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AN INVESTIGATION INTO THE USE OF CREEP VISCOMETRY FOR IN VITRO CHARACTERISATION OF THE RAFT FORMING PROPERTIES OF TABLETS CONTAINING ALGINIC ACID AND ANTACID COMPONENTS

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SUMMARY

The established methods for assessing the strength of rafts formed in-vitro by alginic acid/antacid containing formulations rely on the determination of forces required to disrupt the raft structure. Creep viscometry is proposed as an alternative,non-destructive means of investigating the characteristic parameters of this type of product. Several commercial chewable tablet formulations were investigated using this technique. The instantaneous compliance and the Newtonian viscosity were calculated from the creep compliance curves obtained for these products and were used as raft strength indicators.

Differences found in the raft strength parameters of the different products were attributed to interactions between the formulation components. Additional studies conducted on experimental batches established that such interactions could be estimated using this technique. It was concluded that creep viscometry could be usefully employed in investigations of alginate rafts and,possibly,other oral dosage forms which rely on the formation of visco-elastic structures to modify drug release properties.

INTRODUCTION

Chewable tablets containing alginic acid or its' soluble salts are frequently administered for the treatment of gastric reflux. The ability of alginic acid to form a cohesive gel at low the low pH levels found in the stomach is believed to create a physical barrier to the regurgitation of the stomach contents into the oesophagus. Carbonate salts are also included so that carbon dioxide generated in contact with gastric acid is trapped in the gel structure to create a buoyant raft which floats on the surface of the stomach contents. Antacids are also frequently included to provide relief from the symptoms of hyperacidity.

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It has been demonstrated that aluminium salts can reduce the strength of alginic acid rafts [1,2]. In contrast the presence of calcium ions has been shown to strengthen rafts by increasing polymer cross-linking [3].

Raft strengths are typically assessed by methods which measure the forces required to disrupt the barrier formed by the formulations [4]. This is not unreasonable considering the proposed physical barrier mode of action. However these methods are probably unsuited to evaluating the underlying nature of alginic acid rafts and formulation component interactions which influence the final raft strength. One method which was considered less likely to inflict irreversible changes on the polymeric,cross-linked structure of a raft was that of creep viscometry. Using this technique a small shear stress is applied to a visco-elastic body to produce a characteristic creep compliance curve,providing that the viscoelastic limit is not exceeded. Information on the elasticity and ground state (Newtonian) viscosity,which are considered to be unique characteristics of the materials tested ,can then be calculated [5,6]. Consequently,the possibility of developing of developing a method for the characterisation of alginate rafts and evaluating the effects of formulation variations using this technique was investigated.

MATERIALS AND METHODS

Materials Used

Samples of chewable alginic acid containing tablets were obtained from wholesalers. The products purchased were GASTRON,PYROGASTRONE (Sanofi Winthrop),GAVISCON (Reckitt and Colman) and GASTROCOTE (B.M. Pharmaceuticals). All materials used for experimental formulations were of pharmacopoeial grades.

Manufacture of Experimental Formulations

The effect of variation in the content of three components in experimental alginic acid/antacid formulations was investigated by means of a factorial design procedure [7]. The range of contents for each component was maintained within the limits normally encountered in commercial formulations. A total of eight blends were prepared using combinations of high and low levels of each component (Table 1).

A sufficient quantity of each blend was made to prepare about ten tablets. Approximately 2g. of each blend was compressed using a 2cm. die and flat bevel punches on a KBr press at 2 tonnes compression force and a 5sec. dwell time. The blends were prepared in duplicate to enable repeat experiments to be performed.

Preparation of Rafts

In order to mimic the action of chewing and swallowing the following procedure was used.

The tablets were ground in a mortar to produce coarse granules which were then screened through a 500um. mesh sieve. A 5g. sample was taken from the screened material and wetted with 10ml. of purified water. The resulting slurry was lightly triturated until the raft formed at which point a sample was removed for testing.

Test Procedure

Creep viscometry was performed using a Carri-Med CSL low-shear rheometer (Carri-Med,Dorking,U.K.). The tests were carried out under ambient conditions using a 4cm. parallel plate configuration at a gap setting of 4mm. A

TABLE 1.

The contents of alginic acid,aluminium hydroxide and magnesium trisilicate (mg/tablet) used in experimental tablet formulations. Each tablet also contained sodium bicarbonate 180mg.,magnesium stearate 10mg. and compressible sucrose qs. to 2000mg.

Sample Number	Alginic acid	Aluminium hydroxide	Magnesium trisilicate
1	200	50	25
2	600	50	25
3	200	250	25
4	600	250	25
5	200	50	80
6	600	50	80
7	200	250	80
8	600	250	80

sample of raft material sufficient to fill the gap between the rotating plate and platen of the rheometer was used. The initial shear stress was applied after a brief equilibration period of 30sec. and was maintained at about 2.4N.m-2 for 2min. A further relaxation period of 1min. was given after the shear stress was removed to assess whether elastic recovery had occurred.

The creep compliance curve was derived by the software package provided with the test equipment. Subsequent calculations of the instantaneous compliance and Newtonian viscosity characteristics were also performed automatically by the same software package.

RESULTS AND DISCUSSION

Formulation data and the results for creep viscometry tests of the rafts formed by the commercial products under the conditions specified above are shown in Table 2. Typical creep compliance curves are compared in Fig 1.

GASTRON and PYROGASTRONE,which contain identical quantities of alginic acid,aluminium hydroxide and magnesium trisilicate,gave comparable results for both instantaneous compliance and Newtonian viscosity. GAVISCON and GASTROCOTE both gave higher viscosity values than the other formulations. The instantaneous compliance values appeared to be similar for all of the products.

The raft strength parameters were clearly not directly correlated to the alginic acid content alone. The products which gave the highest viscosity readings,GAVISCON and GASTROCOTE,contained 500mg. and 200mg. of alginic acid respectively,whereas the other products both claim 600mg. alginic acid per tablet. As the proportions of the antacid components were known to be different

TABLE 2.

Details of the contents of active components in four commercial alginate raft forming products and the results obtained from creep viscometry testing. The content of alginic acid,aluminium hydroxide and magnesium trisilicate are given as mg/tablet. The results for viscosity and instantaneous compliance are also shown.

Product	Alginic acid	Aluminium hydroxide	Magnesium trisilicate	Viscosity Pa.s	Instantaneous compliance $Pa^{-1}x10^{-3}$
GAVISCON	500	100	25	13120	3.09
GASTRON	600	240	60	4359	3.34
PYROGASTRONE	600	240	60	2212	6.59
GASTROCOTE	200	80	40	11740	2.66

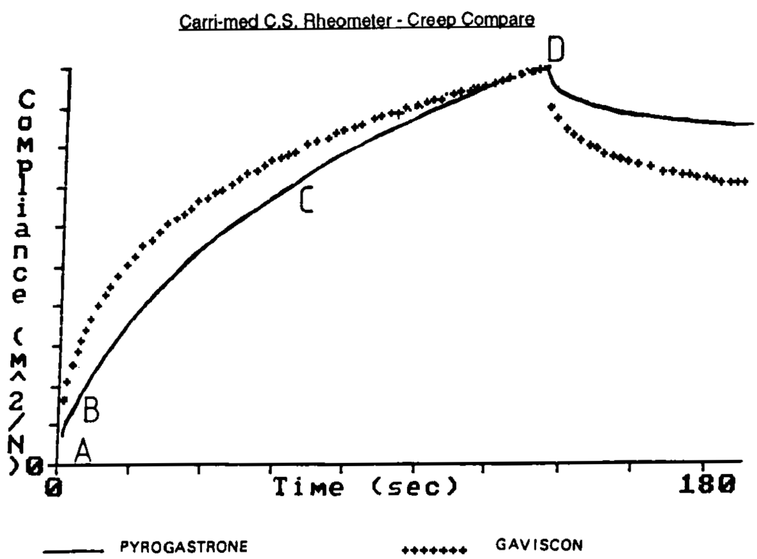

FIGURE 1.

Comparison of the creep compliance curves obtained for alginate raft producing formulations. The instantaneous compliance values were derived from the portion of the curves representing the elastic deformation experienced when a shear stress was first applied (A to B). The linear or Newtonian viscosity was derived from the portion of the curves identified by C to D. Following the removal of the shear stress at point D a certain amount of elastic recovery was demonstrated. These parameters were used to characterise the different formulations.

TABLE 3.

The effect of changing the content of alginic acid,aluminium hydroxide and magnesium trisilicate on raft strength parameters. The levels are expressed as high (H) or low (L) ;the actual quantities used are given in Table 1. Results for the instantaneous compliance and Newtonian viscosity are presented together with a summary of the main and interaction effects on the latter parameter.

Sample number	Alg. acid	Alum. hydrox.	Mag trisil.	Mean viscosity Pa.s	Mean instantaneous compliance Pa-1x10-3	Summary of main effects and interactions on viscosity (Pa.s)
1	L	L	L	13340	3.52	-
2	H	L	L	15905	3.01	+7824
3	L	H	L	3178	9.33	-6087
5	L	L	H	5400	6.70	-3284
4	H	H	L	12120	2.35	+958
6	H	L	H	15505	2.83	+1540
7	L	H	H	1472	11.85	+887
8	H	H	H	9032	3.63	-2231

interactions between the formulation components which affected the raft parameters were considered a possibility.

The effects of the other formulation components in the products examined could not be discounted,however. Accordingly a controlled assessment of the effects of variable formulation parameters was considered necessary to confirm whether creep viscometry could be used to investigate any such interactions.

To achieve this a series of formulations were prepared to a 2^n factorial design (where n = number of variables) in which the levels of alginic acid,aluminium hydroxide and magnesium trisilicate were varied (see Table 1.). The variable component level,test result and estimates of the main effects and interactions on the Newtonian viscosity are summarised in Table 3.

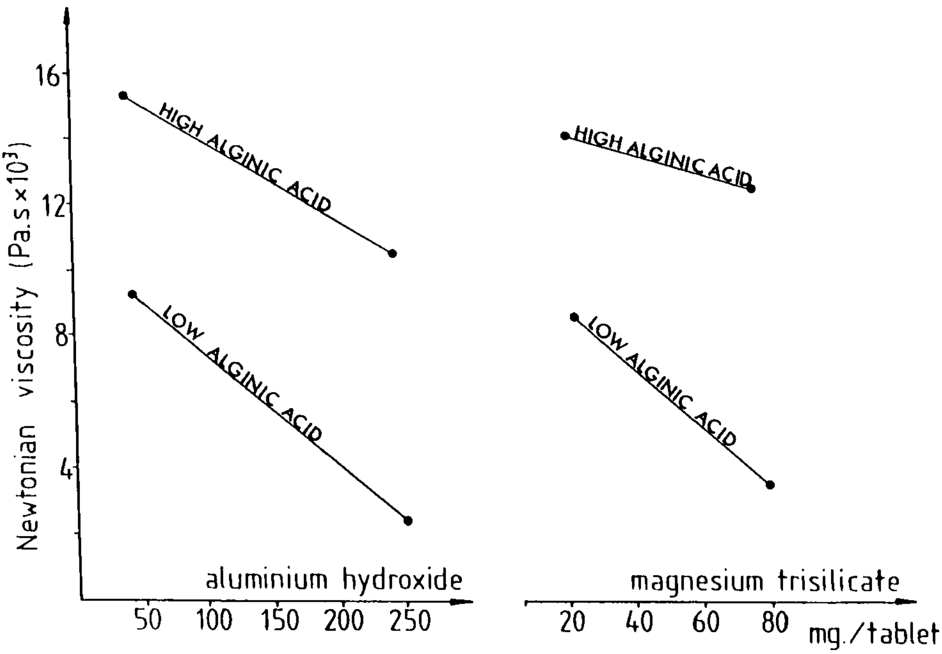

FIGURE 2.

Graphical representation of the main effects of increasing the levels of antacid components in experimental alginate raft forming formulations on raft viscosity. The components and the levels at which they were examined are shown on the X-axis. Two levels of alginic acid were used to assess the extent of interaction. Increasing levels of antacid components tended to reduce the raft viscosity (the main effect) but there is a suggestion of higher-level interaction between magnesium trisilicate and alginic acid as the lines representing the main effects are noticeably divergant.

The main effect of increasing the alginic acid levels was shown to be an increase in the raft viscosity .Increasing the levels of the antacids,however,appeared to reduce the raft strength with the aluminium hydroxide exerting the greater effect. A graphical representation of the main effects is given in Fig 2. These findings support those of Washington et al [2] who suggested that that incorporation of some aluminium salts into raft forming products could reduce the raft strength. It can also be inferred from the divergance of the lines representing the effect of different alginic acid concentrations at increasing proportions of magnesium trisilicate that there is a degree of interaction between these components in this formulation.

Examining the higher level interactions suggested that some benefit may be gained in terms of raft viscosity by adjusting the levels of any two components but not all three. Thus the initial observation that a possible interaction occurs between the alginic acid and the antacid components,resulting in a measurable effect on the measured raft parameters,was supported by these findings.

It should also be noted that the results for instantaneous compliance indicated that the rafts which had the least elastic structure i.e. those with the highest values (samples 3,5 and 7) correlate with the lowest viscosity measurements. This would suggest that the antacids do affect the elastic structure of the rafts. This is considered to be a clear indication that this technique can be used to investigate the structure of the alginate rafts formed in-vitro and perhaps assist in achieving a formulation with optimised characteristics of raft strength and acid neutralising capacity.

CONCLUSION

The results of this investigation suggest that creep viscometry can provide a useful means of evaluating the physical parameters of an alginate raft and the effects of formulation variables. The main advantage offered by this technique is the potential to apply shear stresses below the visco-elastic limit of the gel structure leaving it essentially unaffected. By way of comparison,the method described by Washington[2] uses a wire probe of about 2.5 x 10^{-2}m. long and 6.0 x 10^{-4}m. diameter which is drawn through a raft at 100mm.min^{-1}. This approximates to about 600 Nm^{-2}. This is considerably greater than the shear stress typically applied in the experiments described above (2.4Nm^{-2}). Also,if it is possible to perform tests at shear rates which do not exceed the elastic limit of alginate rafts,then it would be possible to repeat tests on single samples and measure time dependent effects on raft formation.

The general principals of this technique can equally be applied to the investigation of other dosage forms which rely on visco-elastic properties to achieve their effect,such as sustained-release gels. Further investigations into the uses of this technique are,therefore,recommended.

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