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Effect of hydroxypropyl cellulose (HPC) on dissolution rate of hydrochlorothiazide tablets

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Abstract

Hydrochlorothiazide (HCTZ) 60 mg strength tablets containing commonly used excipients and hydroxypropyl cellulose, marketed as either Klucel-EF (HPC, NF from Hercules, USA) or HPC-L (HPC, NF from Nippon Soda, Japan), as a binder were manufactured using identical aqueous wet granulation process. The tablets containing Klucel-EF as a binder exhibited higher dissolution rates than those manufactured using HPC-L. The granulations containing Klucel-EF or HPC-L showed no significant differences in compressibility and compactibility based on analysis performed using the Instron-Stress–Strain Analyzer. Both HPC grades met NF specifications and there were no differences for the NF test results in the certificates of analysis by their respective vendors. Further evaluation of both HPC grades indicated that the cloud point values for Klucel-EF and HPC-L in water were 39(±1) and 48 °C, respectively. The differences in cloud points of Klucel-EF and HPC-L were correlated to the differences in the percent hydroxypropoxy content and the degree of molecular substitution, which were higher for Klucel-EF than for HPC-L. These structural features make Klucel-EF less hydrophilic. Since the cloud point of Klucel-EF was similar to the dissolution medium temperature of 37(±2) °C, it may present a less viscous layer surrounding the HCTZ granules enabling faster dissolution of the drug.

Keywords: Hydroxypropyl cellulose; HPC; Dissolution; Binder; Hydroxypropoxy substitution; Cloud point; Excipient

1. Introduction

Hydroxypropyl cellulose (HPC) is a commonly used binder for the wet granulation method of making tablets. During the development of 60 mg strength hydrochlorothiazide (HCTZ) tablets, it was observed that tablets manufactured using Klucel-EF (HPC from Hercules, USA) exhibited a higher dissolution rate than those manufactured using HPC-L (HPC, from Nippon Soda, Japan). The difference in the dissolution was a concern in light of a commercial need to manufacture the product in different manufacturing plants worldwide using excipients from local sources. Furthermore, there was a concern that if the cause of the difference in dissolution was not identified, even different lots from a same vendor might yield a product with a variable dissolution.

HPC from both vendors met the NF criteria and there was no significant difference in average molecular weight of the HPC sourced from both vendors. Therefore, an investigation was conducted to determine the factor(s) responsible for the difference in dissolution and if possible, to propose a functionality test for HPC so that tablets with reproducible dissolution can be manufactured using HPC from either vendor.

2. Materials and methods

2.1. Materials

The following ingredients were used as received from the suppliers: Hydrochlorothiazide USP (Profarmaco, New York), Lactose Monohydrate NF (Foremost Farms, Baraboo, WI), Corn Starch NF (National Starch and Chemical Co., Bridgewater, NJ), Hydroxypropyl Cellulose NF (Klucel-EF, Hercules, USA

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and HPC-L, Nippon Soda, Japan), Magnesium Stearate NF (Mallinckrodt, St. Louis, MO).

2.2. Methods

2.2.1. Manufacture of tablets

The tablet formulation contained HCTZ, lactose hydrous, HPC, corn starch and magnesium stearate. HCTZ, lactose and corn starch were mixed for about 5 min in a Glatt (GPCG-1) fluid bed granulator and wet granulated using 5% (w/v) HPC solution as a binder in the same equipment at about 75 °C. The batch size was 1.9 kg, which required about 800 g of granulating liquid. The granules were dried in the same fluid bed granulator at about 80–90 °C to 2% (w/w) residual moisture (measured by LOD). The dried granules were milled using a Comil® fitted with 1.2 mm screen and mixed with about 1% (w/w) magnesium stearate in a V-blender for 5 min at 25 rpm speed. The blend was compressed into 60 mg strength tablets weighing 380 mg.

2.2.2. Compaction characteristics of the blends

Tablets were prepared by hand filling the die and compressing with an Instron-Stress–Strain Analyzer. This facilitated control of porosity or solid fraction. Compressibility (Heckel analysis) and compactibility analysis for the two granulations were performed by calculating the extent of volume reduction and gain in tablet strength over a compression pressure range.

2.2.3. Dissolution studies

Dissolution of the tablets ($n = 6$) was conducted in 900 mL 0.1N HCl (pH 1) at 37 °C using the USP apparatus II at 50 rpm paddle speed (Distek Dissolution System, model 5100). The amount of HCTZ dissolved was monitored using a UV spectrophotometer (Hewlett Packard 8453) at wavelength 272 nm. After the 60 min time point, the paddle speed was increased to 100 rpm.

2.3. Characterization of HPC

2.3.1. Cloud point determinations

The HPC solutions were prepared by dissolving 1 g of HPC in 100 mL water or other suitable medium at room temperature. The HPC solutions were clear at room temperature. The Nephelometer (Model 21, Monitek, Hayward, CA) was calibrated using the standards provided by the company. Following the calibration, the HPC solutions were filled into 30 mL vials (supplied by Monitek) at 90% fill and placed in a water bath set at a desired temperature (32–52 °C). The time required for equilibration was 10 min. Each vial was taken out quickly from the water bath and the water was wiped from outside and immediately placed in the Nephelometer. The turbidity reading was recorded. The vial was then placed back into the water bath for equilibration at the next temperature. The water bath temperature was increased gradually until all solutions became turbid. The temperature increment was 2 °C in the beginning and 1 °C as the solution started to show slight turbidity.

2.4. Molecular weight distribution for HPC

Analysis was performed on an Agilent 1100 liquid chromatograph equipped with a refractive index detector. Three columns of TSK-Gel GMPWXL 7.8 mm × 30 cm and one of TSK-Gel G3000PWXL 7.8 mm × 30 cm 6 μm were connected in series from the HPLC pump to the detector. Column flow was constant at 1.0 mL/min with a run time of 75 min. Injection volume was 100 μL. Mobile phase consisted of 0.05 M lithium acetate, pH 4.8. Samples were diluted in the mobile phase containing 1 μL/mL of THF as a marker. Samples were shaken overnight and filtered before analysis. Molecular weight (Mp) of the standards used ranged from 106 to 1,215,000 and in concentrations of 0.4–1 mg/mL.

2.5. Assay for hydroxypropoxy groups

The assay for hydroxypropoxy groups was performed by the USP method (USP 28/NF 23, pp. 3017–3019).

2.6. ^{13}C NMR studies

The ^{13}C NMR spectrum was recorded using a Jeol 400 MHz Eclipse NMR with the pertinent parameters used as follows: 110.54 MHz spectrometer frequency, 2048 transients, 25183 Hz sweep width, 25 °C sample temperature and 32768 points collected. The NMR samples were prepared at a concentration of 100 mg/mL in D_2O. The samples were mixed using a stir bar for at least 6 h to give a homogeneous solution.

3. Results and discussion

As shown in Figs. 1 and 2, HCTZ tablets manufactured using two different lots of Klucel-EF showed faster dissolution than those manufactured using two different lots of HPC-L. The difference was most striking at 20 and 30 min sampling time points and of a concern since these time points are routinely used to set regulatory specifications. The content uniformity and potency data were similar (not shown). As shown in the Figs. 1 and 2, all the drug was released from the tablets when the paddle speed was increased to 100 rpm after the 60 min time point. This indicated that the tablets contained the desired amount of HCTZ,

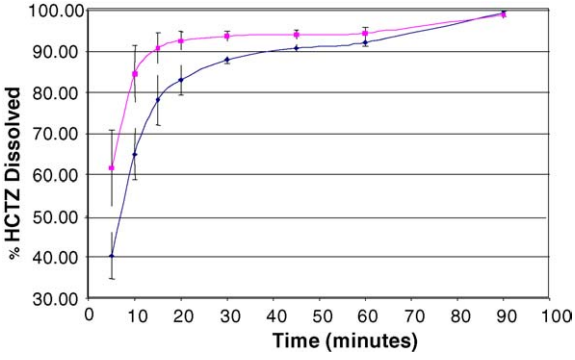

Fig. 1. Dissolution of 60 mg HCTZ tablets made with HPC from Nippon Soda (HPC-L) (♦) lot NBC 0121 and Hercules (Klucel-EF) (■) lot 9150.

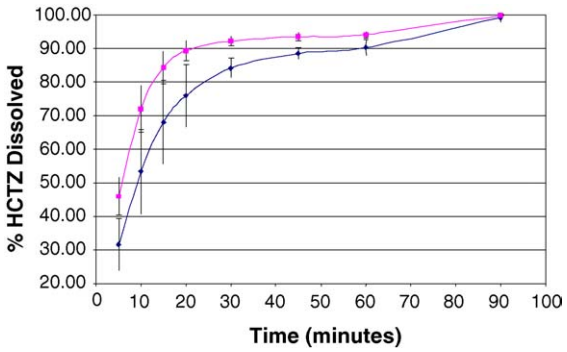

Fig. 2. Dissolution of 60 mg HCTZ tablets made with HPC from Nippon Soda (HPC-L) (♦) lot NJL 1621 and Hercules (Klucel-EF) (■) lot 8210.

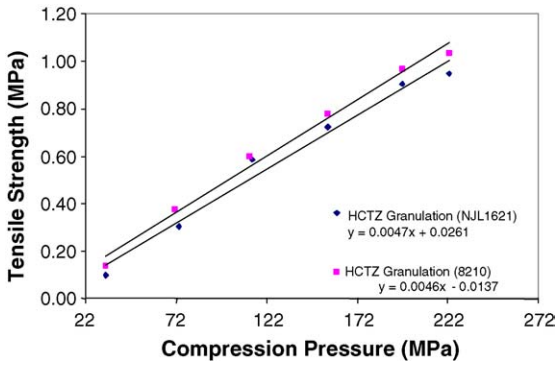

Fig. 4. Compactibility of HCTZ granules prepared using KLucel-EF (lot 8210) and HPC-L (lot NJL 1621) as binders.

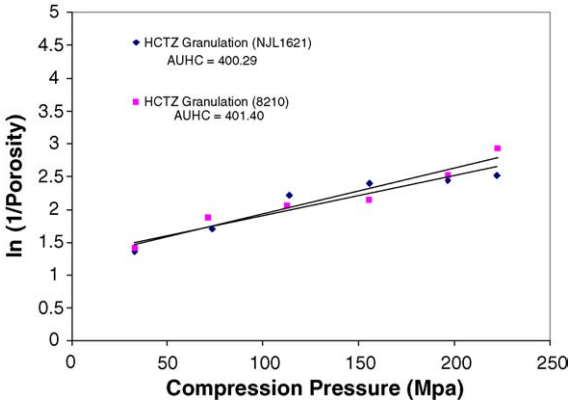

Fig. 3. Compressibility based on Heckel plot of HCTZ granules prepared using Klucel-EF (lot 8210) and HPC-L (lot NJL 1621) as binders.

however the tablets manufactured using HPC-L dissolved more slowly.

The differences in dissolution cannot be attributed to differences in tablet tensile strengths since the tablets manufactured using both binders were compressed at similar tensile strengths. Further analysis of the final blend was performed using the Instron-Stress–Strain Analyzer. Since tablets were prepared by hand filling the die, the differences in granulation flow as a variable was eliminated. Moreover, there was a better control over tablet porosity or solid fraction. As shown in Figs. 3 and 4, compressibility (Heckel analysis) and compactibility analysis for the two granulations were performed. The Area Under Heckel Curve (AUHC) values for the two HCTZ tablet granulations were 400.29 and 401.40 MPa, indicating that the compressibility was similar (Fig. 3). Compactibility of the two batches of HCTZ granulations was also similar, as indicated by the slopes (0.0046 and 0.0047) of the compression force versus tensile strength plot shown in Fig. 4. These results confirmed that the differences in the dissolution rate of tablets cannot be attributed to the tableting operation or physical properties of the granules.

Table 1 shows analytical test results for lots of HPC from both sources. For a given vendor, there was minimal lot to lot variability. The average molecular weight determination using three different media showed that the differences in molecular weight were not significant. No relationship between average molecular weight and cloud points was observed or reported in the literature (Table 1) (Klug, 1971).

The cloud point data on the HPC lots sourced from both vendors are given in Table 1 and Fig. 5. The Klucel-EF lots had 7–9 °C lower cloud point than the HPC-L lots. The cloud point was suppressed slightly in the acidic solution as shown in Fig. 5. For both HPC sources, the cloud points were very consistent for different lots as shown in Table 1. Interestingly, the hydroxypropoxy content of the Klucel-EF lots was about 10% higher than that of the HPC-L lots (Table 1) indicating a higher degree of molecular substitution based on the relationship

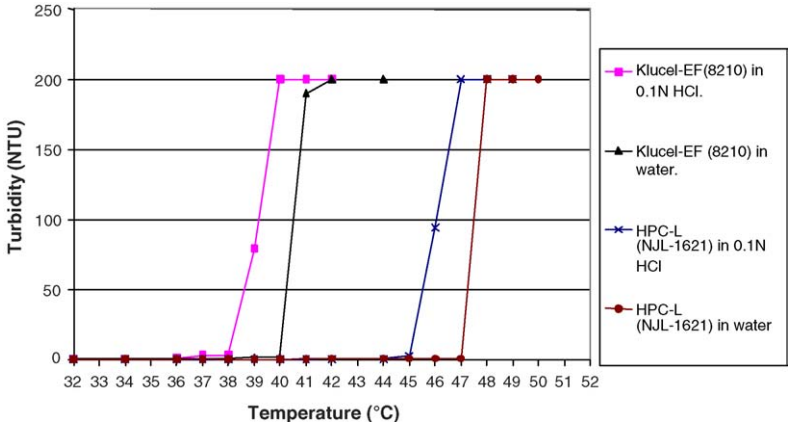

Fig. 5. Cloud point of 1% (w/v) HPC solutions.

Table 1
Properties of various Klucel-EF and HPC-L lots sourced from Hercules and Nippon Soda, respectively

HPC type (source)	Lot number	Hydroxypropoxy group (%) CoA	Molecular substitution (M.S.)	Ratio: outer methyl + single methyl to inner methyl	Molecular weight (weight average)[a], MW at peak max.[b]		Cloud point in water (°C)
					Mobile phase	pH 1.2	pH 4.0	
Klucel-EF (Hercules)	1108	74.4	3.8	1.0	144,000, 62,000	198,000, 60,000	193,000, 58,000	39
	8508	73.4	3.7	1.0	95,000, 57,000	151,000, 60,000	151,000, 59,000	39
	9150	72.8	3.6	1.0	135,000, 97,000	141,000, 70,000	140,000, 67,000	39
	9878	74.4	3.8					39
	8870	71.9	3.5	1.0				39
	9945	74.4	3.8					39
	8210	73.9	3.7					40
HPC-L (Nippon Soda)	NBC-0121	64.3	2.8	1.2				48
	NJL-1621	66.6	3.0	1.2	179,000, 96,000	164,000, 95,000	157,000, 95,000	48

[a] Weight average of molecular weight.
[b] Molecular weight at the peak maximum.

Fig. 6. Relationship between percent hydroxypropoxy and molecular substitution (From the USP 25/NF 20, pp. 2564–2565).

depicted in Fig. 6 (USP 28/NF 23, pp. 3017–3019). Since Klucel-EF had a relatively higher hydroxypropoxy content and higher degree of molecular substitution, it was less hydrophilic and had a lower cloud point in water. The relationship between molecular substitution and cloud point has been well established (Klug, 1971).

The cloud point data, hydroxypropoxy content and molecular substitution are not sufficient to describe the molecular state of the HPC. For instance, the molecular substitution value (Table 1) does not allow for the many substitution isomers to be distinguished. In order to describe the above-mentioned properties at the molecular level, ^{13}C NMR was used to arrive at a schematic for the substitution differences in the HPC-L and Klucel-EF. The structure for hydroxypropyl cellulose with an ideal distribution of hydroxypropoxy units is shown in Fig. 7. A representative ^{13}C NMR spectrum of HPC-L (lot NBC-0121) is shown in Fig. 8. The most down-field resonances are assigned to the methyls from single or outer most hydroxypropoxy units, whereas the more up-field resonances are assigned to the methyls from interior or inner hydroxypropoxy units (Lee and Perlin, 1982). This assignment is consistent with a more down-field shift for the single and outer hydroxypropoxy units owing to the vicinal terminal hydroxyls group as opposed to an ether linkage for the inner hydroxypropoxy units. The previously assigned resonances can be integrated as total down-field/total up-field resonances as shown in Fig. 8. This ratio gives the total moles of outer plus single hydroxypropoxy units relative to the total moles of inner hydroxypropoxy units. The definition of inner outer and single hydroxypropoxy units is shown in Fig. 7.

In order to construct a schematic of the substitution of hydroxypropoxy groups, the molecular substitution (Table 1) and the above-mentioned ratio have been incorporated. Using the molecular substitution to constrain the number of total moles of outer plus single hydroxypropoxy units relative to the total moles of inner hydroxypropoxy units, one can mathematically arrive at an approximate distribution of total moles of outer plus single hydroxypropoxy units relative to the total moles of inner hydroxypropoxy units that are consistent with both the NMR and molecular substitution data. For instance, using the HPC-L schematic (Fig. 9) one can envision two main distributions of HPC that fit the NMR calculated ratio of 1.2 outer plus single to inner total

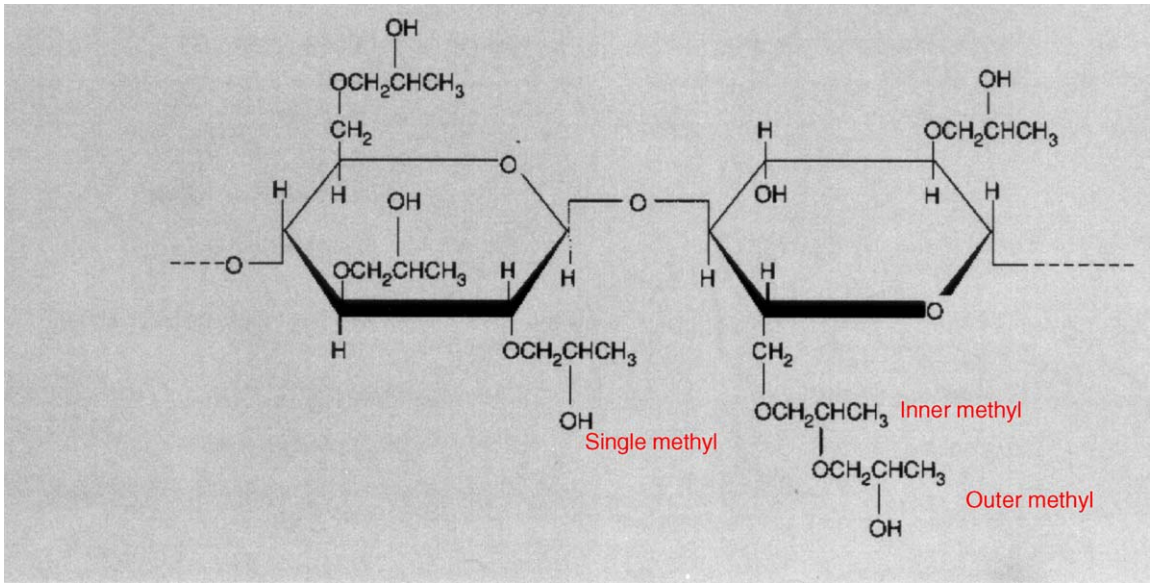

Fig. 7. Structure of hydroxypropyl cellulose (M.S. = 3.0).

moles of outer plus single hydroxypropoxy units relative to the total moles of inner hydroxypropoxy units: approximately 45% giving a ratio of 1/2 outer plus single/inner hydroxypropoxy units (top HPC-L schematic) and approximately 45% giving a ratio of 2/1 outer plus single/inner hydroxypropoxy units (Middle HPC-L schematic). Both distributions have a molecular substitution of three, yet the degree of branching consistent with the NMR data give rise to very different molecular entities and different properties. For instance, the species in the top HPC-L schematic would impart more hydrophilic properties due to less hydroxyl substitution compared to the other two distributions, giving rise to the higher cloud point for the HPC-L material. Likewise, the Klucel-EF material would give rise to a less hydrophilic material, due to more hydroxyl substitution that is consistent with the cloud point data. This information would be hidden in the bulk data, such as cloud point, hydroxypropoxy group percentage, and the molecular weight. Combining the bulk data with molecule specific data (NMR), one can construct a molecular schematic which can explain the experimental results.

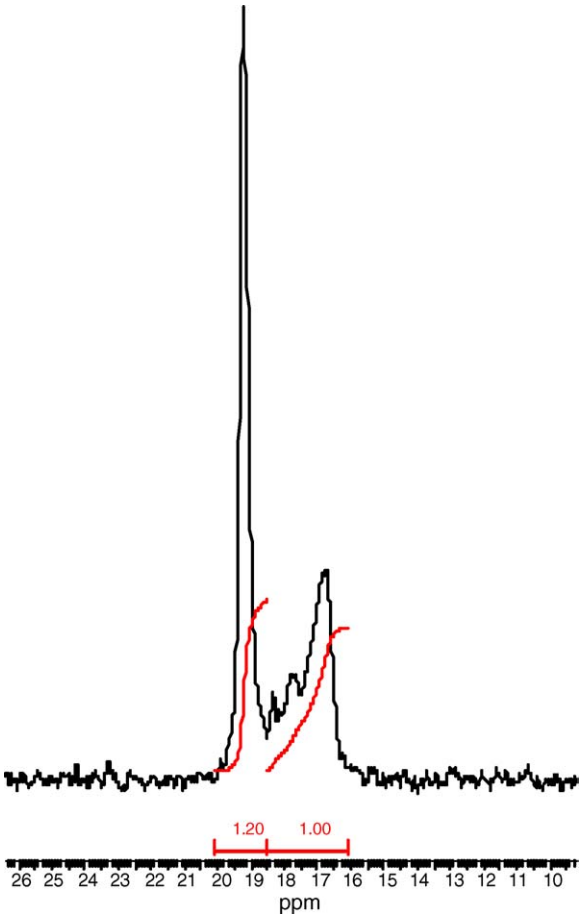

Fig. 8. ^{13}C NMR data on HPC-L lot NBC-0121. Outer + single HPC methyl singlet higher ppm. Inner HPC methyls all the rest. Ratio (outer + single)/(inner).

The schematic (Fig. 9) allows for the relationship between the HPC structure and performance to be drawn. The Klucel-EF material is composed mostly of a more hydroxypropoxy substituted cellulose compared to the HPC-L material. Also, the Klucel-EF material is mostly composed of species which are more substituted (higher hydroxypropoxy content) and less branched than HPC-L. This explains the reduced cloud point of the Klucel-EF (about 39 °C). It is interesting that the cloud point is closer to the temperature of the dissolution medium (37 ± 2 °C). At this temperature the Klucel-EF is likely to phase separate from the dissolution medium and could present a less viscous layer surrounding the HCTZ granules (Stafford et al., 1978). The less viscous layer surrounding the HCTZ granules would enable them to dissolve faster than those containing HPC-L.

Although HPC from both sources met the NF criteria of not more than 80.5% of hydroxypropoxy content, the HPC from both sources differed not only in hydroxypropoxy content and molecular substitution, but also in the degree of branching.

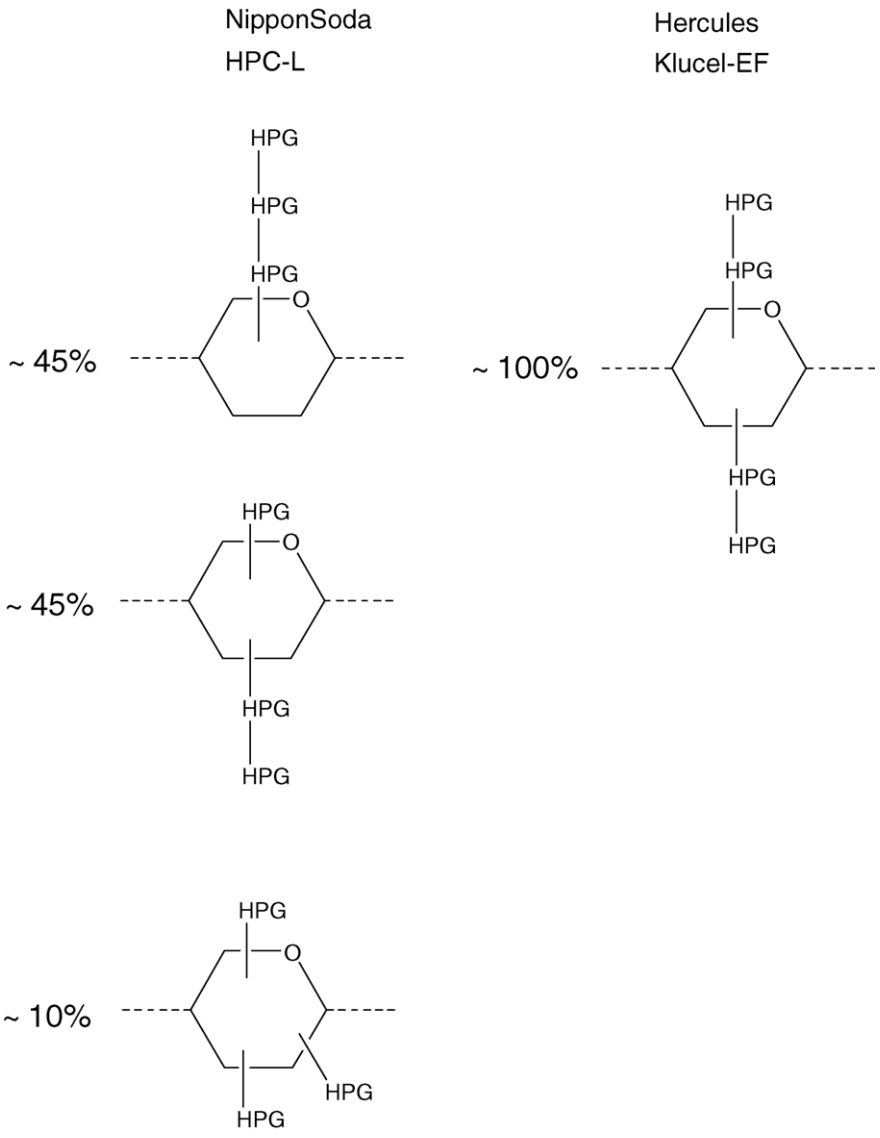

Fig. 9. A schematic of hydroxypropoxy group (HPG) substitution in HPC. The percentage hydroxypropoxy incorporation and the ^{13}C NMR data were used to derive this schematic. Using the two data sets, one can describe the degree of branching as defined by the amount of hydroxypropoxy group substitution on other than the cellulose moiety. Note that the HPC-L contains a larger percentage of highly branched material (top) than that of the Klucel-EF material.

4. Conclusion

Despite the fact that HPC from two different sources met the NF criteria, its performance in tablet formulation was different. In light of such experiences, more emphasis should be given to establishing functional criteria for excipients. In the case of HPC, a cloud point test can be easily performed even as a routine quality control tool. If functional criteria are established where feasible, it will be easier to qualify alternate vendors for excipients.

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