

Adsorption studies on steroid powders

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The adsorption of hydroxyethylcellulose, sodium carboxymethylcellulose, polysorbate 80, glucose and sucrose, by steroid powders has been examined. Hydroxyethylcellulose and polysorbate 80 were adsorbed, but glucose, sucrose and sodium carboxymethylcellulose were not. Hydroxyethylcellulose, which can cross-link with the sedimented particles, caused most caking of the sediment.

CELLULOSE derivatives, sometimes in combination with surfactants, are used extensively in the formulation of pharmaceutical aqueous suspensions. They delay settling of the suspension before administration. Some workers hold the opinion that they are also of value in preventing caking.

It has previously been noted (Steiger-Trippi, 1958) that high molecular weight cellulose derivatives can adversely affect the redispersibility of zinc oxide, talc and titanium dioxide suspensions. Blackadder (1964) also pointed out that polymeric materials capable of linking particles can have a compacting effect on settled suspensions.

The present communication describes a study of the adsorption of certain carbohydrates by the steroid powders in the presence of surfactants. The effect of two cellulose derivatives on steroid suspensions has been examined: hydroxyethylcellulose enhanced the tendency of the settled suspensions to caking.

Experimental and results

The specific surface areas of the hydrocortisone acetate and betamethasone alcohol used were determined by *p*-nitrophenol adsorption from water containing 10% ethanol (Giles, 1962). The specific surface area of hydrocortisone acetate was also determined by BET nitrogen adsorption (at the Paint Research Station) and by air-permeability using the Fisher Sub-sieve Sizer. Adsorption of hydroxyethylcellulose, sodium carboxymethylcellulose, glucose and sucrose by the steroid powders was measured by the anthrone method devised for the assay of carbohydrates by Trevelyan (1952). The adsorption of polysorbate (Tween) 80 was followed by the gravimetric technique of Oliver (1949) (Table 1).

The state of flocculation of the steroid powders in aqueous suspensions containing the various additives was examined by suspending the powders in 2 inch \times $\frac{1}{4}$ inch sample tubes and ascertaining the settling volume, and also by measuring how readily the powders moved from the bottom of the tilted tubes. The results are not precise and serve only as an approximate measure of the effect of the additive (Table 2).

Caking of the suspensions was measured by the number of tilting motions required to remove the sediment from a betamethasone suspension from the bottom of a container 3.3 inches high \times 1.4

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inches diameter. The tilting apparatus was as described by Steiger-Trippi (1961). Suspensions were filled into the containers, which were then allowed to stand upright at room temperature for 30 days before the caking tests were made.

TABLE 1. ADSORPTION BY STEROIDS FROM SOLUTIONS ($\mu\text{g/g}$)

Steroid		Adsorbate [strength of solution (w/v) in brackets]					
Substance	Pre-treatment	P80 (0.5)%	HEC(0.4%) (+ P80, 0.5%)	HEC (0.4%)	NaCMC (0.5%)	Glucose (0.4%)	Sucrose (0.4%)
Hydrocortisone acetate	No surfactant	3,700	0	17,000	0	0	0
Cortisone acetate	No surfactant	6,900	0	8,800	0	0	0
Betamethasone alcohol	Polysorbate 80	0*	0	9,000	0	0	0
Prednisolone acetate	Cetrimide	1,180	0	6,000	0	0	0

P = polysorbate. HEC = hydroxyethylcellulose. NaCMC = sodium carboxymethylcellulose

* See text.

Specific surface area values

Hydrocortisone acetate: *p*-nitrophenol 4.4 m²/g; N₂ 3.3 m²/g; Fisher 1.3 m²/g.

Betamethasone alcohol: *p*-nitrophenol 1.6 m²/g.

Betamethasone suspension with the cellulose derivative required 12 tilting operations (mean of 15 estimations) to clear the sediment. Without the cellulose derivative, 7 operations (mean of 6 estimations) were needed. Two samples of the suspension prepared without the cellulose derivative but with polysorbate 80 required 6 and 4 operations.

TABLE 2. STATE OF FLOCCULATION OF STEROID POWDERS IN AQUEOUS SUSPENSIONS CONTAINING ADDITIVES

Steroid	Treatment (conditions—see Table 1)						
	Water only	P80	HEC/ P80	HEC	NaCMC	Glucose	Sucrose
Cortisone acetate ..	Flocculated free flowing	Low volume	Low volume	Low volume	Flocculated free flowing	Flocculated free flowing	Flocculated free flowing
Prednisolone acetate ..	Low volume	Low volume	Low volume	Low volume	Low volume	Low volume	Low volume
Betamethasone alcohol ..	Low volume	Low volume	Low volume	Low volume	Low volume	Low volume	Low volume
Hydrocortisone acetate ..	Flocculated free flowing	Low volume	Low volume	Low volume	Flocculated free flowing	Flocculated free flowing	Flocculated free flowing

A distribution-free test showed the first two groups to be significantly different at the 5% level. Although there are not sufficient data to place the issue beyond all doubt, there is an indication that the presence of hydroxyethylcellulose produces caking.

Discussion

All the steroid powders adsorb hydroxyethylcellulose from aqueous solution.

For hydrocortisone acetate there are three independent methods of measurement of the specific surface area. The agreement between nitrogen and *p*-nitrophenol adsorption is reasonable, though the Fisher air-permeability method produces a rather lower result.

According to the manufacturer, the hydroxyethylcellulose used has a "repeating unit" with a molecular weight of 442. The projected area of this segment as measured with Catalin models is as follows: Face down = 90\AA^2 . Edge on = 20\AA^2 . Table 1 shows that for hydrocortisone acetate 0.17 g hydroxyethylcellulose is adsorbed per g steroid, thus the area that would be occupied if the hydroxyethylcellulose were adsorbed flat is 21 m^2 , or if adsorbed edge-on, 4.6 m^2 . By the *p*-nitrophenol method the experimentally observed value of the specific surface area was $4.4\text{ m}^2\text{g}^{-1}$.

We have measured the adsorption of hydroxyethylcellulose by the steroid powder at one concentration only, and this is the concentration at which the cellulose derivative is used in the suspension vehicle employed to prepare a typical betamethasone intra-articular injection.

It is obvious that the molecule cannot be adsorbed "flat" in the form of a monolayer. It is also impossible for each segment of the molecule to be attached to the surface, though it would appear that they could be accommodated on the surface.

One of the characteristics of polymer adsorption at solid surfaces is that apparently much more material adheres than corresponds to a flat monolayer (Eirich, 1959). It is generally recognised that the adsorption occurs at only a fraction of the active groups of the polymer molecule. The unadsorbed segments penetrate deeply into the surrounding solution, but are attached to the surface by other units of the same molecule. It would appear that the adsorption of hydroxyethylcellulose on hydrocortisone acetate also occurs in the manner described, since we have shown that a flat monolayer of the cellulose derivative would occupy about four times as much space as is available at the surface of the particles.

For betamethasone alcohol we find the specific surface area by *p*-nitrophenol adsorption to be $1.6\text{ m}^2/\text{g}$ and that the hydroxyethylcellulose adsorbed per g of powder is 0.009 g. These figures give areas for monolayers of 11 m^2 if the derivative is adsorbed flat and 2.4 m^2 if it is adsorbed edge-on. Again, the adsorption is in excess of the area available on the particle surface and the mode of attachment of the derivative to the betamethasone particle surface is probably the same as it is for hydrocortisone acetate.

We note that polysorbate 80 is adsorbed by all the steroid powders, except, as would be expected, the betamethasone alcohol, which had been pre-treated with polysorbate 80. Prednisolone acetate, which had been precipitated in the presence of cetrimide, also gave a low value.

In the presence of polysorbate 80, hydroxyethylcellulose does not appear to be adsorbed (less than $2\mu\text{g}/\text{g}$ was absorbed from a 0.2% w/v solution). It may well be that polysorbate 80 is preferentially adsorbed by the steroids, thus preventing the adsorption of the cellulose derivative.

Sodium carboxymethylcellulose was not adsorbed by any of the powders (limits as above) and at present we can offer no explanation for this.

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A long-chain polymer molecule is adsorbed at many segments along its chain. In order to be desorbed, it must be released from the adsorbing surface simultaneously at each of these points of attachment. This is one of the reasons for the adsorption of long chain polymers, such as hydroxyethylcellulose and the failure of substances such as glucose and sucrose to be adsorbed.

In Table 2 we compare the state of sedimentation of the aqueous suspension with different additives. From column 2, which shows the suspension of the powders in water, we see that only cortisone acetate and hydrocortisone acetate were flocculated and free-flowing after two weeks standing, whereas betamethasone alcohol and prednisolone acetate formed low-volume sediments and were not free-flowing. This is further borne out by data in column 3, which show the effect of polysorbate 80. On the addition of this surfactant, all four steroid powders formed low-volume sediments. The same was true for the addition of hydroxyethyl cellulose alone and also with polysorbate 80.

Sodium carboxymethylcellulose, which was not adsorbed, had no effect on the flocculated sediments of the acetates of cortisone and hydrocortisone, neither did glucose nor sucrose which also had no effect on the two steroids not already deflocculated.

The results of the caking tests support the contention that the presence of a polymer adsorbed by betamethasone enhances the tendency to cake. The caking of a suspension can have many causes, and therefore the omission of hydroxyethylcellulose would not be expected to eliminate caking altogether.

There are indications that when polysorbate 80 is substituted for hydroxyethylcellulose the caking of the suspension is similar to that of the suspension without either of the additives. Both substances produce low-volume sediments, but the hydroxyethylcellulose has a stronger tendency to link the sedimented particles together. It can vary in molecular weight between 40,000 and 350,000, which approximates to molecules of between 600 and 4800 Å in length, while the approximate diameter of a non-ionic surfactant micelle is 100 Å: hence the greater ability of the cellulose derivative to cross-link particles. It should be noted that omission of hydroxyethylcellulose and polysorbate 80 also produces a low volume sediment. As previously indicated (Table 1), the betamethasone alcohol used in these experiments had been pre-treated with the surfactant.

We have thus shown that the presence of the polymer has enhanced the caking tendency of the low-volume sediment.

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