British Journal of Pharmacy

https://doi.org/10.5920/bjpharm.1130

British Journal of Pharmacy

www.bjpharm.hud.ac.uk

Proceedings of the 13th APS International PharmSci 2022

Assessing the effect of moderately increasing medium viscosity on the intrinsic dissolution rate and diffusion coefficient of ibuprofen particles

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ARTICLE INFO

Received: 16/06/2022
Accepted: 28/06/2022
Published: 03/11/2022

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KEYWORDS: dissolution; viscosity; ibuprofen; diffusion

SUMMARY

This study investigated the effects of moderately increasing medium viscosity through two viscosity enhancing agents (VEA) (HPMC and sucrose) on the intrinsic dissolution of a BCS class II drug (ibuprofen). The differences in intrinsic dissolution were characterized through the estimation of a diffusion coefficient (D) of ibuprofen in different media with the Levich equation. Increasing viscosity decreased the intrinsic dissolution rate of ibuprofen with both VEAs. The calculated D from intrinsic dissolution data overestimated the experimental value, but the results suggest that intrinsic dissolution could be used as a tool to estimate a relative change in D in different viscosities.

INTRODUCTION

The viscosity in the fed state is much higher than in the fasted state (Radwan et al., 2014), but the viscosity of the human gastric fluid in the fasted state has been measured to be higher than that of water, ranging from 1.7 to 9.3 mPa.s at a shear rate of 50 s^{-1} (Pedersen et al., 2013). An increase in viscosity could potentially reduce drug dissolution, through a reduction in drug diffusivity, as per the Stokes-Einstein equation.

Intrinsic dissolution allows the characterization of the dissolution rate of drugs by exposing a constant surface area to the medium. The effect of increasing medium viscosity was characterized through intrinsic dissolution testing with two viscosity enhancing agents (VEA), sucrose and hydroxypropyl methylcellulose (HPMC) and the diffusion coefficient of ibuprofen (D) was estimated from these data through the Levich equation (Levich, 1962), which describes the mass transfer to or from a rotating disk, to assess the effect of viscosity on D.

MATERIALS AND METHODS

Intrinsic dissolution tests (Agilent 708-DS apparatus, 50 rpm) were performed using 500 mL pH 6.8 phosphate buffer (PB) with 0.003% w/v Tween 20 (Sigma-Aldrich) as the medium with or without 25% w/v sucrose or 0.3% w/v HPMC (viscosity of 1.4 mPa.s, which is the viscosity of milk (Klein et al., 2004)) or 59% w/v sucrose or 1% w/v HPMC (viscosity of 4.5-5.5 mPa.s, the mid-range viscosity of the human gastric fluid in the fasted state) at 37 °C. 100 mg of ibuprofen (Glentham Life Sciences Ltd) was compressed into a rotating disk (PerkinElmer hydraulic press) by applying 3 tonnes pressure for 1 min. 3 mL samples were taken at 2, 4, 6, 8, 10, 20, 30, 45, 60, 90, 120 min, filtered through 0.45 µm PTFE filters (Fisherbrand), discarding the first mL, and analysed by UV-spectrophotometry (PharmaSpec

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1700, Shimadzu) at 222 nm. Samples were replaced with fresh medium at 37 °C after each sampling time.

The D of ibuprofen in each medium was calculated with the Levich equation (Eq. 1).

$$I \approx 1.9 D^{2/3} \nu^{-1/6} \omega^{1/2} r^2 C_s \qquad \text{Eq.1}$$

Where I is total flow of matter from the disk surface (kg/s), which is determined from each dissolution profile, D is the diffusion coefficient (m^2/s), ν is the kinematic viscosity (m^2/s), that is dynamic viscosity, μ, (Pa.s) divided by fluid density, ρ_f, (kg/m^3), ω is angular velocity (rad/s), r is the disk radius, which was 0.001995 m, and C_s is the saturated solubility of the drug (kg/m^3).

The calculated D values were compared to experimental values (Healy, 1995), and the relative change in the calculated D value from media with and without VEA was used to adjust the baseline experimental value (0.80 x 10^{-9} m^2/s) to assess the relative change in D.

RESULTS AND DISCUSSION

Increasing viscosity led to a reduced intrinsic dissolution rate with both VEAs (Figure 1).

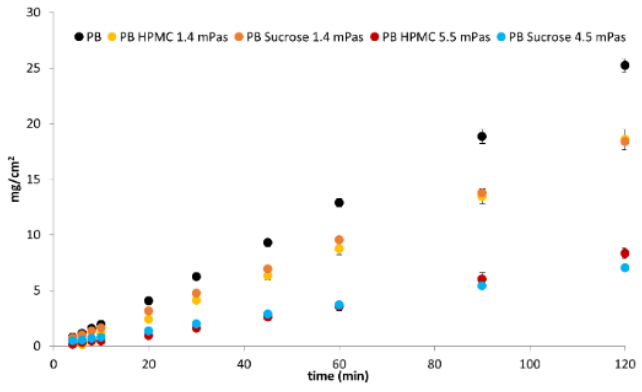

Fig. 1. *Intrinsic dissolution profiles from a rotating disk of ibuprofen in 500 mL of media at 37°C and 50 rpm.*

The calculated D from the Levich equation was overestimated relative to experimental values (Table 1). However, applying the relative change in calculated D to the baseline experimental value led to D values comparable to those experimentally obtained for a viscosity of 1.4 mPa.s using sucrose as VEA (Experimental data: 0.80 x 10^{-9} m^2/s (at 0.7 mPa.s) (baseline value), 0.58 x 10^{-9} m^2/s (at 1.03 mPa.s) and 0.38 x 10^{-9} m^2/s (at 1.66 mPa.s) (Healy, 1995)), with a higher D calculated for HPMC-adjusted medium, suggesting an effect on D from VEA. Results suggest that the Levich equation is useful to relate the effect of viscosity on intrinsic dissolution rates through D.

Table 1. *Calculated D through the Levich equation and experimental D adjusted based on the proportional decrease in calculated D from media with and without VEA.*

Medium	(Levich D±SD) (m^2/s) x 10^9	Adjusted D (m^2/s) x 10^9
PB 0.7 mPa.s	6.40±0.52	-
Sucrose 1.4 mPa.s	3.48±0.06	0.44
Sucrose 4.5 mPa.s	1.53±0.03	0.20
HPMC 1.4 mPa.s	4.36±0.64	0.54
HPMC 5.5 mPa.s	1.45±0.20	0.19

CONCLUSIONS

Moderately increasing medium viscosity reduced the intrinsic dissolution rate of ibuprofen. Although the Levich equation overestimated the experimental D, it led to a comparable relative decrease in D when viscosity was doubled.

ACKNOWLEDGEMENTS

The authors acknowledge funding in the form a research grant from Science Foundation Ireland (SFI), co-funded under the European Regional Development Fund (Grant number 12/RC/2275_P2).

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