Original Article

Technological and Biopharmaceutical Characterization of Carbopol-Based Ketoprofen Emulgels

Petya Peneva[1*], Velichka Andonova[1], Teodora Dimcheva[2], Margarita Kassarova[1]

[1]Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University-Plovdiv, 15A Vassil Aprilov Blvd, Plovdiv 4002, BULGARIA.
[2]Department of Medical Informatics, Biostatistics and E-learning, Faculty of Public Health, Medical University-Plovdiv, 15A Vassil Aprilov Blvd, Plovdiv 4002, BULGARIA.

ABSTRACT

Objective: Emulgels are a combination of emulsions and gels. In this study, the influence of different oil phases and gelling agent concentrations on the technological and biopharmaceutical characteristics of prepared emulgels is assessed. **Materials and Methods:** Light liquid paraffin (various concentrations), cetyl alcohol, isopropyl myristate, and almond oil were used in the oil phase of the emulsions, and Carbopol® 940 (0.5%, 0.75%, and 1% w/w concentrations) was used as the gelling agent for the gel base. The prepared emulgels were characterized in terms of pH, rheological behavior, spreadability, and *in vitro* release of ketoprofen. **Results and Discussion:** All formulations produced stable, white, semisolid forms with smooth homogeneous textures and no phase separations. The pH of the resulting emulgels ranged from 5.5 to 6.5. An increase in the carbopol concentration led to an increase in viscosity, and all prepared emulgels exhibited pseudoplastic flow. The spreadability of semisolid dosage forms improved by reducing the concentration of the gelling agent. Results from the *in vitro* study indicated that 88.48%-99.11% of the ketoprofen was released within 150 min. **Conclusion:** The prepared emulgels are in semisolid form, and hence suitable for topical application.

Key words: Carbopol, Emulgels, Ketoprofen, Topical application.

INTRODUCTION

Ketoprofen [KP; (2RS)-2-(3-benzoylphenyl) propanoic acid] is a widely used non-steroidal anti-inflammatory drug (NSAID) that is effective for the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.[1] The physicochemical properties of KP are considered as ideal, with a molecular weight of 254.29 Da, pKa of 5.94, and partition coefficient of 0.97. KP is practically insoluble in water, and freely soluble in acetone, ethanol (96%), and methylene chloride.[2] Various dermal formulations for KP have been developed, including gels,[3,4] ointments,[5] plasters,[6] and microemulsions.[7] In a study evaluating the efficacy and skin permeability of nine topical NSAID formulations, Komatsu and Sakurada found that KP has potent anti-inflammatory and analgesic properties as well as high skin permeability.[8]

Emulgels are emulsions incorporated into a gel base. The presence of a gelling agent in the aqueous phase of an emulsion increases its stability.[9] Both hydrophilic and hydrophobic drugs can be incorporated into emulgels, which enhances skin permeation and allows controlled release of the therapeutic agent.[10] Emulgels have several favorable properties: they are greaseless, easily spreadable, easily removable, emollient, feasible to produce, and have a pleasing appearance, long shelf-life, and low preparation cost.[11,12,13]

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Correspondence:
Dr. Petya Peneva,
Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University-Plovdiv, 15A Vassil Aprilov Blvd, Plovdiv 4002, BULGARIA.
Phone no: 0886358683
E-mail: pharmpeneva@abv.bg

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The present study investigates the influence of different oil phases and gelling agent concentrations on the technological and biopharmaceutical characteristics (viscosity, spreadability, and *in vitro* drug release) of the prepared emulgels.

MATERIALS AND METHODS

MATERIALS

This study utilized analytical-grade KP (≥ 99%; Sigma-Aldrich, USA), Carbopol® 940 (The Lubrizol Corporation, USA), propylene glycol (PG; Sigma-Aldrich, USA), ethanol 95% (v/v), Span® 65 (Sigma-Aldrich, USA), Tween® 60 (Sigma-Aldrich, USA), light liquid paraffin (LLP, Ph. Eur.), cetyl alcohol (CA; Sigma-Aldrich, USA), isopropyl myristate (IPM; Sigma-Aldrich, USA), almond oil (AO), triethanolamine (TEA), and purified water.

Preparation of emulgels

The emulsion and carbopol dispersion were prepared separately. The oil phase of the emulsion included a hydrophobic substance (LLP, CA, IPM, and AO) with dissolved Span 65. The hydrophilic phase contained PG, Tween 60, and purified water. KP was dissolved in ethanol and added to the hydrophilic phase of the emulsion. Both the oil and the hydrophilic phases were heated to a temperature of 70–80°C; the oil phase was then added to the hydrophilic phase with continuous stirring (300 rpm). Carbopol was dispersed in purified water at room temperature with continuous stirring (300 rpm). The obtained emulsion and the dispersed carbopol were mixed at a 1:1 ratio, after which the pH was adjusted to 5.5–6.5 with TEA. The compositions of the various formulations are presented in Table 1.

Evaluation of emulgels

Physical examination of emulgels

The prepared emulgels were inspected visually for their color, homogeneity, consistency, and phase separation.

Determination of pH

The pH values of 10% aqueous solutions of the prepared emulgels were measured by a pH meter (inoLab pH 720), which was calibrated with standard buffer solutions.[14] The measurements were conducted three times for each formulation, with the pH presented as mean ± standard deviation (SD).

Determination of drug content

Drug content in the emulgel formulations was determined as follows: 0.100 g of the emulgel formulation was dispersed in freshly prepared phosphate buffer (pH 5.5) in 100 mL volumetric flasks under ultrasonic impact; 5 mL of this dispersion was filtered and diluted to 25 mL with phosphate buffer (pH 5.5).[15,16] The drug content was determined at 260 nm using a UV-Vis spectrophotometer, Ultrospec 3300 pro (Biochrom Ltd., Cambridge, UK). The measurements were conducted three times, with the results presented as mean ± SD.

Determination of viscosity

Viscosity of the prepared emulgels was determined using a Selecta STS-2011 viscometer (J.P. SELECTA, s.a., Spain) at 25 ± 0.5°C. A spindle R6 was used at 1, 2, 3, 4, 5, 6, and 10 rpm. The results, presented as mean ± SD, were plotted after triplicate measurements.

Determination of spreadability

A 350 mg sample of the emulgel preparation was weighed on a glass slide (10/5 cm). Another glass slide (10/5 cm and 6 ± 1 g) was then placed on top. Gel type was defined based on the diameter of the resulting circle after 1 min: > 2.4 cm, fluid gel; 1.9 to 2.4 cm, semi-fluid gel; 1.9 to 1.6 cm, semi-stiff gel; 1.6 to 1.4 cm, stiff gel; and < 1.4 cm, very stiff gel.[17]

In vitro drug release studies

In vitro analysis of KP release from the prepared emulgels was performed using Dissolution Apparatus 1 (Basket apparatus, Sotax) under sink conditions.[18] A ~300 mg emulgel sample was applied on a cellulose membrane affixed to a basket.[14] Freshly prepared phosphate buffer (300 mL, pH 5.5) was used as the test medium. The experiment was conducted at 32 ± 0.5°C and 50 rpm. Samples of 5 ml were taken at appropriate time intervals. The amount of KP released was determined spectrophotometrically at $\lambda = 260$ nm.

To evaluate the drug release kinetics and better understand its release mechanisms, the data obtained from the *in vitro* dissolution tests were fitted to zero-order, first-order, Higuchi, and Korsmeyer-Peppas models.

Determination of stability

Stability of the prepared emulgels was assessed in accordance with International Council for Harmonisation guidelines. Emulgels were packed in tightly closed plastic containers and stored at 30 ± 2°C/65 ± 5% RH. After 6 months, the samples were evaluated for physical appearance, pH, and drug content.

Statistical analysis

Data were analyzed by one-way analysis of variance (ANOVA) using GraphPad InStat (ver. 3.10). A P-value < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Preparation and evaluation of emulgels

In this study, we prepared emulgels using various oil phases (LLP, CA, IPM, and AO) and carbopol concentrations Table 1. All formulations were white, viscous, and creamy with a smooth and homogeneous texture. The consistency of all emulgels was suitable for dermal application. Phase separation was not observed. The pH values of the formulations, ranging from 5.62 ± 0.02 to 6.42 ± 0.01, were optimal for dermal application.

The drug content of the emulgels ranged from 98.56 ± 0.01% to 99.72 ± 0.26%, indicating full incorporation of KP in the emulgels Table 2.

Determination of viscosity

Viscosity behavior as a function of shear rate is presented in Figure 1. Viscosity was influenced by the oil phase and carbopol concentration of the emulgel. The highest viscosity was observed with formulation F4 (CA and 1% carbopol). Increases in the quantity of LLP (F1: 5%; F2: 6%; F3: 7.5%) were associated with reduced viscosity. This effect has also been observed with miconazole nitrate emulgels.[19] Formulations F5 and F6 had lower viscosities than F1–F4, likely due to the different oil phases used (IPM and AO). Similar less pronounced trends were observed with F7–F12, prepared with 0.75% carbopol, and F13–F18, prepared with 0.5% gelling agent. Therefore, the type and amount of oil phase play important roles in viscosity. Reductions in the gelling agent concentration led to a change in viscosity in the following order: F1–F6 > F7–F12 > F13–F18. Thus, an increase in carbopol concentration is associated with an increase in viscosity. This could be explained by the mechanism of gelation of carbopol. Reaction of the carbomer carboxyl groups with hydroxyl groups of PG and ethanol leads to the formation of hydrogen bonds.[20] A higher carbopol concentration results in a higher number of hydrogen bonds, resulting in higher viscosity.

At the lowest shear rate (1 rpm), no significant difference in viscosity was observed between groups F1–F6 and F7–F12 ($P>0.05$). However, a significant difference in viscosity was observed between F1–F6 and F13–F18 ($P<0.001$), and between F7–F12 and F13–F18 ($P<0.01$). At the highest shear rate (10 rpm), significant differences were observed between F1–F6 and F13–F18 ($P<0.05$), and F7–F12 and F13–F18 ($P<0.05$), but not F1–F6 and F7–F12 ($P>0.05$).

The prepared emulgels demonstrated non-Newtonian shear thinning pseudoplastic flow (i.e., the increase in shear rate was related to the reduction in viscosity). As shear stress increases, the long polymer chains are arranged in the direction of flow. This orientation of the long axes reduces the internal resistance of the material, thereby decreasing viscosity.[14]

Determination of spreadability

The spreadability of emulgels is an important technological characteristic. The formulations prepared with 1% carbopol (F1–F4) were defined as semi-stiff gels, while F5 and F6 were semi-fluid gels Table 2. This is likely due to the oil phase used (IPM vs. AO). Reducing the gelling agent concentration reduces viscosity and increases spreadability, as observed with the categorization of formulations F7–F12 as semi-fluid gels (excluding F10, defined as a semi-stiff gel as it was prepared with CA). The formulations prepared with a lower concentration of carbopol, F13–F18, were characterized as fluid gels (with the exception of F16, which was prepared with CA and characterized as a semi-fluid gel). Overall, the results indicate that the spreadability of emulgels is improved by reducing the concentration of carbopol.

The Tukey-Kramer multiple comparison test assumes that the differences among the SDs for F1–F6, F7–F12, and F13–F18 are extremely significant ($P = 0.0005$). If the value of q is greater than 3.674, the P value is < 0.05 Table 3.

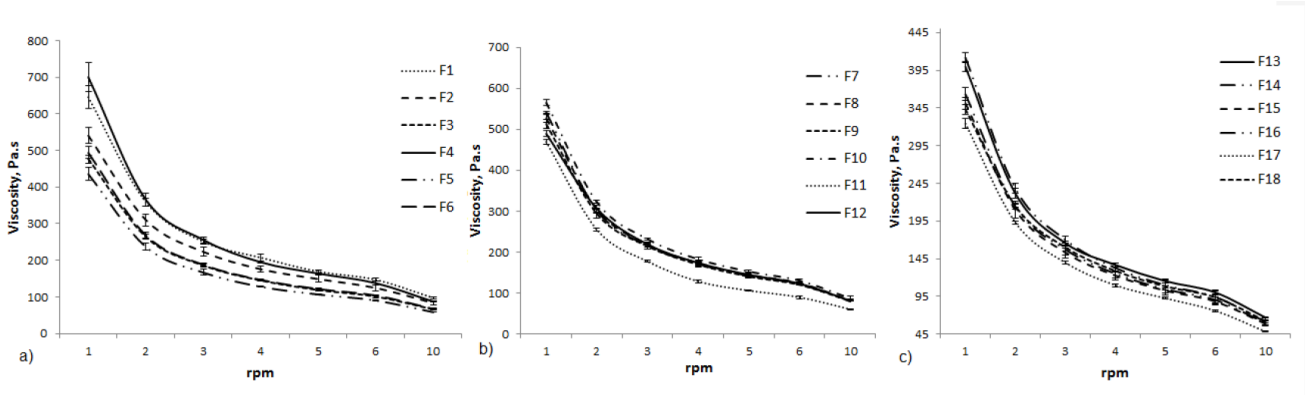

Figure 1: Effect of shearing on viscosity.

In vitro drug release

The results of the cumulative drug release assessment are presented in Table 2. The *in vitro* KP release profiles of the emulgels are shown in Figure 2. The amount of drug released after 150 min was high, ranging between 88.48 ± 0.82% and 99.11 ± 0.69%. The reduction in viscosity leads to increases in the amount of drug released and the release rate. Our results support previous findings with zidovudine emulgels.[21] The type of oil phase had no effect on the KP release profile. The highest cumulative drug release was observed with F18, the formulation prepared with AO and 0.5% carbopol.

Drug release mechanisms and kinetics were determined by the application of zero-order, first-order, Higuchi, and Korsmeyer-Peppas models. Goodness of fit was evaluated using determination coefficient (R^2) values. According to the R^2 values, the *in vitro* release data were in favor of first-order kinetics. For all the tested models, the "n" value was below 0.5, demonstrating that the mechanism controlling the drug release was the quasi Fickian diffusion. First-order release kinetics for KP was obtained using a series of simple gels containing HPC and carbosil that varied in solvent composition.[22]

Stability study

F18 was identified as the most promising emulgel formulation. After 6 months of storage, no changes in color, consistency, and homogeneity were observed in the selected sample. Drug contents before and after storage were 99.69 ± 0.10% and 98.96 ± 0.18%, respectively. The pH value decreased from 5.73 ± 0.02 to 5.65 ± 0.01. The minor changes in pH value and drug content, as well as the lack of any changes in physical appearance, highlight the stability of the emulgel.

Table 1: Composition of ketoprofen emulgel formulations (% w/w).

Formulation	KP	Carbopol	LLP	CA	IPM	AO	Span 65	Tween 60	PG	Ethanol	Purified water
F1	1	1	5	-	-	-	0.69	1.31	5	10	q.s.
F2	1	1	6	-	-	-	0.69	1.31	5	10	q.s.
F3	1	1	7.5	-	-	-	0.69	1.31	5	10	q.s.
F4	1	1	-	5	-	-	0.14	1.86	5	10	q.s.
F5	1	1	-	-	5	-	0.69	1.31	5	10	q.s.
F6	1	1	-	-	-	5	0.69	1.31	5	10	q.s.
F7	1	0.75	5	-	-	-	0.69	1.31	5	10	q.s.
F8	1	0.75	6	-	-	-	0.69	1.31	5	10	q.s.
F9	1	0.75	7.5	-	-	-	0.69	1.31	5	10	q.s.
F10	1	0.75	-	5	-	-	0.14	1.86	5	10	q.s.
F11	1	0.75	-	-	5	-	0.69	1.31	5	10	q.s.
F12	1	0.75	-	-	-	5	0.69	1.31	5	10	q.s.
F13	1	0.5	5	-	-	-	0.69	1.31	5	10	q.s.
F14	1	0.5	6	-	-	-	0.69	1.31	5	10	q.s.
F15	1	0.5	7.5	-	-	-	0.69	1.31	5	10	q.s.
F16	1	0.5	-	5	-	-	0.14	1.86	5	10	q.s.
F17	1	0.5	-	-	5	-	0.69	1.31	5	10	q.s.
F18	1	0.5	-	-	-	5	0.69	1.31	5	10	q.s.

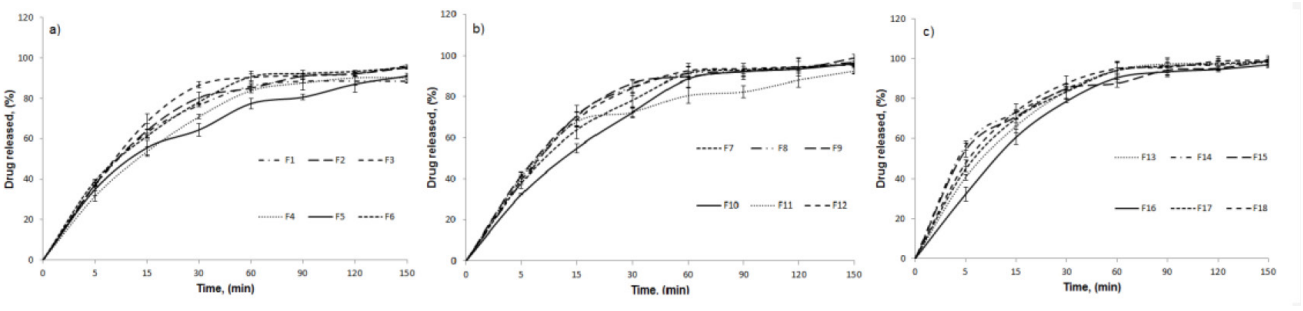

Figure 2: *In vitro* cumulative drug release (%) of emulgels.

Table 2: Summary of pH values, drug content (%), spreadability (cm), and cumulative drug release (%) of emulgels.

Formulation	pH	Drug content, (%)	Spreadability, (cm)	Cumulative drug release at the 150 min, (%)
F1	5.62±0.02	98.91±0.01	1.60±0.1	88.48±0.82
F2	5.98±0.02	99.01±0.02	1.63±0.06	95.19±0.58
F3	6.13±0.02	99.25±0.01	1.87±0.06	96.14±0.27
F4	6.09±0.01	98.56±0.01	1.77±0.15	90.14±2.14
F5	5.99±0.02	98.99±0.02	2.07±0.06	91.01±0.26
F6	5.87±0.02	99.72±0.26	1.93±0.06	95.31±0.64
F7	5.77±0.01	98.69±0.12	2.07±0.06	95.92±4.68
F8	5.87±0.01	99.05±0.15	2.13±0.06	96.8±1.9
F9	6.01±0.01	99.25±0.11	2.20±0.06	98.92±0.53
F10	6.03±0.01	98.56±0.05	1.85±0.06	96.16±1.19
F11	5.95±0.01	99.26±0.10	2.30±0.06	92.4±1.48
F12	6.02±0.01	98.99±0.13	2.35±0.1	95.54±0.97
F13	6.42±0.01	98.66±0.21	2.40±0.1	98.46±3.07
F14	6.22±0.01	98.95±0.15	2.47±0.15	98.02±2.26
F15	5.89±0.01	99.45±0.06	2.55±0.06	99.03±0.56
F16	5.81±0.01	98.81±0.07	1.93±0.06	96.94±0.27
F17	5.66±0.01	99.01±0.08	2.67±0.06	98.54±0.78
F18	5.73±0.02	99.69±0.10	2.63±0.06	99.11±0.69

Table 3: Statistical data (mean difference, q, and P value) obtained from the comparison of F1–F6, F7–F12, and F13–F18.

Comparisons	Mean Difference	q	P value
F1-F6 vs. F7-F12	-0.3383	3.866	P<0.05
F1-F6 vs. F13-F18	-0.6300	7.200	P<0.001
F7-F12 vs.F13-F18	-0.2917	3.333	not significant

CONCLUSION

The KP emulgels were white, viscous, and creamy with excellent homogeneity and pH suitable for dermal application. Increasing carbopol concentrations in the gel base led to an increase in viscosity, and all emulgels exhibited pseudoplastic flow. The spreadability of the semi-solid dosage forms was improved by reducing carbopol concentrations. Based on the *in vitro* drug release analysis, F18 was the formulation of choice with a maximum drug release of 99.11 ± 0.69% after 150 min. Based on the results obtained, we can suggest that the drug release from F18 can provide a prolonged therapeutic effect, with a reduced number of applications and improved patient compliance. After 6 months of storage, the F18 formulation remained stable. Thus, carbopol emulgels are a promising topical delivery system for therapeutic agents like KP.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS USED

AO: almond oil; **CA:** cetyl alcohol; **IPM:** isopropyl myristate; **KP:** ketoptofen; **LLP:** light liquid paraffin; **NSAID:** non-steroidal anti-inflammatory drug; **PG:** propylene glycol; **SD:** standard deviation; **TEA:** triethanolamine.

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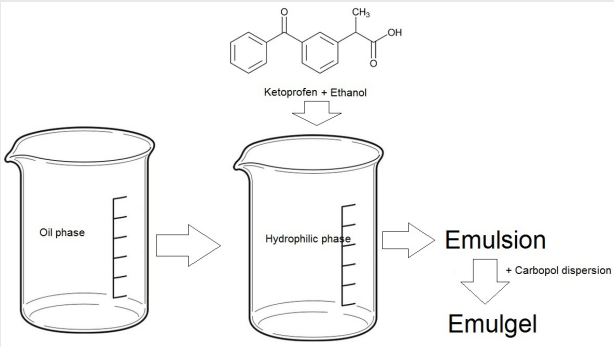
PICTORIAL ABSTRACT



SUMMARY

- Emulgels with different oil phases (such as light liquid paraffin, cetyl alcohol, isopropyl myristate, and almond oil) and Carbopol 940 (various concentrations) as a gelling agent were prepared.
- All formulations produced stable, white, semi-solid forms with smooth homogeneous textures and no phase separations.
- An increase in the carbopol concentration led to an increase in viscosity, and all prepared emulgels exhibited pseudoplastic flow.
- The spreadability of emulgels is improved by reducing the concentration of carbopol.
- The reduction in viscosity leads to increases in the amount of drug released and the release rate.
- Carbopol emulgels are a promising topical delivery system for therapeutic agents like KP.

About Authors

Ms. Petya Peneva: Is an assistant professor in Pharmaceutical Technology and Biopharmacy, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University-Plovdiv. Her scientific interests are in the field of semi-solid dosage forms as well as the development and evaluation of nanoparticles.

Dr. Velichka Andonova: Is a chief assistant professor in Pharmaceutical Technology and Biopharmacy, Department of Pharmaceutical Sciences, Faculty of Pharmacy, Medical University-Plovdiv. Her scientific interests are in the field of nanotechnologies (polymeric and nobble nanoparticles); microencapsulation of active pharmaceutical ingredients; dosage forms for ophthalmic administration; and semi-solid dosage forms for topical administration.

Dr. Teodora Dimcheva: Is a chief assistant professor at the Department of Medical informatics, Biostatistics and eLearning, Faculty of Public Health since 2012. Scientific and research activity: healthcare management; management of COPD; medical statistics; Quantitative methods; IT in healthcare; E-learning and education.

Prof. Margarita Kassarova: Is a Head of Department of Pharmaceutical Sciences and Chief Secretary of the Faculty of Pharmacy, Medical University-Plovdiv. She is a professor in Pharmaceutical Technology and Biopharmacy. She is also PhD mentor as well as a head of many scientific projects

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