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Influence of dissolution media composition on drug release and in-vitro/in-vivo correlation for paracetamol matrix tablets prepared with novel carbomer polymers

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Abstract

The influence of dissolution media composition on drug release kinetics and in-vitro/in-vivo correlation (IVIVC) for hydrophilic matrix tablets based on Carbopol 971P and Carbopol 71G was investigated. A number of buffered and unbuffered media differing with respect to their pH value, ionic strength and ionic species was evaluated. The observed in-vitro drug release profiles were compared with the hypothetical drug release profiles in-vivo calculated by numerical deconvolution from the results of an in-vivo study. The obtained IVIVC plots were examined using linear and non-linear (proportional odds, proportional hazards and proportional reversed hazards) mathematical models. Although the studied sustained release agents were chemically identical, they exhibited pronounced differences in drug product behaviour both in-vitro and in-vivo. The use of non-linear modelling resulted in an improved level of correlation, especially in the case of Carbopol 71G matrices. The obtained results indicated the susceptibility of drug release kinetics and hence IVIVC in the case of anionic polymer matrices to media composition, and emphasized the need for thorough evaluation of applied media during the development of biorelevant dissolution methodology. Although the use of non-linear modelling could be advantageous, the need for a simple and meaningful non-linear relationship is pointed out.

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Introduction

In-vitro/in-vivo correlation (IVIVC) has long been sought as a way of reducing the number of in-vivo studies in humans, thus decreasing the overall time and expense necessary for the development of optimal drug formulations. This is considered a difficult prospect but is possible to achieve and worth the effort (McGilveray 2003). IVIVC is defined as a rational, quantitative relationship between a biological property or a parameter derived from a biological property produced by a dosage form and a physicochemical property or characteristic of the same dosage form (USP 26). As the physicochemical property most commonly used is the in-vitro dissolution behaviour of a dosage form, the establishment of drug release methodology that would be predictive of in-vivo drug product behaviour is important, especially in the case of modified release preparations. Among the factors that should be considered when developing dissolution test methodology, composition of the dissolution media and applied hydrodynamics should be thoroughly evaluated (Khan 1996; Jorgensen & Bhagwat 1998; Costa & Sousa Lobo 2001; Corrigan et al 2003). Regarding the drug release media, use of buffered solutions containing hydrochloric acid, acetate, citrate or phosphate salts, over the pH range 1.0–7.8 (or 6.8) is recommended (FIP 1995; Jorgensen & Bhagwat 1998). The influence of media composition is well recognized and documented (Mitchell et al 1990; Bodmeier et al 1996; Khan 1996; Corrigan et al 2003; Qiu et al 2003; Wagner et al 2003), however being drug and product specific, no general conclusions can be made. The buffer media composition, its pH, ionic strength and ionic species may significantly affect drug release kinetics of ionizable drugs, as well as the ionizable excipients present and, thus, the formulated pharmaceutical product. Corrigan et al (2003) recently demonstrated the importance of dissolution media composition on ketoprofen release from

multiparticulate extended release formulation and establishment of a correlation between the in-vitro and in-vivo data. It was suggested that the observed shift in the obtained in-vitro profiles could be attributed to the differences in buffer capacity of the applied media.

The currently accepted methodology for the evaluation of IVIVC involves the development and in-vitro and in-vivo evaluation of several drug product formulations with different release rates, assessment of the hypothetical drug dissolution profile in-vivo using an appropriate deconvolution technique and linear regression of the two sets of data obtained, namely in-vitro and in-vivo drug release profiles, in order to establish a quantitative, mathematical relationship between them (USP 26; FDA/CDER 1997; EMEA/CPMP 1999). Although the linear regression analysis that is officially recommended represents the most simple relationship and thus the most appropriate to consider first, it has been recognized that IVIVC should not be limited to only linear relationships (Polli et al 1996; Dunne et al 1997; Sirisuth et al 2002). Attempts to develop a general model covering the linear as well as non-linear relationship between the in-vitro and in-vivo data have been reported (Polli et al 1996; Dunne et al 1997). Polli et al (1996) proposed the model equation derived assuming first-order dissolution and permeation after oral drug administration. Dunne et al (1997) proposed the general mixed effects models based on the assumption that in-vitro and in-vivo distributions of time at which a drug molecule enters solution could be related to one another using a proportional odds, proportional hazards or proportional reversed hazards model. Sirisuth et al (2002) reported the use of linear and non-linear (quadratic, cubic and sigmoid) correlation models in order to develop an IVIVC for a diltiazem multiparticulate bead extended release formulation.

This report is focused on the case study of hydrophilic matrix tablets prepared with novel polyacrylate polymers, Carbopol 971P and Carbopol 71G. Carbopol 71G is manufactured by dry granulation of Carbopol 971P and introduced as a matrix-forming excipient for sustained release tablets with improved flowability and compressibility. It could be expected that owing to its ionic nature, drug release from Carbopol matrices would be media dependent. In this study, a number of different buffered and unbuffered drug release media were evaluated. The non-salicylate analgesic and antipyretic, paracetamol, which is voluminous and poorly compressible, was used as a model drug. Paracetamol is generally classified as a drug with high solubility that shows high permeability throughout the intestinal tract, meeting the criteria of a class I substance according to the Biopharmaceutics Classification System (Lobenberg & Amidon 2000). The absorption of class I drugs should be dependent on their in-vivo dissolution, controlled by the kinetics of drug release from the dosage form; thus class I drugs are candidates for positive IVIVC when formulated in controlled-release dosage forms. Paracetamol was chosen because it is readily absorbed throughout the gastrointestinal tract and is present in a non-ionized form in the physiological pH range ($pKa = 9.5$).

Materials and Methods

Materials

The following materials were obtained from commercial suppliers and used as received for matrix tablet preparation: paracetamol (Merck, Germany), Carbopol 971P, Carbopol 71G (Noveon Speciality Chemicals, USA), lactose monohydrate (Fluka Chemie, Switzerland), polivinylpirolidone (Kollidon 30; BASF, Germany), microcrystalline cellulose (Emcocell XLM 90; Penwest, USA), colloidal silicium dioxide (Aerosil 200; Degussa, Germany), sodium stearyl fumarate (Pruv; Penwest).

Drug release media were prepared using hydrochloric acid (Zorka Pharma, Serbia), potassium dihydrogenphosphate (Merck-Alkaloid, Macedonia), sodium hydrogen phosphate (Merck-Alkaloid), sodium hydroxide (Zorka Pharma), sodium acetate (Merck-Alkaloid), acetic acid (Zorka Pharma), citric acid (Zorka Pharma).

For HPLC analysis of paracetamol in urine samples, ethylacetate (Merck) and acetonitrile (Merck) were applied.

Dosage forms

Two prototype sustained-release matrix tablet formulations containing 325 mg paracetamol were selected for in-vitro and in-vivo evaluation following the results of previous studies. Tablet samples were prepared by a conventional wet granulation method. A paracetamol/lactose mixture (80:20) was granulated with a 5% PVP aqueous dispersion. The amount of 15% w/w of Carbopol 971P (sample P) and 22.5% Carbopol 71G (sample G) was added extragranularly, as well as the other excipients (Emcocell XLM 90 as filler, Aerosil 200 as glidant and Pruv as lubricant). Sample tablets were compressed on an excenter tablet press (Korsch EK0; Korsch, Germany) using flat-faced punches with a 12-mm diameter. The compression force was adjusted to provide tablets with hardness between 50 and 60 kN. A commercially available paracetamol solution (Febricet syrup; Panfarma, Serbia) was used as a reference formulation in the bioavailability study.

In-vivo study

The study was conducted as an open label, fasting, single dose, three-treatment crossover trial. Nine healthy volunteers (female, aged 27–40 years (32.1 ± 4.6), 55–75 kg (62.4 ± 7.3)) were enrolled in the study and received three formulations (two sustained-release tablets and paracetamol oral solution) in a randomized order. The study was reviewed and approved by the Ethical Committee of the Military Medical Academy, Belgrade, Serbia and Montenegro. The volunteers were fully informed and provided written informed consent before entering the trial. The study was conducted in three phases, separated by a 1-week washout interval. Drug formulations were administered under fasting conditions, and urine samples were collected before and 1, 2, 3, 4, 6, 8, 10, 14, 18 and 24 h after dosing. The volunteers were instructed to increase fluid intake in

order to ensure adequate diuresis. They were also instructed to record the exact time of sampling (in the case of deviation from the stated time schedule) and total volume of urine excreted at all sampling points during the collecting period. The collected samples were stored at −20° C until analysis. Drug concentrations in urine samples were determined by a validated reversed-phase high-performance liquid chromatographic method proposed by Lo & Bye (1979).

In-vivo data analysis

Cumulative urinary excretion–time profiles were calculated for each formulation and for each volunteer. The hypothetical in-vivo dissolution profiles were calculated as an input function by applying numerical deconvolution to the urinary excretion data obtained after administration of the investigated sustained-release formulations and oral solution, for each volunteer individually. The mean in-vivo dissolution profiles were than calculated and identified as targeted drug release profiles.

In-vitro evaluation

In-vitro drug release studies were conducted in a paddle apparatus (Erweka DT70; Erweka, Germany) at 200 rev min^{-1}. High steering speed was selected following the results of a preliminary study (Parojčić et al 2003), and was in accordance with the data reported for hydrophilic matrix tablet formulations (Sako et al 1996; Abrahamson et al 1998; Halsas et al 2001). A number of dissolution media with different composition and pH values were used: distilled water, 0.1 M HCl, 0.05 M KH_2PO_4 (pH ≈ 4.5), USP acetate buffer pH 4.5, USP phosphate buffers pH 5.8 and 6.8, and Ph Eur phosphate buffers pH 5.8 and 6.8 (containing 773 mL 0.15 M $Na_2HPO_4 \times 12H_2O$ (71.5 g L^{-1}) and 227 mL citric acid (21 g L^{-1})). All tests were performed with six tablets. Samples were collected at 1-h intervals, filtered, properly diluted and assayed spectrophotometrically at 243 nm.

In-vitro/in-vivo correlation

In order to assess the relationship between the in-vitro and in-vivo data, a level A approach was applied. The percent of drug dissolved in-vivo at the specified time points, as calculated by numerical deconvolution, was plotted against the percent dissolved in-vitro at the same time points. The obtained correlation plots were evaluated using linear regression analysis, the non-linear proportional odds (Equation 1), proportional hazards (Equation 2), proportional reversed hazards models (Equation 3) (Dunne et al 1997), and segmented regression, or the "broken-stick" approach as proposed by Farrell et al (2003) (Equations 4–5).

$$\frac{F_{i2}(t)}{1-F_{i2}(t)} = \alpha_i \frac{F_{i1}(t)}{1-F_{i1}(t)} \quad (1)$$

$$1 - F_{i2}(t) = (1 - F_{i1}(t))^{\alpha i} \quad (2)$$

$$\log(F_{i2}(t)) = \alpha_i \log(F_{i1}(t)) \quad (3)$$

where F_{i1} and F_{i2} are distribution functions for in-vitro and in-vivo dissolution times, respectively.

The linearization of the proposed equations was performed in order to estimate the regression parameters.

$$t \le bp\ tscaled_{vitro} = \alpha + \beta_1 t \quad (4)$$

$$t > bp\ tscaled_{vitro} = (\alpha + \beta_1 t) + (t - bp)\beta_2 \quad (5)$$

where bp represents the time of break point, $tscaled_{vitro}$ represents the transformed (scaled) time axis in-vitro, α is the intercept of the first linear phase, β_1 is the slope of the first linear phase, and β_2 is the slope of the second linear phase.

Drug release profiles obtained in-vitro under different experimental conditions and the hypothetical in-vivo drug release profile were also compared according to the value of the similarity factor (f_2) as proposed by Moore & Flanner (1996) (Equation 6).

$$f_2 = 50 \log\left\{\left[1 + \frac{1}{n}\sum_{n=1}^{t}(R_t - T_t)^2\right]^{-0.5} \times 100\right\} \quad (6)$$

where R_t and T_t are the percent drug dissolved at each time point for the reference and the test product, respectively.

Results and Discussion

Drug release data obtained using various dissolution media, as well as the targeted, hypothetical in-vivo dissolution profile calculated by numerical deconvolution, are presented in Figures 1 and 2 for tablet samples P and G, respectively. In the case of Carbopol 971P matrices, the observed drug release profiles both in-vitro and in-vivo followed linear, near zero-order kinetics. Certain differences among the obtained profiles were noticed, with

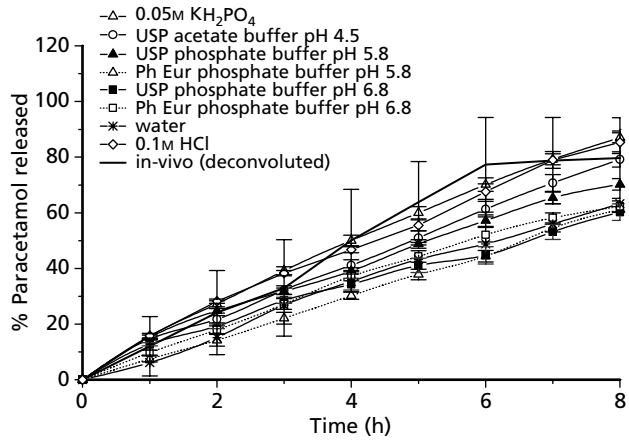

Figure 1 Drug release profiles in various dissolution media and the targeted in-vivo dissolution profile calculated by numerical deconvolution for sample P.

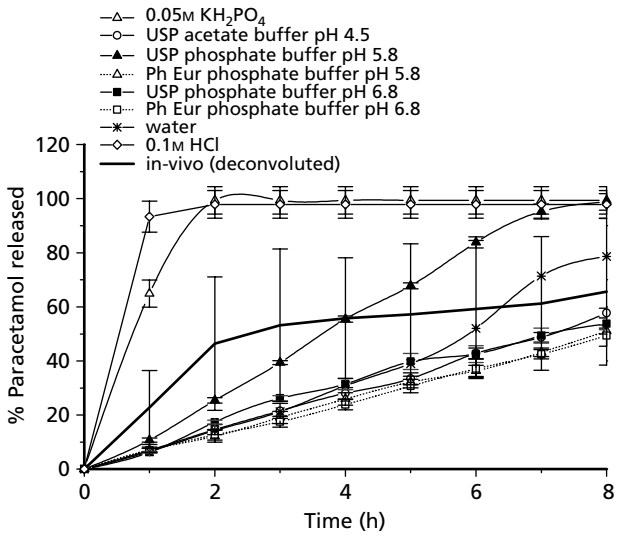

Figure 2 Drug release profiles in various dissolution media and the targeted in-vivo dissolution profile calculated by numerical deconvolution for sample G.

maximum deviation over the range 20–30% observed after 6 h of investigation. The hypothetical in-vivo dissolution profile was similar to the in-vitro profiles obtained in unbuffered 0.05 M KH_2PO_4 solution, 0.1 M HCl, USP acetate buffer pH 4.5, USP phosphate buffer pH 5.8, and Ph Eur phosphate buffer pH 6.8, as characterized with the values of the similarity factor, f_2, close to or higher than 50 (Table 1). The most rapid drug release was observed in 0.05 M KH_2PO_4 and 0.1 M HCl, where, after 8 h of investigation, the majority of drug has been released. Drug release in water and phosphate buffers was slower, leading to total amount of 60–70% of paracetamol dissolved after 8 h.

Although the evaluated sustained-release agents were chemically identical, their in-vitro behaviour exhibited more or less pronounced differences depending on the dissolution media applied. In the case of Carbopol 71G matrices, drug release data obtained in various drug release media revealed the significant influence of dissolution media composition on drug release. The hypothetical drug release profile in-vivo, calculated by numerical deconvolution, exhibited obvious biphasic pattern. Furthermore, according to the values of the similarity factor (Table 1), neither of the investigated in-vitro conditions resulted in a dissolution profile that could be considered similar to the targeted, deconvoluted, in-vivo drug dissolution profile. In-vitro tests conducted in the 0.1 M HCl and unbuffered KH_2PO_4 resulted in an extremely rapid drug release followed by the complete disintegration of the matrices during the first 2 h of investigation. In pH 4.5 acetate buffer, drug release was slow and incomplete, with less than 60% of drug dissolved after 8 h. The trials conducted in USP phosphate buffers pH 5.8 and 6.8 (differing with regard to the amount of sodium hydroxide added in order to adjust the pH value of the media) demonstrated the retardation of drug release, which was in proportion to the amount of base added. The use of Ph Eur buffer solutions pH 5.8 and 6.8 resulted in almost superimposed release profiles regardless of media composition and ionic strength.

Table 1 Comparison of the hypothetical in-vivo drug release profile and profiles obtained in-vitro under various experimental conditions using the similarity factor (f_2).

Medium	Similarity factor (f_2)	
	Sample P	Sample G
Distilled water	37.2	33.6
0.1 M HCl	61.7	14.1
0.05 M KH_2PO_4	65.6	16.2
USP acetate buffer 4.5	53.4	33.3
USP phosphate buffer 5.8	47.2	33.2
USP phosphate buffer 6.8	36.0	34.6
Ph Eur phosphate buffer 5.8	34.5	29.7
Ph Eur phosphate buffer 6.8	54.2	29.1

The results indicated that the observed pronounced differences among the drug release kinetics obtained in various media could not be attributed solely to the media pH, its ionic strength or buffer capacity. The observed effect of dissolution media could be attributed to the rate at which formation of the gel layer (which acts as the barrier for drug diffusion) occurs on the tablet surface, given that this is the process that mainly governs release of highly soluble drugs from swellable matrices (Colombo et al 2000). If the polymer gels slowly, the solvent can penetrate deep into the glassy matrix, thus dissolving the drug and leading to the disintegration of the matrix. In the case of carbomer polymers, the swelling of the polymer is greater at higher pH values (above the polymer's pKa value), resulting in the rapid formation of the gel layer and thus slower and more prolonged drug release. At lower pH values, such as in 0.1 M HCl, the degree of swelling is less, leading to the initially rapid penetration of the medium into the pores of the polymer matrix and diffusion of the drug through these pores prior to complete gel formation. A similar phenomenon is also reported for media containing potassium salts (Mitchell et al 1990; Durrani et al 1994). The presence of potassium ions, regardless of media pH, may cause a reduced and slower degree of polymer swelling as a result of its affinity to bind the water molecules, thus reducing the amount of water available for hydration of the polymer matrix. With regard to the differences in drug release profiles obtained in various dissolution media for matrices prepared with chemically identical Carbopol 971P and Carbopol 71G polymers, it can be postulated that the observed phenomenon is attributed to the difference in particle size of the polymeric excipient. It can be supposed that in the case of granular polymer (Carbopol 71G), slow formation of the gel layer around the individual polymeric granules (in 0.1 M HCl and 0.05 M KH_2PO_4 applied as drug release media) facilitates penetration of the medium into the matrix, leading to the rapid and complete dissolution of paracetamol and matrix disintegration. In the case of matrices prepared with Carbopol 971P, slower formation

of the gel layer resulted in an initially greater drug release rate, which tended to tail off as hydration of the matrix and gel formation occurred, sealing the pores on the tablet surface. On the other hand, in media with higher pH values, rapid formation of the gel layer led to slower drug release, which was similar in the case of both granular and powdered polymers.

Correlation plots constructed when the percent of drug dissolved in-vivo at a given time was plotted against the percent dissolved at the same time in-vitro in various media are presented in Figures 3 and 4 for tablet samples P and G, respectively. In the case of sample P, certain deviations from the ideal 1:1 relationship (represented with the straight line with slope = 1) were observed. However, in the case of sample G, differences between drug release kinetics in-vitro and in-vivo were much more pronounced and even simple visual inspection of the correlation plots presented in Figure 4 indicated apparent deviation from the linear relationship. With regard to the obvious poor linear correlation and biphasic character of the in-vivo drug release profile obtained in the case of sample G, the recently proposed "broken-stick" approach of Farrell et al (2003) was used.

Statistical parameters obtained after performing the linear and non-linear regression analysis are presented in Tables 2 and 3 for tablet samples P and G, respectively. The results obtained for the sample P, characterized by the correlation coefficients of linear regression higher than 0.97, indicated relatively high level A IVIVC. The calculated values of the slope of the regression line were also close to unity, especially when unbuffered 0.05 M KH_2PO_4 and 0.1 M HCl solutions were employed as dissolution media (1.044 and 1.065, respectively). Regarding the results obtained for non-linear modelling, the highest coefficients of correlation were obtained when data were fitted to the proportional reversed hazards model. However, the obtained values were not significantly improved when compared with data obtained for linear regression.

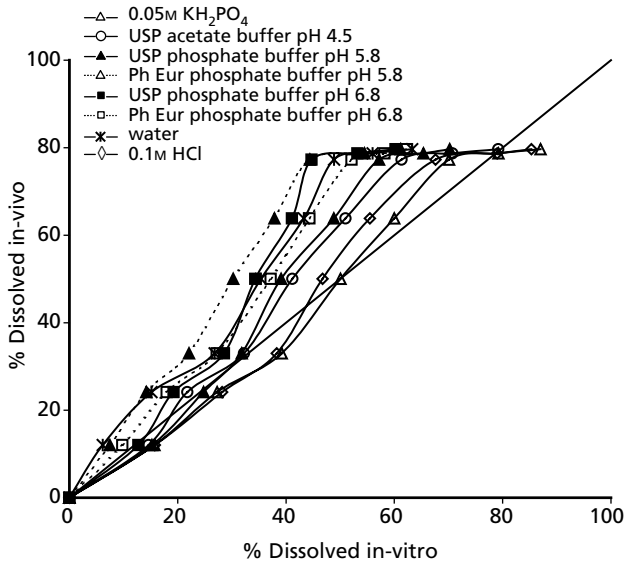

Figure 3 In-vitro/in-vivo correlation plots for tablet sample P in various dissolution media.

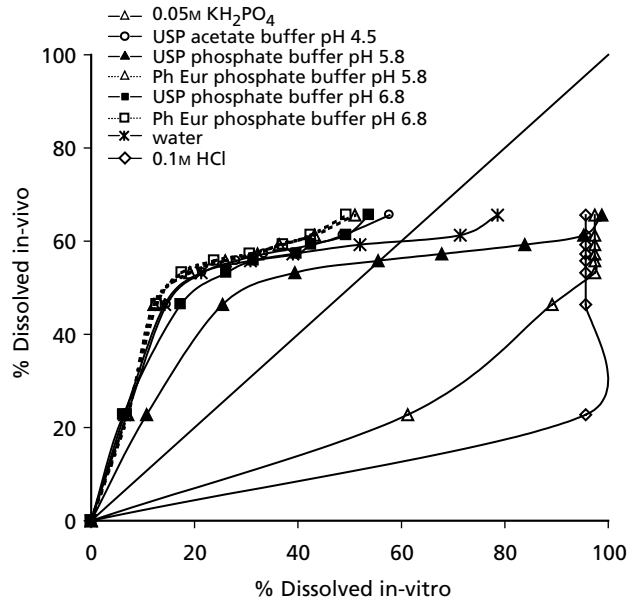

Figure 4 In-vitro/in-vivo correlation plots for tablet sample G in various dissolution media.

In the case of sample G, the obtained values of the linear regression correlation coefficients were lower than 0.95, indicating a poor level A IVIVC. Application of non-linear modelling led to an improved level of correlation, characterized by coefficients of correlation obtained for the proportional reversed hazards model of greater than 0.95 in the cases when 0.05 M KH_2PO_4, 0.1 M HCl and USP phosphate buffer pH 6.8 were used as drug release media.

It is interesting that in both cases studied, the highest correlation coefficients were obtained for the proportional reversed hazards model, which assumes that the fraction dissolved in-vivo and the fraction dissolved in-vitro correspond to the relationship given by the relatively simple power law function. In the view of recent suggestions that IVIVC should be modelled using various non-linear mathematical functions such as quadratic, cubic or sigmoid (Sirisuth et al 2002), the need for simple and generally applicable non-linear relationship should be pointed out.

Farrell et al (2003) proposed that in cases where biphasic drug release is postulated in-vivo, approaches based on the segmented linear regression should be applied in order to develop linear IVIVC. This concept is based on the assumption that different linear models should be applied to different regions of the data. It was applied to the data obtained for sample G in the present investigation. After performing the corresponding mathematical transformations involved in the "broken-stick" approach, notable improvement of level A IVIVC was achieved, as represented

Table 2 In-vitro/in-vivo correlation: statistical parameters of the applied mathematical models (tablet sample P).

In-vitro experimental conditions	Linear regression		Proportional odds		Proportional hazards		Proportional reversed hazards		
	a	r	α	r	α	r	a	α	r
Distilled water	1.319	0.9810	2.692	0.9512	1.802	0.9684	2.359	0.862	0.9894
0.1 M HCl	1.065	0.9750	0.728	0.8942	0.926	0.9441	0.469	1.188	0.9886
0.05 M KH_2PO_4	1.044	0.9837	0.639	0.8828	0.885	0.9494	0.509	1.160	0.9934
USP acetate buffer 4.5	1.125	0.9753	1.166	0.9128	1.155	0.9523	0.653	1.138	0.9855
USP phosphate buffer 5.8	1.333	0.9817	1.973	0.9626	1.562	0.9748	0.388	1.288	0.9895
USP phosphate buffer 6.8	1.363	0.9708	2.899	0.9470	1.891	0.9615	1.907	0.942	0.9911
Ph Eur phosphate buffer 5.8	1.586	0.9676	3.244	0.9380	2.146	0.9548	0.508	1.278	0.9845
Ph Eur phosphate buffer 6.8	1.334	0.9906	1.807	0.9727	1.501	0.9833	0.268	1.351	0.9963

α, constant of proportionality; a, slope of the regression line; r, correlation coefficient.

Table 3 In-vitro/in-vivo correlation: statistical parameters of the applied mathematical models (tablet sample G).

In-vitro experimental conditions	Linear regression		Proportional odds		Proportional hazards		Proportional reversed hazards		
	a	r	α	r	α	r	a	α	r
Distilled water	0.407	0.8006	0.298	0.7976	0.366	0.7932	15.027	0.356	0.8973
0.1 M HCl	0.500	0.9547	0.012	0.8340	0.141	0.9111	2.2029	0.712	0.9769
0.05 M KH_2PO_4	0.992	0.9055	0.007	0.7765	0.147	0.8491	0.003	2.142	0.9530
USP acetate buffer 4.5	0.997	0.8954	0.805	0.8747	0.445	0.9248	11.754	0.659	0.8576
USP phosphate buffer 5.8	0.357	0.8727	0.012	0.6606	0.126	0.7712	10.151	0.413	0.9370
USP phosphate buffer 6.8	0.755	0.9174	1.218	0.9417	0.948	0.9284	10.829	0.462	0.9702
Ph Eur phosphate buffer 5.8	0.750	0.8544	1.350	0.9101	0.994	0.8822	12.022	0.452	0.9006
Ph Eur phosphate buffer 6.8	1.408	0.9056	1.015	0.8749	0.455	0.8989	12.076	0.756	0.8452

α, constant of proportionality; a, slope of the regression line; r, correlation coefficient.

Table 4 Statistical parameters of the segmented regression analysis ("broken-stick" model) and the obtained in-vitro/in-vivo correlation for tablet sample G.

In-vitro experimental conditions	"Broken-stick" regression analysis					
	bp	α	β_1	β_2	a	r
Distilled water	4.500	−0.1015	0.3588	2.3830	0.889	0.9466
0.1 M HCl	1.152	−0.4443	1.8641	8.0164	1.105	0.8630
0.05 M KH_2PO_4	0.558	0.0141	2.7893	10.893	0.753	0.8853
USP acetate buffer 4.5	6.554	0.0328	0.2965	2.3467	0.983	0.9933
USP phosphate buffer 5.8	3.340	−0.1253	0.6123	3.8024	0.977	0.9899
USP phosphate buffer 6.8	6.110	0.0399	0.3370	1.1433	0.984	0.9908
Ph Eur phosphate buffer 5.8	7.208	0.0497	0.2614	2.0465	0.929	0.9869
Ph Eur phosphate buffer 6.8	7.336	0.0262	0.2598	1.7933	0.872	0.9806

See Equations 4 and 5 for the definition of terms bp, α, β_1 and β_2. a, slope of the regression line; r, correlation coefficient.

by the coefficients of correlation greater than 0.98 and values of the regression line close to unity (see Table 4). However, considering the somewhat arbitrary selection of the break point and need for additional transformation of the experimental data, and current trends that IVIVC should not be limited to the linear relationship, it is questionable whether there is a need for abundant mathematical manipulation forcing the achievement of linearity.

Conclusion

This study showed the susceptibility to media composition of drug release kinetics and hence IVIVC in the case of anionic polymer matrices and emphasizes the need for thorough evaluation of applied drug release media in the development of biorelevant dissolution methodology. It should also be noted that physical changes, such as the particle size resulting from the process of dry granulation, of the chemically identical polymers used as sustained release agents could lead to the pronounced differences in drug product behaviour both in-vitro and in-vivo. The obtained results indicate that IVIVC should not be limited to the linear mathematical model, however the need for simple and generally applicable non-linear relationship should be pointed out.

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