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Research Article

Determining the Polymer Threshold Amount for Achieving Robust Drug Release from HPMC and HPC Matrix Tablets Containing a High-Dose BCS Class I Model Drug: *In Vitro* and *In Vivo* Studies

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Abstract. It is challenging to achieve mechanically robust drug-release profiles from hydrophilic matrices containing a high dose of a drug with good solubility. However, a mechanically robust drug release over prolonged period of time can be achieved, especially if the viscosity and amount of the polymer is sufficiently high, above the "threshold values." The goal of this research was to determine the hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) polymer threshold amount that would enable robust drug release from matrix tablets containing a high dose of levetiracetam as a class I model drug according to the Biopharmaceutical Classification System (BCS). For this purpose, formulations containing HPC or HPMC of similar viscosity range, but in different amounts, were prepared. Based on the dissolution results, two final formulations were selected for additional *in vitro* and *in vivo* evaluation to confirm the robustness and to show bioequivalence. Tablets were exposed to various stress conditions *in vitro* with the use of different mechanically stress-inducing dissolution methods. The *in vitro* results were compared with *in vivo* results obtained from fasted and fed bioequivalence studies. Under both conditions, the formulations were bioequivalent and food had a negligible influence on the pharmacokinetic parameters C_{max} and area under the curve (AUC). It was concluded that the drug release from both selected formulations is mechanically robust and that HPC and HPMC polymers with intrinsic viscosities above 9 dL/g and in quantities above 30% enable good mechanical resistance, which ensures bioequivalence. In addition, HPC matrices were found to be more mechanically robust compared to HPMC.

KEY WORDS: HPC; HPMC; matrix tablets; mechanically robust dissolution; threshold amount.

INTRODUCTION

In the development and production of hydrophilic matrix tablets, hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) are the most frequently used polymers. The mechanism of drug release from HPMC- or HPC-based matrices has been studied and reviewed in the literature as well as in our previous work (1–5). Considering the solubility interplay between the drug and polymer, the release is diffusion-controlled if the solubility of the incorporated drug is greater than the solubility of the polymeric matrix. In contrast, the release is more erosion-controlled if the solubility of the polymeric matrix is greater than the solubility of the incorporated drug (2). Applying this theory, for drugs with good solubility (Biopharmaceutical Classification System (BCS) class I), the release would be generally more diffusion-controlled, especially if the tablet contains a high amount of high-viscosity–grade polymer. In this way, formation of a robust gel layer enables mechanically robust drug release over prolonged time and also contributes to lowering the initial burst release of highly soluble API. Therefore, these types of formulations are not expected to be mechanically influenced by GI motility or to exhibit any significant food effect related to mechanical physiological differences between a fasted state (drug taken on an empty stomach) and a fed state (drug taken shortly after a meal).

GI motility is different under fasted and fed conditions. In the fasted state, the mechanical stress exerted on a tablet during GI transit mostly depends on the migrating myoelectric complex (MMC). The movement of tablets during the first and second MMC phase is relatively slow; however, during the short gastric emptying phase (phase III), which cycles every 90 to 120 min and lasts 15 to 20 min, tablets are prone to greater mechanical stress because stomach contractions are intense (6–8). Pressures during the gastric emptying phase have been measured and can be about 60 Pa in the fasted state and up to 96 Pa in the fed state (9). In the fed state, gastric motility after food intake is also elevated, which exerts greater mechanical stress on matrix tablets (9–11).

In vitro tests should be designed considering different *in vivo* gastrointestinal conditions. The goal of bio-relevant *in vitro* testing is to establish an *in vitro–in vivo* correlation and

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to reflect any possible differences between formulations tested before conducting bioequivalence studies (12–14). The ionic strength and pH of the media may influence drug release from hydrophilic matrices; however, the hydrodynamic and mechanical conditions around the matrix tablets are the most relevant for mimicking *in vivo* gastrointestinal forces. This is particularly true in the case of more erosion-controlled matrix tablets, but less for diffusion-controlled systems.

In vitro tests simulating different hydrodynamic conditions are difficult to develop using only conventional dissolution methods. So far, some modifications to the conventional dissolution apparatus, as well as novel dissolution methods for elucidating mechanical stress, have been proposed (11, 14–17). The use of USP dissolution Apparatus 3 (reciprocating cylinder, BioDis) has also been suggested for simulating the mechanical conditions within the GIT (18–20).

In our previous work, we tested the HPMC and HPC tablet robustness, correlating it with intrinsic viscosity of the polymer based on the method described by Sako *et al.* (15). It was confirmed that an increased intrinsic viscosity of the HPMC or HPC polymer value resulted in decreased mechanical susceptibility of predominately diffusion-controlled matrices containing a low-dose model drug with a solubility of about 0.1 mg/mL in aqueous media. Furthermore, a minimum threshold value of intrinsic viscosity that ensures a controlled, non-accelerated drug-dissolution profile was determined and was set to about 9 dL/g for HPMC and to about 10 dL/g for HPC (21).

A USP 3 apparatus in combination with plastic beads was also used to apply additional mechanical stress to HPMC matrices with a model drug with low solubility (22). It was shown that applying the stress using the beads was crucial in discriminating the tablets *in vitro* and in establishing a good correlation with *in vivo* data. In this case, however, the drug release was more erosion-controlled.

Studies were performed to determine polymer threshold amounts that ensure mechanically robust drug release while keeping the polymer viscosities fixed above previously determined threshold values. The hypothesis was that HPMC or HPC with high viscosity grades and in a similar range would enable robust drug release profiles in a wide polymer amount range considering the rule for intrinsic viscosity values in correlation with mechanical susceptibility established in our previous work (21). For this purpose, we prepared formulations containing different amounts of HPC and HPMC with an incorporated high dose of a BCS class I model drug. Two final formulations were selected based on the dissolution results and were additionally evaluated for robustness with stress-inducing *in vitro* tests and *in vivo* bioequivalence studies under fasted and fed conditions. The *in vivo* and *in vitro* results were compared and discussed to confirm the robustness of the selected formulations with respect to their mechanical resistance.

MATERIALS AND METHODS

Materials

The antiepileptic drug levetiracetam with molecular weight 170.21 g/mol and pH-independent solubility in aqueous media 1 g/mL was purchased from Hetero Drugs Ltd. The excipients used in the formulations were as follows: HPMC, hypromellose USP Type 2208 with apparent viscosity 11,250–21,000 mPas and intrinsic viscosity 8.98 dL/g (21) (DOW Chemical Company, Midland, MI, USA); HPC, hydroxypropyl cellulose with apparent viscosity 14,000–18,000 mPas and intrinsic viscosity 10.2 dL/g (21) (Hercules, Aqualon, Wilmington, DE, USA); polyethylene glycol 6000 (Clariant GMBH, Germany); Aerosil 200 colloidal silica dioxide (Degussa, Germany); and magnesium stearate (Mallinckrodt Chemical Inc., USA). Reagents for the dissolution testing were NaOH, ethanol (96% *v*/*v*), and KH_2PO_4. For HPLC NaH_2PO_4, acetonitrile, and H_3PO_4 (Merck, Germany) were used.

Tablet Preparation

High-dose (750 mg per tablet) levetiracetam and a selected amount of the controlled release rate polymer HPC for formulations A1–A5 (Table I) or HPMC for formulations B1–B5 (Table I) were blended and granulated with purified water in a Glatt fluid bed granulator GPCG 30 (Glatt, Germany). After drying, granulate was sieved with a Frewitt MG 636 (Key International, USA) oscillating sieve, mesh size 0.71 mm. The granulate loss on drying (LOD) was 0.5% tested 20 min at 80°C using loss on drying balance (Mettler-Toledo International Inc.). The granulate obtained was mixed with PEG 6000 and Aerosil 200 colloidal silica dioxide using a bin blender (Erweka, Germany). Magnesium stearate was then added and the entire composition was blended again to obtain the final mixture (Table I). The final mixture was compressed into tablets with punches measuring 21.0×10.0 mm using a tablet press (Fette 2090, Germany) to obtain tablets with hardness from 180 to 250 N (Kraemer automatic tablet tester, Germany). The difference in hardness was due to different polymer amounts in the formulations that were not compensated for with another excipient. It was confirmed that hardness in a range from 150 to 250 N has no significant influence on the dissolution profiles. The percent of polymer A (HPC) or B (HPMC) in the matrices was 10, 15, 20, 25, or 30%. Various authors suggest the use of at least 20% polymer to achieve robust drug release (23). However, for HPMC, the supplier suggests the use of 30 to 40% polymer (24).

In Vitro Testing

Dissolution Testing

All formulations were tested using the FDA-suggested method: Apparatus 1 (USP), 100 rpm in a pH 6.0 phosphate buffer media (DT1, Table II) (http://www.accessdata.fda.gov/scripts/cder/dissolution/). The mechanical robustness of formulations was further evaluated using additional *in vitro* stress-inducing dissolution methods (DT2–DT4, Table II).

Dissolution tests DT1–DT3 were performed with Apparatus 1 using a dissolution tester (Erweka DT6, Germany) coupled with an automatic sampler (Vankel VK8000, USA). Standard vessels with baskets were utilized at stirring rates of 100 rpm with 900 mL of dissolution media. The dissolution media temperature was set to 37±0.5°C prior to starting the test. For each time point, 1.7 mL of sample was automatically collected and filtered through 4.0-μm tip filters (Erweka, Germany) into 2.0-mL vials. The dissolution medium was not replaced.

In test DT2, additional mechanical manipulation with glass beads was introduced. After 1 h 30 min from commencing the

Table I. Compositions of the Tablet Formulations Studied in Milligrams (A for HPC-Type and B for HPMC-Type)

Formulation A, B	1	2	3	4	5
Levetiracetam	750.0	750.0	750.0	750.0	750.0
HPC (A) or HPMC (B)	85.4	135.7	192.3	256.3	329.6
Colloidal silica dioxide	5.5	5.5	5.5	5.5	5.5
Polyethylene glycol 6000	11.0	11.0	11.0	11.0	11.0
Magnesium stearate	2.5	2.5	2.5	2.5	2.5
Target mass	854.4	904.7	961.3	1025.3	1098.6
Polymer amount (%)	10	15	20	25	30

test, tablets were transferred to 50-mL plastic tubes containing 10 mL of medium and 10 g of glass beads with a density of approximately 2.5 g/mL and 1 cm in diameter. The tubes were shaken vertically for 10 min on a laboratory shaker (IKA, Staufen, Germany) at 300 strokes per min. After this manipulation, the tablets were transferred back to baskets in vessels and the dissolution test continued. This test was used previously by Sako *et al.* (15) and also by us (21).

Test DT3 was performed in the same way as test DT1; only the media was changed to 40% (*v*/*v*) ethanol solution. The selected ethanol concentration was the highest one that is suggested based on FDA guidelines for evaluating burst release in the presence of ethanol (25).

Test DT4 was done with a USP 3 apparatus containing plastic beads to exert high mechanical stress on the tablets. This test was developed in our group and is only briefly presented here (22). A total of 250 mL of dissolution media was poured into each dissolution vessel and placed in a water bath to maintain a temperature of 37±0.5°C. Next, beads to fill approximately one fourth of the vessels (8 g) were weighed and placed into reciprocating cylinders. The tablets were weighed and placed on top of the beads and the cylinders were attached to the BioDis. The stainless steel mesh size screen on the top and bottom of the cylindrical vessels was 2000 μm. The dipping speed was set to 25 DPM.

Dissolution test data were further manipulated and analyzed using Excel software. The non-linear least squares method was used to fit the different dissolution profiles. The Korsmeyer–Peppas release rate constant k (kinetic constant) and the exponent n (diffusion coefficient) were calculated by fitting the dissolution curves to Eq. 1 (26).

$$Q_t = kt^n \quad (1)$$

In addition, the dissolution profiles were fitted using the Peppas–Sahlin equation (Eq. 2) (27, 28). Origin software from OriginPro labs was used.

$$Q_t = K_d t^m + K_r t^{2m} \quad (2)$$

Q_t is the percentage of drug released at a given time point t, and k is a kinetic constant characteristic of the drug/polymer system. The exponent n was calculated from Eq. 1 and the diffusion and relaxation rate constants K_d and K_r (Eq. 2) were used as a criterion to evaluate the release-mechanism kinetics and to compare the formulations. Exponent m represents a purely Fickian diffusion exponent for a device of any geometrical shape, and it was selected at 0.45 for cylindrical shapes (2, 32).

HPLC Assay

An HPLC system, the Waters 2695D separation module (Waters, USA) with UV detection at a wavelength of 200 nm, was used to analyze the collected samples. The chromatographic column C18, 3.5 μm with dimensions 150×4.6 mm X-Bridge (Merck, Germany), was thermostated at 30°C during the analysis. The mobile phase had a composition of phosphate buffer pH 7.0 to acetonitrile in a ratio of 90:10 (volume ratio). The phosphate buffer solution pH 7.0 was prepared by dissolving 1.4 g of Na_2HPO_4 in 1000 mL of purified water. The pH was set with 85% H_3PO_4. The flow rate of the mobile phase was 1.0 mL/min and 10 μL of sample solution was injected from the vials maintained at 4°C. The retention time of levetiracetam was around 4 min; the total run time of the analysis was 6 min. The HPLC method was validated.

In Vivo Bioequivalence Studies

Study Design

Formulations A and B were tested in two separate single-dose, randomized, open-label, two-period crossover studies on 14 healthy male volunteers aged 18–55 years under fasting or fed conditions. The volunteers received an oral dose of 1×750 mg of formulation A or B with 240 mL of water according to randomization schedule. There was a washout period of 7 days between each dosing.

In the fasting study, formulation A/B was administered following a 10-h overnight fasting period. Volunteers were required to fast for at least 4 h after dosing, and water was restricted from 1 h prior to dosing until 1 h post dosing except

Table II. Dissolution Testing Methods to Evaluate Mechanical Robustness of the Tablets

Test	DT1	DT2	DT3	DT4
Test type	Apparatus 1	Apparatus 1+glass bead manipulation	Apparatus 1	Apparatus 3 with plastic beads
Setting	100 RPM	100 RPM	100 RPM	25 DPM
Sampling times (h)	1, 2, 4, 8, 12	1, 2, 4, 8, 12	1, 2, 4, 8, 12	1, 2, 4, 8, 12
Medium	Phosphate buffer pH 6.0	Phosphate buffer pH 6.0	Ethanol 40%	Phosphate buffer pH 6.0

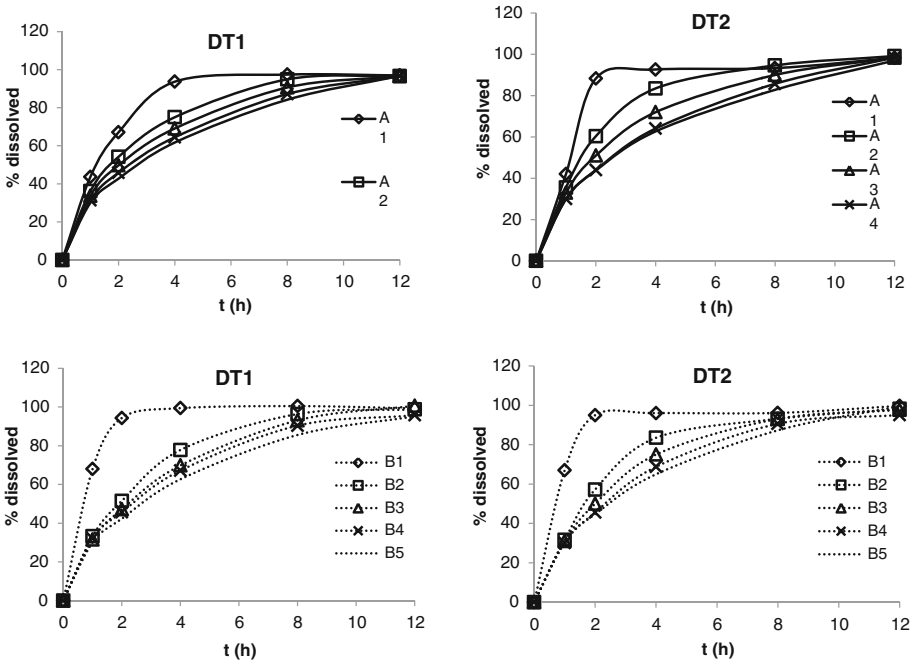

Fig. 1. Dissolution profiles for formulations A1–A5 containing HPC (*straight lines*) and for formulations B1–B5 containing HPMC (*dotted lines*) obtained from dissolution testing methods DT1 (*left*) and DT2 (*right*). RSD values (n=3) were below 3% and are not presented

for the water provided for the drug administration. After 4-h fasting period, subjects were given standardized meals at scheduled times. Blood samples were collected prior to and at 1, 2, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, 12, 16, 24, 30, and 36 h after dosing in each study period.

In the fed study, 10-h overnight fasting period was followed by an FDA-recommended high-fat, high-calorie breakfast. Volunteers received either formulation 30 min after the start of the breakfast. No food was allowed for further 4 h after dosing, and then standardized meals were provided. Water restriction period lasted from 1 h prior to dosing to 1 h post dosing. Blood samples were collected prior to and at 1, 2, 3, 3.5, 4, 4.5, 5, 5.5, 6, 7, 8, 10, 12, 16, 24, 30, and 36 h after dosing in each study period.

The levetiracetam in the plasma was determined by high-performance liquid chromatography connected to mass spectrometry.

Statistical Analysis

ANOVA was performed for ln-transformed AUC_t, AUC_{inf}, and C_{max}; T_{max} was analyzed using an additional non-parametric test. The 90% confidence intervals for A/B ratios of geometric means for AUC_t, AUC_{inf}, and C_{max} were calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA.

RESULTS AND DISCUSSION

It is known that development of prolonged-release matrix tablet formulations with a high dose of a highly soluble active pharmaceutical ingredient is very challenging. Therefore, polymers enabling constant prolonged release should be very effective at a relatively low percentage. Among them, some cellulose ethers such as high-viscose HPMC and HPC are highly efficient. The release from HPC and HPMC matrix tablets is usually a combination of gel erosion and the diffusion of the dissolved drug from the swollen gel layer on the tablet. However, if the solubility of the compound is greater than the solubility of the polymeric matrix, the release is predominately diffusion-controlled (1, 2). Our goal was to determine appropriate polymer amounts that would enable robust release and prevent food and mechanical influences that occur *in vivo*.

Our previous work confirmed that an increased intrinsic viscosity value of HPMC or HPC polymer value resulted in a

Table III. Calculated Slopes (%/h) of Dissolution Profiles Between the 1st and 2nd Hour with Corresponding Differences Δ (DT2−DT1) for HPC-Type Formulations

	A1	A2	A3	A4	A5
DT2	46.2	24.8	18.0	15.5	13.8
DT1	23.4	18.0	16.0	14.0	12.7
Δ	22.8	6.8	2.0	1.5	1.1

Table IV. Calculated Slopes (%/h) of Dissolution Profiles Between the 1st and 2nd Hour with Corresponding Differences Δ (DT2−DT1) for HPMC-Type Formulations

	B1	B2	B3	B4	B5
DT2	28.0	25.6	19.0	15.5	13.7
DT1	26.3	18.3	15.6	13.6	12.3
Δ	1.7	7.3	3.4	1.9	1.4

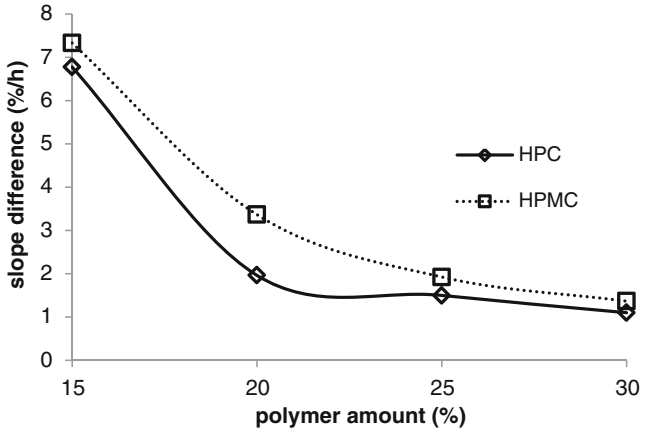

Fig. 2. The difference between slopes (%/h) of dissolution profiles obtained in tests DT2 and DT1 for HPMC and HPC formulations with different polymer amount. Note that the 10% amount is not shown because the HPMC formulation releases about 70% of the drug within the 1st hour and the slope between the 1st and 2nd hour is less descriptive of the profile acceleration

decrease in the mechanical susceptibility of hydrophilic matrices containing a low dose (1 mg) of drug with a solubility of 0.1 mg/mL. The threshold intrinsic viscosity value was set between 9 and 10 dL/g (21). The same rule for intrinsic viscosity was also assumed in this study, and a further assumption was that matrix tablets containing a sufficiently high-viscosity type should have robust *in vitro* dissolution profiles if tested with different mechanically "stress enhancing" dissolution methods. However, the polymer amount that is the "threshold amount" for enabling robust drug release was yet to be determined. To test whether our assumptions were valid and selected polymer amounts were correct, different *in vitro* stress tests as well as a bioequivalence study under fasted and fed conditions were performed.

Dissolution Testing Results

All formulations were tested with a conventional dissolution testing method (DT1) and a glass bead manipulation method (DT2). The results are shown in Fig. 1.

Observation of the profiles in Fig. 1 leads to the following conclusions. Increasing the polymer amount decreases the drug release. Comparing the profiles of DT1 with those of DT2, it can be observed that in the case of a lower polymer amount (below 20%), the mechanical susceptibility is greater because the dissolution rates are faster under conditions of stress DT2 compared to DT1. Comparison of the dissolution profiles reveals that above a certain polymer amount, the profiles obtained with the DT1 and DT2 test methods become similar. To address this in greater detail, the slopes of dissolution profiles between the 1st and 2nd hour were calculated and compared. The slope between the 1st and 2nd hour is the most descriptive because the mechanical stress manipulation was performed at 1 h 30 min. When the difference between the calculated slopes approaches zero for the same formulation under both methods, the mechanical susceptibility was considered small. In contrast, the greater the difference between slopes, the greater the mechanical susceptibility (Tables III and IV). The differences between slopes are graphically presented in Fig. 2.

Comparison of slopes and slope differences shows that at a higher polymer amount, the mechanical susceptibility is low

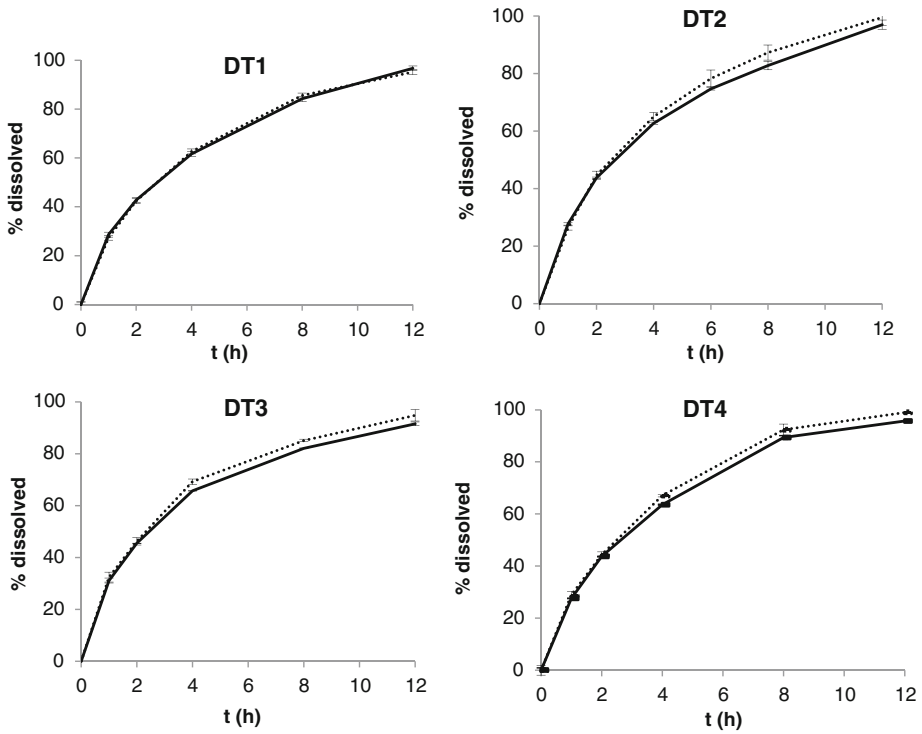

Fig. 3. Dissolution profiles for formulation A5 containing HPC (*straight line*) and formulation B5 containing HPMC (*dotted line*) with SD error bars ($n=3$) obtained from various dissolution testing methods numbered from DT1 to DT4 (*Table II*)

and it is the lowest at 30% of polymer content. This polymer amount in both cases ensures robust drug release *in vitro*. Considering slope differences, a polymer amount of 25% in the HPC formulation (A4) might be sufficient to achieve the desired robust drug release similar to the HPMC formulation (B5) with 30% polymer.

Formation of more robust gel layer on the surface of HPC tablets in comparison to HPMC was even more expressed, when 10% of the polymer was incorporated into matrix tablets. In this case, the difference in slopes was high for HPC (A1) and low for HPMC (B1). Slope differences between HPC (A1) and HPMC (B1) are a consequence of different drug release in the first 60 min (Fig. 1). In a formulation with 10% HPMC (B1), about 70% of the drug is released in 1 h, whereas in a formulation with the same HPC amount (A1), only about 40% (Fig. 1). This confirms that at low polymer amounts, the differences in mechanical robustness of gel layers are more expressed, meaning that HPMC forms a less robust gel compared to HPC. The difference may be attributed to higher intrinsic viscosity of HPC compared to HPMC even if apparent viscosities are in a similar range. The HPC that was used has an intrinsic viscosity of about 10 dL/g whereas that of HPMC is about 9 dL/g (21). Since the intrinsic viscosity values are very similar, the differences in robustness at high percentages of incorporated polymers are not seen. However, at lower percentages, the differences are more pronounced because the gel layer is composed of smaller amount of polymer molecules and here, the intrinsic viscosity of each molecule is important in formation of gel layer.

As seen above, formulations A4 and B5 exhibit similar *in vitro* robustness and could be used for further *in vivo* studies. However, to evaluate the impact of polymer type, formulations with 30% polymer (A5 and B5) were selected for additional comparative *in vitro* testing and final *in vivo* bioequivalence study. The complete dissolution testing results for the selected formulations are presented in Fig. 3.

The dissolution results in Fig. 3 show that there is no significant difference between both formulations studied regardless of the method used. However, formulation B5 exhibits slightly faster drug release in all of the tests.

The tablet drug release robustness was tested in a different way, also using a high concentration of ethanol. Namely, ethanol may influence the drug release and cause dose dumping (29, 30). Dose dumping by ethanol could have serious consequences in certain types of medicines (29). In the case of epilepsy treatment with levetiracetam, the different drug release due to concomitant alcohol abuse may lead to additional complications in the therapeutic efficacy (31). In this sense, it was rational to also test the levetiracetam matrix tablets for dose dumping as a consequence of ethanol. However, the results show that ethanol (DT3) did not have a different influence on both formulations and did not cause matrix disintegration.

Furthermore, the robustness of both formulations was tested using a modified BioDis method using plastic beads (DT4) and agitation of 25 dpm. As evident in Fig. 3, the differences between profiles remain the same as in previous tests.

To present differences more explicitly, the ratio of A5/B5 in percent dissolved for each time point was calculated (Table V). The ratio of A5/B5 is less than 100% for most dissolution time points, especially at 4 and 8 h, where 60 to 80% of the drug was dissolved, meaning that the B5 formulation with HPMC exhibits slightly faster release compared to A5 with HPC. It was also seen that the discrimination between A5 and B5 is the smallest under test conditions of DT1.

Table V. Ratios of Percent Dissolved from Formulation A5 and Percent Dissolved from Formulation B5 for all Time Points in Different Dissolution Tests

t (h)	DT1	DT2	DT3	DT4
1	104.6	105.3	96.0	95.5
2	100.9	98.0	98.5	98.4
4	98.5	96.5	94.9	94.8
8	98.4	94.8	96.5	95.7
12	101.6	97.5	96.5	100.5

Table VI. Diffusion Coefficient *n* and the Ratio Between Relaxation and Diffusion Constants K_r/K_d for Formulations A5 and B5 Tested with Different Dissolution Methods (DT1–DT4)

	n		K_r/K_d	
Test	A5	B5	A5	B5
DT1	0.549	0.590	0.089	0.169
DT2	0.570	0.619	0.126	0.234
DT3	0.537	0.556	0.070	0.107
DT4	0.586	0.605	0.158	0.203

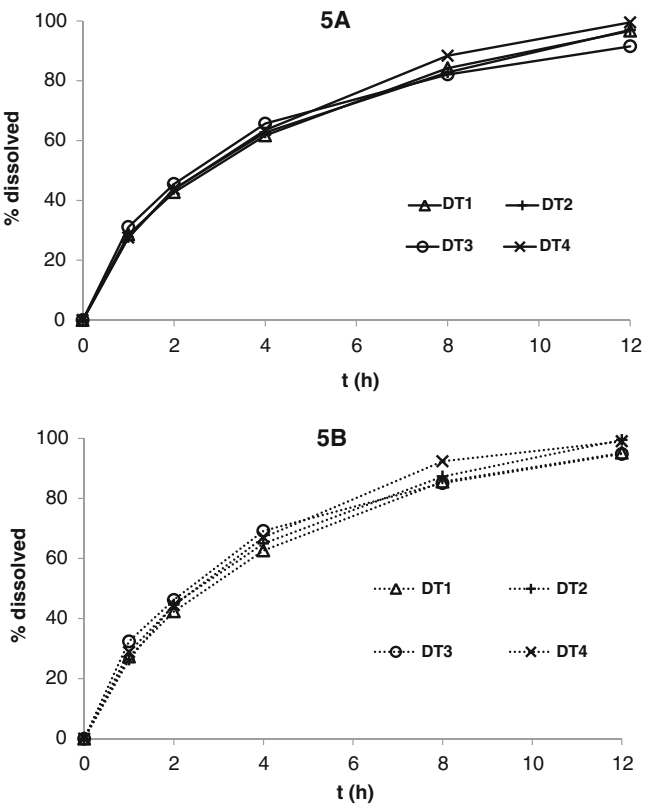

Fig. 4. Dissolution profiles for formulation A5 containing HPC (*0*) and for formulation B5 containing HPMC (*right*) obtained from various dissolution testing methods DT1–DT4 (Table II)

Table VII. Main Pharmacokinetic Parameters of Levetiracetam Obtained from the Fasted Bioequivalence Study (n=14)

	AUC_t (h ng/mL)	AUC_i (h ng/mL)	C_{max} (ng/mL)	T_{max} (h)
Form A5				
Mean	153.3	165.9	8.57	4.46
CV (%)	19.2	20.8	14.1	18.6
Form B5				
Mean	158.3	168.8	9.01	4.54
CV (%)	21.6	23.1	17.8	21.3
Ratio of form A5/form B5 (%)	96.8	98.24	94.89	

To evaluate the release mechanism, the diffusion coefficient n was calculated using the Korsemeyer–Peppas approach (Table VI). In addition, we also calculated the ratio of K_r/K_d after fitting the dissolution data using the Peppas–Sahlin equation (27, 28). For all of the calculations, we used dissolution data for which approximately 60% of the drug was dissolved. This is a common approach described in the literature (26).

In general, if n=0.45, the release is diffusion-controlled; if n=0.89, the release is erosion-controlled; and for n between 0.45 and 0.89, the release is a combination of both mechanisms meaning that drug is released by diffusion trough the formed gel layer as well as by erosion of the polymer matrix on the tablet surface. These are the values determined for cylindrical type systems or tablets (2, 32). The diffusion coefficients in Table V show that the drug release from both formulations in all tests is close to the first order, indicating predominately diffusion-controlled drug release. However, the diffusion coefficients for HPMC formulation B5 are higher compared to HPC formulation A5, which could lead us to conclude that the formulation with HPMC is more susceptible to surrounding mechanical forces compared to the formulation with HPC.

In addition, higher ratios of K_r/K_d for the HPMC-type formulation compared to HPC also indicate that drug release for HPMC-type matrices is more erosion-controlled because the relaxation constant K_r is higher than the diffusion constant K_d.

Higher HPMC susceptibility was also shown with calculated slopes and differences between slopes under two dissolution-testing methods (Tables III and IV; Fig. 2). By comparing the dissolution profiles for the same formulation tested under different dissolution methods, a robustness can be proven. If the dissolution profiles obtained under various test conditions are similar, the drug release may be considered mechanically robust, and thus, no significant changes between tested formulations in fasted or fed states are expected and bioequivalence is expected. Figure 4 presents the dissolution profiles for selected formulations A5 and B5 obtained from different dissolution methods.

The dissolution profiles in Fig. 4 show that the drug release from both formulations is robust. All of the profiles are comparable regardless of the method used. However, a detailed visual inspection of the profiles reveals that slightly greater variability is seen for formulation B5, which may be attributed to a lower intrinsic viscosity value of HPMC compared to HPC formulation A5.

Based on the above *in vitro* findings, it can be concluded that *in vitro* drug release from both formulations is robust, despite the small differences observed between them. However, it is not absolutely straightforward that the formulations would be bioequivalent *in vivo* because the observed differences *in vitro* may be more pronounced under *in vivo* conditions. This is reflected in poor IVIVC models because it is often the case that IVIVC fails due to differences in formulation behavior under *in vitro* conditions compared to *in vivo* conditions, especially if an *in vitro* model is not descriptive enough (12, 14).

In Vivo Results and Comparison with *In Vitro* Data

To confirm the assumptions of tablet robustness based on *in vitro* data, two bioequivalence studies were performed. The main pharmacokinetic results from fasted and fed BE studies are presented in Tables VII and VIII, respectively.

The results of the fasted BE study show that formulations A5 and B5 are bioequivalent as the 90% confidence interval for the ratio between formulations tested is contained within the acceptance interval of 80–125% for AUC and C_{max} (33, 34). However, all pharmacokinetic values were slightly, but not significantly, lower for formulation A5. This difference was mostly pronounced in C_{max}, for which the ratio of A5/B5 was 94.89%. This correlates well with *in vitro* study findings, in which we showed that formulation B5 exhibits slightly faster drug release compared to formulation A5 (Fig. 3, Table V).

Table VIII. Main Pharmacokinetic Parameters of Levetiracetam Obtained from the Fed Bioequivalence Study (n=14)

	AUC_t (h ng/mL)	AUC_i (h ng/mL)	C_{max} (ng/mL)	T_{max} (h)
Form A5				
Mean	165.5	176.4	9.16	6.3
CV (%)	10.6	12.3	9.5	25.9
Form B5				
Mean	167.1	176.9	9.85	7.32
CV (%)	10.4	12.3	13.3	23.4
Ratio of form A5/form B5 (%)	99.05	99.70	92.96	

Moreover, the intra-subject variability (CV) for all parameters, especially C_{max}, is higher for formulation B5. Again, this correlates well with *in vitro* findings, in which formulation B5 showed greater variability if one compares plots under different testing conditions (Fig. 4).

The results of the fed BE study also show that formulations A5 and B5 are bioequivalent. From the fed study, however, the pharmacokinetic values for both AUC were almost equal, but the C_{max} was higher for formulation B5. The same applies for the intra-subject variability (CV). In the fed study, the C_{max} ratio of A5/B5 was 92.96%, which is lower than in the fasted study. This difference can be explained with *in vitro* study results and the mechanism of release. We have shown that according to the calculated diffusion parameter *n* (Table VI), the release from both formulations is mostly diffusion-controlled, but the addition of erosion to the overall drug release is higher from formulation B5 compared to formulation A5. In this case, the matrix tablet is more susceptible to the surrounding mechanical stress. It is known that in the fed state, the mechanical stress exerted on the tablets is greater compared to the fasted state, which again confirms that HPMC formulation B5 has lower mechanical resilience (9, 10).

Interestingly, the intra-subject variability of pharmacokinetic parameters was lower in the fed study. This may be explained with more similar gastric emptying time of the test subjects after food intake. Namely, in the fasted state, migrating myoelectric complex (MMC) cycle movements are observed in the stomach and since individuals are in different MMC cycle phases at the time of tablet administration, different gastric emptying times are expected and this could be the cause of higher variability. For example, one subject could be in the MMC cycle phase just before gastric emptying (phase III) whereas another is just in the cycle after the gastric emptying phase at the time when the tablet is administered. It is known that the gastric emptying phase occurs every 90 to 120 min (7, 8). Thus, emptying differences in addition to quite fast drug release (T_{max} about 5 h) may be reflected in higher variability. In the fed state, however, the gastrointestinal movement changes to peristaltic mode, therefore gastric emptying of tablets is more inter-individually similar, which may lead to lower variability.

T_{max} is also longer in the fed state, which is a common understanding of the interference of food with a tablet. It can be concluded that absolute pharmacokinetic parameters are greater in the fed state compared to a fasted state, but not significantly.

The comparison between *in vitro* and *in vivo* results in this study showed that important pharmacokinetic data from *in vivo* studies correlate well with *in vitro* data. It has to be pointed out that predication of *in vivo* results based on *in vitro* data can be successful only when *in vitro* tests simulating *in vivo* conditions are performed also using non-conventional dissolution methods. The use of non-conventional dissolution methods is therefore important in IVIVC research.

Our results thus indicate that a high-dose BCS class I drug with HPC or HPMC polymer with an intrinsic viscosity above 9 dL/g and in an amount above 30% is likely to result in matrix tablets with a robust drug release that has low susceptibility to mechanical stress. Formulations of this type have a high probability of achieving bioequivalence.

CONCLUSION

Two mechanically robust formulations containing a BCS class I model drug were developed and tested with *in vitro* stress-inducing methods and *in vivo* bioequivalence studies. Our studies confirmed that it is possible to achieve a mechanically robust drug release profile in the case of a drug with high dose and high solubility if the viscosity or intrinsic viscosity values of the polymer are above 9 dL/g and in an amount above 30%. Based on *in vitro* results, HPC matrices exhibited more robust drug release at lower polymer loading compared to HPMC. Detailed study of the results also showed a good correlation of *in vitro* results with pharmacokinetic parameters obtained from *in vivo* findings. In spite of the good results presented in this paper thorough *in vitro* evaluation of tablets before commencing *in vivo* study should be carried out, particularly with mechanically stress-inducing dissolution methods for each matrix formulation type and compound.

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