

**FLOATING AND SWELLING CHARACTERISTICS OF VARIOUS  
EXCIPIENTS USED IN CONTROLLED RELEASE TECHNOLOGY**

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**ABSTRACT**

During the past few years, great interest was developed in the subject of floating. In the present study, the floating and swelling characteristics of several excipients used controlled release technology were examined. The floating behavior was evaluated with resultant weight measurements, while a gravimetric method was employed for studying their swelling. The experiments were carried out in two different media, i.e. deionized water and simulated meal in order to monitor possible differences. The results indicated that higher molecular weight polymers and slower rates of polymer hydration are usually followed by enhanced floating behavior. The floating characteristics of all evaluated excipients were improved when simulated meal medium was used. Finally, the combination of resultant weight measurements and swelling experiments can be used to determine in vitro the buoyancy, weight and

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volume changes of orally administered dosage forms and to predict floating behavior.

## **INTRODUCTION**

Gastrointestinal (GI) residence time depends on many factors such as the density of the dosage form (1, 2, 3), the size of the dosage form (1, 3), meal intake (4, 5, 6), nature of the meal (4, 7), sleep (8), posture (9), exercise (10), etc.

Many researchers (11, 12, 2, 13, 14) have suggested that a floating dosage form may either prolong GI residence time or at least prevent erratic gastric emptying during the digestive phase (1). Moreover, during the past few years, several dosage forms, like the Hydrodynamically Balanced System (HBS) (11), were designed to prolong GI residence time due to their floating capabilities. Under that scope, it would be useful to examine the floating and swelling characteristics of several excipients used in controlled release technology. To achieve that, resultant weight and water uptake measurements of several dosage forms, immersed in specific media, were performed, and volume changes were monitored at various time intervals.

## **MATERIALS AND METHODS**

All excipients were filled volumetrically, by a manual method, into size 2 hard gelatin capsules (Capsugel AG, CH).

The excipients used were: Hydroxypropyl methylcellulose (HPMC): Methocel grades K, E and F (Colorcon, U.K.), sodium carboxymethylcellulose: CMCNa, (Aqualon, U.S.A.), hydroxypropylcellulose: HPC grade H (Nisso, Japan), Polycarbophil: Noveon AA1 (BF.Goodrich, U.S.A.), poly(ethylene)oxide: Polyox grades WSR N-750 and WSR-303 (Union Carbide, U.S.A.), sodium alginate: Protanal LF 20/200 and Protanal LF 120M (Protan Biopolymer A/S, Norway).

Valrelease<sup>R</sup> capsules (Hoffmann-La Roche) were also evaluated.

### **Test Media**

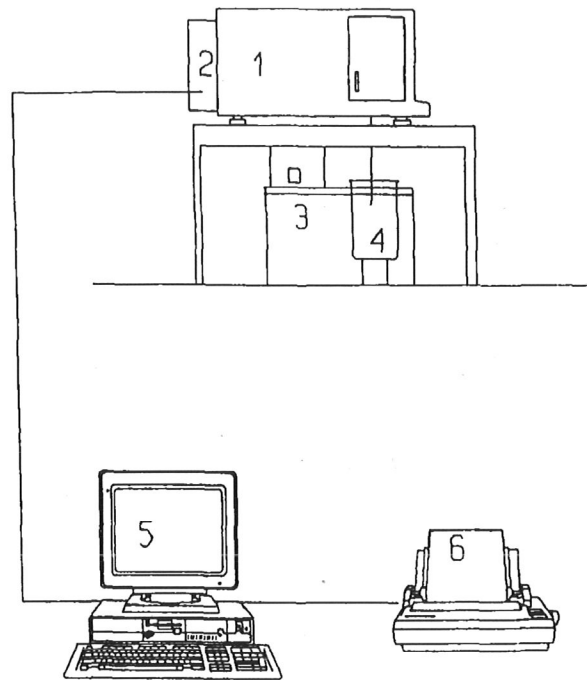
- Air free deionized water (D.W.) (density=0.997gr/ml)
- Simulated meal medium (S.M.M.), prepared by mixing the complete nutrition product Ensure<sup>R</sup> (Abbott Laboratories, Hellas) with the adequate amount of deionized water (5.0/4.6) (density= 1.033gr/ml).

### **Floating Measurements**

The floating characteristics of the above excipients were evaluated with resultant weight measurements. Resultant Weight Force (FRW) is a vertical force and represents the vectorial sum of the buoyancy ( $F_B$ ) and gravity ( $F_W$ ) forces which act on an object when it is immersed in a specific medium (15) (Equation 1).

$$F_{RW} = F_B - F_W = > RW.g = B.g - W.g = > R.W = B - W = df.V - W \quad (1)$$

where:  $g$  is the acceleration of gravity,  $df$  is the fluid density and  $V$ ,  $W$  are the volume and the weight of the object respectively.  $RW$  was measured in vitro. Each excipient was examined at least three times. The apparatus used, which



1. Balance
2. Interface
3. Water-bath
4. Test medium
5. Computer
6. Printer

**Figure 1: The resultant weight measurement apparatus.**

is shown in Figure 1, was based on the one developed recently by Timmermans and Moes (16,17,18). The most important difference was that the balance (Mettler AE200) was connected through an RS 232C interface to a Personal Computer and the recorder was substituted by a printer. Thus, at any time an exact indication (gr) of the RW value was available. The

apparatus was validated through comparison of theoretical and experimental data for spherical objects. The difference between the mean experimental and the mean theoretical value of RW was not greater than 0.87%. A standard deviation (SD) of less than 0.0042 was calculated between five subsequent measurements.

### **Swelling Measurements**

A gravimetric method (19, 20, 21, 22) was considered to be the most suitable in order to study the swelling behavior of the excipients. The capsules, containing the excipients, were kept in USP dissolution baskets without rotation. The wet weight of the swollen dosage form was recorded at specific time intervals. Swelling characteristics were expressed in terms of water uptake (WU) (%) (22, 23) according to the equation 2:

$$\text{WU}(\%) = \frac{(\text{W of swollen form} - \text{initial W of the form})}{\text{initial W of the form}} \times 100 \quad (2)$$

### **RESULTS AND DISCUSSION**

The selected excipients are polymeric materials that can absorb a significant amount of water (more than 20% of their dry weight), while maintaining a distinct three-dimensional structure. As a result, they conform to the definition of hydrogels provided by Gehrke et al, (24). When a dosage form is immersed in a specific medium and after the dissolution of the gelatin capsule, an outer gel layer is formed, accompanied by an increase of its volume. The process of erosion, due to dissolution of the gel formed or to

deaggregation (20), and the creation of new gel layers affect both the volume and the weight of the dosage form.

The RW force which is responsible for floating depends on both the weight and the buoyancy forces, as shown in equation 1. Water uptake and, consequently, weight gain should be compensated by adequate swelling in order to keep the dosage form at buoyant state. RW data for each dosage form were plotted versus time. Representative graphs are shown in Figures 2 and 3. In all cases RW decreased in a step-like pattern, due to the periodic release of air bubbles created by the substitution of air, enclosed in pores of the formulation, by the test medium. Such a phenomenon does not take place in the case of Valrelease (Figure 2), which maybe due to the compression of the capsule contents. This observation is in agreement with previous findings of Timmermans et al (16,17,18). In each graph, the horizontal zero baseline represents the measurement obtained by the apparatus when no dosage form was immersed. The point where an RW graph crosses the zero baseline indicates the Maximum Floating Time (MFT), namely, the time period a dosage form remains at buoyant state, when immersed in a specific medium. An additional criterion applied in the evaluation of excipients was the Area Under the Curve (AUC), i.e. the area between the RW curve and the zero baseline. These data are summarized in Table 1.

According to Table 1, it can be derived that different viscosity grades of the same polymer display significant differences both in AUC and MFT values.

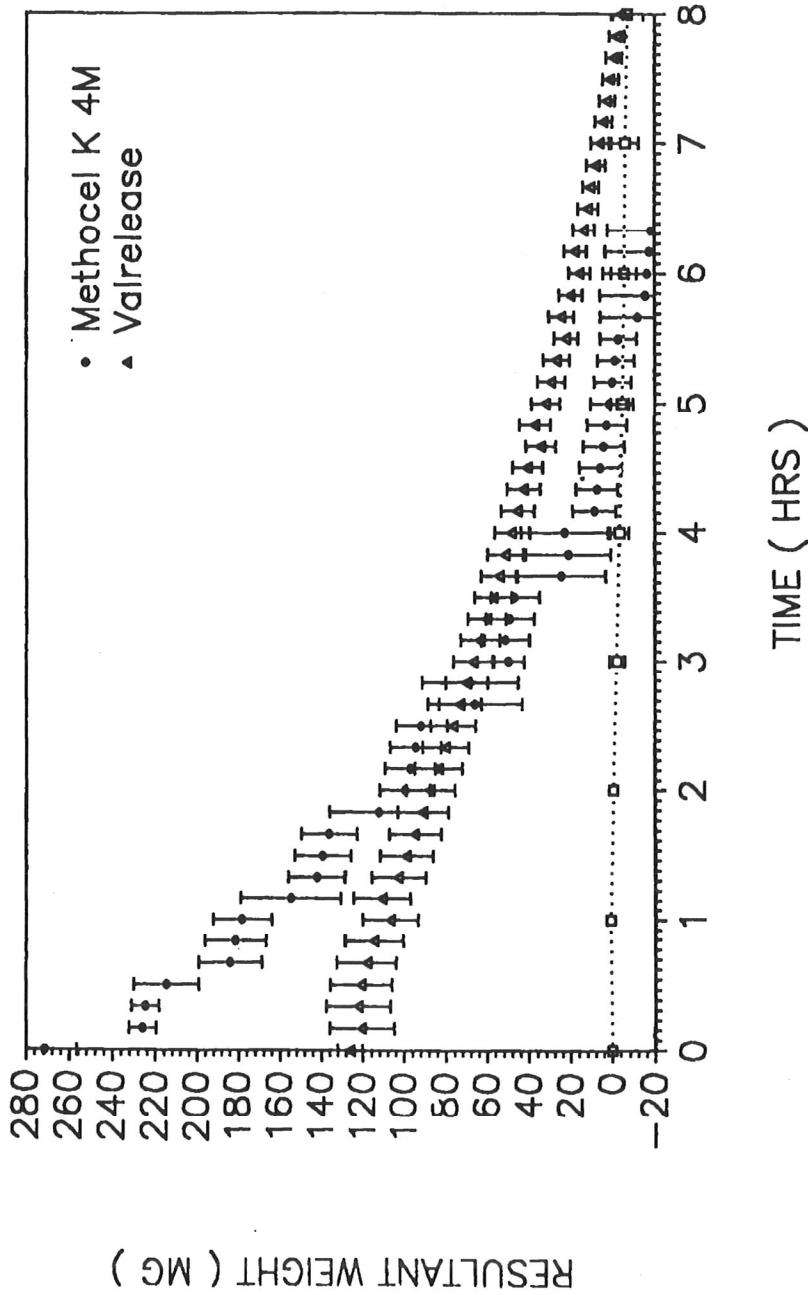


Figure 2: Resultant Weight measurements versus time for Methocel K 4M size 2 hard gelatin capsules and Valrelease capsules in water. Bars indicate SD. Dotted line represents baseline.

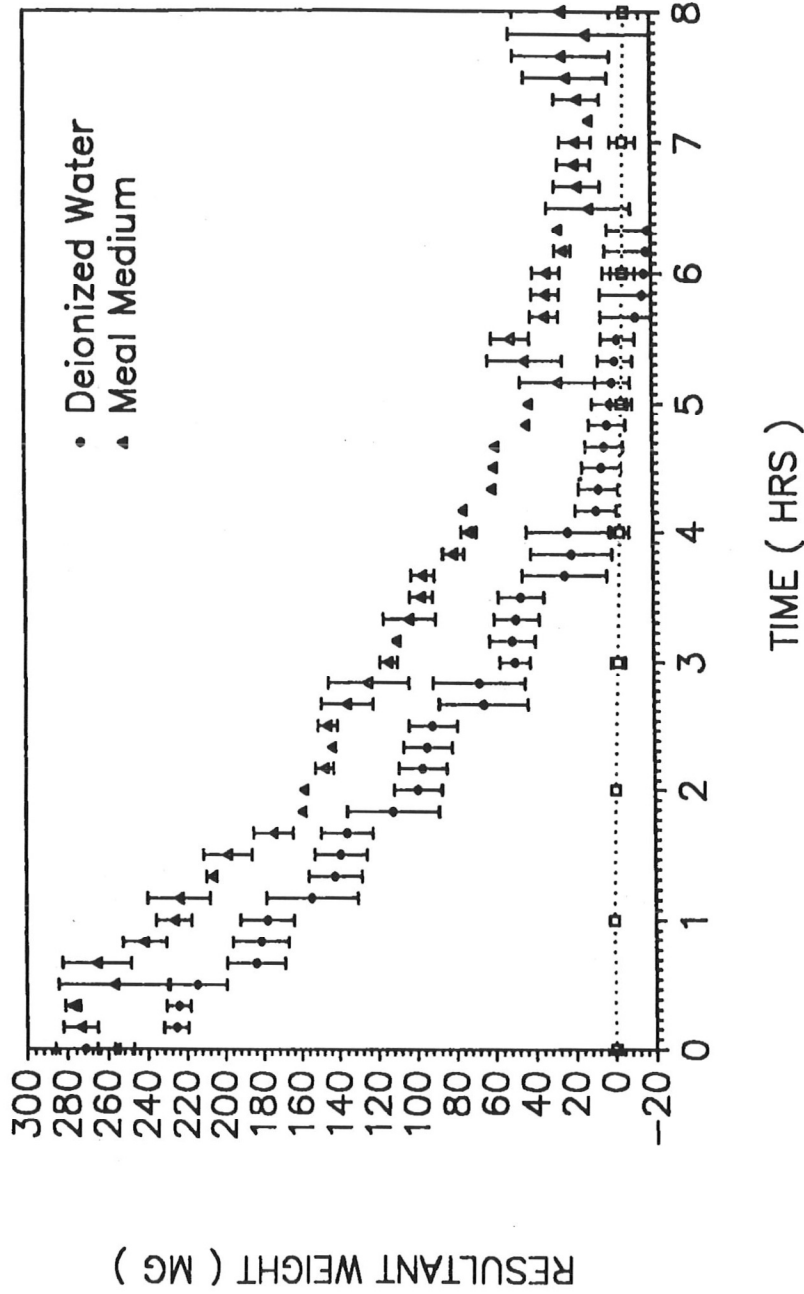


Figure 3: Resultant Weight measurements versus time for Methocel K 4M size 2 hard gelatin capsules in water and meal medium. Bars indicate SD. Dotted line represents baseline.



Table 1: Area Under the Curve (AUC) and Maximum Floating Time (MFT) derived from Resultant Weight measurements of dosage forms. Parentheses indicate SD.

| Dosage Form        | Medium | AUC (MG HR)    | MFT (HR)  |
|--------------------|--------|----------------|-----------|
| Methocel K 4M      | D.W.   | 487.9 (65.8)   | 5.1 (0.5) |
| Methocel K 4M      | S.M.M. | 844.7 ( 6.3)   | >8        |
| Methocel K 100M    | D.W.   | 716.2 (52.8)   | 6.9 (0.2) |
| Methocel K 100M    | S.M.M. | 1026.1 (102.0) | >8        |
| Methocel K 100M CR | D.W.   | 632.1 (44.2)   | 6.3 (0.9) |
| Methocel K 100M CR | S.M.M. | 620.1 (18.9)   | >8        |
| Methocel E 4M      | D.W.   | 624.8 (21.5)   | 6.1 (0.3) |
| Methocel E 4M      | S.M.M. | 739.1 (18.1)   | 7.2 (0.8) |
| Methocel E 10M CR  | D.W.   | 992.3 (15.7)   | >8        |
| Methocel F, 4M     | D.W.   | 692.1 (38.7)   | 7.9 (0.1) |
| CMC Na             | D.W.   | 456.8 ( 9.5)   | 6.1 (0.1) |
| HPC H              | D.W.   | 171.5 ( 9.8)   | 3.8 (0.2) |
| Noveon AA1         | D.W.   | 35.8 ( 0.5)    | 0.4 ( 0 ) |
| Polyox 750         | D.W.   | 115.1 ( 2.2)   | 1.7 (0.7) |
| Polyox 303         | D.W.   | 711.7 (36.0)   | >8        |
| Polyox 303         | S.M.M. | 1120.2 (64.0)  | >8        |
| Protanal LF 20/200 | D.W.   | 247.5 (17.7)   | 2.1 (0.2) |
| Protanal LF 120M   | D.W.   | 259.6 ( 2.0)   | 2.4 (0.5) |
| Protanal LF 120M   | S.M.M. | 286.1 ( 6.7)   | 4.5 (0.3) |
| Valrelease         | D.W.   | 439.9 (30.0)   | 7.9 (0.1) |
| Valrelease         | S.M.M. | 661.6 (20.2)   | >8        |

D.W. : Deionized Water  
S.M.M.: Simulated Meal Medium

Particularly, Methocel K 100M displays better floating capabilities compared to Methocel K 4M (46.7% greater AUC, 34.3% longer MFT). According to the product's information pamphlet (25), Methocel K 100M has greater Molecular Weight (MW) than Methocel K 4M. The same was observed in the case of Polyox polymers (Table 1). Polyox 303 (M.W. 7.000.000) shows 618.3% greater AUC and more than 479% longer MFT compared to Polyox 750 (M.W.: 300.000). From the above observations, it can be concluded that as the M.W. of these polymers increases, their floating characteristics are enhanced.

Chemical substitution of Methocel polymers seems to affect the floating characteristics as well. According to the product's information pamphlet (25) the differences in chemical substitution result in different rates of hydration. The lowest percentage of the hydrophobic substituent (methoxyl group) and the highest amount of hydrophilic (hydroxypropoxyl) substitution give to Methocel K series the fastest rate of hydration compared to E and F series. The findings displayed on Table 1 indicate that there might be some kind of correlation between the rate of hydration and floating characteristics among polymers of the same viscosity grade. Methocel K 4M, for instance, which has the fastest rate of hydration displays 21.9% smaller AUC and 16.4% shorter MFT compared to Methocel E 4M, which is the next fastest. Methocel K 4M also shows 29.5% and 35% smaller AUC and MFT values respectively when compared to F 4M, which has the slowest rate of hydration. It should be mentioned, however, that the above explanation contradicts with previously conducted research (26) which indicated that the rates of hydration between HPMC series are not significantly different.

From Table 1, it can be concluded that Methocel K 100M (90% passed through a 40 mesh screen) exhibits more than 13.3% longer MFT and 9.5% larger AUC compared to Methocel K 100MCR (99% passes through an 100 mesh screen). A similar effect of particle size is also observed in the case of sodium alginate. Protanal LF 120M (99% passes through 120 mesh screen) displays 10.1% and 32.3% larger AUC and MFT values respectively (Table 1) compared to Protanal LF 20/200 (99% passes through a 200 mesh screen). Although the polymer's particle size seems to have some effect on floating behavior, the differences were not found significantly different ( t test,  $p < 0.01$ ).

The floating behavior of the various dosage forms depends upon the medium used as well (Table 1). This has also been suggested by Timmermans et al (16,17,18). Dosage forms displayed larger AUCs and longer MFTs when immersed in SMM. The higher density of SMM compared to DW leads to higher buoyancy values for the same dosage form volume. Moreover, this effect may be attributed to the presence of fatty substances which delay water uptake. Excluding Methocel K 100M CR which showed similar AUC in both DW and SMM, the rest of excipients displayed an at least 10% higher AUC when immersed in SMM compared to DW. All excipients increased their MFT for at least 18% in SMM. It should also be mentioned that all members of Methocel K series under evaluation remained buoyant for more than 8 hours when the test medium was SMM.

Swelling measurements were performed separately in order to collect data on the weight increase of the various forms over time and also to examine if

there is any correlation with the previous findings on the floating behavior of excipients. Water Uptake (%) (Equation 2) data were plotted versus time (Figures 4, 5). The above graphs express the swelling behavior of a range of excipients both in DW and SMM. It should be pointed out that such data alone cannot provide accurate information on floating characteristics, which is depicted by the fact that dosage forms such as Polyox 303 and Valrelease, with radically different WU profiles, display both excellent floating behavior.

To investigate further the previous findings Buoyancy (B) has been also estimated. Based on Equation 1, B can be calculated by adding RW and the weight (W) of the dosage form at a specific time point. Both B and W data were plotted versus the square root of time. Then regression analysis was performed. In all cases, regression lines for B versus the square root of time displayed greater intercept and smaller slope values compared to W versus the square root of time lines. At the point where the regression lines of B and W cross each other, i.e. when B equals W, the dosage form starts sinking (Figure 6). Therefore, that point represents MFT, and, thus the above regression equations can be applied effectively in calculating mathematically MFT. Additionally, the volume (V) of a dosage form can be calculated by dividing B by the test medium density. Since the volume of orally administered dosage forms could influence GI residence time (27) the above measurements can be very useful. The calculated volumes at various time points of several dosage forms, after immersion in a specific medium, are shown in Table 2. According to this Table, Polyox 303 acquires after eight

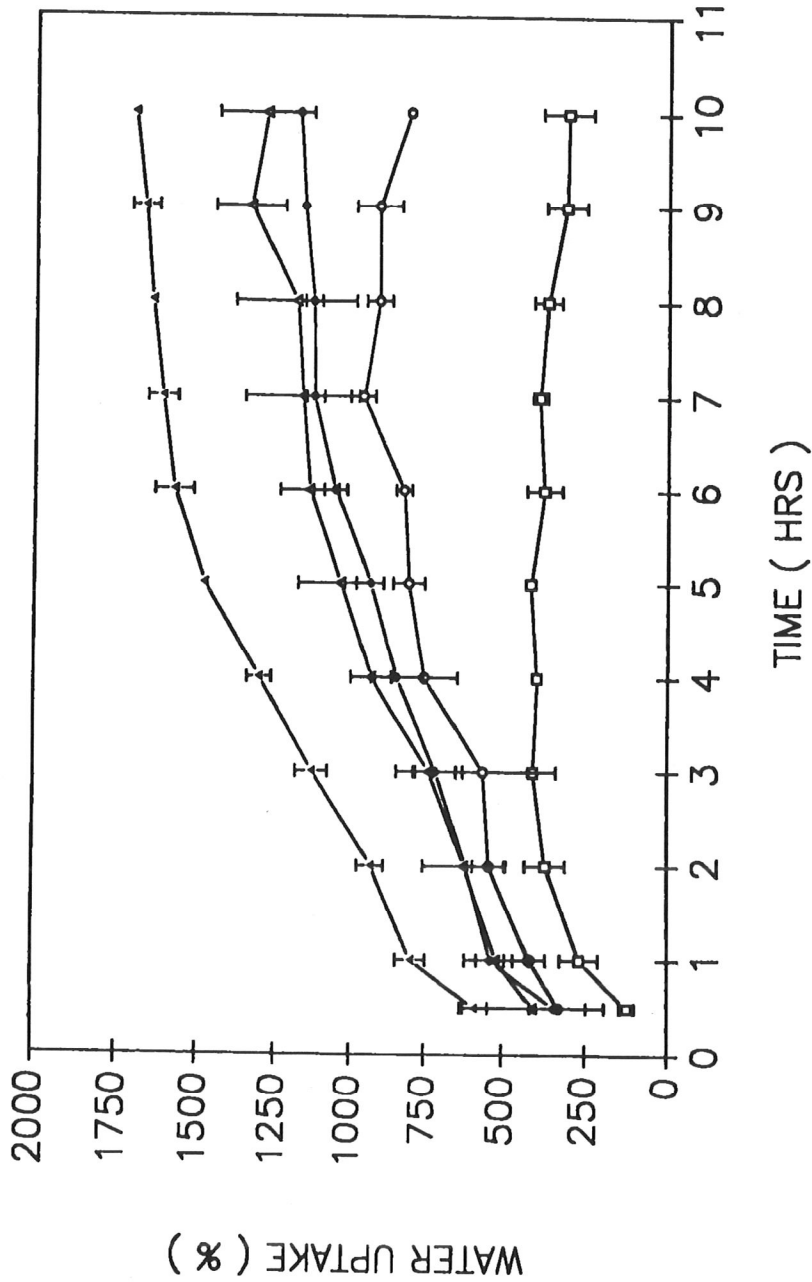


Figure 4: Water Uptake ( % ) for a series of excipients, filled in size 2 hard gelatin capsules, in deionized water. Bars indicate SD.  
 (•—•) Methocel K 4M, (◊—◊) Methocel K 100M, (▲—▲) Methocel K 100M cr, (◻—◻) Polyox 303, (▼—▼) Valrelease.

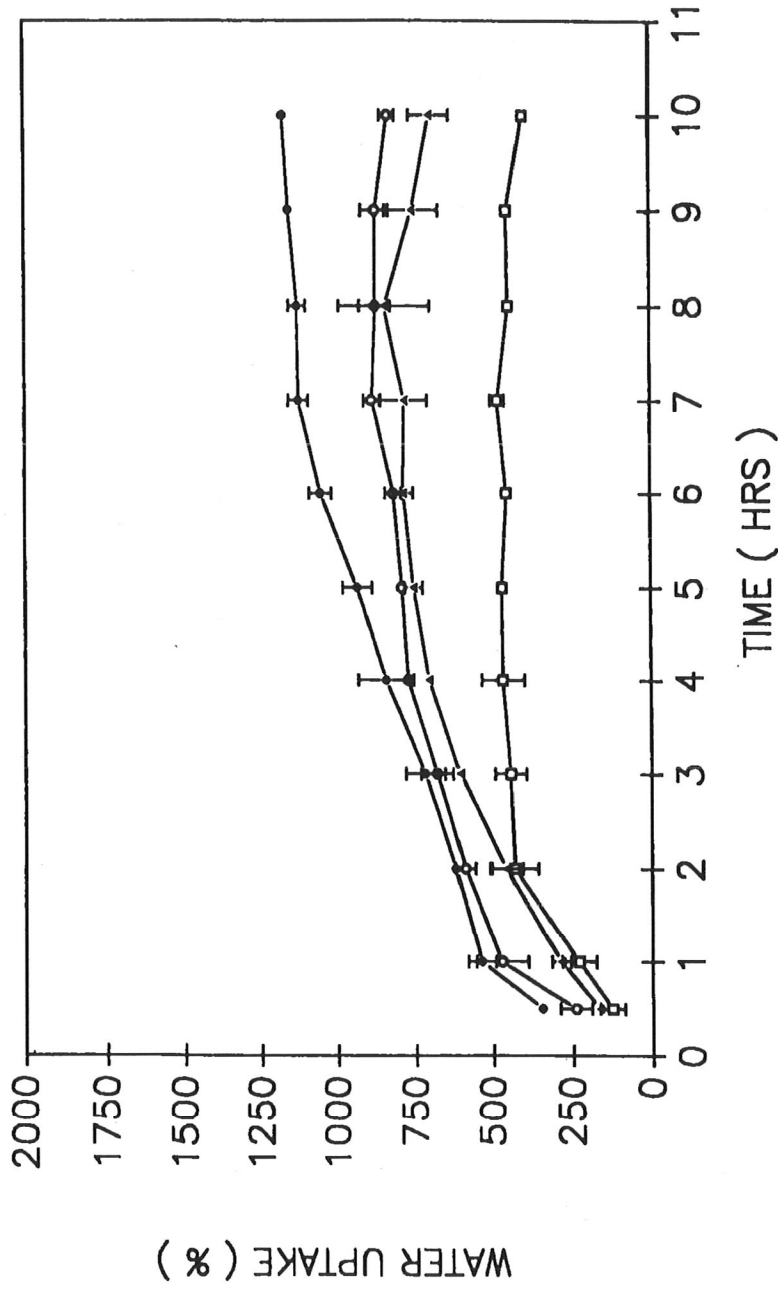


Figure 5: Water Uptake ( % ) for a series of excipients, filled in size 2 hard gelatin capsules, in meal medium. Bars indicate SD. (•—•) Methocel K 4M, (◦—◦) Methocel K 100M, (▲—▲) Polyox 303 and (◻—◻) Valrelease.

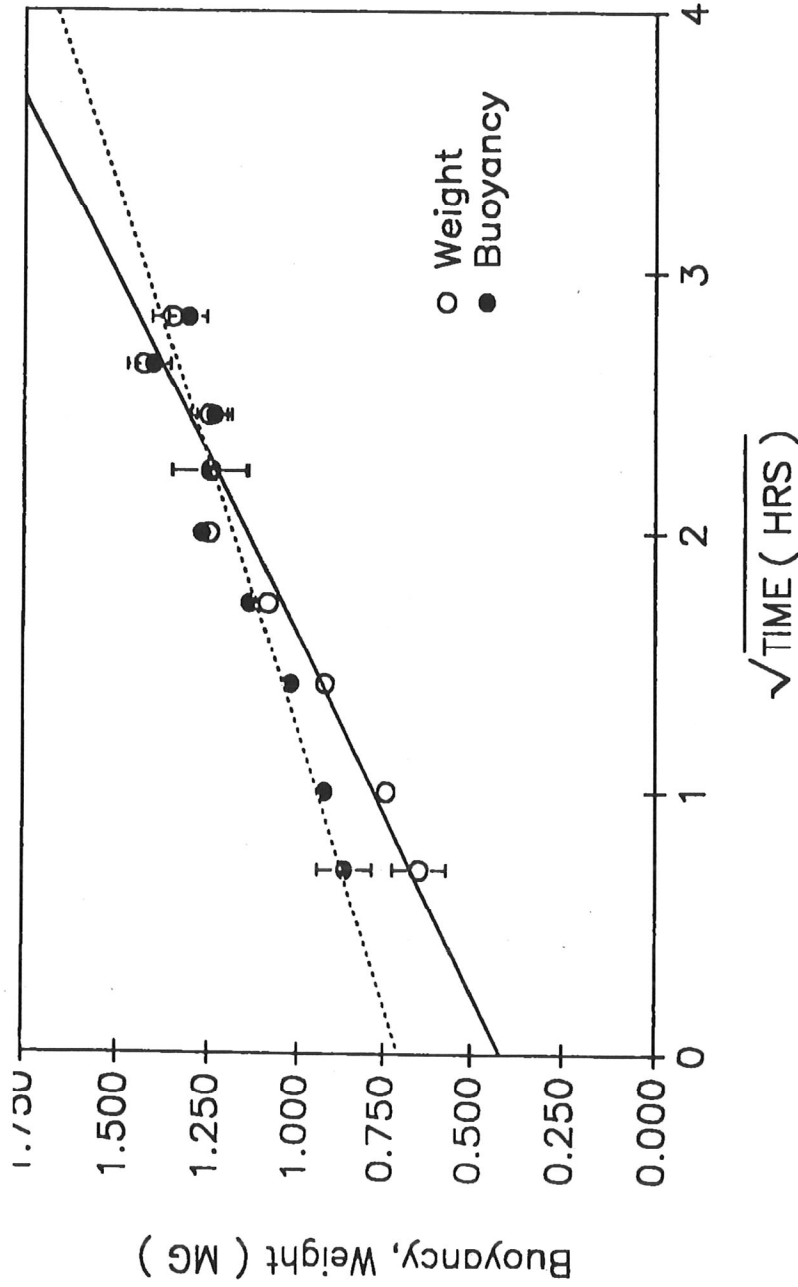


Figure 6: Buoyancy and Weight versus  $\sqrt{\text{time}}$  for Methocel K 4M size 2 hard gelatin capsules, in water. The continuous and dotted lines represent the regression lines for Buoyancy and Weight respectively. Bars indicate SD.

Table 2: Volume of several excipients filled in size 2 hard gelatin capsules after immersion in a particular medium. Bars indicate SD.

|                    |        | Volume (ML)   |               |               |
|--------------------|--------|---------------|---------------|---------------|
| Time (HR)          |        |               |               |               |
| Dosage Form        | Medium | 1.0           | 4.0           | 8.0           |
| Methocel K 4M      | D.W.   | 0.930 (0.014) | 1.275 (0.027) | 1.312 (0.055) |
| Methocel K 4M      | S.M.M. | 0.959 (0.074) | 1.201 (0.025) | 1.278 (0.122) |
| Methocel K 100M    | D.W.   | 0.969 (0.060) | 1.404 (0.068) | 1.864 (0.175) |
| Methocel K 100M CR | D.W.   | 1.170 (0.106) | 1.591 (0.059) | 1.979 (0.204) |
| Methocel K 100M CR | S.M.M. | 1.045 (0.050) | 1.333 (0.116) | 1.669 (0.064) |
| Methocel E 4M      | D.W.   | 1.002 (0.099) | 1.349 (0.083) | 1.521 (0.083) |
| Methocel E 4M      | S.M.M. | 1.205 (0.042) | 1.575 (0.147) | 1.482 (0.122) |
| Methocel E 10M CR  | D.W.   | 1.083 (0.057) | 1.983 (0.197) | 2.173 (0.279) |
| Methocel F 4M      | D.W.   | 1.013 (0.021) | 1.298 (0.113) | 1.317 (0.103) |
| Polyox 303         | D.W.   | 1.901 (0.054) | 2.812 (0.047) | 3.432 (0.084) |
| Polyox 303         | S.M.M. | 0.973 (0.070) | 1.710 (0.001) | 1.789 (0.125) |
| Valrelease         | D.W.   | 0.733 (0.058) | 1.425 (0.013) | 1.292 (0.124) |
| Valrelease         | S.M.M. | 1.043 (0.077) | 1.577 (0.176) | 1.477 (0.040) |

D.W. : Deionized Water  
S.M.M.: Simulated Meal Medium



Table 3: Slopes of the regression lines of Weight (Slope W) and Volume (Slope V) versus the square root of time, for excipients filled in size 2 hard gelatin capsules. Parentheses indicate SD.

| Dosage Form        | Medium | Slope W       | Slope V       | $\frac{\text{Slope W}}{\text{Slope V}}$ |
|--------------------|--------|---------------|---------------|---|
| Methocel K 4M      | D.W.   | 0.406 (0.079) | 0.287 (0.088) | 1.41                                    |
| Methocel K 4M      | S.M.M. | 0.371 (0.080) | 0.247 (0.084) | 1.50                                    |
| Methocel K 100M    | D.W.   | 0.591 (0.044) | 0.500 (0.707) | 1.18                                    |
| Methocel K 100M CR | D.W.   | 0.593 (0.042) | 0.477 (0.039) | 1.24                                    |
| Methocel K 100M CR | S.M.M. | 0.523 (0.053) | 0.401 (0.052) | 1.30                                    |
| Methocel E 4M      | D.W.   | 0.482 (0.033) | 0.353 (0.018) | 1.36                                    |
| Methocel E 4M      | S.M.M. | 0.359 (0.027) | 0.221 (0.016) | 1.63                                    |
| Methocel E 10M CR  | D.W.   | 0.706 (0.242) | 0.626 (0.243) | 1.13                                    |
| Polyox 303         | D.W.   | 1.016 (0.089) | 0.967 (0.093) | 1.05                                    |
| Polyox 303         | S.M.M. | 0.648 (0.057) | 0.547 (0.051) | 1.18                                    |

D.W. : Deionized Water  
S.M.M.: Simulated Meal Medium

hours of immersion in DW the larger V, 8.7 times greater compared to its initial V. Moreover, the measurement of V helps identifying which of the two processes -weight gain or volume expansion- is more important for a particular excipient. For that purpose, W and V were plotted versus the square root of time and regression analysis was performed for the first eight hours. The slopes of these regression lines, for some of the excipients used, are shown

in Table 3. In all cases, the slopes of W increase versus the square root of time were larger than those of V increase. The slower rate of V increase compared to W increase indicates that after a particular time point, V expansion can not generate a buoyancy force substantial enough to counteract W increases. It should also be mentioned that the slopes of both W and V are decreased in SMM compared to DW. In order to investigate further the above findings, the ratio of the slope of W over the slope of V ( $\text{slopeW}/\text{slopeV}$ ), versus the root of time was calculated. This ratio seems to correlate with the floating behavior of the excipients. More specifically, the lower the value of the ratio, the better the floating characteristics. As a consequence, the floating behavior of an excipient can be predicted by monitoring W and V over a time period.

### **CONCLUSION**

Resultant Weight measurements of excipients, widely used in controlled release technology, show that higher molecular weight polymers and slower rates of polymer hydration are usually followed by enhanced floating behavior. Therefore, the selection of high molecular weight and less hydrophilic grades of polymers seem to improve floating characteristics. The floating behavior of all evaluated excipients was enhanced when simulated meal medium was used instead of distilled water. The resultant weight measurements combined with swelling experiments can be used to determine in vitro the buoyancy and volume changes versus time of various orally administered dosage forms. The

slopes of weight, volume and buoyancy of dosage forms versus the square root of time provide important information on their behavior, when immersed in a specific medium, and can be effectively applied to predict floating behavior.

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