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Full Length Research Paper

Evaluation of base for optimal drug delivery for iontophoretic therapy: Investigation of quality and stability

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Increasing the penetration rates of active substances from transdermal preparations to skin is a major goal for the pharmacy technologists. Higher concentration of the active substance in the skin is commonly associated with higher treatment quality. The aim of this study was to model an optimal pharmaceutical iontophoretic delivery form and to examine the dependency of its quality and stability on different parameters (that is, polymer type and concentration used for formulation, the viscosity of the vehicle, and its electrical conductivity). Gels have been intended to be used for 5-aminolevulinic acid (5-ALA) incorporation. The optimization of the vehicles has been performed without 5-ALA insertion due to its high price and very large standard concentration according to dermatologic protocols; but the gels have been evaluated accordingly to 5-ALA chemical properties. Different concentrations (0.25 to 10%) of four polymers (carbopol (CP), methylcellulose (MC), hypromellose (HM), and hydroxypropylcellulose (HPC)) have been selected for the formulations, and they produced wide range of dynamic viscosity (1.5 to 10000 mPa×cm). The highest shear viscosity has been measured in CP gels; dynamic viscosity was the highest in MC gels. 1000 to 5000 mPa×s was identified as the optimal dynamic viscosity for the iontophoretic gels. The following polymer concentrations have been singled out as optimal ones: 1% for carbopol, 4% for methylcellulose, and 3% for hypromellose. PH values of 5 and 7 have been identified as the most suitable for 5-ALA incorporation.

Key words: Gel, iontophoresis, viscosity, conductivity, rheology.

INTRODUCTION

Iontophoresis is a method of using small electric charge for delivery of chemical substances, including medicines, through skin (Guy et al., 2000). Nowadays, iontophoresis is most commonly employed for enhancing the penetration of medicines through skin (Merclin et al., 2000; Gelfuso et al., 2008). Iontophoresis focuses on hydrophilic molecules and optimal pharmaceutical forms that induce the active substance flow and increase cumulative active substance concentration present in the skin (Armoskaite et al., 2011). Production of suitable pharmaceutical forms is one of the major milestones for successful iontophoresis. Iontophoretic pharmaceutical form must be water-based,suitable for hydrophilic molecules, easy, and non-irritantly applied on the patient s' skin. It also has to be easily modified in the terms of conductivity and pH (Kalia et al., 2004). Conductivity for iontophoretic pharmaceutical forms is of major importance, because the transportation rate of the medicine with electric current is directly associated with it (Gelfuso et al., 2008; Panchagnula et al., 2004). The molecule of the drug must be ionized for export to the skin. Several studies have been performed while applying carbopol (CP) as a suitable gelling polymer (Lopez et al., 2003; Merclin et al., 2004; Chandra et al., 2008). Its acrylic acid origin, a cross-linked structure with polyalkenyl ethers or divinyl glycol, tendency to absorb water, and gelatinize makes it a potential candidate for

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use in controlled release drug delivery system (European Pharmacopoeaia, 2008; Rowe et al., 2003). These studies have identified that it was a suitable vehicle for active substance (e.g. 5-ALA) incorporation and delivery through iontophoretic system. On the other hand, only CP gels have been mainly used for iontophoretic studies (Papp et al., 2010, Huang et al., 2005; Fang et al., 1996; Chang et al., 2010; Fang et al., 1999; Raghavan et al., 2000). High substituted hydro-xypropyl cellulose (HSHPC) has been applied as a gelling agent in two studies (Valenta et al., 2005; McCarron et al., 2006). Multiple pharmaceutical forms (e.g. microemulsions (Araujo et al., 2010), patches (Morrow et al., 2010), and solutions (Donnelly et al., 2006)) have been formulated, but the opportunity to perform a study while comparing different polymers for the iontophoretic pharmaceutical form selection has not been taken.

In this study, methods such as addition of excipients/penetration enhancers or dermabrasion, microneedles, laser that would irritate the skin (Lee et al., 2010; Zhang et al., 2011) were not used. Therefore, the main aim of this study was to design an optimal pharmaceutical form for the delivery of anticancer drugs (including, 5-ALA) into skin by iontophoresis and to evaluate their rheologic properties, stability, optimal pH, viscosity and conductivity. The main task of this study was to evaluate whether CP gels have better features for iontophoretic gel formulation in comparison to cellulose gels and whether cellulose gels can be a suitable alternative for pharmaceutical base. For this reason, the 3 following cellulose polymers corresponding to the principal factors of quality (suitability for gel formulations, lubrication and stability) (Bourne, 2002; Ghosh and Jatsi, 2005) have been selected for the formulation of the vehicle: methylcellulose (MC), hypromellose (HM), and low substituted hydroxypropyl cellulose (LSHPC). CP gels have been produced for comparison as gels belonging to different polymer group.

MATERIALS AND METHODS

Carbopol 980 (CP) has been purchased from Lubrizol, USA. Methylcellulose (Metholose SM) (MC), hypromellose (Metholose SH) (HM), and low substituted hydroxypropyl cellulose NF (LSHPC) have been received from Shin-Etsu (Japan) as a gift. Potassium hydroxide (BDH Laboratory Supplies, England) and hydrochloric acid (Sigma-Aldrich, Germany) have been used for the adjustment of pH.

Optimization of the composition of the gel base

This method is based on the complex evaluation of the pharmaceutical form with several different tests (e.g. pH, viscosity, conductivity, and rheology). The selection of polymer concentration range is performed accordingly to the literature data. Afterwards, the physical properties of gels and their compatibility with 5-ALA physical and chemical features are being evaluated. Additional measures, such as mixing and water heating are being estimated as well.

PH stability test

PH stability has been evaluated with pH/mV meter Delta OHM HD 2105.1 (Delta OHM, Italy) pH-meter for semisolid preparations. PH adjustment is performed by adding 0.1 N NaOH and 0.1 HCl solutions while stirring the gel. The measurements before adjustment and after it have been performed 3 times per each sample.

The pH adjustment is performed three days after the formulation becomes stable. Before stabilization, polymer swells, dissolves in the water and forms a colloidal system (Michailova et al., 1999). PH re-adjustment is performed one day after the adjustment and repeatedly pH is measured after 1 month.

Viscosity analysis

Dynamic viscosity is measured with SV Series Sine-wave Vibro Viscosimeter (A & D Company, Japan) in standard conditions (25°C, 760 mmHg) or in the presence of temperature (heating with water bath) up to 60°C.

For the evaluation of gel resistance to temperature and the influence of temperature on the dynamic viscosity of CP gels, few pH values which will be used for the formulation of pharmaceutical form are selected accordingly to the literature data. The specimens for this study are selected accordingly to the ability to sustain the stability of 5-ALA (which will be incorporated into the formation) and the non-irritability to the skin (Elfsson et al., 1999; Robinson et al., 2005). Shear viscosity is evaluated with rheometer Carri-med CLS100 (TA Instruments, Germany) at 40°C.

Conductivity analysis

Conductivity is evaluated with WTW InoLab series conductometer (WTW Wissenschaftlich-Technische Werkstätten GmbH, Germany), while using magnetic stirrer MSC basic (IMLAB, Belgium). Conductivity is estimated for the gels without 5–ALA incorporation due to reasons mentioned earlier.

Rheological flow behavior test

Rheologic properties have been determined with rheometer Carri-med CLS100 (TA Instruments, Germany) by using plate-cone geometric system (the diameter of the cone, 40 mm; angle, 2°; thickness of the sample on the cone, 150 µm) at 40°C temperature by applying the deformation rate increasing from 0 to 500 s^{-1} in 2 min or adequately deformation rate from 0 to 500 s^{-1} in 25 s (to obtain more precise results as most relevant changes take place in this interval).

Statistical analysis

All the measurements have been performed 3 times per sample. Data was analyzed with programs Microsoft Excel and Statistical Package for Social Sciences (SPSS) 16.0 by applying Student t-test, analysis of variance (ANOVA), post-hoc analysis and curve fit test. Mathematical models for rheology studies have been calculated with Statistica 6.0 software.

RESULTS AND DISCUSSION

Four polymers have been analyzed for the formulation of the iontophoretic gel matrix. One polymer, CP, is of a

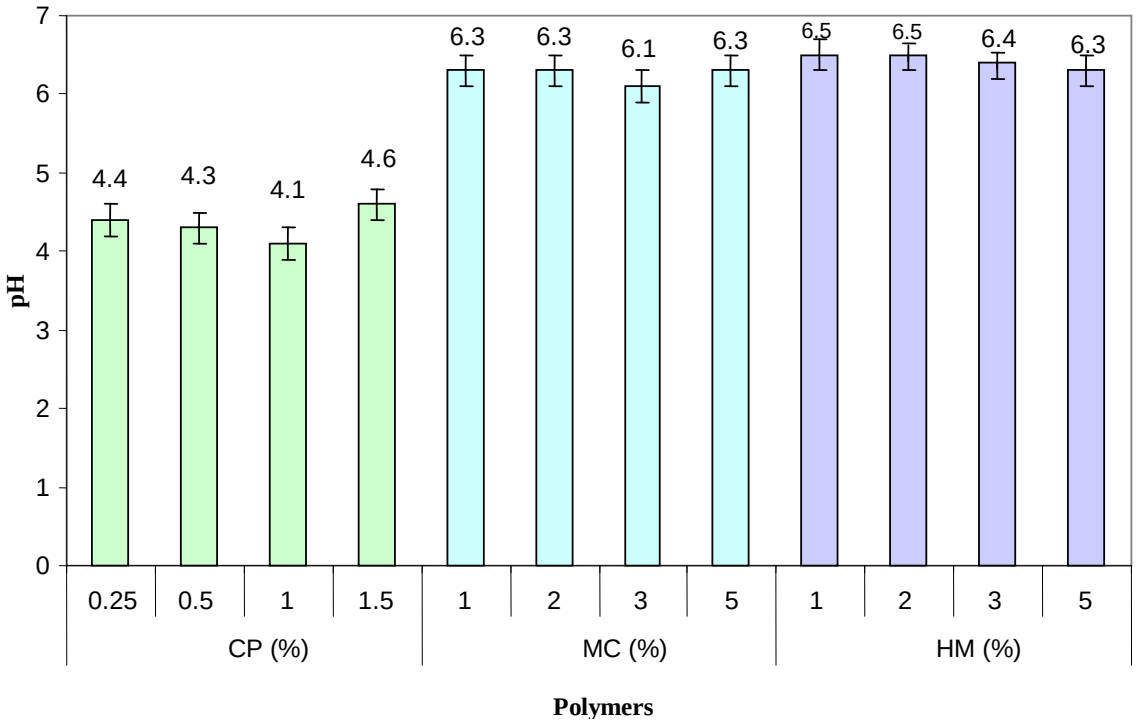

Figure 1. Investigation of pH value dependency on the concentration of the polymer in the vehicle. CP: Carbopol; MC: methylcellulose; HM: hypromellose.

polyacrylic nature, the other three (MC, HM, and LSHPC) are cellulose derivatives. Optimal concentration of these polymers and additional measures (mixing, heating) for formulation of the gel have been selected as follows: primary test of polymer concentration has been carried out in the following ranges (0.25 to 1.5% for CP, 1 to 10% for MC, 1 to 10% for HM, and 1 to 10% for LSHPC). After that, shorter intervals of the polymer amount in the formulation have been chosen for detailed analysis: 0.5 to 1% for CP; 3 to 5% for MC, and 1 to 3% for HM. These concentrations produced the following values of dynamic viscosity: 213 to 9580 mPa×s for CP, 671 to 4850 mPa×s for MC, and 127 to 3290 mPa×s for HM. LSHPC has been declined as a possible candidate, because it formed a suspension instead of homogenous gel. Water, heated up to 70°C, has been added to MC, HM, and LSHPC gels for formulation, but still LSHPC polymer was not able to form suitable gel. Mixing has been applied to all the gels and it increased the dynamic viscosity by 15 to 20%. In this stage, LSHPC polymer has been rejected as a candidate for gel formulation, so it was shown that HSHPC is suitable for gel formulation (as the literature suggests), but LSHPC is not.

CP and cellulose gels contained suitable properties for iontophoretic gel formulation; therefore, they have been selected for further pharmaceutical form development.

While dissolving different concentrations of polymer in the water, it formed vehicles with different pH values (RSD = ±5%). pH values, obtained by gels with different polymer concentration are as shown in Figure 1.

As shown in Figure 1, CP gels have average pH of 4.4, MC have average pH of 6.3, and HM have average pH of 6.4. All are of acidic nature; the acidity is more obvious in CP gel of acrylic origin. Cellulose gels have higher pH than CP gels; therefore, their acidic nature is expressed less than CP gels. ANOVA test has been applied for statistically relevant difference analysis with critical points of $P < 0.05$ and $F > Fcrit$. ANOVA analysis has shown that CP gels within different concentration levels differ significantly ($P = 0.025$; $F = 5.40$; $Fcrit = 4.07$) in their own group. Therefore, a post-hoc analysis with least significant difference (LSD) test has been applied. The test has shown that significant difference exists between the pH values of 0.25% CP and 1% CP gels ($P = 0.053$); 0.5% CP and 1.5% CP gels ($P = 0.026$) and 1% CP and 1.5% CP gels ($P = 0.005$). MC gels ($P = 0.158$; $F = 2.27$; $Fcrit = 4.07$) and HM ($P = 0.184$; $F = 2.06$; $Fcrit = 4.07$) gels did not show significantly relevant difference within their own groups.

Afterwards, ANOVA and post-hoc analysis with LSD test has been used to evaluate the significance of pH value differences among the gels of the selected polymers. Post-hoc test has shown differences between pH values of CP and MC as well as CP and HM polymers ($P < 0.05$). There was no significantly relevant difference between cellulose polymers ($P = 0.121$). The results have

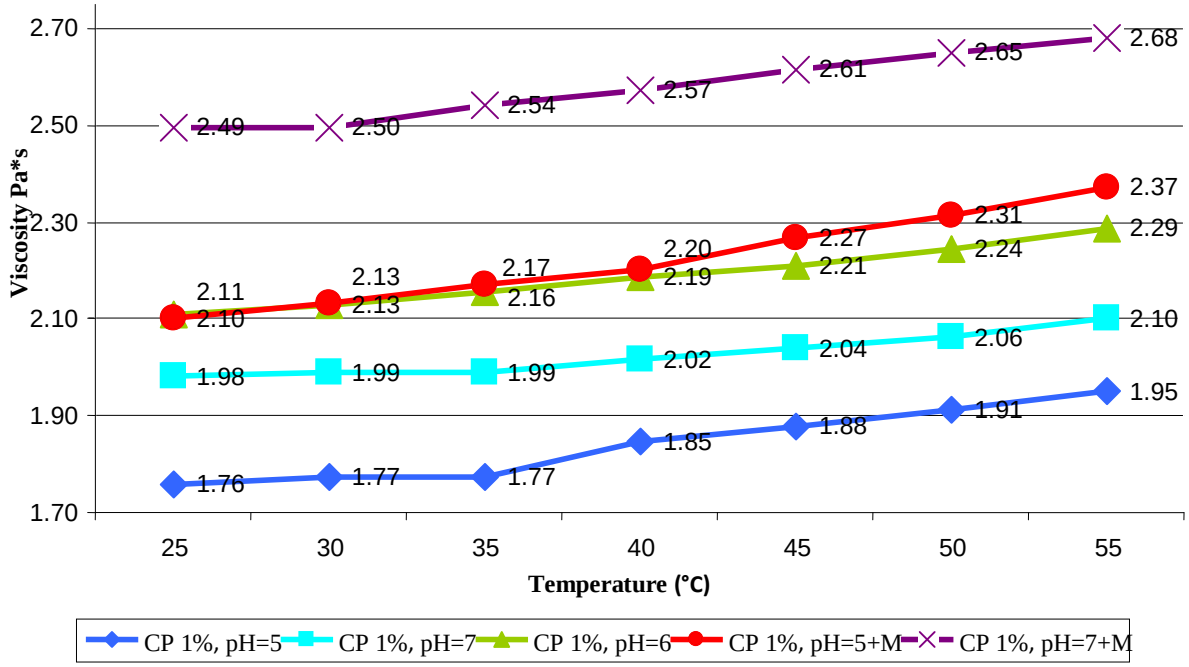

Figure 2. The influence of temperature and mixing on the dynamic viscosity. CP: carbopol; MC: methylcellulose; HM: hypromellose; M: mixing.

been confirmed by Student t-test that also identified statistically relevant differences between CP and MC ($P = 7.45 \times 10^{-13}$) as well as CP and HM ($P = 2.45 \times 10^{-10}$) gels. There was no statistically relevant difference accordingly to t-test between various pH values of MC and HM ($P = 0.06$) gels.

After that, the gels were adjusted to standard pH values and later on re-adjustment was applied. Re-adjustment identified that mostly the difference of the manufactured gels from the required pH meanings was few decimals or none before re-adjustment. Maximum difference was up to 1 pH unit after pH adjustment which results in RSD = ±20%. Therefore, re-adjustment always must be performed. After re-adjustment, the pH was measured in the period of one month (week-to-week study): it was identified that the real pH value varied statistically irrelevantly from the theoretical value. The differences between the real and theoretical values varied from 0.1 to 0.3 units per sample (RSD = ±5%).

After pH adjustment, it was decided to test the temperature influence on the CP gel dynamic viscosity. The results of this experiment are as shown in Figure 2.

In general, the viscosity (resistance) should decrease while temperature increases, but CP gels are complex polymer formulations; therefore, in the influence of temperature the structure transforms. The increase of viscosity in the presence of rising temperature has been enrolled (Figure 2). The distribution of particles in a gel and ability to form the colloidal system was higher in mixed gels. Mixed gels had higher viscosity of about 15 to 20%. Mixing increased the viscosity of CP gels (pH=5 and pH=7)) (Figure 2). The highest viscosity of non-mixed CP gels is typical for pH=6 gel, but other gels are suitable for iontophoresis as long as they form the vehicle of suitable viscosity, stability and retain these properties after the incorporation of active substance. The change in viscosity under the influence of temperature (it rises by 30° from 25 to 55°C) varies from 3.9 to 9.3%. Normally, the gels do not reach mentioned temperature conditions while storing, so it is considered that the gels are stable transdermal forms in room temperature. Thermal stability conditions for HM and MC gels were found in the specification supplied by the producer; therefore, it has not been tested.

Afterwards, while measuring dynamic viscosity of the produced gels, it has been decided to examine the correlation between polymer percentage in the formulation and the dynamic viscosity values. As it is shown in Figure 3, MC has the highest viscosity features in all the polymer concentration points, as well as CP has the lowest ones. The viscosity of each formulation has been evaluated 3 times with the average deviation listed in brackets MC gels (4.7%), HM gels (4.2%), and CP gels (3.9%). Following optimal concentrations were excluded excluded after the viscosity and organoleptic evaluation (the optimal concentration are shown in brackets): CP (1%), HM (3%), and MC (4%). These viscosity values were chosen for further studies.

The acid-base balance has different effects on gel preparations. This study has shown that dynamic viscosity of the gel increases with higher concentration of polymer in the formulation. Curve estimation has been

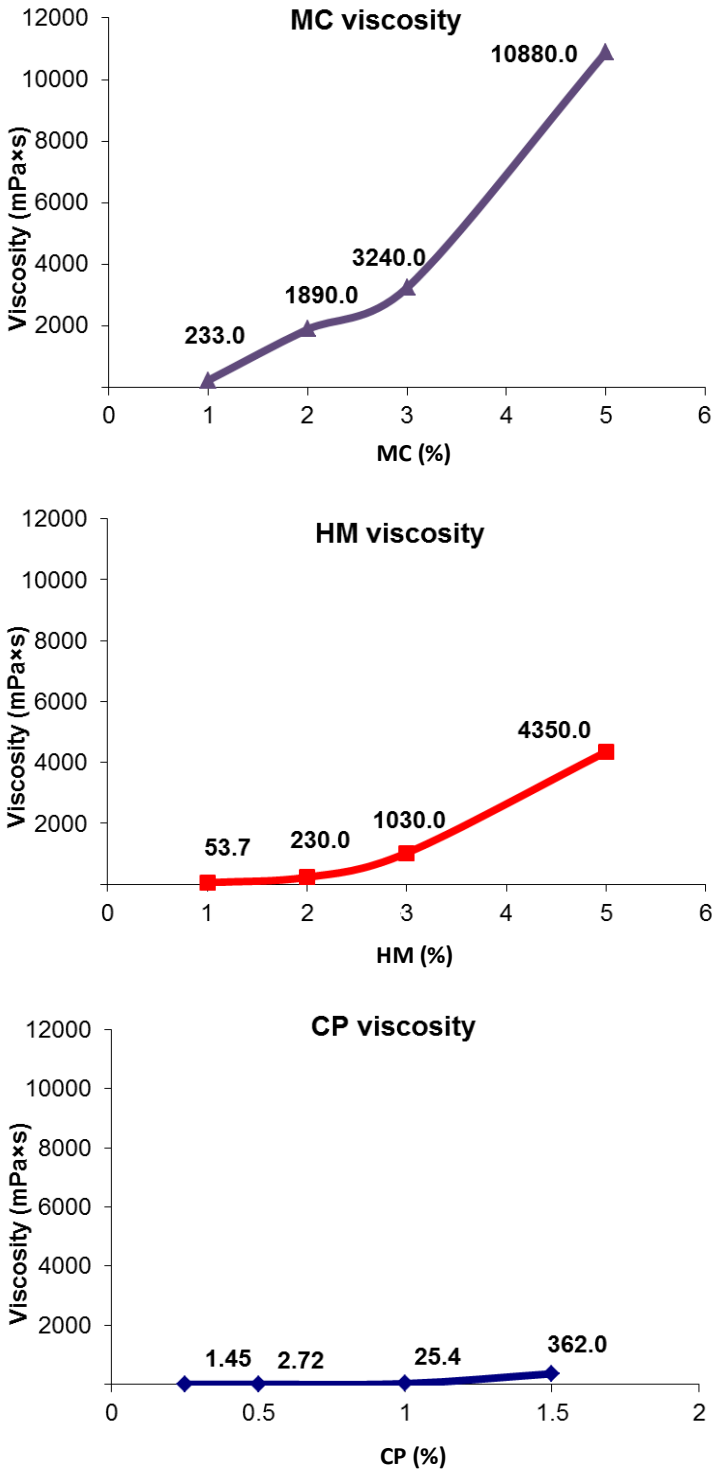

Figure 3. Dependence of dynamic viscosity value on polymer percent in gel formulation. CP: carbopol; MC: methylcellulose; HM: hypromellose.

performed for all the polymer gels with SPSS curve fit analysis and it has shown that the best fitting model for all the curves was the cubic one ($R^2 = 1$). Cubic model was better fitting for CP gels than the logistic and exponential ($R^2 = 0.989$) and quadratic one ($R^2 = 0.980$). It also showed higher correlation in MC gels than the

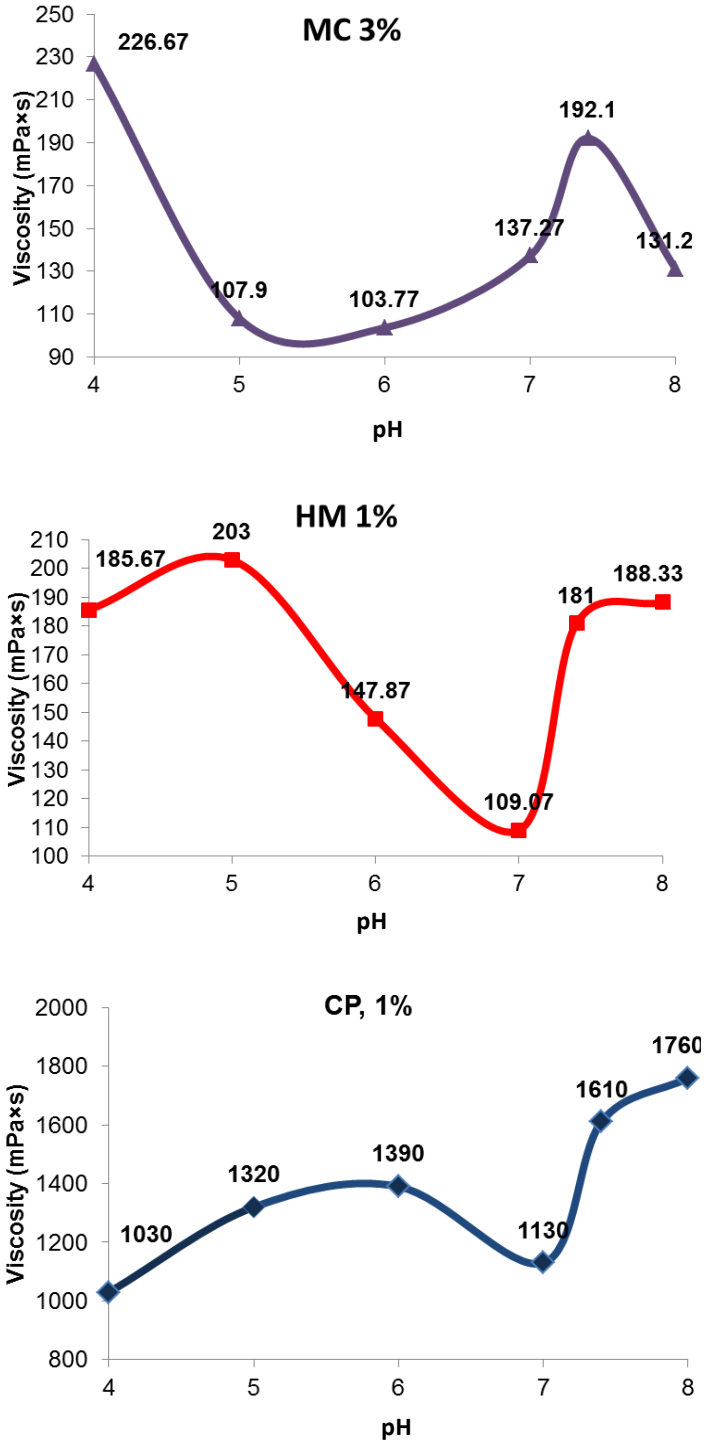

Figure 4. The dependency of dynamic viscosity on the pH value of gels. CP: Carbopol; MC: methylcellulose; HM: hypromellose.

quadratic (R^2 = 0.995) and linear (R^2 = 0.946) models. In HM gels, it was the same as quadratic regression (R^2 = 1) and higher than exponential regression (R^2 = 0.961).

After evaluation of polymer concentration effect on the formulation, it was decided to estimate the pH effect on the dynamic viscosity of the formulations. Figure 4 represents the chaotic dependence of 1% CP, 1% HM, and 3% MC gel dynamic viscosity on their pH values. In Figure 4, the viscosity for CP is increasing up to pH=8 value except one point (pH=7) where it drops. For MC,

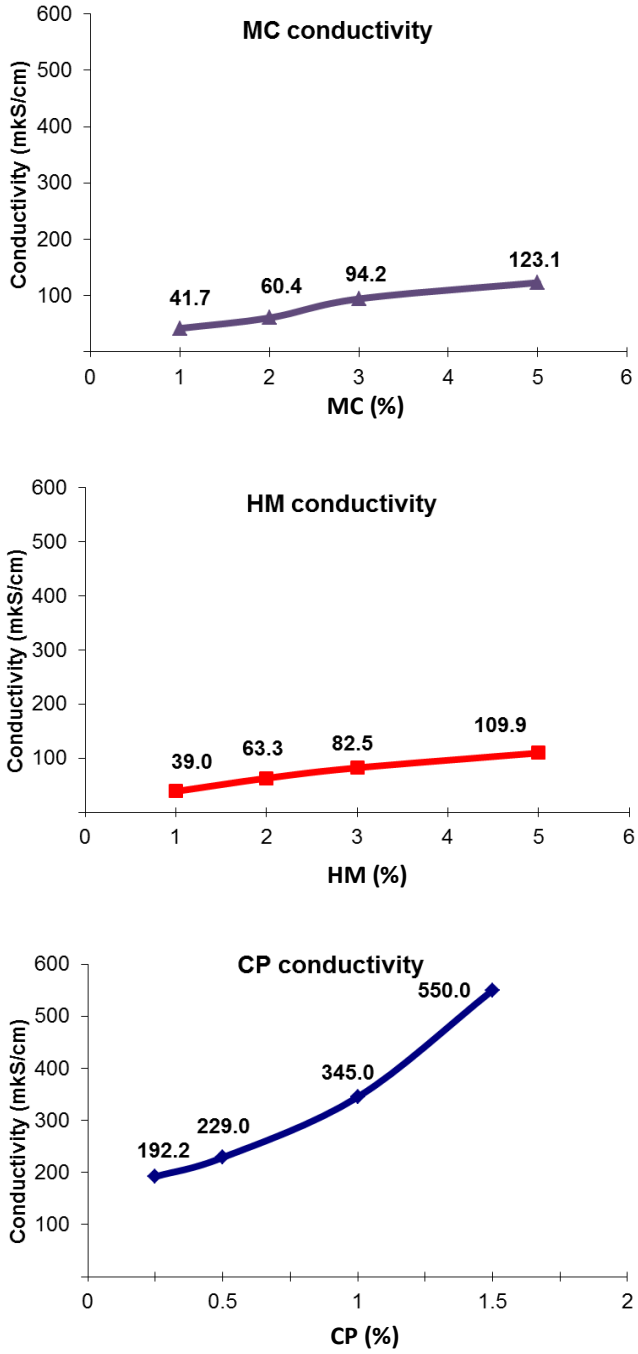

Figure 5. Correlation between the percentage of polymer, used for gel preparation and conductivity.

the viscosity decreases to pH=6, then it increases up to pH=7.4 and drops at pH=8. Viscosity is also chaotic considering the HM curve. The highest value of the viscosity might appear at any pH. Considering other concentrations or polymers, the same rules apply; there is no tendency on the pH increment or decrease because polymers have a complex structure that is sensitive to pH changes.

Iontophoresis is always dealing with electric currents, which is a very important factor while considering that 5-ALA hydrochloride is a hydrophilic molecule with logP = -0.929; so the molecule of the drug must be ionized to gain the transportation tendencies in application of electric current; therefore, conductivity test has been performed. As shown in Figure 5, the correlation between increasing percentage of polymer in the composition of

Table 1. Rheologic parameters of gels for iontophoresis.

Gel type, concentration of polymer (%), pH	Yield stress (a), Pa	Consistency (b), ($Pa \cdot s^n$)	Rate index (c)	Regression	Mathematical model
CP, 1, pH=5	18.26	46.51	0.362	0.983	HB
CP, 1, pH=7	9.9	90.9	0.311	0.970	HB
HM, 3, pH=5	4.63×10^{-12}	73.5	0.331	0.957	HB
HM, 3, pH=7	3.17×10^{-11}	87.97	0.309	0.961	HB
MC, 4, pH=5	1.35×10^{-8}	23.41	0.510	0.995	PL
MC, 4, pH=7	6.28×10^{-10}	23.86	0.508	0.993	PL

CP: Carbopol; MC: methylcellulose; HM: hypromellose; HB: Hershey-Buckley; PL: power low.

the gel and conductivity has been established. While comparing Figure 5 to Figure 3, it is evident that lower viscosity produces higher conductivity.

The regression between the polymer concentration and conductivity has been evaluated while applying curve fit analysis (SPSS 16.0). The analysis revealed that cubic regression was the most appropriate one for all the polymers. The R^2 was 1 for all the polymers and it exceeded (or rarely was equal to) other curve models, that is, quadratic regression (R^2 = 0.984) and linear equation (R^2 = 0.971) for MC gels; quadratic (R^2 = 1) and logarithmic (R^2 = 0.988) for HM gels, and quadratic (R^2 = 1) as well as exponential and logistic equations (R^2 = 0.0997) for CP gels.

Also, lower viscosity is associated with higher conductivity; although, the correlation is not very strong. Correlation coefficients for different groups or polymers and their different concentrations vary: for HM the strongest correlation is in HM 1% concentration (-0.63), medium correlation. Adequately, for MC 1%, the value is -0.69 (medium) and CP 0.5% (-0.73) (strong). In other cases, the correlation is mostly weak and reverse. Rheologic properties (yield stress, consistency, and rate index) of gels (pH 5 and 7) have been determined for evaluation of their resistance to deformation force. This is relevant for spreadibility and consistency for pharmaceutical form estimation (San Taberner et al., 2002). The rheologic characteristics of gels are displayed in Table 1.

It is evident from Table 1 that CP and HM gels behave as expected, that is, non-Newtonian pseudoplastic fluids and Herschel-Bulkley model is designated to them. MC gels have stronger fluidic properties (Power Low model is designated to these gels). Highest values of yield stress are characteristic to CP gels. It indicates that it is the most resistant base to the effect of external deformation force. Cellulose gels have statistically significantly higher meanings of yield stress in comparison to cellulose gels; therefore, yield stress is a characteristic for separating the gels accordingly to the polymer origin (CP, polyvinyl carboxy polymer; MC and HM, cellulose gels).

Consistency index indicates the viscosity of the system. The higher it is, the higher force and pressure must be applied to the vehicle for it to become runny and possible to evaluate dynamic properties. Therefore, the highest viscosity was determined for CP and HM gels, the lowest for MC gels. Rate index (C) indicates the similarity of the base to Newtonian fluids. Therefore, according to the experiment data, MC gels possess the characteristics closest to Newtonian fluids out of all these gels.

Evaluation of rheological parameters of gels made from different polymers with different pH has been performed as well. The resistance of CP and HM gels within their group to stress is highly influenced by pH values. This information has been provided in flow behavior curves in Figure 6. It is evident from Figure 6 that the proportion of shear stress and shear rate of CP gels is highly influenced by pH values. Gels made from 1% of CP (pH value 7) have the highest viscosity. On the other hand, the viscosity of CP gels (pH=5) has the lowest value out of all the gels from different polymers as well. The viscosity of HM gels highly depends on the pH value as well: the resistance of HM gel is the highest once the pH reaches value 7. The resistance of CP and HM gels is very similar at pH =7. The resistance of MC gels does not depend on the pH value (the curves are almost the same for both pH values). The following presumptions have been approved with statistical analysis. ANOVA and post-hoc analysis with LSD test have been performed to estimate the differences among flow behavior curves by analyzing shear stress of the gels. ANOVA analysis has shown that there are significant differences among all the gels ($P = 6.06 \times 10^{-26}$, F = 28.00, Fcrit = 2.23). Post-hoc analysis identified that the following 4 pairs of gels had no significantly relevant difference between them: CP=1%, pH=5 and MC=4%, pH=5 (P = 0.103); CP=1%, pH=5 and MC=4%, pH=7 (P = 0.08); CP=1%, pH=7 and HM=3%, pH=7 (P = 0.392); MC=4%, pH=5 and MC=4%, pH=7 (P = 0.906). Other pairs were significantly different from each other.

The analysis of the relationship between shear stress of the studied systems and their shear rate shows that, increasing shear rate disrupted the structure of the system, resulting in increasing shear stress at temperature of 40°C. At first, shear stress increased significantly, but later on, while the system was becoming

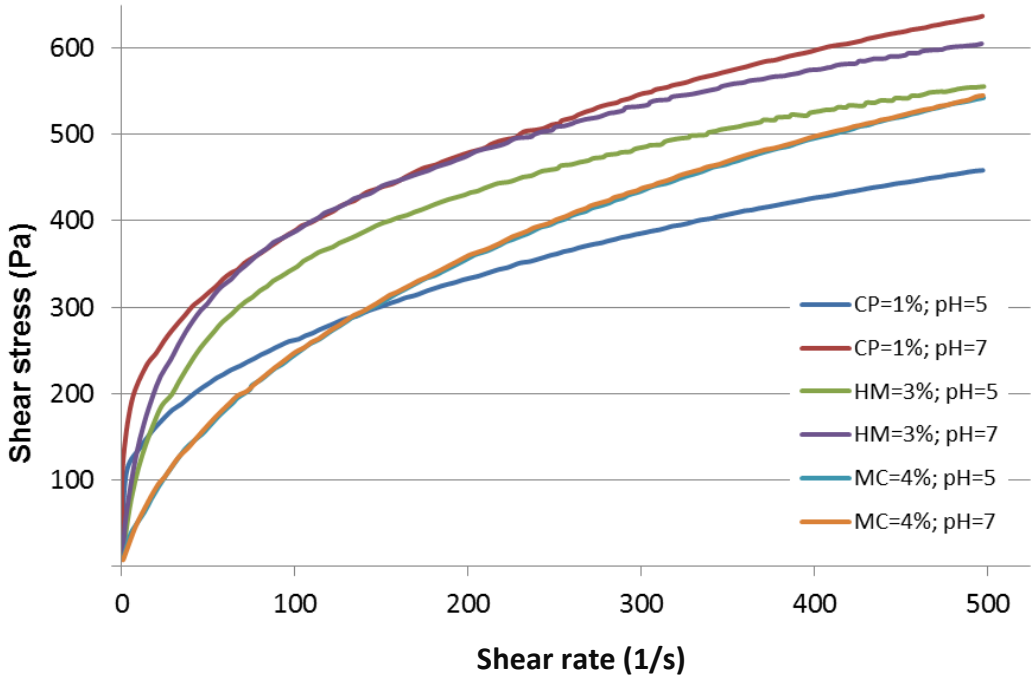

Figure 6. Flow behavior curves for different polymer gels with different pH. CP: Carbopol; HM: hypromellose; MC: methylcellulose.

more uniform, the increase in shear stress became more even due to newly formed properties of the more uniform gel (disrupted initial structure and lower resistance to deformation). The dependency of shear viscosity on the shear rate (while share rate is increased from 0 to 100 s^{-1} in 25 s and from 0 to 100 s^{-1} in 25 s for cellulose analysis for more thorough analysis) was measured with Rheometer Carri-med CLS100; it is displayed in Figure 7.

While applying mild shear rate (up to 0.5 s^{-1}), CP gels demonstrated the highest shear viscosity (resistance to deformation). This peak appeared after about 2 s from the start of application of deformation and it was visible in HM and CP gels. As shown in Figure 7b, the highest shear viscosity was significantly higher in CP gels (the exact meanings of this "peak" shear viscosity are the following ones: for CP 1% (pH=5), 113.5 Pa×s; CP 1% (pH=7), 340.5 Pa×s; HM 3% (pH=5), 16.52 Pa×s; HM 3% (pH=7), 25.92 Pa×s). While Figure 7b singles out that the viscosity of cellulose gels is significantly lower in comparison to CP 1%, pH=7 gels. This hypothesis has been tested with ANOVA and post hoc analyses (with LSD test). P value (0.01) and F evaluation (F(2.88) > Fcrit (2.23)) for shear viscosity has shown that there is a significantly relevant difference between different gels. Post hoc analysis singled out only CP 1%, pH=7 as the only group that differs significantly from the other gels (p value varying for different groups forms 0.001 to 0.25). The lowest difference was between both CP gels, although, either way it was still significant. Application of higher shear rate (s^{-1}) to MC gels does not produce the peaks in the diagrams. This is a major difference from CP and HM gels. It seems that MC gels do not have any "yield peaks" and do not try to resist the deformation force at the start of it (it is flowable before applying the deformation force). It seems that CP and HM have a different polymeric structure and bonds in comparison to MC gels: CP and HM gels possess a stronger bond; therefore, higher deformation force must be applied for the gel to assume the properties of a running fluid. The diagram of MC gels indicates that they are closest to Newtonian fluids out of all these gels. Analysis with rheometer Carri-med CLS100 also provided additional data about shear viscosity; therefore, we had an opportunity to compare it to the dynamic viscosity, measured with Sine-wave Vibro Viscosimeter (A & D Company, Japan). Both methods have different approaches towards viscosity; therefore, the results differ. By using rheometer Carri-med CLS100, the highest viscosity is determined for CP gels. Therefore, it is assumed that CP gels have the highest resistance to shear deformation (shear stress) in comparison to HM and MC gels. Experiments performed with Series Sine-wave Vibro Viscosimeter (A & D Company, Japan) identify that the highest values of dynamic viscosity are measured for MC gels (HM and CP have lower values). Also, the differences in temperature (samples with rheometer are measured at temperature 40°C and viscosimeter measures are performed at room temperature with 25°C) must be taken into account as well. In ideal conditions, the dynamic viscosity should concur

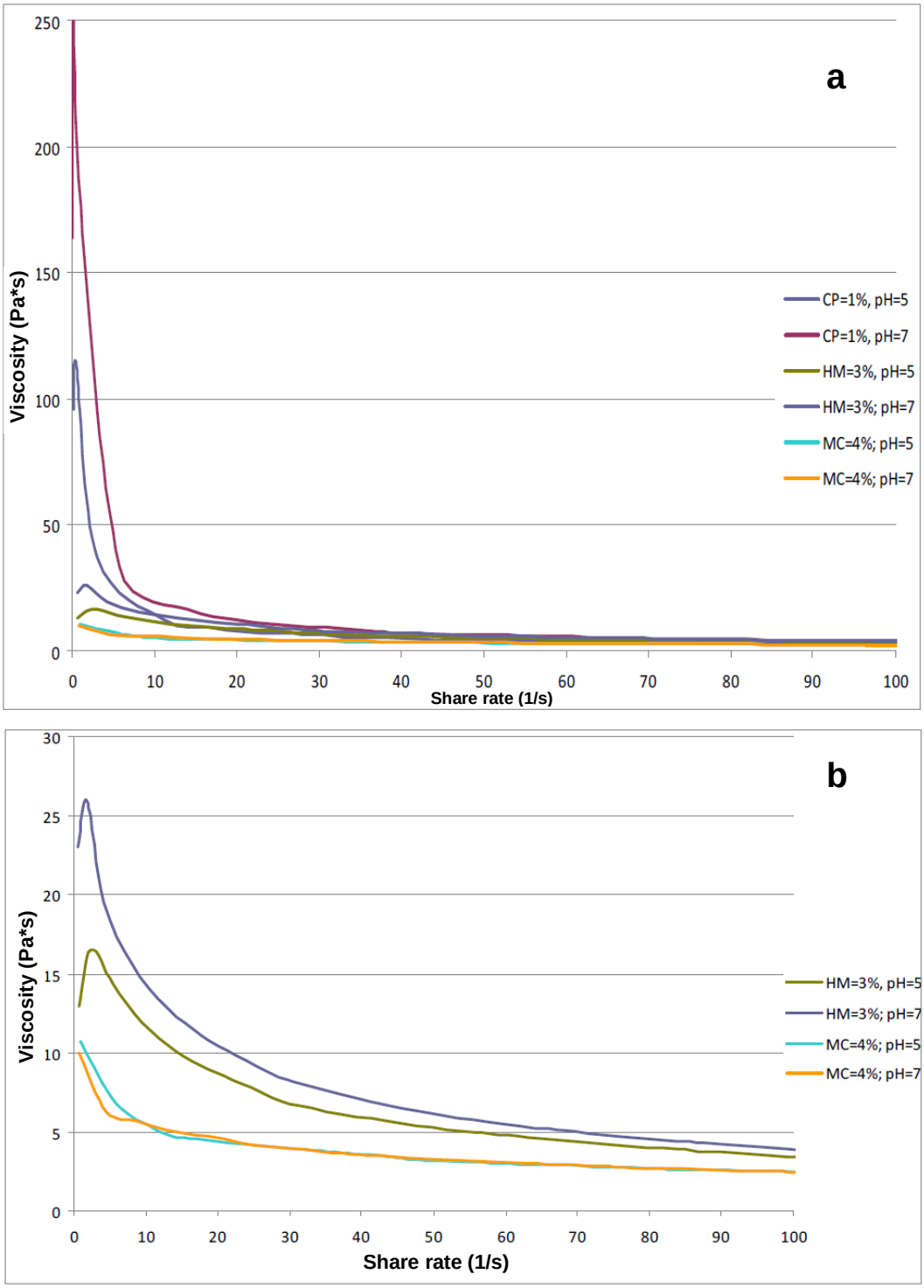

Figure 7. The dependency of shear viscosity on the shear rate in gels (share rate is increased from 0 to 100 s^{-1} in 25 s): a) all gel analysis; b) cellulose gel analysis. CP: carbopol; HM: hypromellose; MC: methylcellulose.

with shear viscosity at shear rate 0, but the experiments show that due to different temperature regimens and real conditions, they differ.

Conclusions

After polymer screening and primary tests, the following

optimal polymer concentrations in gels have been selected: CP 1%, HM 3%, and MC 4%. These pH values (pH=5 and pH=7) have been selected as optimal ones accordingly to physical features of the incorporated active substance as well as viscosity and conductivity tests. It has been evaluated that there is no statistically clear conductivity and viscosity dependence on the pH, (the calculated correlations were weak and they were not stable through the whole series of gels). The correlation between conductivity and viscosity exists as well, although, mostly, it is reverse and weak. Curve fit analysis identified that the dependency of dynamic viscosity on the polymer concentration (as well as conductivity on the polymer concentration) is the most precisely described with cubic equation. Rheologic properties singled out CP gels as the most stable ones in terms of resistance to stress and indicated that according to the rheologic parameters and model, these gels are the closest to non-Newtonian fluids. Dynamic viscosity has been the highest for CP gels; and static viscosity was the highest in MC gels. In terms of quality and stability, manufactured gels of optimal concentration and pH have been identified to be suitable for incorporation of the drug and application for iontophoretic therapy.

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