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Compaction Characteristics of Ethylcellulose in the Presence of Some Channeling Agents: Technical Note

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INTRODUCTION

Polymers are frequently used in drug delivery systems. By using polymer combinations, formulators may be able to develop sustained-release drug dosage forms with better performance than is shown by the individual polymer components. Various polymer blends have been studied in order to achieve the desired release kinetics.[1] The presence of more than one polymer in a formulation may result in a spatial configuration, but it is also possible that a polymer additive may become part of the gel network.[2] The externally adsorbed water in the insoluble polymers can assist in the formation of liquid bridges between the particles. Any soluble component in the formulation could dissolve in these liquid bridges and thus assist in the formation of solid bridges between the particles on drying, which would sustain the granule integrity and alter the physicotechnical properties of the matrixing agent. These polymers can be expected to experience an aqueous environment in production and in vivo. The water-polymer and polymer-polymer interactions and their distribution and/or configuration within a formulation are critical to their applications in wet massing techniques.[2,3]

Ethylcellulose (EC) is a water-insoluble polymer used in controlled-release dosage forms. In the absence of polymer swelling ability, EC compactibility becomes a key factor in such systems, because release kinetics would depend largely on the porosity of the hydrophobic compact.[4] Although EC is considered insoluble, it can take up water.[5] This is because of its hydrogen bonding capability with water due to the polarity difference between the oxygen atom and the ethyl group of the polymer.[3]

EC, like other water-insoluble polymers used in drug delivery systems, more often than not requires the incorporation of release modifiers, which create channels through which drug leaches out, increase the wetting of the hydrophobic barriers of the matrix, or modify the barrier properties of the absorbing membrane.

While the compaction characteristics of EC[4] and the effects of various additives on the release properties of EC have been studied,[6] the effects of such interactions on the compaction characteristics of EC have not been studied.

In the present study, the effects of 4 commonly used hydrophilic additives—polyethylene glycol (PEG) 4000, PEG 10 000, sorbitol, and mannitol—on the compaction characteristics of EC were investigated using density measurements and the Heckel equation.[7,8] The Heckel equation is widely used for relating the relative density, D, of a powder bed during compression to the applied pressure, P. It is written as follows:

$$Ln\,[1/1 - D] = KP + A \qquad (1)$$

The slope of the straight-line portion, K, is the reciprocal of the mean yield pressure, P_y, of the material. From the value of the intercept, A, the relative density, D_a, can be calculated using the following equation[9]:

$$D_a = 1 - e^{-A} \qquad (2)$$

The relative density of the powder bed at the point when the applied pressure equals zero, D_o, is used to describe the initial rearrangement phase of densification as a result of die filling. The relative density, D_b, describes the phase of rearrangement at low pressures and is the difference between D_a and D_o:

$$D_b = D_a - D_o \qquad (3)$$

MATERIALS AND METHODS

Materials

The materials used were EC (Aldrich Chemical Company, Inc, Milwaukee, WI), PEG 4000 and PEG 10 000 (Fluka, AG, Buchs, Switzerland), sorbitol, and mannitol (Evans, Lagos, Nigeria).

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Methods

Preparation of Granules

Granules were prepared with EC as a matrix former using the wet granulation method. EC alone or with the additive was mixed in a blender (Braun, Frankfurt, Germany). The powder mixtures consisting of 99% EC and 1% magnesium stearate additive, or 95% EC and 5% additive, were mixed for 10 minutes using a tumbler mixer (Karl Kolb, Dreieich, Germany) and granulated with water for 5 minutes using an Erweka granulator (Erweka, Heusenstamm, Germany) fitted with a 1.6-mm mesh. Granules were dried at 40°C for 60 minutes in a hot air oven (Salvis, Reussbuehl, Switzerland). The dried granules were rescreened through a 1.7-mm sieve and lubricated with 1% magnesium stearate for 5 minutes using the tumbler mixer.

Three hundred–milligram compacts were produced by compressing the granules for 60 seconds with predetermined loads (at various compression pressures) using a Manesty tablet machine (Tianxiang and Chentai Pharmaceutical Machinery Co Ltd, Shanghai, China) fitted with a 10.5-mm flat punch and die set. Twenty tablets were compressed at each pressure, and all readings are the average of 3 measurements. After ejection, the tablets were stored over silica gel in a dessicator for 24 hours to allow for elastic recovery and hardening to prevent falsely low yield values,[10] and dimensions of the compact were determined with a Mitutoyo model IDC1012EB (Mitutoyo Corporation, Kawasaki, Japan) thickness gauge to the nearest 0.01 mm. The Heckel plots were done and statistically analyzed using Microsoft Excel software. The composition of the prepared tablets is shown in Table 1.

RESULTS AND DISCUSSION

Figure 1 shows the effect of the various additives (PEG 4000, PEG 10 000, sorbitol, and mannitol) on the Heckel plots of EC. EC alone showed better compressibility than formulations with additives. An unusual Heckel plot resulting in a negative slope was noticed in formulations without any additive. Three phases of compression are discernible (Figure 1), with the second phase commencing at ~17.5 kN and showing a higher correlation coefficient of ~0.900. The intercept, A, was determined from the extrapolation of the line. The values of the mean yield pressure, P_y, D_o, D_a, and D_b for the formulations are presented in Table 2. The D_o value, which represents the degree of initial packing in the die as a result of die filling, decreased in the presence of additives. Formulations containing no additives (batch 1) had the highest D_o value, while those containing mannitol had the lowest. These results indicate that EC alone exhibited the highest degree of packing in the die, because of die filling, with the addition of mannitol reducing the extent of packing the most.

Table 1. Ethylcellulose Tablet Composition (mg)

	1	2	3	4	5
Ethylcellulose	297	285	285	285	285
Polyethylene glycol 4000	—	15	—	—	—
Polyethylene glycol 10 000	—	—	15	—	—
Sorbitol	—	—	—	15	—
Mannitol	—	—	—	—	15
Magnesium stearate	3	3	3	3	3

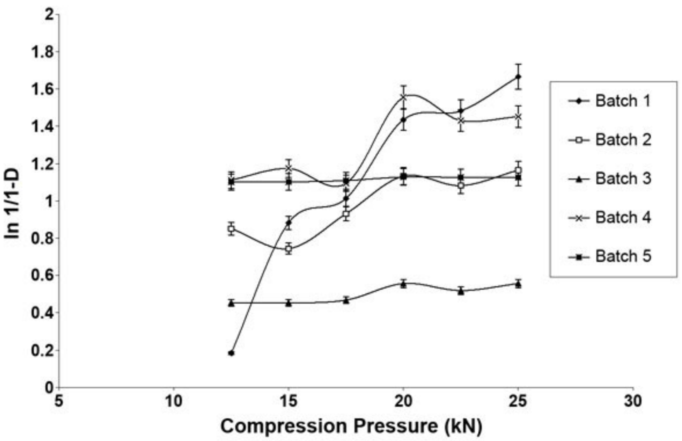

Figure 1. Effect of the channeling agents on the Heckel plot of ethylcellulose.

The D_a values, which represent the total degree of packing at zero and low pressure, decreased in the presence of all the additives except mannitol, which increased the value. The order of decrease was PEG 10 000 > PEG 4000 > sorbitol > EC > mannitol. The D_b value represents the particle rearrangement phase in the early compression stages and tends to indicate the extent of particle or granule fragmentation, although fragmentation can occur at the same time as plastic and elastic deformation of constituent particles. The formulation containing mannitol exhibited the highest value—that is, increased the initial D_b value (batch 1); the formulation containing PEG 4000 showed the lowest values, that is, decreased the D_b values. These results indicate that EC granule fragmentation decreased in the presence of PEG 4000, PEG 10 000, and sorbitol but increased in the presence of mannitol. Furthermore, the values of D_b were usually higher than those of D_o because granule fragmentation and the subsequent filling of void

Table 2. Heckel Constants for the Formulations

	1	2	3	4	5
Py	9.07	31.45	108.70	29.85	400.00
Da	0.62	0.32	0.28	0.49	0.66
Db	0.45	0.17	0.19	0.36	0.63
Do	0.17	0.15	0.09	0.13	0.03

spaces between particles occurred extensively at low pressures. The loose packing of the large granules at zero pressure tended to yield low D_o values.[11] It was observed that in contact with water (during granulation), the EC without additives (batch 1) swelled rapidly, which resulted in large granular sizes (and hence, increased values of D_o), which drastically (depending on the type of additive) reduced upon addition of the additives (batches 2-5). The order of increase in D_o values was batch 1 > batch 2 > batch 4 > batch 3 > batch 5. These values indicate that the presence of additives in the EC matrix facilitated the initial packing of granule formulations in the die.

The mean yield pressure is related inversely to the ability of a material to deform plastically under pressure. The value of P_y for the EC formulation without additives (batch 1) was much lower than the values for formulations containing additives (batches 2-5). This finding implies that the onset of plastic deformation in the EC formulation without additives occurred at much lower pressures. The presence of additives in EC formulations drastically increased the pressures at which plastic deformation of EC granules occurred. The extent of this increase depended on the type of additive, with mannitol, the nonhygroscopic additive, imparting the highest resistance to deformation of EC granules, and sorbitol the least. The change of the essentially type B plot for EC without additives, to type A in EC with mannitol (Figure 1), in which a linear relationship is observed at all applied pressures, indicates densification apparently only by plastic deformation. The removal of the fragmentation portion of the plot is due to softening or increased malleability. Such a change in plot character resulting from the change in the mode of incorporation of some surfactants in an herbal formulation has been reported.[12] This observation is, however, quite different from the work of Al-Omran et al,[13] who found that PEG 600 imparted greater elasticity to EC microcapsules. PEGs also marketed as Carbowax and polyglycols are waxlike solids with a molecular weight greater than 1000. PEGs' water solubility, hygroscopicity, and vapor pressure decrease with increasing average molecular weights. PEGs exhibit different physicochemical properties, which influence their behavior in a formulation; for example, PEG 6000 is the least reactive of all PEGs.[14]

SUMMARY AND CONCLUSION

This study investigated the effect of some commonly used release enhancers on the compaction characteristics of EC. The wet granulation method of massing and screening was used, and compacts were produced by compressing granules for 60 seconds at various compression pressures. The Heckel equation, used for the analysis of results, showed that EC alone showed better compressibility than formulations with additives. The hygroscopic additives, sorbitol and PEG 4000, produced unusual Heckel plots, while the nonhygroscopic additives, PEG 10 000 and mannitol, produced biphasic Heckel plots. The results also indicate that EC alone exhibited the highest degree of packing in the die, with the addition of mannitol reducing the extent of packing the most. The presence of additives in EC formulations increased the pressures at which plastic deformation of EC granules occurred. The extent of this depended on the type of additive, with mannitol imparting the highest resistance to deformation of EC granules and sorbitol the lowest. It can be concluded that additives such as PEG 4000, PEG 10 000, sorbitol, and mannitol, which are often used as channeling agents in sustained-release formulations containing hydrophobic matrix formers, affect the deformation characteristics of EC, with the extent and nature of the effect dependent on the nature of the additive.

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