dose local (intracervical or vaginal) administration in a viscous gel or a lipid-based pessary (5, 6).

The prostaglandin E_2 regimen is simple and highly acceptable to patients, causing no significant side effects and improving the prospects of labor. There is now extensive evidence of the efficacy and safety of this method (7–9). The obstacle to wider utilization lies in the inherent lability of prostaglandin E_2 compared to the less effective prostaglandin $F_{2\alpha}$ (10). Existing formulations in simple gels and pessaries do not provide sufficient long-term stability and involve problems concerning homogeneity, sterility, and dosage safety (11, 12).

The absence of a suitable delivery vehicle and a standardized preparation of the gel has discouraged commercial production and hindered clinical usage of the prostaglandin E_2 technique. This report presents a new prostaglandin E_2 gel delivery system and affords a definite solution to the problems afflicting the practical handling of the drug for local administration. This system consists of drug distributed in the matrix of a cross-linked starch derivative. The properties of the starch powder provide a stabilizing milieu for the labile prostaglandin E_2 and, by addition of saline, a ready-to-use gel for immediate local administration.

The safety and efficacy of the starch gel prepared with prostaglandin E_2 in cervical ripening were established in clinical trials (13), and this paper outlines the pharmaceutical aspects involved in the development of such a delivery system.

EXPERIMENTAL

Materials—Prostaglandin E_2[1](I) was used in the crystalline form. [1-^{14}C]Prostaglandin E_2[2] (specific activity 2.07 GBq/mmole) was supplied as a solution in ethanol–water (7:3). The cross-linked starch polymer[3] was supplied as a dry powder (particle size 50–100 μm). All reagents were analytical grade.

Gel Formulations—The prostaglandin E_2 gel powder was prepared under aseptic conditions. A freshly prepared, sterile-filtered solution of I (50 mg) in 80% (v/v) aqueous ethanol (25 ml) was added to 50 g of the heat-sterilized (160° for 1 hr) cross-linked starch powder. During the subsequent manual mixing for 10 min, the starch material swelled to twice its original volume. After lyophilization and homogenization, the prostaglandin E_2 gel powder was dispensed in 0.5-g portions (0.5 mg of I/dose) in sterile, disposable, 10-ml syringes.

The radiolabeled prostaglandin E_2 gel powder was prepared in a similar manner with the addition of 92.5 KBq of [1-^{14}C]prostaglandin E_2 to the solution of I. For practical reasons, this batch was prepared at one-half the scale (*i.e.*, 50 doses) and under nonaseptic conditions.

The ready-to-use-gel for clinical administration was prepared by adding 2.2 ml of sterile saline *via* a hypodermic needle to the prostaglandin E_2 gel powder in the syringe. A uniform gel consistency was obtained without agitation within 30 sec.

The prostaglandin E_2 gel fortified with X-ray contrast medium was prepared by adding 1 ml of saline and 2 ml of contrast medium (6.75 g of metrizamide[4] dissolved in 7.8 ml of 0.6 m*M* sodium bicarbonate) to

[1] The Upjohn Co.
[2] The Radiochemical Centre.
[3] Perstorp AB.
[4] Amipaque, Nyegaard & Co., Oslo, Norway.

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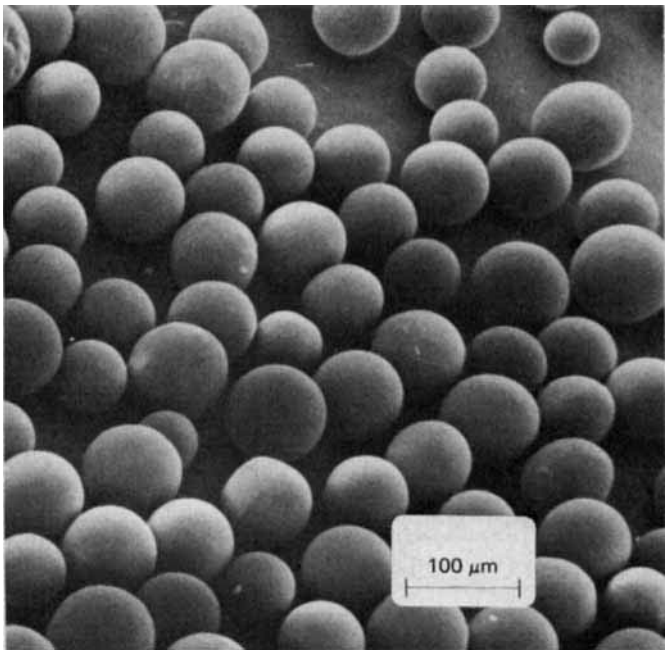

Figure 1—*Scanning electron micrograph of the dry starch microspheres prepared with I (×150).*

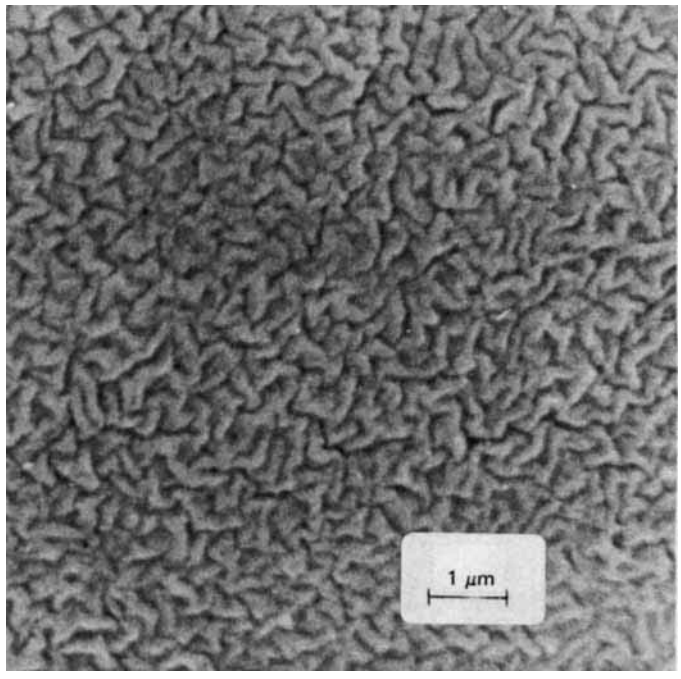

Figure 2—*Scanning electron micrograph of the sphere surface structure (×10,000).*

the prostaglandin E_2 gel powder. The gel was administered to a 28-year-old II-gravida at a gestational age of 30 weeks with an intrauterine dead fetus.

Characterization of Prostaglandin E_2 Gel Powder—The water content in the powder was determined by Karl Fischer titration. Particle-size fractionation was performed using a mechanical oscillating sieve[5]. The pH measurements were made using a standard pH meter[6]. The absorption capacity was determined using the method described by Granath and Flodin (14). Micrographs were taken using a scanning electron microscope[7]. Sterility tests on five batches were performed according to the European Pharmacopoeia.

Homogeneity Studies—Twenty samples of 100.0 mg of the radiolabeled I gel powder were selected randomly according to the table of random numbers[8]. After addition of 10 ml of gel scintillation fluid[9] to each sample, the radioactivity was measured using a liquid scintillation spectrometer[10]. The absence of quenching due to the starch powder was verified by measuring the radioactivity in successively increasing amounts (10–300 mg) of the I gel powder from the same samples.

The distribution of I in the swollen, ready-to-use gel was determined in a similar manner by measuring the radioactivity of ~300.0-mg portions of the gel when expelled in a standard manner from the syringe.

Stability Studies—Compound I was tested for stability in the dry powder and in the swollen, ready-to-use viscous gel. Stability was monitored at 4 and 23° in the dry powder for 12 months and at 4, 20, and 37° in the freshly prepared, ready-to-use viscous gel for 24 hr.

Assay and Analytical Procedure—Compound I was determined by extraction from the gel, separation from the degradation products by TLC, and spectrophotometric assay[11] after conversion to prostaglandin B_2 by alkali treatment.

Aqueous ethanol (80% v/v) was prepared, and 2.00 ml was added to 500.0 mg of the dry I gel; after vortexing for 2 min, 50 μl of the supernate was applied to a silica gel thin-layer plate[12] together with standards of 80% (v/v) aqueous ethanol solutions of known concentrations of I. The plate was developed in a solvent system of chloroform–methanol–acetic acid–water (90:9:1:0.65). This system separates I from its major degradation products, prostaglandin A_2 and the ethyl esters (15).

The zone of I was visualized by spraying the standards at the edge of the plate with 10% phosphomolybdic acid in ethanol. The areas corresponding to I were removed from the plate, and I was eluted with methanol (3 × 2.00 ml). The sample was treated with potassium hydroxide to give a final concentration of 1 *M* and then was heated at 50° for 1 hr. The absorbance at 277 nm was read against a blank (containing a corresponding amount of silica gel treated similarly) and compared with the standards.

RESULTS AND DISCUSSION

The described formulation procedure results in an off-white, free-flowing powder consisting of microspheres of 50–100 μm in diameter (Fig. 1). Each microsphere is a highly hydrophilic, three-dimensional network of a cross-linked starch derivative. Scanning electron micrographs show a regular matrix surface structure (Fig. 2). The hydrophilic nature of the starch microspheres is illustrated by the absorption capacity in polar liquids. For example, upon addition of saline, the I gel powder swells to assume a gel consistency, with absorption up to eight times the original weight of the dry powder. Upon addition of 80% aqueous ethanol, the starch powder swells to about twice its own volume as the microspheres enlarge in size. The solution is absorbed by the microspheres and incorporated as intraparticulate liquid. The solution of I thus is distributed

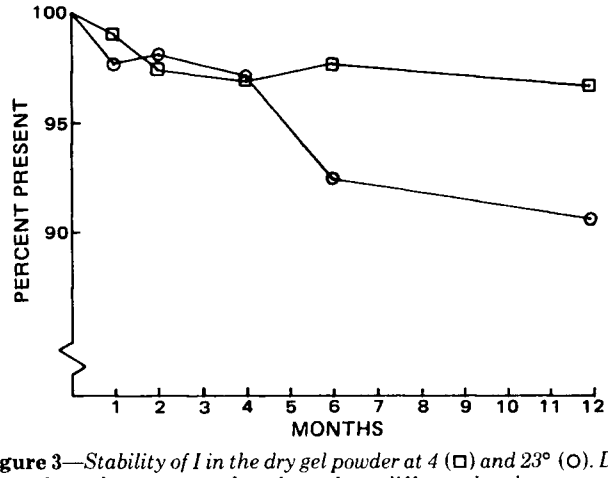

Figure 3—*Stability of I in the dry gel powder at 4 (□) and 23° (○). Data plotted are the average values from three different batches.*

[5] Retsch plane model 330.
[6] Radiometer model 26, Copenhagen, Denmark.
[7] ISM-4S Jeol Ltd., Tokyo, Japan.
[8] See "Geigy Scientific Tables," Ciba-Geigy Ltd., Basel, Switzerland.
[9] Lumac Systems AG, Basel, Switzerland.
[10] Tri-Carb, Packard No. 3320.
[11] Cary model 110 spectrophotometer.
[12] Merck No. 5721 TLC plates.

Table I—Stability of Prostaglandin E_2 (I) in the Freshly Prepared Ready-to-Use I Gel [a]

Incubation, hr	Recovered I, %		
	+4°	+20°	+37°
4	99.1 ± 7.0	99.3 ± 6.9	91.8 ± 5.6
24	94.7 ± 5.4	88.5 ± 4.8	78.0 ± 1.5

[a] Each value is the mean ± *SD* of four samples from the same batch.

throughout the gel bed. During the subsequent lyophilization, the solvent is removed and the starch microspheres are restored to their original size, thereby facilitating the even distribution of I throughout the starch gel powder.

The water content of the I gel powder is ~2–4% and, when protected from moisture, does not significantly alter during storage in plastic syringes.

The results of studies to determine the intrabatch distribution of I in the dry radiolabeled I gel powder prepared at the 50-dose scale showed a relative standard deviation of 2.1% (mean ± *SD*, 24,053 ± 507 dpm/100 mg of dry powder). This value reveals good homogeneity and suggests that the I gel powder can be manufactured commercially with a satisfactory intrabatch variation. The homogeneous nature of the swollen I gel is illustrated by the distribution of radioactivity throughout the gel bed, having a relative standard deviation of 15% (mean count ± *SD*, 11,836 ± 1800 dpm/300 mg). This finding suggests that, in clinical routine, I is distributed satisfactorily in the gel when administered, for example, into the cervical canal.

The solid-state stability of I in the gel delivery system is shown in Fig. 3. The stability profile presents a promising trend and shows little difference between storage temperatures of 4 and 23° for up to 1 year. This finding may be of significance when considering storage conditions for preparations to be used clinically. The stability pattern of the bulk drug presents an increasing degradation rate beginning at 6 months at room temperature (16) and has a 6-month shelflife. In sharp contrast, I in the gel delivery system was quite stable at room temperature for at least 1 year. The starch gel powder functions not only as a delivery vehicle for I but also as a stabilizer for this labile substance. The mechanism controlling the long-term stability of I probably is related to the inherent hydrophilic nature of the starch powder. The degradation rate of the bulk I powder seems to increase and indeed be catalyzed by the presence of the degradation products.

It is likely that I is distributed throughout the starch gel powder and is diluted to such an extent that the degradation products formed have no catalytic effect on the stability profile of I. Moreover, the individual microspheres probably present a very large surface area onto which I adheres to increase the dilution effect. Furthermore, the three-dimensional network probably provides a means of distributing I throughout the whole matrix of the starch microspheres, thereby stabilizing the drug by enclosure. Work is in progress to determine the precise mechanism involved in stabilizing I.

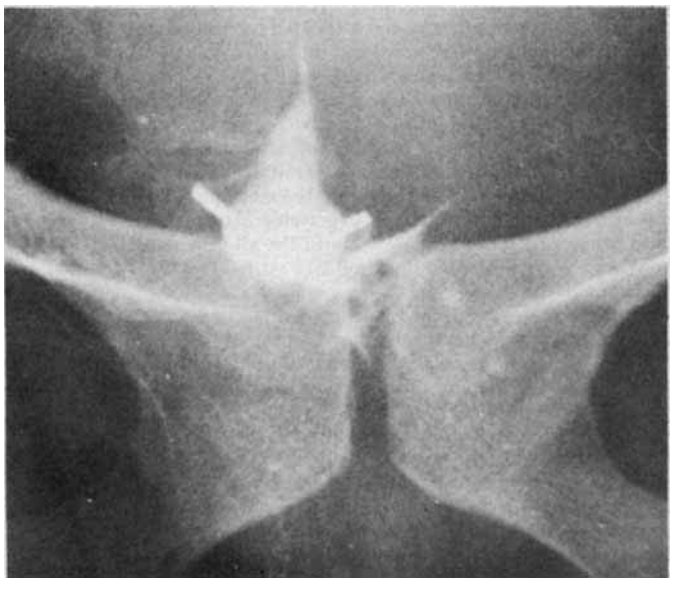

Figure 4—*X-ray picture illustrating the intracervically located gel. Clips were applied at the level of the external os.*

The stability of I in the freshly prepared gel after addition of saline is shown in Table I. Even at elevated temperatures, I is stable in the gel preparation for at least 4 hr, after which the degradation pattern follows the trend seen for the drug in other solvent systems (17). In clinical practice, once the gel is constituted by addition of saline, no further preparative steps are necessary, and the preparation is ready for use. Therefore, the stability of the drug in the swollen gel at room temperature is satisfactory for a sufficient period prior to administration.

The results of sterility testing of five batches showed no microbiological contamination throughout the testing period of 1 year. Thus, the more standardized method of preparation of the I gel powder, compared with more involved methods of I gel preparation, and the dry form of the final product contribute to lowering the risk of microbiological contamination during preparation and subsequent storage.

After the addition of 2.2 ml of saline, the viscous I gel has a final pH of 6.9; therefore, from this point of view, the preparation presents no risk for tissue irritation in the cervix canal when used clinically. Figure 4 shows an *in vivo* X-ray photograph of the viscous I gel located in the cervical canal of a 28-year-old II-gravida. The X-ray, taken 10 min after intracervical administration, shows that the gel clearly adheres to the surface of the cervical canal walls and illustrates the unique property of the gel in facilitating strict intracervical delivery of I.

The new prostaglandin E_2 gel delivery system offers the following advantages over existing gel preparations: (*a*) the final dosage form is a sterile, homogeneous, and clinically ready-to-use preparation for local administration; (*b*) the shelflife of the preparation is at least 12 months at room temperature; and (*c*) the delivery system has a gel consistency, so strict intracervical administration is possible.

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