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Research Article

A Study on the Impact of Hydroxypropyl Methylcellulose on the Viscosity of PEG Melt Suspensions Using Surface Plots and Principal Component Analysis

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Abstract. An understanding of the rheological behaviour of polymer melt suspensions is crucial in pharmaceutical manufacturing, especially when processed by spray congealing or melt extruding. However, a detailed comparison of the viscosities at each and every temperature and concentration between the various grades of adjuvants in the formulation will be tedious and time-consuming. Therefore, the statistical method, principal component analysis (PCA), was explored in this study. The composite formulations comprising polyethylene glycol (PEG) 3350 and hydroxypropyl methylcellulose (HPMC) of ten different grades (K100 LV, K4M, K15M, K100M, E15 LV, E50 LV, E4M, F50 LV, F4M and Methocel VLV) at various concentrations were prepared and their viscosities at different temperatures determined. Surface plots showed that concentration of HPMC had a greater effect on the viscosity compared to temperature. Particle size and size distribution of HPMC played an important role in the viscosity of melt suspensions. Smaller particles led to a greater viscosity than larger particles. PCA was used to evaluate formulations of different viscosities. The complex viscosity profiles of the various formulations containing HPMC were successfully classified into three clusters of low, moderate and high viscosity. Formulations within each group showed similar viscosities despite differences in grade or concentration of HPMC. Formulations in the low viscosity cluster were found to be sprayable. PCA was able to differentiate the complex viscosity profiles of different formulations containing HPMC in an efficient and time-saving manner and provided an excellent visualisation of the data.

KEY WORDS: hydroxypropyl methylcellulose; polymers; principal component analysis; surface plot; viscosity.

INTRODUCTION

Polymer rheology plays a crucial role in polymer processing and polymer manufacturing. In recent years, there has been increasing interest in the study of polymer systems rheology, whether in the form of solutions or melts (1). Many pharmaceutical processes such as hot melt extrusion (2–5) and spray congealing (6–8) and products such as solid dispersions (9,10), suppositories (11) and pessaries utilize polymer melts. The rheological properties of polymer melts in these processes, if uncontrolled, may lead to a blockage or high backpressure in the extrusion system, clogging of the spray delivery system or inadequate filling of melts into moulds, which often necessitate the termination of the process. As such, an understanding of the rheological behaviour of these melts has become increasingly important for successful process development and formulation of the desired product (12,13). Although polymers have been studied over the years, polymer rheology is a difficult subject to comprehend (1). Most pharmaceutical formulations have multi-components, such as matrix materials, additives and active pharmaceutical ingredients, and they collectively make the rheological profile of composite polymer melt suspensions complex and difficult to classify.

Celluloses such as hydroxypropyl methylcellulose (HPMC) are used in many pharmaceutical applications as sustained release agents, tablet binders, suspending agents, thickening agents, viscosity-increasing agents and film-coating (14). They exist in different viscosity grades, containing different percentages of methyl and hydroxypropyl substitutions (15). The differences in the substituent contents affect the viscosity of the HPMC solution. In polymer melt suspensions, different HPMC grades affect the viscosity to various extents when different concentrations and/or temperatures are used. Furthermore, batch to batch variations of HPMC exist and can potentially alter the rheological properties of the polymer melt suspensions, necessitating readjustment of process parameters during manufacturing to achieve the desired final product. Therefore, it is important to study the effects of both concentration and temperature on the viscosity of melt suspensions holistically by the use of surface plots. A good understanding of the viscosity profiles of changing concentrations and grades of HPMC in molten polyethylene glycol (PEG) enables greater accuracy in predicting potential processing and formulation problems. This would lead to potential cost savings for manufacturers.

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Viscosity data are typically analysed by comparing single points of different formulations or observing plotted viscosity graphs for trends. Even though these techniques are useful for extracting information from the different viscosity profiles, it may be increasingly complex and time-consuming when many formulations are involved and the plots overlap with one another. Conventional statistical method, such as analysis of variance (ANOVA), allows the comparison of each data point to other points at a particular temperature. However, such method is unable to consider the whole curve and provide a fair comparison over a temperature range. Therefore, to further distinguish the viscosities of the composite polymer melt suspensions, multivariate analysis may be the best approach. Multivariate or chemometric analysis has been increasingly used in different pharmaceutical applications to process data which are usually large and too complex to be easily interpreted (16). One of such method is principal component analysis (PCA) which allows the visualisation of the most important information contained in the data set (17). Principal component analysis has been applied in the pharmaceutical industry to detect differences in production batches when process parameters changed (18), evaluate characteristics of excipients (19,20) and assess effects of formulation parameters on granule and tablet properties (21,22) and in the non-pharmaceutical industries (23–25). However, to the authors' knowledge, PCA has not been applied to evaluate the viscosity of polymer melt suspensions. The use of PCA as a tool for rapid viscosity screening of composite formulations allows for potentially better control of parameters during manufacturing, resulting in improved process robustness and less product variation from batch to batch.

The viscosity of polymer melt suspensions can be expressed by Einstein's equation where the resultant viscosity (η) is a function of the viscosity of the suspending liquid or molten polymer (η°), Einstein coefficient (k_E) and volume fraction of suspended particles (ϕ) (26):

$$\eta = \eta^\circ(1 + k_\mathrm{E}\phi) \qquad (1)$$

The Einstein coefficient depends on the geometry and orientation of the entities that make up the dispersed phase, *e.g.* fibres and other non-spherical particles. In this study, the viscosity of the composite polymer melt suspension can be variable given that fibrous HPMC particles can have assorted orientations in the molten polymer. Therefore, to ensure a higher productivity rate and a product of consistent quality, it is essential to employ an analytical tool capable of evaluating the viscosities of polymer melt suspensions.

To date, very few studies have been carried out to understand the influence of HPMC on the rheology of PEG melts. As polymer melt suspension viscosity is also dictated by the volume of suspended particles (Eq. 1), it is of interest to investigate the changes in viscosity with various concentrations of HPMC of different grades. In the present study, the influence of ten different grades of HPMC at various concentrations on the viscosity of PEG melt suspension at different temperatures was evaluated using surface plots. Metronidazole (MNZ) was included as the model drug, as most pharmaceutical formulations contain at least one active pharmaceutical ingredient. The suitability of PCA as an analytical tool was assessed before its application to differentiate the different viscosities of the polymer melt suspensions. This study provided insights on the effects of HPMC concentration and process temperature on viscosity of PEG melt suspensions and the application of PCA as a method for the fast classification of formulation viscosity.

MATERIALS AND METHODS

Materials

Metronidazole (BP grade), a yellowish crystalline powder, was obtained from Sunward Pharmaceutical, Singapore. Polyethylene glycol (PEG; MW 3350) was supplied by Clariant, Sulzbach, Germany. Ten different grades of HPMC from four different series and HPMC K15M of various mesh size fractions were obtained from Dow Chemical (Michigan, USA) (Table I). In the nomenclature of HPMC grades, an initial letter (K, E, F) identifies the different substitutions of methoxyl and hydroxypropyl groups in the polymer. The number following the letter identifies the viscosities in millipascal seconds of that grade measured at 2% concentration in water at 20°C (15). The letter "M" is used to represent 1,000 while "LV" refers to low viscosity. A special grade of Methocel VLV, developed for coating purposes, was also included in this study.

Preparation of Molten Mixtures

An appropriate amount of PEG was weighed in a glass beaker and heated in an oven (UL 40, Memmert, Schwabach, Germany) at 70°C to form a melt to which HPMC and/or MNZ was added. The mixture was stirred to obtain a homogeneous dispersion. Both HPMC and MNZ were poorly soluble in molten PEG and existed predominantly as dispersed particles in the polymer melt.

Table I. Properties of the Various Grades of HPMC and Their Corresponding Codes Represented in PCA

HPMC grades	Methoxyl substituent (%)	Hydroxypropyl substituent (%)	Nominal viscosity (mPa·s)	Codes in PCA[a]
K-series				
K100M	22	8.1	100,000	xKa
K15M	22	8.1	15,000	xKc
K4M	22	8.1	4,000	xKd
K100 LV	22	8.1	100	xKb
E-series				
E4M	29	8.5	4,000	xEa
E50 LV	29	8.5	50	xEb
E15 LV	29	8.5	15	xEc
F-series				
F4M	28	5.0	4,000	xFa
F50 LV	28	5.0	50	xFb
Special series				
Methocel VLV	–	–	<2	xM

HPMC hydroxypropyl methylcellulose, *PCA* principal component analysis

[a] x concentration of HPMC

Two different sets of formulations were prepared (Table II). The first set, composed of ternary formulations, was employed to investigate the influence of various grades of HPMC at different concentrations on the viscosities of PEG melt suspensions containing MNZ. The second set, composed of binary formulations of PEG with low (5%) and high (25%) concentrations of the ten grades of HPMC, was employed to assess the suitability of PCA in differentiating rheologically different dispersions. A total of 44 ternary formulations and 20 binary formulations were prepared. Each formulation was prepared in triplicates for measurements.

Rheological Analysis

The viscosity of the polymer melt suspension was measured using a rheometer (AR-G2, TA Instruments, USA) with a parallel plate system (20 mm diameter) at a gap of 1,000 μm and temperature range of 70 to 120°C. The shear stress was set at 6.37 Pa. Each sample was transferred to the rheometer plate and excess removed with a spatula. The measurements were triplicated. The rheological data obtained was then converted to surface plots using the graphical software DPlot (V2.3.0.9 HydeSoft Computing).

Morphology of HPMC Particles

The morphology of the HPMC particles of various grades was visualised using a scanning electron microscope (JSM-6010LV, Jeol, Japan). The particles were mounted on aluminium studs using conductive carbon tapes and examined at 1.5 kV under vacuum.

Particle Size and Size Distribution Analysis

Sizing of HPMC particles was carried out by laser diffractometry (LS230, Coulter, USA) with the dry powder module. Size determinations were triplicated and the results averaged. Size distribution curves were plotted, and the median particle size, d_{50}, was obtained.

Table II. Composition of Binary and Ternary Formulations of Polymer Melt Suspensions

Formulations	PEG (%, *w*/*w*)	HPMC (%, *w*/*w*)	MNZ (%, *w*/*w*)
Ternary			
1	75	5	20
2	70	10	20
3	65	15	20
4	60	20	20
5	55	25	20
Binary			
Low	95	5	–
High	75	25	–

PEG polyethylene glycol, *HPMC* hydroxypropyl methylcellulose, *MNZ* metronidazole

Assessment of Molten Mixture Sprayability

The sprayability of the molten mixture was assessed by evaluating its product yield obtained after the spray congealing process. A formulation was considered sprayable if a reasonable product yield was obtained without choking of the delivery system. Spray congealing of selected molten mixtures was carried out using a laboratory scale spray congealer (Mobile Minor 2000, Niro, Denmark). A pneumatic two-fluid nozzle, with a 2.0-mm nozzle tip, was used for the atomisation of molten mixture into the cooling chamber. The cooling chamber was maintained at 5–10°C by introducing cool air produced from an air chiller (ALFA ST 21, Air Blue, Italy). Atomisation air temperature was set at 80°C. Air was extracted from the chamber by an exhaust fan. Atomising air pressure of 2 bars was used.

Statistical Analysis

PCA was performed on the rheological data obtained to extract useful information using the statistical software Unscrambler (X 10.2 CAMO Software AS) and PCA scores plot was generated. In this study, the full rheological profile of each formulation ranging from 70 to 120°C was used for comparison. For more detailed comparison, rheological profiles can be analysed within the required temperature range, but it was not the objective of this study. The codes shown in Table I were used to represent the different grades of HPMC and provided a more effective visualisation of the data points in the scores plot. With the aid of a statistical analysis software (SPSS, version 13.0, USA), one-way analysis of variance (ANOVA) at level of significance 0.05 was used where appropriate.

RESULTS AND DISCUSSION

Effects of Various Concentrations of HPMC and Temperatures on the Rheological Properties of Ternary Polymer Melt Suspensions

The viscosity of the formulations with HPMC concentrations from 5 to 25% could be determined by the rheometer, except for a few grades of HPMC at very high concentrations. The polymer melt suspensions consisting of K100M beyond 15% and F4M, K100 LV, K4M and K15M beyond 20% were too viscous for accurate measurements. These few formulations appeared almost like a semi-solid paste and would not flow. The formulations of F50 LV, E15 LV, E50 LV, E4M and Methocel VLV were relatively less viscous even at high HPMC concentrations. Generally, the lower viscosity grades permitted a higher load of HPMC before becoming too viscous compared to higher viscosity grades. However, K100 LV, a low viscosity grade, did not permit high HPMC loading. Therefore, viscosity grades of HPMC and the viscosity of PEG melt suspensions were not well correlated. As the concentration of MNZ was kept constant, the differences observed could be largely attributed to HPMC.

Surface plots were used to study the effect of HPMC concentration and temperature on the viscosity of the ternary formulations (Figs. 1 and 2). It was observed that the viscosity of the formulations generally increased proportionally with

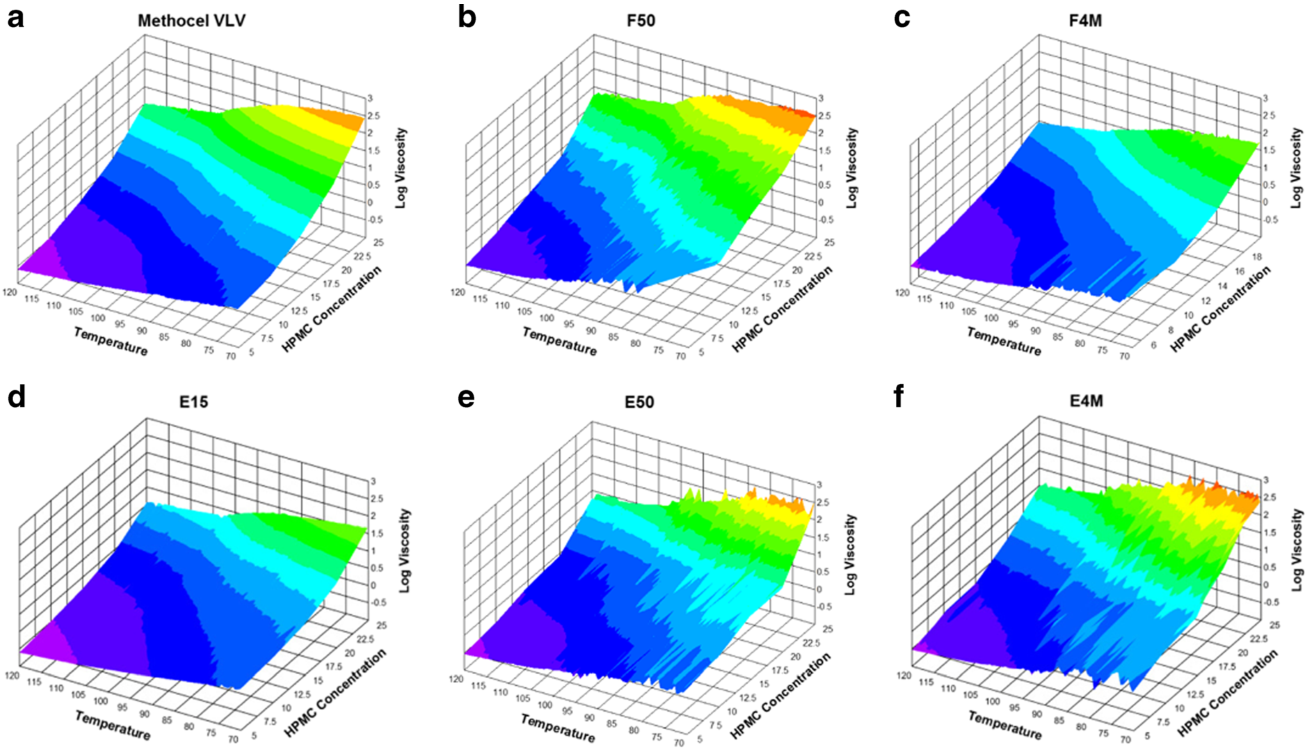

Fig. 1. Surface plots of log viscosity with temperature (°C) and HPMC concentration (%, *w*/*w*) for HPMC **a** Methocel VLV, **b** F50 LV, **c** F4M, **d** E15 LV, **e** E50 LV and f E4M

HPMC concentration but inversely with temperature. A higher concentration of solids in the polymer melt retarded the flow of the melt, resulting in higher viscosity. On the other hand, an increase in temperature increased the kinetic energy of the molecules, resulting in greater molecular mobility and reduction in viscosity. A combination of both the HPMC concentration and temperature effects affected the viscosity of the polymer melt suspensions to the greatest extent. Viscosity markedly increased for all grades of HPMC when a high concentration and low temperature was used. For all grades of HPMC, the increase in HPMC concentration resulted in a more drastic rise in the viscosity compared to temperature. This implies that HPMC concentration is the primary factor affecting the viscosity of the polymer melt suspensions. Therefore, the control of viscosity of PEG melt suspension is more readily achieved by modifying the amount of solids rather than regulating the temperature of the process. The surface plots also provided other useful information as discussed below.

Methocel VLV is a recently developed special grade of very low viscosity HPMC. Its viscosity is lower than that of E15 LV at 2% concentration in water at 20°C. However, the PEG melt suspensions consisting of Methocel VLV had consistently higher viscosity compared to the corresponding melt suspensions consisting of E15 LV (Fig. 1). The surface plot of melt suspensions of Methocel VLV was found to be more comparable to those of F50 LV and E50 LV, indicating a similarity in viscosity between these grades when used in PEG melt suspensions. Hence, the viscosity of the HPMC in water and its viscosity in molten PEG are different and cannot be inferred to be the same when substituting different grades in the PEG formulation. Methocel VLV had similar median particle size and size distribution as E50 LV and F50 LV (Fig. 3a–b). This explained their similarity in viscosities among the grades as indicated in the surface plots. A detailed discussion on the effects of particle size and size distribution will be provided in later sections.

The E15 LV grade had the lowest solution viscosity among the different grades of HPMC (excluding Methocel VLV) (Table I). Comparing the corresponding melt suspensions, those consisting of E15 LV also had the lowest viscosity. When the HPMC concentration of E15 LV was varied from 5 to 25%, the change in melt suspension viscosity was the least compared with all other grades. Even with a high loading of 25% *w*/*w*, the viscosity remained low compared with other grades at the same loading. Therefore, the E15 LV grade would be useful in melt formulations where a high concentration of solids is needed. The melt dispersion could be more efficiently conveyed or atomised if its viscosity is not excessively high.

Within the E-series HPMC, the viscosities of the melt suspensions increased from E15 LV<E50 LV<E4M. This is in agreement with their corresponding solution viscosities (Table I). The F-series also showed a similar trend with melt suspensions of F50 LV having a lower viscosity than F4M.

The K-series HPMC showed the expected trend of increasing melt suspension viscosity: K4M<K15M<K100M (Fig. 2). However, at 20%, K100 LV had similar viscosity to K15M but higher viscosity than K4M. This is in agreement with earlier observations that K100 LV resulted in an unusually high viscosity during the preparation of molten mixtures. This finding further substantiated that the viscosity of HPMC in polymer melts may differ from that in solution. The

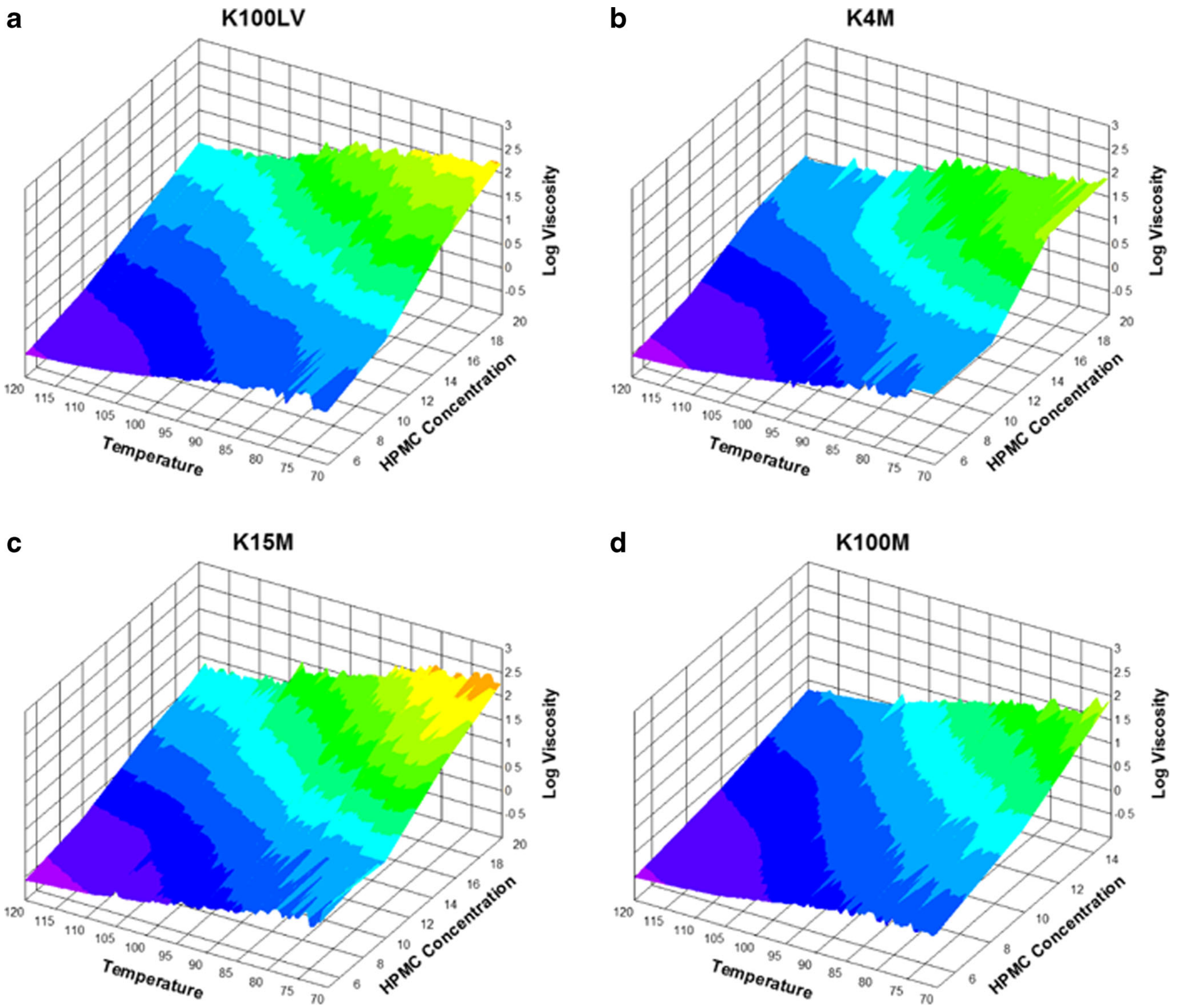

Fig. 2. Surface plots of log viscosity with temperature (°C) and HPMC concentration (%, w/w) for HPMC **a** K100 LV, **b** K4M, **c** K15M and **d** K100M

drawback of comparing the surface plots with one another is that trends are not easily distinguished. The comparison of different grades of HPMC at different concentration and temperature would also be more tedious and time-consuming.

Effects of HPMC Particle Size and Size Distribution on the Viscosities of Melt Suspensions

Figure 3a–b shows the median particle size and particle size distribution of the various grades of HPMC. To investigate the effect of HPMC particle size on the viscosity of melt suspensions, the surface plots were converted to line plots (Fig. 4). Within the F-series, F50 LV resulted in higher melt suspension viscosity than F4M at each corresponding concentration from 5 to 15% (Fig. 4a). However, at 20% concentration, the viscosity of F4M surpassed that of F50 LV. The median particle size of F50 LV was found to be significantly lower than that of F4M ($p<0.05$). The particle size distribution of F50 LV was also relatively narrower than that of F4M. At the same concentration, HPMC grade with smaller particles would be present in larger number in the melt suspension. The larger number of particles retarded the flow of molten PEG. This accounted for the trend observed from 5 to 15% HPMC concentrations. At higher concentrations, the HPMC particles were closely packed and particle-particle interactions took place. Particle-particle interactions are dependent on the surface area available for contact, which is affected by the particle shape and size distribution. The particle shapes of the different HPMC grades were found to be variable, albeit generally elongated (Fig. 5). Nevertheless, the trends observed suggested that particle-particle interactions were largely affected by particle size and particle size distribution. At 20% HPMC, F4M resulted in a higher resistance to flow compared to F50 LV, alluding to the association of greater surface area for interaction with larger particle size and broader size distribution. Particle size and size distribution exerted more than one effect, and its influence on melt suspension viscosity was not straightforward. An increase in particle size and size distribution favoured particle-particle interaction, which in turn

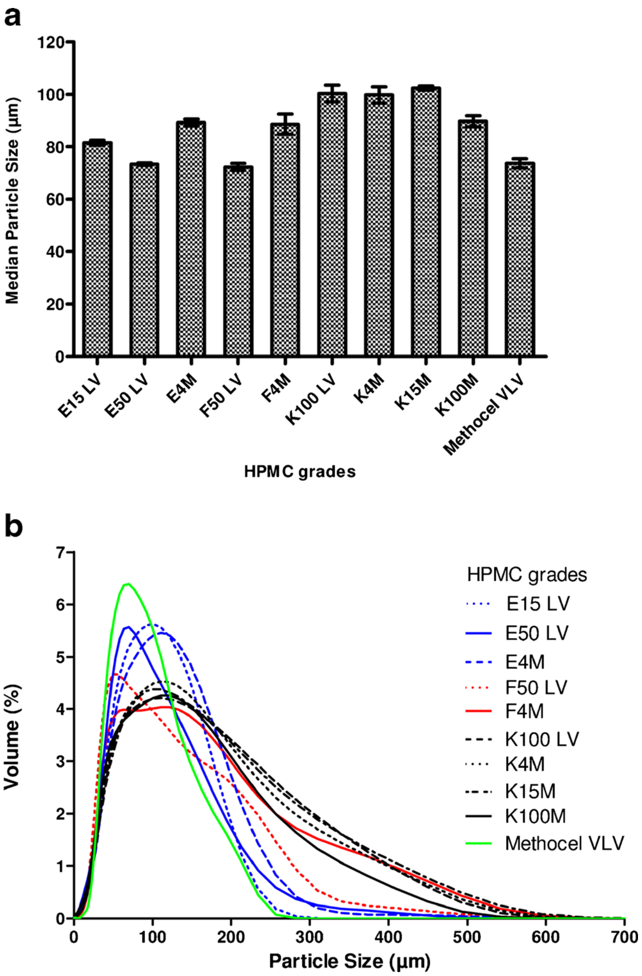

Fig. 3. **a** Median particle size and **b** size distribution of various grades of HPMC

increased viscosity. On the other hand, increase in particle size reduced the number of particles for the same HPMC concentration and reduced retardation of flow.

Similar findings were found with the E-series HPMC. Having smaller median particle size and narrower size distribution than E4M, E50 LV demonstrated higher melt suspension viscosity than E4M from 5 to 15% (except 10%) concentrations (Fig. 4b). Above the concentration of 15%, melt suspension viscosity of E4M was higher than that of E50 LV. Interestingly, the viscosity of E50 LV remained consistently higher than that of E15 LV at each corresponding concentration from 5 to 25%. Since E15 LV had greater median particle size than E50 LV, E15 LV was expected to exhibit greater particle-particle interactions and higher melt suspension viscosity than E50 LV at high concentrations. However, this was not observed. The results alluded that E15 LV did not exhibit particle-particle interaction. The median particle size of E15 LV (81 µm) was higher than that of E50 LV (73 µm), but lower than that of E4M (89 µm). Therefore, it could be postulated that a reasonable physical size was necessary for particle-particle interaction to occur. In the present situation, the HPMC should have median particle size greater than 81 µm before particle-particle interactions could occur.

Within the K-series, the melt suspension viscosities of K100M were consistently higher than those of K100 LV, K4M and K15M at each corresponding concentration from 5 to 15% (Fig. 4c). K100M had significantly smaller median particle size than the other three grades ($p<0.05$), as well as slightly narrower particle size distribution. Hence, at the same concentration, K100M particles were numerically larger in number, resulting in greater retardation to flow. At 20% HPMC concentration, K100 LV and K15M had higher viscosity than K4M even though the median particle sizes and size distributions for all three grades were similar ($p>0.05$). It is likely that the variation in the particle shapes of the different HPMC grades affected particle-particle interactions to a certain extent.

To gain a deeper understanding of the effects of HPMC particle size on viscosity of PEG melt suspensions, a further investigation using HPMC K15M of distinctly different particle sizes was carried out. The median particle size of the various HPMC mesh size fractions were determined from the size distribution curves (Fig. 6). A low concentration of HPMC (5%) was employed to avoid the confounding effect of concentration on viscosity. Figure 7 shows the impact of particle size on the viscosity of melt suspensions. HPMC of the smallest size fraction (33 µm) had a melt suspension viscosity of 0.47 Pa·s. When the particle size increased to 58 µm, the viscosity of the melt suspension decreased. As mentioned earlier, at the same concentration, HPMC with a smaller particle size would be present in a larger number which would retard the flow of molten PEG. At a slightly larger HPMC size, the particles would be further apart, accounting for the drop in viscosity. However, the HPMC network was discontinuous at this stage. The particles in the melt suspension were dispersed and existed as individual, separated particles. When the HPMC particle size employed was doubled (114 µm), it resulted in a significant spike in viscosity of the melt suspension (0.494 Pa·s, $p<0.05$). The spike in viscosity substantiated earlier observation that particle-particle interaction occurred when HPMC was of a certain particle size. At this stage, the HPMC network would be continuous as the particles might be close enough to be in contact with one another, resulting in a great resistance to the flow of molten PEG. Interestingly, it was found that the continual increase in particle size led to a remarkable decrease in viscosity ($p<0.05$). Larger HPMC particles would interact and form irregular particle clusters/aggregates in the melt suspension, resulting in a reversal of the continuous to discontinuous network. This phenomenon is known as particle flocculation/aggregation, where the particles were sufficiently large to adsorb onto another particle leading to aggregation (27,28). Furthermore, at the same concentration, larger HPMC particles would be present in a lower number which might be insufficient to form a continuous network. When the size of the HPMC particle was very large (275 µm), the viscosity increased slightly. Though the network was not continuous, the larger clusters formed would still be able to retard the flow of molten PEG, albeit to a lower extent than if a continuous network was formed.

The viscosities of the melt suspensions at different HPMC concentrations and temperatures for a particular grade of HPMC are shown in the respective surface plots (Figs. 1 and 2). Detailed comparison of the viscosities at each and every temperature and concentration between the various

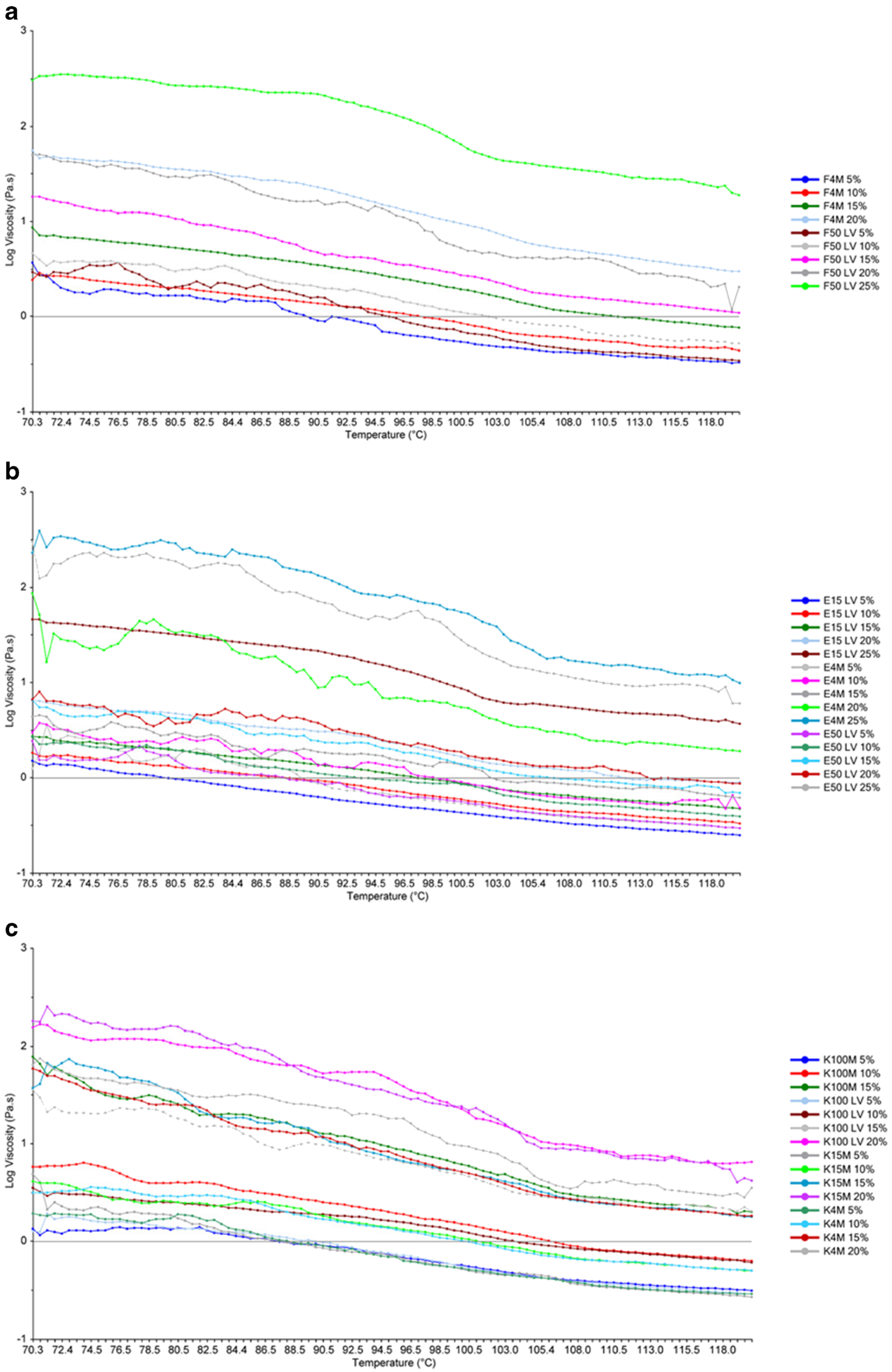

Fig. 4. Line plots of melt suspension viscosities with increasing temperature for **a** F-series, **b** E-series and **c** K-series

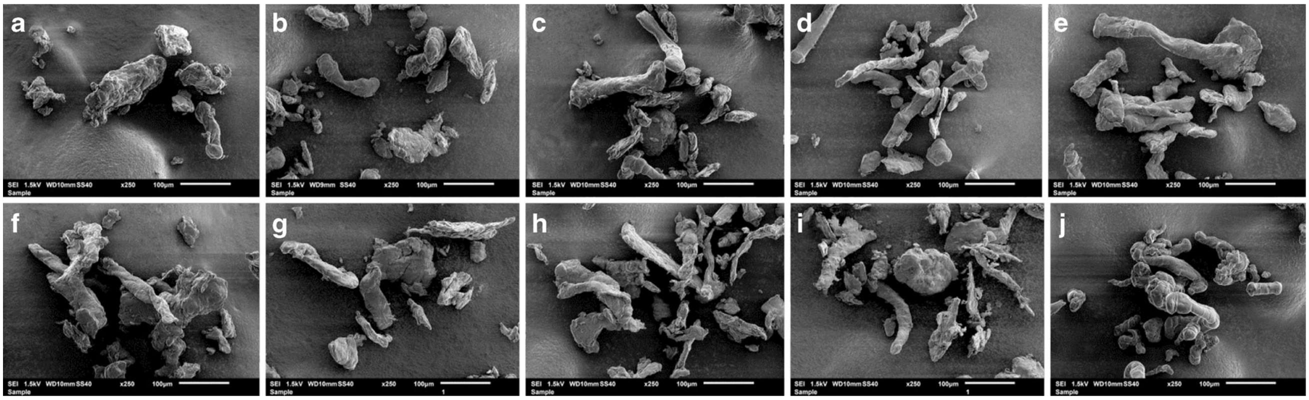

Fig. 5. Photomicrographs of HPMC **a** E15 LV, **b** E50 LV, **c** E4M, **d** F50 LV, **e** F4M, **f** K100 LV, **g** K4M, **h** K15M, **i** K100M and **j** Methocel VLV

grades of HPMC was very tedious and time-consuming. Therefore, the use of principal component analysis was explored to compare the viscosity profiles of the various formulations. Such analysis would also provide useful information on the possibility of substituting one HPMC grade with another without affecting the manufacturing process and final product.

Assessment of Principal Component Analysis as a Suitable Analytical Tool to Evaluate Viscosity Profiles of Melt Suspensions

The ability of PCA to differentiate the viscosity profiles of different formulations was examined. Binary formulations were prepared, and their viscosities were determined using a rheometer. The viscosity profiles generated from the rheometer were then analysed using PCA. The scores plot generated from PCA was a two-dimensional scatter plot which gave information about patterns in the sample. The two axes in the scores plot represent the principal components (PCs), which are variables used to differentiate the data. As viscosity was the only variable in this study, the first principal component would have close to 100% variance explained. The closer the samples were in the scores plot, the more similar they were. Conversely, samples far away from each other were different from each other. The plot was used to interpret differences and similarities among samples. The correlation between the viscosity profiles obtained using the rheometer and the PCA scores plot was employed to establish the suitability of PCA as an analytical tool for classifying the viscosity profiles of melt suspensions.

The effect of temperature on the viscosity of low (5%) and high (25%) concentrations of various grades of HPMC was examined (Fig. 8). Four distinct groups of viscosity profiles obtained using the rheometer were observed. These groups were numbered 1 to 4. Group 1 represented the formulations whose viscosities were the highest and group 4 the lowest. Melt of PEG alone had the lowest viscosity among the formulations. Groups 1 to 3 consisted of formulations containing 25% HPMC of various grades. This observation demonstrated that the resultant viscosity varied with the HPMC grade. It is interesting to note that the viscosity profiles of the formulations with high HPMC concentration were grouped according to the E-, F- and K-series with the exception of K100M. As mentioned previously, particle-particle interaction predominated at high HPMC concentration, but the extent differed from grade to grade. The viscosity profiles suggested that the F-series generally had more extensive particle-particle interactions compared to the K-series, followed by the E-series at the same concentration. Within each series, it was difficult to rank the grades according to the extent of particle-particle interactions, as their viscosity

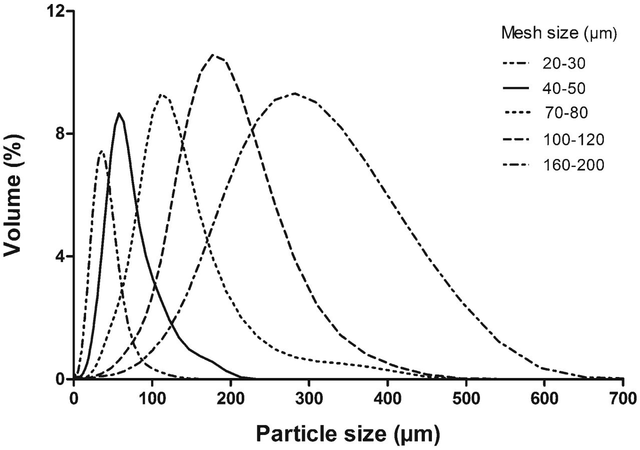

Fig. 6. Particle size distribution of various HPMC K15M mesh sizes

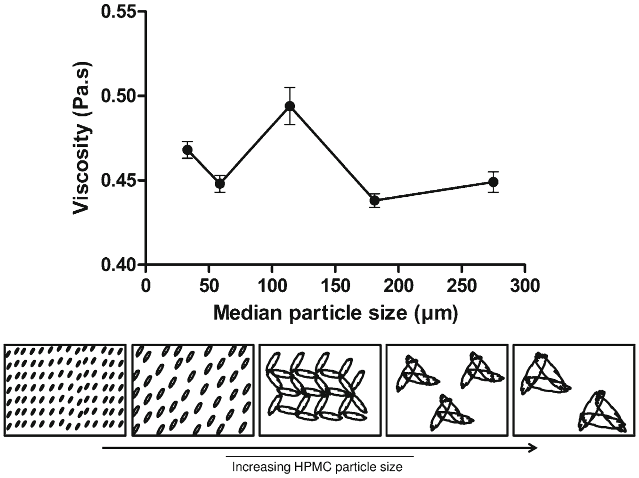

Fig. 7. Viscosities of PEG melt suspensions containing HPMC of increasing particle size

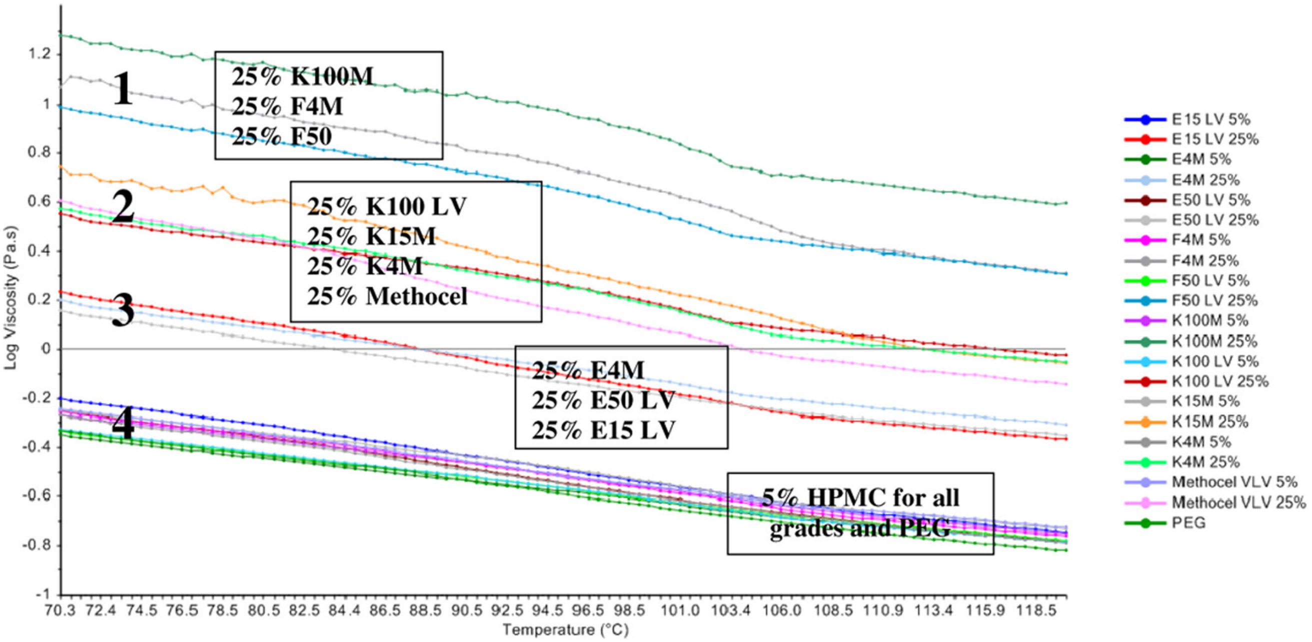

Fig. 8. Viscosity profiles of the various formulations with increasing temperature

profiles intersected with one another at various temperatures. For example, viscosity profile of 25% K15M intersected with 25% K100 LV at 109°C. The overlapping of viscosity profiles was also seen in group 4, which consisted of formulations containing 5% HPMC concentration regardless of grades. Within this group, viscosities of the various formulations were similar. The viscosity of a particular HPMC grade might not be consistently higher or consistently lower than that of another grade throughout the whole temperature range. This finding showed additional complexity of polymer-HPMC or HPMC-HPMC interactions at the different temperatures, resulting in difficulties to generalise.

Interestingly, the viscosity profiles of formulations with high HPMC concentrations generally exhibited a biphasic curve. This effect was not seen at low concentrations of HPMC. The viscosity profile of PEG alone exhibited linear curve. The point of deflection was postulated to coincide with maximum disentanglement of all the polymer chains of PEG. Under such a situation, there was a lower resistance to flow, which explained the smaller decrease in viscosity as tempera-

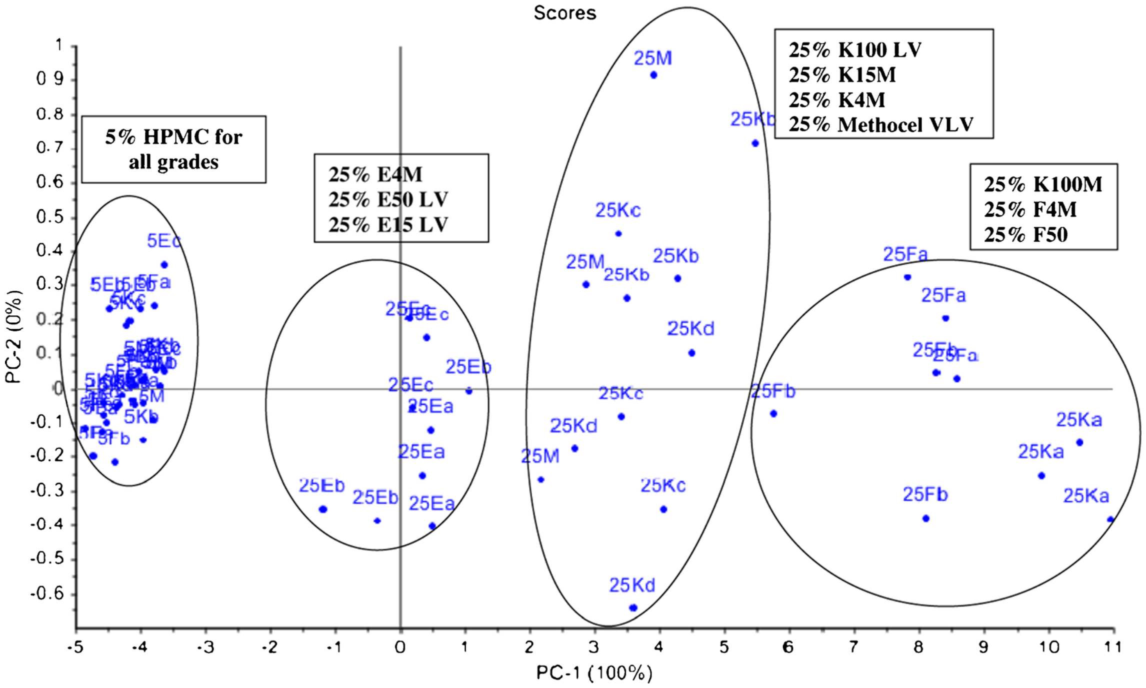

Fig. 9. Scores plot of the viscosity profiles of binary formulations. Codes represent the different formulations as shown in Table I

ture increased. The PEG chains disentangled easily when HPMC was not present or at low concentrations. A high concentration of HPMC hindered the disentanglement of the PEG chains.

The viscosity profiles were analysed using PCA, and the corresponding scores plot of the formulations are shown in Fig. 9. Each formulation consisting of triplicates is represented by three data points. In the PCA scores plot, four distinct groups of formulations were also observed (circled). The low viscosity formulations clustered to the left while those with higher viscosities to the right. The formulations within each group in line plot (Fig. 8) were compared with those in the scores plot and were found to match. The good correlation between the scores plot generated and viscosity profiles determined using a rheometer established that PCA was able to successfully compare various viscosity profiles and differentiate them into clusters of similar viscosities. Therefore, the use of better and faster analytical method, such as PCA, can be suitable for studying the viscosity profiles of ternary melt suspensions.

Evaluation of Ternary Polymer Melt Suspensions Using PCA

The PCA scores plot enabled better and faster comparison between the different grades and concentrations of HPMC used. The scores plot of the various formulations showed the presence of three clusters when the viscosity profiles of ternary melt suspensions were evaluated using PCA (Fig. 10). All the formulations within the same cluster had comparable viscosity profiles.

Table III. Classification of Various Ternary Formulations According to Viscosity Profiles

HPMC grade	Clusters[a] Low	 Moderate	 High
Methoce VLV	5, 10, 15	20	25
E15 LV	5, 10, 15, 20	25	–
E50 LV	5, 10, 15, 20	–	25
E4M	5, 10, 15	20	25
F50 LV	5, 10	15, 20	25
F4M	5, 10, 15	20	–
K100 LV	5, 10	15	20
K4M	5, 10	15, 20	–
K15M	5, 10	15	20
K100M	5, 10	15	–

HPMC hydroxypropyl methylcellulose

[a] Numerical value denotes the concentration of HPMC used

Table III lists the formulations in the scores plot according to the clusters of low, moderate and high viscosities relative to each other. In the high viscosity cluster, K100 LV and K15M at a concentration of 20% had viscosity profiles comparable with most of the other grades at 25%. Avoidance of high viscosity in melt suspension formulations required the HPMC concentrations to be below 20% for K100 LV and K15M and below 25% for the other grades in the group. In the moderate viscosity cluster, K4M and F50 LV grades had similar viscosity profiles at HPMC concentrations of 15–20%. Thus, increasing the HPMC concentration from 15 to 20% would not be effective in increasing the viscosity of the melt suspension. For all four grades of the K-series, HPMC concentration of 15% resulted in similar melt suspension viscosities. Viscosity of E15 LV remained moderate even at 25% concentration and comparable to other grades at lower

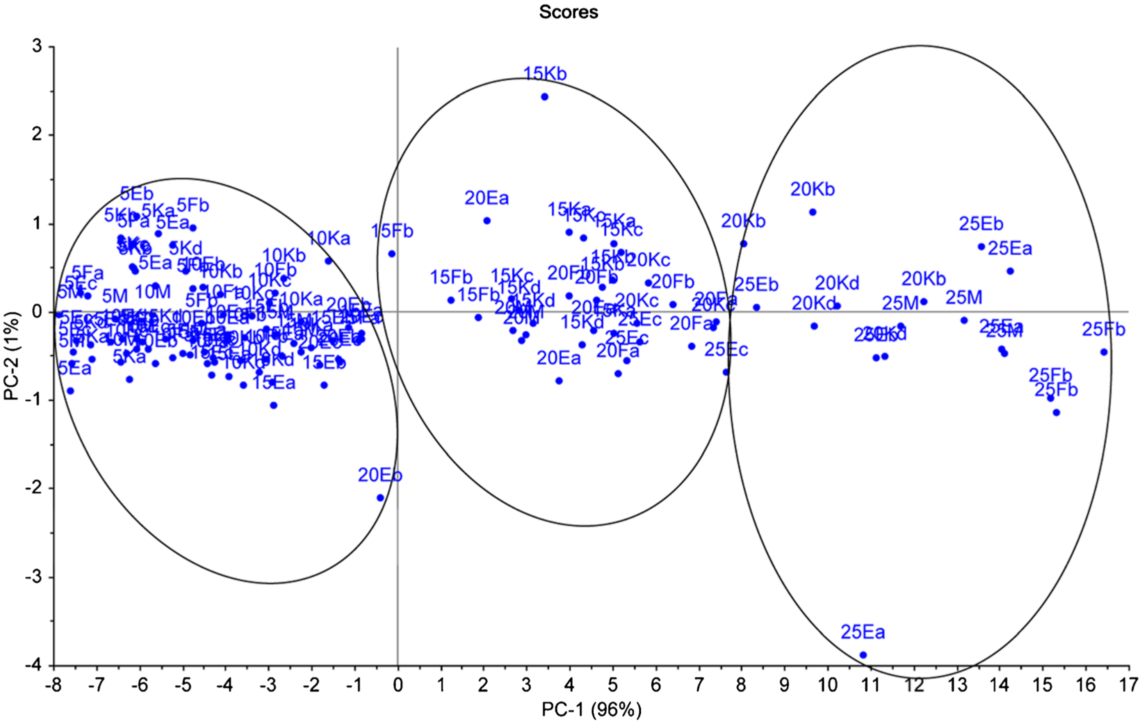

Fig. 10. Scores plot of the viscosity profiles of the various ternary formulations. Codes represent the different formulations as shown in Table I

HPMC concentrations. Hence, E15 LV would be the most appropriate grade to use when a need for high HPMC concentration, yet maintaining a suitable viscosity, is required. Being in the same cluster, all these grades at various concentrations can be used interchangeably when a similar viscosity is required. In the low viscosity cluster, HPMC grades of E15 LV and E50 LV had similar viscosities when used at concentrations of 5–20%. E50 LV showed a remarkable increase in melt suspension viscosity, moving from low to high viscosity cluster, when HPMC concentration was increased beyond 20%. This implied that the concentration used should be less than 20% to avoid non-flowable high viscosity formulations for this grade. The viscosities of Methocel VLV, E4M and F4M were similar when used at 5–15%, thus allowing the use of higher HPMC concentrations without the concern of increasing formulation viscosity significantly. The HPMC grades of K-series had similar viscosity to F50 LV at 5–10%. It seemed that regardless of the grades in the K-series, all of them can be used interchangeably.

No particular trend was observed when comparing the scores plot of the ternary and binary formulations. It is vital to note in both plots that HPMC of low concentrations (5%) were all grouped together. At higher concentrations (25%), binary formulations were differentiated into more clusters compared to ternary formulations. The different grades (Methocel VLV, E50 LV, E4M and F50 LV) which were previously separated in scores plot of binary formulations were clustered together in scores plot of ternary formulations. This showed that addition of MNZ, despite in the same amount in all formulations, increased the melt suspension viscosities to different extents. It cannot be assumed that the viscosity trends will remain consistent when more components are added to the formulation. This observation reflected the complex interactions affecting viscosity when different components are used in a formulation and reinforces the need of using PCA to evaluate the various formulations.

Sprayability of Ternary Melt Suspensions

Several formulations were selected from each cluster of low (20% E15 LV, 10% F50 LV and 10% K4M), moderate (20% F4M and 15% K4M) and high (25% E50 LV and 20% K15M) viscosity and were subjected to the spray congealing process to determine their sprayability. Sprayability in spray congealing refers to the ability to atomise a formulation of suitable viscosity to obtain a reasonable yield of microparticles without choking of the delivery system. Formulations in the low viscosity clusters (0.93 to 5.62 Pa·s) were successfully spray congealed. Above that viscosity, choking problems occurred. Therefore, formulations in the low viscosity cluster were classified as sprayable while those in moderate and high viscosity were not sprayable.

CONCLUSION

Principal component analysis successfully classified the ternary polymer melt suspensions into three clusters of low, moderate and high viscosity. Formulations in the low viscosity cluster were found to be sprayable. Principal component analysis was able to differentiate the complex viscosity profiles of different formulations in an efficient and time-saving manner and provided an excellent visualisation of the data. This enabled the selection of an appropriate grade and concentration of HPMC to achieve the desired viscosity in the pharmaceutical process.

For all grades of HPMC, the amount of HPMC added to molten PEG was found to play a more crucial role than temperature in changing the viscosity of PEG melt suspensions. Particle size and size distribution of HPMC played important roles in the viscosity of melt suspensions with smaller particles leading to a greater viscosity than larger particles. HPMC exhibited a propensity for particle-particle interaction at a certain particle size, leading to the formation of a continuous network and higher viscosity. Above this particle size, HPMC formed clusters, resulting in a discontinuous network and lower viscosity. Furthermore, the extent of interaction differed among the grades, with the F-series having the greatest extent, followed by the K-series and E-series at the same concentration.

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