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CROSSLINKED STARCH AS SUSTAINED RELEASE AGENT

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ABSTRACT

Different types of crosslinked starches and pregelatinized-crosslinked starches were evaluated for their use as hydrophilic matrices. Some fundamental properties of these chemically modified starches, e.g. granule swelling power and viscosity of the dispersion in function of pH and ionic strength, were studied. Dissolution tests and the rate and amount of water uptake were evaluated on tablets containing theophylline and modified starch (40/60 w/w), compressed on an instrumented tablet press at three different pressures (50,200 and 300 MPa.). Theophylline releasing profiles were determined using the paddle system at a rotational speed of 50 rpm.. Water, simulated gastric fluid, and simulated intestinal fluid were used as dissolution media. Crosslinked starches showed a poor swelling power and dispersion viscosity in comparison to pregelatinized starch and pregelatinized-crosslinked starches. The pregelatinized-crosslinked starches developed less swelling power than the pregelatinized

starch, but they showed higher dispersion viscosity than the pregelatinized starch. The viscosity of all starch dispersions was not affected by ionic strength. An alkaline pH dramatically increased the dispersion viscosity of pregelatinized starch and pregelatinized-crosslinked starches. Drug dissolution rate was lower for tablets containing pregelatinized starch than for tablets containing pregelatinized-crosslinked starches. This phenomenon can be related to the rate and amount of water uptake. The dissolution rate seemed not to be influenced by the compression force nor by the composition of the dissolution media. The results indicate that crosslinked starches, either pregelatinized or not, are not suitable as sustained release agents.

INTRODUCTION

Starch, in its native and modified form, is used extensively throughout the pharmaceutical industry as a disintegrating agent, as a binder, or as a diluent in the tabletting process. Starches can be gelatinized to make them cold water swellable.[1] When formulated as a tablet, these starches can form a hydrophilic gel matrix prolonging the release of an active ingredient. Only some investigators mentioned the possibility to use these modified starches in this field.[2,3,4,5] Cold water swellable starches, known as pregelatinized starches can be produced in many ways. The most widely used technique is drum drying in which the aqueous suspensions of nongelatinized native or chemically modified starches are poured onto hot drums. Other techniques include spray drying and extrusion.[1]

Thermal treatment is not the only way to modify starches. For many years, a number of chemical modification have been developed to improve the properties of starches. Because of an abundance of hydroxyl groups in the polymer, crosslinking occurs when starch is treated with a bifunctional or multi-functional reagent, such as acid anhydride, aldehyde, ethylenic compound etc. Crosslinking reinforces hydrogen bonds holding the granule together. This produces considerable changes in the gelatinization properties of the starch granule and leads to a restriction in swelling properties.[6]

The reaction conditions for making cross-linked starches vary widely depending upon the specific bi- or polyfunctional reagent used for the cross-linking. In general, most of the reactions are run on aqueous suspension of starches at temperatures ranging from room temperature up to about 50°C. The reactions are normally carried out in neutral to fairly alkaline conditions. When the desired level of crosslinking is reached, the starch suspensions are neutralized, filtered, washed with water to remove any unreacted reagent and other impurities produced by side reactions of the crosslinking reagents and finally dried.[7] Phosphate crosslinked starch can be produced by reaction of starch granules in aqueous suspension with either phosphorus oxychloride or sodium trimeta-phosphate under alkaline condition.[7] Adipate crosslinked starch are made by esterifying granular starch in aqueous suspension under mildly alkaline condition with adipic anhydride.[7] It is difficult to determine directly the level of crosslinking because the amount of crosslinking chemicals introduced into the starches are usually very low compared to the

weight of the starches and the total number of anhydroglucose units present in the granules. Therefore, the crosslinked starches must be physically characterized by the measurements of viscosity, rheology, swelling power etc. to determine the level of crosslinking during the production.[6]

In this work, some fundamental properties such as granule swelling power and viscosity of the starch dispersions were evaluated. Dissolution rate of a model drug from tablets containing these starches, and the rate and amount of water uptake by the tablets made with pure starches were investigated in order to characterize and determine the possible use of cross-linked-modified starches as sustained release agent.

MATERIALS

All starches used in this work are waxy-corn starches containing only the branched anhydroglucose polymer : 'amylopectin'. Native waxy-corn starch was modified by pregelatinization only, pregelatinization and crosslinking or by crosslinking only. All these modifications were performed by CERESTAR (Vilvoorde, Belgium). Table 1 summarizes the different types of modified starches evaluated in this work.

Two types of crosslinks were used : phosphate and adipate. The native starches were crosslinked both at a low and high level. The pregelatinized starches were crosslinked only at a high level. However, it must be emphasized that in term of chemical substitution, both levels of crosslinking ('low' and 'high') are low.[8]

TABLE 1

Modified starches used in this study

Types of starches	Pregelatinized	phosphate crosslinked	Adipate crosslinking
-Pregelatinized	+		
-Pregelatinized-phosphate cross-linked	+	+	
-Pregelatinized-adipate cross-linked	+		+
-Crosslinked			
low level		+	+
high level		+	+

METHODS

Granule swelling power

The granule swelling power of each starch was examined by determining the water retention capacity and the swelling capacity in water.

1. Water retention capacity - 15.0 ml. of 5.0 % (w/w) starch dispersions prepared in deionized water, at room temperature were centrifuged at 4,500 rpm. for 30 minutes (Christ UJ-2 centrifuge, West-Germany). Next, the supernatant was decanted and the sedimented paste was weighed, dried at 75°C until constant weight and weighed again. The values of wet and dry weight were used in order to calculate the water retention capacity which is the ratio of wet weight to dry weight of sedimented pastes.[9,10]

2. Swelling capacity - For each starch, 5.0 g. was weighed in a 100.0 ml. graduated cylinder. The initial volume (bulk volume) was noted before shaking

with 80.0 ml. of deionized water until all particles were well dispersed. Subsequently, the dispersion was adjusted to 100.0 ml. and the sedimented volume of swollen starch was read after 24 hours. The swelling capacity is the ratio of the swollen volume to the bulk volume.[11]

Influence of ionic strength and pH on the viscosity of starch dispersions

10% (w/w) starch dispersions were prepared in different media using a homogenizer (Silverson Laboratory Mixer Emulsifier , Waterside, Chesham, Bucks, England). After a two hours swelling period, the viscosity was measured at 25°C by a rotational viscosimeter (Haake RV12, Karlsruhe, West-Germany) using a MV1 body with a variable speed depending on the viscosity of starch dispersions. In the case of starch dispersions having a viscosity higher than 50,000 mPa., a Brookfield rotational viscosimeter with a spindle (number 7) was used at 2.5 rpm. (Brookfield ; type HAT, Massachusetts, U.S.A.). All values were read after ten minutes.

The influence of ionic strength was determined by the differences in viscosity of starch dispersions in distilled water, 0.9% sodium chloride solution (μ = 0.154 M), and 3.0% sodium chloride solution (μ = 0.505 M), respectively.

The influence of pH was examined using buffer solutions of pH 3 (phthalate buffer), 7 (phosphate buffer), 8 (phosphate buffer), and 9 (borate buffer) according to USP.XXI. The ionic strength of all these

buffers was equalized at μ = 0.136 M by the addition of sodium chloride.

Dissolution Test

Anhydrous theophylline (≤180μm, Laboratoria Flandria, Belgium) and pregelatinized starch (≤180μm), anhydrous theophylline and pregelatinized-phosphate-crosslinked starch (≤180μm), or anhydrous theophylline and pregelatinized-adipate-crosslinked starch (≤180μm) all in a 40:60 (w/w) ratio were mixed for 10 minutes by a Turbula mixer (Type T2A, W.A.Bachofen, Basel, Switzerland). 250 mg. of each blend was compressed at three different pressures (50 MPa., 200 MPa. and 300 MPa.) on an instrumented tablet press equipped with 11 mm. flat faced punches (Ateliers Ed. Courtoy Tablet Press;type A.C.27, Mons, Belgium). The dissolution rate was determined in water, simulated gastric fluid (USP.XXI), and simulated intestinal fluid (USP.XXI) at 37°C by the paddle system (USP.XXI, method 2) at a rotational speed of 50 rpm. The extinction of the dissolved theophylline was continuously measured by a spectrophotometer (Zeiss PM6, Carl-Zeiss, Oberkochen, West-Germany) set at 273 nm. and recorded on a multi-point recorder (Philips PM 8235, Eindhoven, The Netherlands).

Water Uptake

The rate and amount of water uptake was determined on a pure starch tablet of 13 mm. weighing one gram and compressed on flat-face punches at 150 MPa.(Erweka Tablet Press:type EKO, Frankfurt, Germany).

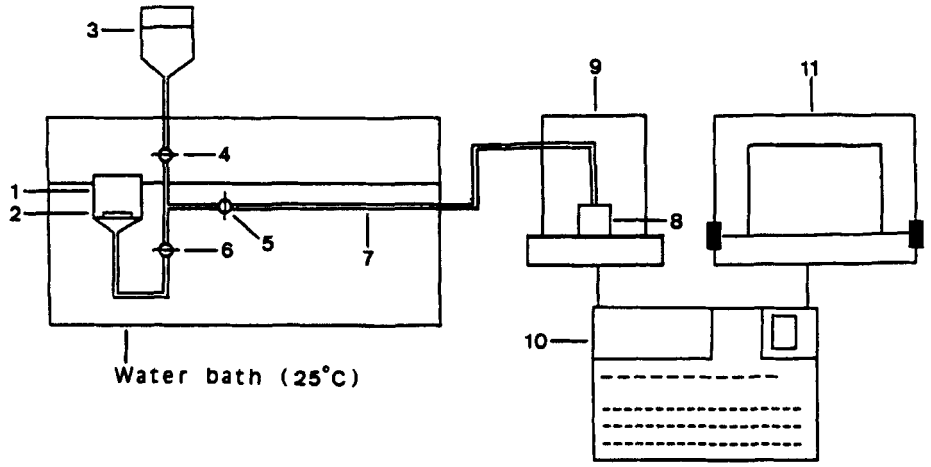

FIGURE 1

Modified water uptake apparatus
[1.Buchner funnel with filter (pore size 20-40 µm); 2.Filter (pore size 10 µm); 3.Reservoir; 4,5,6.Valve; 7.Burette; 8.Container; 9.Balance; 10.Microcomputer; 11.Printer]

The determination was done on an apparatus adapted from the instrument designed by H.V. van Kamp et al.[11] The apparatus (Figure 1) consists of a Buchner funnel with a filter which has pore size of 20-40 µm (1). On that filter, another filter with a 10 µm pore size (2), on which the tablet is put during the experiment, is fixed. Before the measurement, the water level of the filter (2) and container (8), which are directly connected by a burette (7) must be in equilibrium, thus, no passive water transport takes place. To equilibrate the system, water can be added from a reservoir (3) by valves (4) (5) and (6). The water surface in the container (8) is covered with an oil layer to prevent water evaporation during measurement. The water uptake by the tablet can be measured as the weight loss of the container placed on an electronic balance (Mettler AJ100, Greifensee, Switzerland) (9), connected by an

interface (RS232C) to a microcomputer (Epson PX4 portable computer, Nagano, Japan) (10). At precise time intervals, weighing results are collected in the memory of the computer and printed out on a printer (Epson LX80 printer, Nagano, Japan) (11). At the end of the measurements, the amount of water uptake are calculated and presented as water uptake curves in function of time.

RESULTS and DISCUSSION

Granule Swelling Power

The granule swelling power is the expression used to define the extent of swelling of the starch granules.[7] The results of these measurements (Table 2) showed that the pregelatinized starches, with or without crosslinking, swell in cold water while purely crosslinked starches do not. The only crosslinked starches showed a very low and nearly identical swelling power. As the pregelatinized waxy starch was water miscible, an unmeasurable high swelling capacity was obtained. Because the crosslinking is responsible for blocking the swelling of the starch granules [13], the pregelatinized-crosslinked starches showed a lower swelling capacity (6.0 and 10.5 for phosphate and adipate cross-linking, respectively) than the pregelatinized starch.

No important difference in the water retention capacity was observed between the different types of pregelatinized-crosslinked starches (15.3 and 15.7 for phosphate and adipate crosslinked, respectively).

TABLE 2

Granule swelling power of several modified starches.(n=3)

types of starches	Water retention capacity (±SD.)	Swelling capacity (±SD.)
pregelatinized	23.8 ± 0.2	*
pregel.+phosphate crosslinked	15.3 ± 0.1	6.0 ± 0.2
pregel.+adipate crosslinked	15.7 ± 0.1	10.5 ± 0.2
low - phosphate crosslinked	2.3 ± 0.0	0.9 ± 0.0
high - phosphate crosslinked	2.2 ± 0.0	0.8 ± 0.0
low - adipate crosslinked	2.2 ± 0.0	0.9 ± 0.1
high - adipate crosslinked	2.2 ± 0.0	0.9 ± 0.0

* cannot be determined because highly miscible with water

However, the water retention capacity of the pregelatinized starch (23.8) was higher. This can be explained by the fact that pregelatinized starch does not contain any crosslinks. The crosslinking agents reacted with the starch granules at the hydroxyl groups in the anhydroglucose units to form the crosslinked starches, thus, more hydroxyl groups were left in the pregelatinized starch allowing the pregelatinized starches to absorb more water.[6]

Viscosity

Viscosity data (Table 3) showed that the viscosity of crosslinked starch dispersions were not affected by the composition of the dispersing media and were very low and nearly identical due to the absence

TABLE 3

Influence of pH and ionic strength on the viscosity of 10% (w/w) starch dispersion of crosslinked starches (mPa.s ± SD. ; n=3)

Dispersing medium	Phosphate crosslinked		Adipate crosslinked	
	low level	high level	low level	high level
distilled water	8.6 ± 0.5	9.1 ± 0.9	8.8 ± 0.3	9.1 ± 0.0
0.9% NaCl solⁿ	8.9 ± 0.6	9.1 ± 0.5	8.8 ± 1.7	10.0 ± 1.1
3.0% NaCl solⁿ	8.9 ± 0.8	9.3 ± 0.3	8.4 ± 0.8	9.3 ± 0.3
buffer pH3	8.9 ± 0.8	8.6 ± 0.5	9.3 ± 1.4	9.3 ± 1.1
buffer pH7	9.1 ± 1.9	8.6 ± 0.3	8.4 ± 0.3	9.3 ± 0.8
buffer pH8	7.9 ± 1.4	8.4 ± 0.3	8.4 ± 2.0	8.6 ± 0.0
buffer pH9	10.4 ± 0.6	7.3 ± 0.8	9.7 ± 0.5	8.9 ± 0.8

Table 4

Influence of pH and ionic strength on the viscosity of 10 % (w/w) starch dispersion of pregelatinized starches, with and without crosslinking. (mPa.s ± SD. ; n=3)

Dispersing medium	Pregelatinized starches		
	without crosslinked	phosphate crosslinked	adipate crosslinked
distilled water	193 ± 14	5304 ± 13	3770 ± 22
0.9% NaCl solⁿ	154 ± 5	5126 ± 210	3449 ± 18
3.0% NaCl solⁿ	143 ± 2	6220 ± 196	3541 ± 52
buffer pH3	148 ± 5	5505 ± 68	3043 ± 81
buffer pH7	117 ± 0	5716 ± 229	3043 ± 18
buffer pH8	241 ± 6	68654 ± 1793	34487 ±4495
buffer pH9*	66135 ±1707	1339200 ±15839	632000 ±2262

* Brookfield Viscosimeter

of a cold water swelling capacity. Pregelatinized starch and pregelatinized-crosslinked starches, gave more viscous dispersions.(Table 4) However, one should remark that the pregelatinized-crosslinked starches dispersions, either phosphate or adipate crosslinked, showed a higher viscosity than the pregelatinized starch dispersion. This can be explained by the fact that, in contradiction to the pregelatinized starch, the swollen granules of the pregelatinized-crosslinked starches are still kept intact by the crosslinks during the swelling of these starches, even when the hydrogen bonds which keep the granules together are disrupted.[7]

The viscosity of all starch dispersions was not affected by ionic-strength, while on the contrary a distinct influence of pH was observed. An alkaline pH (pH 8 or pH 9) dramatically increased the viscosity of pregelatinized and pregelatinized-crosslinked starch dispersions in comparison to an acidic (pH 3) or neutral pH (pH 7) medium. The viscosity at pH 9 was about 400 times higher than at pH 3 for the pregelatinized starch dispersion and 250 times higher in the case of the pregelatinized-phosphate or adipate crosslinked starch dispersions. This could be explained by a change in configuration of the starch molecule in an alkaline medium from a compact coil to an expanded random coil due to the disruption of hydrogen bonds situated between the hydroxyl groups of adjacent chain units.[14]

Dissolution Test

The dissolution tests were performed only on tablets containing pregelatinized starch and pregelati-

TABLE 5

Comparison of the time (h ± SD.) for 80% dissolution (T_{80}) of theophylline from tablets made with pregelatinized starch and pregelatinized-crosslinked starches. (n=3)

Compression forces (MPa)	Dissolution media	Pregelatinized starches		
		no crosslinked	Phosphate crosslinked	Adipate crosslinked
50	water	13.4 ± 0.7	2.3 ± 0.1	2.4 ± 0.2
	SGF.	13.5 ± 1.5	3.5 ± 0.1	2.3 ± 0.3
	SIF.	14.1 ± 1.0	3.7 ± 0.2	3.0 ± 0.4
200	water	13.5 ± 1.7	2.7 ± 0.2	2.8 ± 0.3
	SGF.	11.9 ± 1.0	3.9 ± 0.2	2.6 ± 0.1
	SIF.	13.7 ± 1.9	4.2 ± 0.3	3.9 ± 0.2
300	water	13.1 ± 2.8	3.0 ± 0.2	2.7 ± 0.4
	SGF.	12.3 ± 0.7	3.6 ± 0.3	2.4 ± 0.1
	SIF.	14.1 ± 0.3	4.1 ± 0.6	3.9 ± 0.1

nized-crosslinked starches because the granule swelling power test pointed out that the crosslinked starches showed inability to swell and to form a hydrophilic gel. Dissolution data (Table 5) showed that the release rate of theophylline from the tablets containing a mixture of theophylline and pregelatinized starch was dramatically lower (T_{80} about 12-14 hours) than from the tablets containing pregelatinized-crosslinked starches(T_{80} about 2-4 hours). The release rate was not influenced by the difference in compression forces (50 MPa., 200 MPa.and 300 MPa.) (Figure 2)

However, at the same pressure the dissolution rates in simulated gastric fluid seemed to be slightly higher than in simulated intestinal fluid. In simulated intestinal fluid (pH 7.5), the starches swell and form a more viscous gel than in the acidic conditions

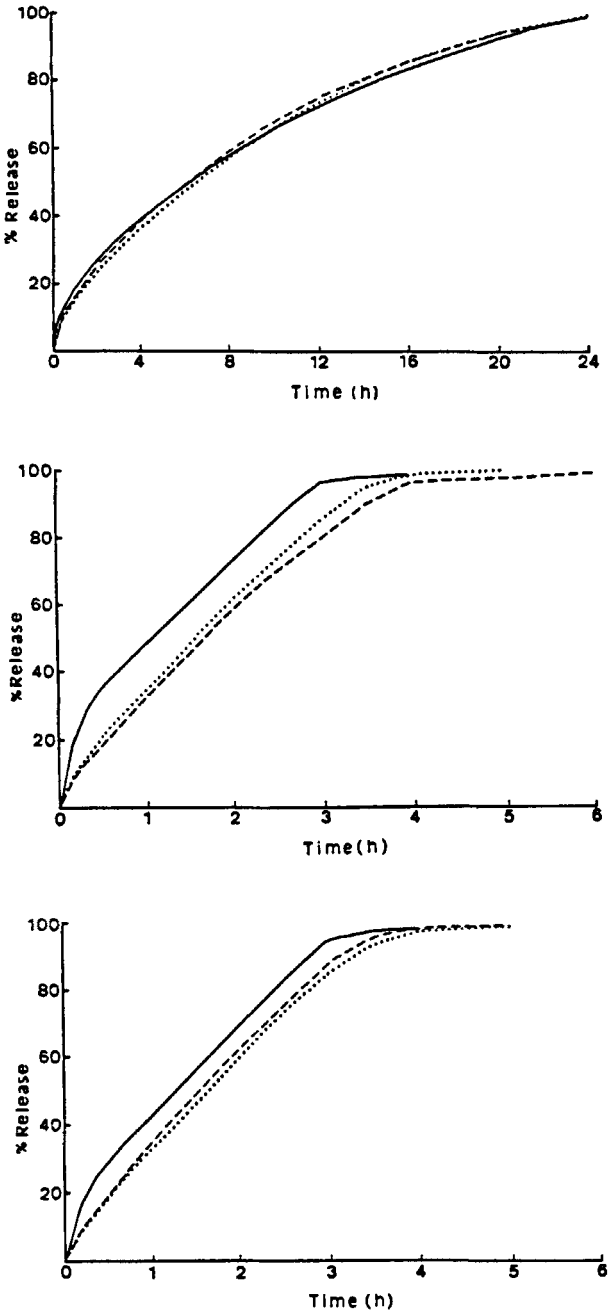

FIGURE 2

Dissolution profile in water of tablets containing 40% theophylline and different types of starch, compressed at three different pressures. (—— 50 MPa., ···· 200 MPa., --- 300 MPa.)
(A=Pregelatinized starch; B=Pregelatinized-phosphate crosslinked starch; C=Pregelatinized-adipate cross-linked starch)

of the simulated gastric fluid (Table 4). The formation of a viscous gel decreased the diffusion rate of dissolved theophylline through the swollen matrix tablets.

In simulated intestinal fluid, no difference in drug release rate could be observed for tablets containing different types of pregelatinized-crosslinked starches suggesting that the type of crosslinking did not influence the release rate in simulated intestinal fluid. On the contrary, in simulated gastric fluid, the pregelatinized-adipate crosslinked starch showed a faster dissolution than the pregelatinized-phosphate crosslinked starch.(Table 5) This could indicate that the pregelatinized-phosphate crosslinked starch is more resistant to an acidic medium than the pregelatinized-adipate crosslinked starch.

Water Uptake

Although the pregelatinized starch has a higher granule swelling power, the water uptake of tablets prepared from a mixture of theophylline and pregelatinized-crosslinked starches were faster than the tablets containing a mixture of theophylline and pregelatinized starch (Figure 3). This can be explained by the fact that the pregelatinized starch granules swell and form a viscous gel barrier in contact with water. This viscous gel blocks the tablet pores hindering further water uptake. The pregelatinized-crosslinked starches also swell and form a viscous gel but because of the crosslinking, the formation of a coherent gel is prevented and the pores

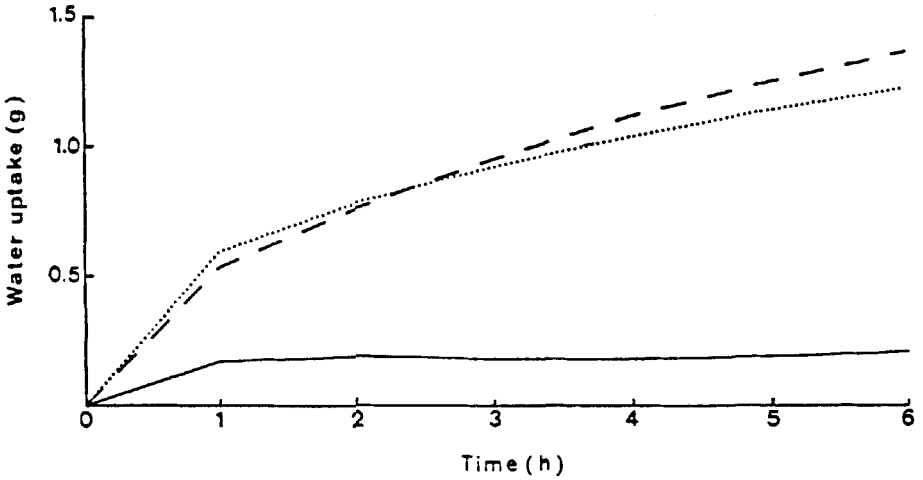

FIGURE 3

Water uptake in function of time for tablets prepared from 40% theophylline and different types of starches (——— = Pregelatinized starch; ····· = Pregelatinized-phosphate crosslinked starch; ---- = Pregelatinized-adipate crosslinked starch)

are not completely blocked, thus the tablets can still take more water. No difference in water uptake for the tablets prepared with different types of pregelatinized-crosslinked starches was observed.

CONCLUSION

This study indicates that crosslinked-modified waxy corn starches, either pregelatinized or not, in comparison to purely pregelatinized waxy-corn starch are not suitable to use as hydrophilic matrix in sustained release formulation.

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