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FORMULATION OF A CONCENTRATED DISPERSION AS A CARRIER FOR THE DELIVERY OF PROSTAGLANDIN E2 IN THE CERVICAL CANAL.

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SUMMARY

The use of a concentrated dispersion of swollen polydextrin particles as carrier for the delivery of PGE2 into the cervical canal has been studied. This dispersion should be easily made and expellable from a syringe. However, expelling a concentrated dispersion of swollen polydextrin particles in an 0,9% saline solution through a catheter is problematic since phase separation occurs. Increase of the viscosity of the continuous phase of the dispersion medium on the one hand and interaction of a water soluble polymer with the polydextrin particles on the other hand will prevent phase separation.

Formulation studies on such a dispersion were performed. The studies included the wetting/swelling characteristics, the forces needed to expel the dispersion from a syringe and explanation of these forces by rheological measurements. It was found that the addition of 3% Dextran 70 to 0,9% saline resulted in a viscous dispersion of polydextrin particles that was easy to expel from a syringe through a catheter and which met all the requirements for use as a product for the administration of PGE_2 into the cervical canal.

INTRODUCTION

Prostaglandin E2 is administered into the vagina or cervical canal for the induction of cervical "ripening" (that is softening and effacing) in labour. Therefore there is a need for carriers for the instillation of prostaglandin E2 (PGE2) that are free from interactions with the target site and remain in-situ long enough to deliver the active compound. Many systems for the delivery of prostaglandin E2 and its derivatives have been studied and reported. Examples of delivery systems are gels of methylhydroxycellulose (1,3) triacetin (2,8), sodium carboxymethylcellulose (3), dextran 70 (7) and sulprostone gel containing also pluronic F127^{R} (7). In addition, lipid pessaries based on cocoa rubber or Witepsol^{R} (4), and pessaries of cross-linked poly(ethylene oxide) (5) were studied as well as vaginal films based on water-soluble polymers (6) and drug-reservoir membrane devices (9). However, these carriers show disadvantages such as: relatively high amounts of PGE2 are needed to achieve a clinical effect, instability of the active compound in the carrier, unwanted rheological behaviour and inconveniency of application of the final formulation.

A concentrated dispersion for the delivery of PGE2 into the cervical duct has been described by Harris et. al (10,11). The disperse phase of this dispersion consisted of swollen particles of polydextrin (a cross-linked starch polymer), whereas the continuous phase was an aqueous saline solution. This dispersion was found to be very effective in the delivery of PGE2 into the cervical duct and forms the basis for the product Cerviprost^{R} (12). The basic pharmaceutical concept of Cerviprost is that after the dispersion is prepared in a syringe it has to be expelled from it through a catheter into the cervical canal.

Constitution of the final dispersion with water or saline is possible, but expelling such a dispersion through a syringe tip or a catheter of approximately 2 mm internal diameter was found to be difficult. The main cause was phase separation. The force applied on the dispersion in the syringe is transferred to the continuous liquid phase (the medium). Restrictions such as a narrow syringe tip or

catheter causes the liquid phase to separate from the dispersed polydextrin particles resulting ultimately in blockage of the syringe delivery system.
It was envisaged that increasing the viscosity of the liquid phase of the final dispersion should result in a medium in which phase separation is reduced (14).
Furthermore, upon mixing of polydextrin particles with water, the polydextrin particles swell up to twice their original diameter due to water absorption. When instead of water an aqueous polymer solution is added to the polydextrin particles, then, after swelling and water uptake by the polydextrin particles, the aqueous phase is enriched by polymer. The effect is then an increased viscosity of the aqueous phase, high concentration of polymer on the particle surface due to adsorption and an increased interaction between polydextrin particles and water and between the polydextrin particles due to bridging (15). Phase separation will then be eliminated.
Formulation studies were therefore focussed on the preparation of a viscous dispersion with the following characteristics:

- good wetting and establishment of the dispersion within one minute
- no phase separation during expulsion
- easy to expel
- viscosity high enough for the product to remain in situ after application.

MATERIALS AND METHODS

Polydextrin particles were obtained from Perstorp AB, Sweden, and had a mean particle size of 80 μm. The adjuvant polymers Gelatin A, Gelatin B, Hydroxymethylpropylcellulose and Dextran 70 were obtained from different suppliers and were used as supplied.
In all experiments demineralized water was used.
Viscosities were measured with the Brookfield RVT viscosimeter using Helipath stand D and spindle type T-F.
Forces needed to expel the dispersion were measured with the

Universal Tensile tester of J.J. Lloyd. Wetting and swelling of the polydextrin particles were assessed qualitatively, the target being that complete wetting and swelling of the polydextrin particles should be accomplished within one minute. Complete wetting means absence of dry spots in the constituted dispersion and complete swelling means that the constituted dispersion appears to be completely established and homogeneous.

RESULTS AND DISCUSSION

The selected polymers were dissolved in 0,9 % saline. In Table 1 the qualitative assessment of the wetting/swelling character is given. After establishment of the dispersion in a syringe (Terumo^{R}, 5 ml disposable syringe) the nature of the dispersion during expelling was judged with special attention to phase separation. These results are also included in Table 1.

From Table 1 it is apparent that gelatin A and B and Dextran 70 are suitable polymers for the establishment of the final concentrated dispersion. However, when the volume of the added solution is taken into consideration then Dextran 70 is the polymer of choice for further formulation studies.

The forces needed to completely expel the dispersion from the syringe were determined and results are given in Table 2. It is important to note that the difference between the initial force required to move the plunger in the syringe and the force at the end of the ejection should be as small as possible, since this will achieve the most convenient means of administering the product to the patient.

In this experiment glass bodied syringes based on the final sale concept, i.e. a type dual compartment syringe (supplier Vetter) were used. The inner diameter of the syringe tip was 0,9 mm. In all tests 2 ml of liquid phase containing the polymer solution were added to 0,5 g of polydextrin particles.

TABLE 1: Qualitative assessment of wetting and expulsion characteristics of the dispersion.

Composition			Wetting and swelling complete withine one minute	Homogeneity during expulsion after the one minute wetting/ swelling period
Medium	Polymer concentration (% w/v)	ml of solution per 0,5 g of poly-dextrin		
Water	-	2,5	yes	bad
0,9% saline	-	2,5	yes	bad
0,9% saline plus:				
Gelatin A	1,0	2,2	no	-
	1,0	2,5	yes	good
Gelatin B	1,0	2,2	no	-
	1,0	2,5	yes	good
HMPC	1,0	2,5	no	-
Dextran 70	1,0	2,0	yes	bad
	1,0	2,5	yes	bad
	1,5	2,0	yes	moderate
	1,5	2,5	yes	moderate
	2,0	2,0	yes	good
	2,0	2,5	yes	good
	3,0	2,0	yes	good
	3,0	2,5	yes	good
	6,0	2,0	no	-
	6,0	2,5	no	-

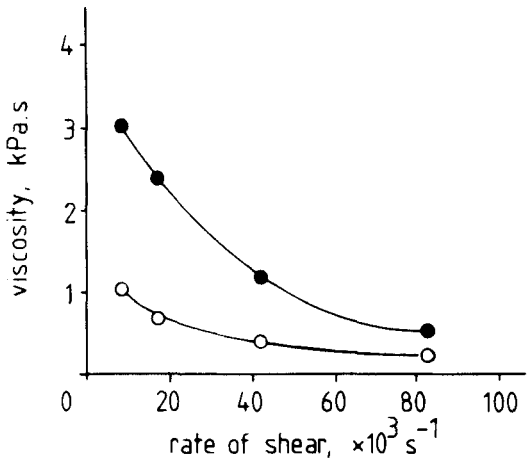

FIGURE 1: Viscosity versus shear rate of a dispersion of polydextrin particles in 0,9 % saline (●) and in 3% Dextran 70 in 0,9 % saline (o), 2 ml of liquid phase per 0,5 g of polydextrin.

Comparing the results given in Table 2 with the results of the qualitative assessment in Table 1 it is apparent that a relationship exists between a bad homogeneity during expulsion and the increase of force during expulsion. A bad homogeneity complies with a relatively high increase of force during expulsion.

To obtain better insight into the factors which are involved, the rheological behaviour of the dispersion constituted with 3% Dextran 70 in 0,9% saline was assessed and compared to that of the dispersion constituted only with 0,9% saline. The results of the viscosity measurements are shown in Figure 1.

The viscosity of the dispersion containing Dextran was lower than that containing only saline and viscosity was found to decrease with increasing rate of shear. When the rate of shear is plotted against the shear stress, the viscosity profiles produced showed typical plastic flows (13), see: Figure 2. Moreover, a yield stress was found.

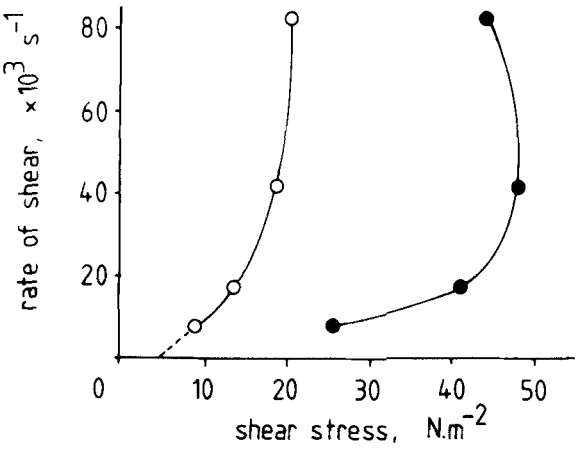

FIGURE 2: Rate of shear versus shear stress of a dispersion of polydextrin in 0,9 % saline (●) and in 3% dextran 70 in 0,9 % saline (o), 2 ml of liquid phase per 0,5 g of polydextrin.

TABLE 2: Forces needed to expel the dispersion, in Newtons (N), (average of 3 syringes).

Composition	Force at begin of expulsion N	Force at end of expulsion N	Increase of force during expulsion N
0,9 % saline	11	57	46
0,9 % saline plus:			
Dextran 70, 1%	11	35	24
Dextran 70, 1,5%	10	31	21
Dextran 70, 3%	23	37	14

These results explain the forces which were measured in the expulsion experiments with syringes (Table 2). The increase in the force required to expel the product for dispersion constituted with the saline Dextran solution is less than with saline only. In addition, it was found that a yield force is needed to move the plunger initially. The yield

stress is significant and has clinical relevance, i.e. after application the dispersion will remain in-situ and will not leak from the application site.

CONCLUSIONS

The aim of the present investigation was to study formulation aspects of a concentrated dispersion of polydextrin particles. The following characteristics should be achieved:

- good wetting on rapid establishment of the dispersion
- no phase separation during expulsion
- easy to expel from a syringe/catheter system
- high enough viscosity for the product to remain in-situ after application.

The results established that a solution of 3% Dextran 70 in 0,9% saline solution, when combined with polydextrin in the ratio of 2,0: 0,5, produces a dispersion which has these characteristics.

The final dispersion of swollen polydextrin particles shows a minor increase in the force needed to expell the product from a syringe. Furthermore, the final dispersion has a yield value which is of clinical importance.

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