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Effect of drug concentration and agitation rate on drug release from thixotropic gels for hard gelatin capsules

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Renewed interest in liquid filling or semi-solid matrix (SSM) technology is evident, however, processing and drug release from these systems is poorly understood, particularly with respect to formulations filled at ambient temperature. This work is part of an investigation of thixotropic gels prepared from semi-synthetic triglycerides (Miglyols (M); Hüls) and colloidal silicon dioxide (Aerosil (A); Degussa), with reference to manufacture at ambient temperature and drug release of SSM filled capsules. Drug release from the gel formulations in hard gelatin capsules (HGC) has been shown to be related to silicon dioxide type and concentration (Walters et al, 1991) and drug solubility and viscosity of the oil (Ellison et al, 1995). An unexpected pattern of drug release was observed from M829/A200 gels. Release rate was dependent on A200 concentration with the minimum rate obtained with 4% w/w gels indicative of a change of release mechanism at this concentration. Walters et al (1992) indicated that drug release was controlled by a gel viscosity dependent diffusional process for silica concentration up to 4% w/w, whereas a mechanism related to enhanced liquid penetration was predominant for gels of higher A200 concentration. The aim of this investigation is to provide further evidence towards an explanation of the change of mechanism. M829 gels prepared with 3% and 8% w/w A200 and containing 25, 50 and 100 mg of propantheline bromide (PBr; Sigma) were filled (400 mg) into size 1 HGC. Dissolution testing was performed in triplicate for at least 3 hours, or to 100% release, using BP apparatus I (Model 8ST, Caleva) in 1 litre of distilled water, with basket rotation rate of 100 rpm, and also 50 and 200 rpm for capsules containing 50 mg PBr. Drug analysis was by UV spectroscopy (CE 5501, Cecil Instruments) at 243 nm. Results were compared using dissolution efficiency at 160 minutes (DE_{160}); (Khan and Rhodes, 1972). Table 1 summarizes the effect of agitation conditions where PBr release from 8% w/w A200 gels was relatively unaffected, in contrast to release from 3% w/w systems. This suggests that matrix erosion and diffusion makes a more significant contribution to drug release for gels containing less than 4% w/w silicon dioxide.

Table 1. The effect of agitation rate on dissolution efficiency for 3% and 8% w/w A200/M829 gels at 37°C .

	$DE_{(160)}$ (%)	
Agitation rate (rpm)	3% w/w A200	8% w/w A200
50	14.2	48.5
100	26.4	54.3
200	39.0	54.2

Rate and extent of PBr release was greater from the more viscous 8% w/w A200 gels than from 3% w/w systems at all drug concentrations and conditions of agitation as shown in Tables 1 and 2. This provides further evidence that the release mechanism above 4% w/w A200 is neither diffusion controlled nor directly related to gel viscosity. Results also show that increased hydrophilic drug concentration improves release rate regardless of mechanism (Table 2). The increased concentration gradient promotes drug release by diffusion from M829/A200 gels with up to 4% w/w silica, and above this concentration the drug enhances the effect of A200, increasing penetration of the gel by aqueous media. This work therefore supports the hypothesis that the hydrophilic character of the formulation and gel viscosity are important in the control of drug release from SSMs.

Table 2. The effect of PBr content on dissolution efficiency for 3% and 8% w/w A200/M829 gels at 37°C .

	$DE_{(160)}$ (%)	
PBr content (mg)	3% w/w A200	8% w/w A200
25	23.6	46.9
50	26.4	54.3
100	40.5	70.6

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