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COMMUNICATION

TITANIUM DETERMINATION AS A METHOD OF QUANTIFYING FILM-COAT APPLICATION ON TO TABLETS

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ABSTRACT

A method for assessing the extent and uniformity of film-coat application on to tablets by the determination of titanium is reported. The method is utilised to determine the ideal charge of tablets in a 24" Accela-Cota for the application of a water insoluble film-coat which is intended to be rate controlling. The results are compared with those obtained using conventional methods of process optimisation ie dissolution testing.

INTRODUCTION

In recent years there has been considerable interest in the preparation of tablet formulations where the release of the active medicament is either wholly or partially controlled by the application of a film-coat. To ensure reproducibility of the dissolution characteristics of these formulations it is essential to minimise any variation in coat uniformity that may occur as a result of the film-coating process. Conventionally for controlled release preparations this is performed by monitoring dissolution profiles for tablets coated under various conditions. However this may be an involved process requiring the analysis of large numbers of tablets over extended time frames to give meaningful results. An alternative approach is to use marker compounds and quantitative analytical techniques to define the level of film-coat required to give the desired release profile and then monitor the effect of process variables on such factors as extent of film-coat application, inter-tablet variation etc.. Utilisation of such methods can be more efficient and additionally allows the possibility of performing extensive optimisation studies on placebo products where drug supply is critical. If the marker compound is also an integral component of a marketable formulation it will provide additional control information on production processes on an on-going basis.

Several methods for quantifying the amount of film-coat applied to a tablet by the incorporation of marker compounds into the coating medium have been reported and potassium bromide (1), tartrazine (2), and FD&C Blue #1 (3) have all been considered for this purpose. In each case, the coat was removed from the tablet by dissolution in an aqueous medium and the marker detected using appropriate methodology. Such methods are not suitable where the film-coat is formulated to have limited aqueous solubility, eg ethylcellulose and in these instances coat removal in an organic solvent may be required. Furthermore, tartrazine and to a lesser extent FD&C Blue 1, do not have general pharmaceutical acceptability and their use may therefore be limited to development processes only.

Titanium dioxide is a pharmaceutical excipient with wide regulatory approval, commonly used to pigment and opacify tablet film-coats and for which assay methodology is well documented in standard chemistry texts. We report how the determination of titanium has been adapted to investigate the influence of tablet charge in a 24" Accela-Cota on the extent and uniformity of application of a release controlling ethylcellulose film-coat. These results have been compared with those obtained by monitoring the dissolution of an active ingredient from the same batches of film-coated tablets.

MATERIALS AND METHODS

Tablet manufacture. Tablets consisted of MK-458 Hydrochloride (a research compound under development by Merck Sharp and Dohme) 1.725mg, Hydroxypropylmethycellulose 4000cps (Methocel K4M, Colorcon Ltd, Orpington, England) 80mg, Hydrous Lactose BP 112.775mg, Citric Acid Monohydrate BP 5mg and

Magnesium Stearate BP 0.5mg and were compressed to 200mg using 5/16" diameter, normal concave tooling.

Film-coating materials. The film-coating suspension consisted of a proprietary aqueous dispersion of Ethylcellulose (Aquacoat^{tm} FMC Corp. Philadelphia, USA) 38.7%w/w, Distilled Acetylated Monoglycerides (Myvacet 9-40tm Eastman-Kodak, Kingsport, USA) 2.6%w/w, titanium dioxide BP 1.3%w/w and Purified Water to 100%w/w.

Film-coat application. Tablets were coated in a 24" Accela-Cota (Manesty Machines Ltd, Liverpool, England) using an inlet air temperature of 50-55°C, an exhaust air of 30-33°C and a pan speed of 12.5rpm. The film-coat was applied via a Schlick Model 930/7 gun fitted with a 1.2mm insert (Schlick, Coburg, West Germany) using a spray rate of 24-26g per minute and an atomising air pressure of 20psi. To determine optimal batch loading, charges consisting of between 6 and 14kg of tablets were coated separately with a theoretical coat application of 38.4mg of suspension equivalent to 0.5mg titanium dioxide. The coating suspension was stirred continuously throughout the process to maintain homogeneity.

Analytical reagents. Methanol (Fisons, Loughborough, UK), t-butyl methyl ether (Fisons, Loughborough, UK) concentrated sulphuric acid (Fisons, Loughborough, UK) and hydrogen peroxide 100 volumes (Fisons, Loughborough, UK) were all of analytical reagent grade.

Titanium determination. Coated tablets were placed in separate glass centrifuge tubes with 2ml of t-butyl methyl ether and sonicated until the film coat was stripped (2 minutes). The decoated tablets were removed and carefully washed with t-butyl methyl ether. The combined solution and washings were centrifuged at 4000rpm for 5 minutes and after discarding the supernatant, the residue was further washed with 2x2ml aliquots of methanol with sonication, centrifugation and decanting being performed after each addition. Having dried the residue for 2 minutes on a steam bath, 2ml of 70%v/v sulphuric acid were added and the tube sonicated for 2 minutes prior to transfer to a 50ml beaker. The tube was rinsed with a further 2 x 1ml aliquots of acid and the resultant suspension heated over a Bunsen burner until the titanium dioxide dissolved and any yellowness had been removed. The cooled solution was transferred to a 10ml volumetric flask which was adjusted to volume with rinsings of distilled water. A 5ml aliquot of this solution was pippetted into a glass test tube and 2 drops of Hydrogen Peroxide added and mixed prior to centrifuging at 4000rpm for 5 minutes. The absorbance of the supernatant was determined at 410nm using an HP-8451A UV/visible diode array spectrophotometer using the solution remaining in the volumetric flask as a blank. Using spiked solutions, this procedure was shown to give a linear response (correlation coefficient = 0.9996) over the range 0 to 1.5mg titanium dioxide. Sample solutions at all stages throughout the procedure were found to be stable for at least 48 hours. For each batch loading 15 individual tablets were assayed for titanium in this manner.

Assay validation. For control purposes the recovery from 15 replicate samples of placebo tablets spiked with 0.5mg titanium dioxide in a Myvacet 9-40/Aquacoat suspension was found to be 100.2% with a relative standard deviation of 1.78%.

Dissolution Testing. Dissolution of MK-458 from active tablets was performed using USP XXI Apparatus 2, paddles rotating at 50rpm with 500ml 0.1M Hydrochloric Acid as dissolution medium. Samples were removed at appropriate time intervals and analysed by reversed phase HPLC with UV detection at 280nm.

RESULTS AND DISCUSSION

The results of the individual and mean assay values for titanium dioxide of 15 replicate samples of tablets at each 24" Accela-Cota charge together with percentage recovery of the theoretical quantity of coat applied and relative standard deviation are presented in Table 1. It is immediately apparent that the quantity of titanium dioxide applied to individual tablets increases significantly to a maximum level of coverage at a charge of 11kg before declining slightly at a charge of 14kg. For loads of 8kg and less the actual quantity of titanium dioxide applied to the tablets is of the order of 50% of the theoretical value rising to nearly 90% for an 11kg load. Losses to the exhaust system

Table 1

Analysis of the Titanium Content of Coated Tablets as a Function of Charge in the 24" Accela-Cota

	ACCELA-COTA CHARGE							
	6 Kg		8 Kg		11 Kg		14 Kg	
SAMPLE NUMBER	TITANIUM CONTENT (mg/tab)	%RECOVERY OF CLAIM	TITANIUM CONTENT (mg/tab)	%RECOVERY OF CLAIM	TITANIUM CONTENT (mg/tab)	%RECOVERY OF CLAIM	TITANIUM CONTENT (mg/tab)	%RECOVERY OF CLAIM
1	0.304	60.8	0.241	48.2	0.480	96.0	0.435	87.0
2	0.219	43.8	0.288	57.6	0.482	96.4	0.488	97.6
3	0.276	55.2	0.271	54.2	0.426	85.2	0.427	85.4
4	0.214	42.8	0.294	58.8	0.424	84.8	0.434	86.8
5	0.280	56.0	0.262	52.4	0.447	89.4	0.397	79.4
6	0.308	61.6	0.231	46.2	0.433	86.6	0.376	75.2
7	0.231	46.2	0.267	53.4	0.442	88.4	0.369	73.8
8	0.243	48.6	0.295	59.0	0.434	86.8	0.403	80.6
9	0.278	55.6	0.269	53.8	0.479	95.2	0.427	85.4
10	0.245	49.0	0.299	59.8	0.484	96.8	0.433	86.6
11	0.236	47.2	0.266	53.2	0.429	85.8	0.461	92.2
12	0.191	38.2	0.254	50.8	0.432	86.4	0.365	73.0
13	0.241	48.2	0.236	47.2	0.473	94.6	0.382	76.4
14	0.223	44.6	0.290	58.0	0.414	82.8	0.448	89.6
15	0.268	53.6	0.281	56.2	0.427	85.4	0.400	80.0
MEAN	0.250	50.1	0.270	53.9	0.449	89.4	0.416	83.3
RELATIVE STANDARD DEVIATION	13.60%		8.14%		5.65%		8.56%	

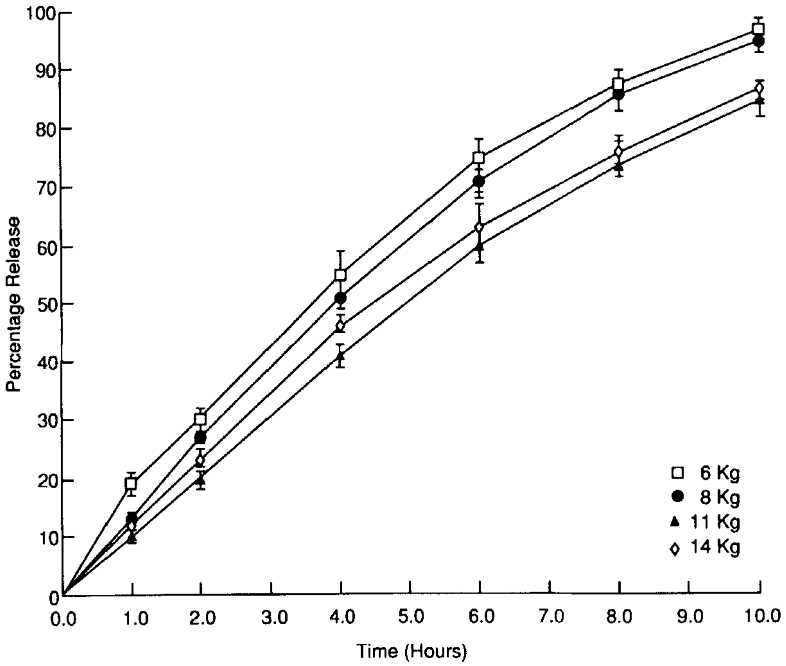

FIGURE 1

Dissolution Profiles for the Release of MK-458 as a Function of Charge in the 24" Accela-Cota (n = 6)

and to coating of the Accela-Cota drum probably account for these unexpectedly low values. These results correlate well with those obtained for conventional dissolution testing (Figure 1) where it is seen that the release rate of tablets coated as part of an 11kg charge is considerably slower than those coated as part of an 8kg charge suggesting a higher level of coat application to the former. There is also some evidence to indicate that the lower titanium dioxide recoveries from the 14kg batch relative to the 11kg batch is reflected in a slower dissolution rate of the latter. For this formulation, the function of the film-coat was to restrain release during early times to allow hydration of the HPMC matrix before rupturing at approximately one hour. Thus, dissolution results at the two hour time interval are of particular interest and once again good correlation between the two sets is evident.

In all cases the determination of titanium for individual tablets showed a significantly higher standard deviation than the control sample at the 95% confidence level thus indicating that considerable inter-tablet variation of film-coat application is a real effect. Not surprisingly this was most marked in samples taken from the lowest charge. However there is some indication that for the highest loading inter-tablet variation again increases suggesting that a load of 14 Kg may be beyond the optimal range. Results suggesting significant inter-tablet variability of film-coat application are barely supported by dissolution testing with the range bars on Figure 1 showing that the individual dissolution profiles of 6 tablets rarely deviated by more than 4% from the mean at a given time point. By way of comparison it may be noted that for titanium determination, deviations from the mean were as large as 23% for the 6 kg load decreasing to around 8% for the 11 kg load. From this information it would appear that measurement of titanium level is a more sensitive measure of the extent of film-coat application.

As with all experiments of this nature, it is assumed that the extent of application and adhesion of titanium dioxide is the same as for the other components of the film coat. While this assumption may not be wholly valid it is apparent that in this instance determination of titanium as a method of assessing extent of film coat application correlates well with conventional dissolution test methods. While assay methodology for titanium is necessarily involved due to its insolubility, the process is capable of batch scale-up thus increasing efficiency. As a commonly used tablet coating excipient it is envisaged that utilisation of this analysis would be appropriate in all stages of tablet development, process optimisation and as a control method during manufacture.

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