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Investigating drug release from two types of HPMC capsule in various dissolution media

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A Self Emulsifying Drug Delivery System (SMEDDS) formulation was developed to deliver an acidic BCS class 2 compound (cLogP 8.78, pK_a 3.74) in a bio-enhanced formulation. Suppliers' literature has suggested that some components of SMEDDS are incompatible with gelatin capsules. Differences between gelatin and HPMC Capsules are well documented (Podczeck & Bones 2002; Cole 2004). Hard HPMC capsules were selected and two types of HPMC capsules were considered (Capsugel V Caps and Shionogi Qual-V Caps). Both capsules utilised hydroxypropyl methylcellulose (Hypromellose) as the polymer. Capsugel capsules use gellan gum as gelling agent and have a pK_a of 3.4. Shionogi capsules use carageenan as gelling agent and have a pK_a of < 2. Both capsule types use potassium ions as a gelling promoter. All capsules used in this investigation were size '00'. This work describes the differences observed in dissolution performance associated with the two types of HPMC Capsule. Dissolution media of various pH, ionic strength and buffer types were considered in the development of a QC dissolution method. Dissolution was performed on the USP II Apparatus using 500 mL of Simulated Gastric Fluid (SGF) pH 1.6 (BP) at 75 rpm. Table 1 shows Shionogi capsules demonstrate faster release and dissolution of the active compound than Capsugel capsules. It was also observed that Shionogi capsule rupture occurs more rapidly than for Capsugel capsule. To assess affects of varying ionic strengths, pH and presence of phosphate ions; dissolution was performed using USP II dissolution equipment, a 900 mL volume and 75 rpm paddle speed in a range of media. Capsugel capsule rupturing and breakage were assessed. This work demonstrated that increasing ionic strength and phosphate ions affects the disintegration rate of the Capsugel HPMC capsules. It is evident that a higher acetate concentration retards capsule breakage to a greater degree than presence of phosphate ions. Increased surfactant concentration encourages capsule rupture. Water containing 2% w/v sodium dodecyl sulphate (SDS) was selected as the QC method for Capsugel HPMC capsules. This medium proved most efficient for disintegration and dissolution of both the capsule shell and the SMEDDS formulation.

Table 1 Comparison of release from Capsugel and Shionogi Capsules in SGF pH 1.6

Time (min)	Capsugel	Shionogi
15	0	38
30	25	71
45	34	73
60	59	73

Table 2 Comparison of dissolution rates utilising different media

Dissolution media	% Drug dissolved			
	15 min	30 min	45 min	60 min
100 mM Ammonium acetate (pH 7.0)	0	5	31	50
100 mM Sodium acetate (pH 5.8)	0	8	24	48
FaSSIF (5 mM phosphate)	19	74	101	103
FaSSIF (30 mM phosphate)	0	3	69	73
2%SDS in water	29	70	89	95
5 mM Sodium phosphate (pH5.8)	58	71	82	85

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Effect of fed and fasted simulated intestinal fluids on drug permeability in Caco-2 monolayers

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Simulated intestinal fluid representing the fasted state in the intestinal lumen (FaSIF) has been used as a biorelevant medium in permeability experiments using the Caco-2 drug absorption model (Ingels et al 2004). The use of FaSIF resulted in a reduction in the permeability lipophilic drugs compared with permeability measured using standard transport medium. The recently reported development of a biocompatible simulated intestinal fluid to represent the fed state in the intestinal lumen (FeSIF; Patel et al 2006) provides an opportunity to investigate the effect of using a wider range of biorelevant conditions on drug permeability in the Caco-2 system. The aim of this study was to measure the permeability of propranolol, metoprolol, imipramine and digoxin in Caco-2 cells using FaSIF and FeSIF as biorelevant media and Hanks' balanced salt solution (HBSS) as standard test medium. Caco-2 cells (passage 60–73) were seeded in polyester Transwell cell culture inserts (pore diameter 0.4 μm, surface area 1.13 cm^2) at a seeding density of 6.6×10^4 cells/cm^2 and grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% v/v foetal bovine serum, 1% v/v non-essential amino acids (100×), 1% v/v L-glutamine (200 mM) and gentamicin (50 mg/mL). Cells were cultured at 37°C in an atmosphere of 5% CO_2 and used for experiments at 21–28 d. Test solutions containing 0.02–0.05 mM radiolabelled drug were prepared in FaSIF, FeSIF and HBSS and absorptive permeability was measured over 2 h as described previously (Patel et al, 2006). Transepithelial electrical resistance (TER) was measured before and after experiments and drug recovery was calculated. No change in TER (> 400 ω cm^2) was measured over the course of the experiments. The transport rate of each compound was linear under all experimental conditions used. Metoprolol and digoxin recovery was complete and was not affected by the donor matrix. The mass balance (% recovery) for propranolol and imipramine was low in HBSS (77 and 50%, respectively), higher in FaSIF (86 and 76%, respectively) and complete in FeSIF (101 and 93%, respectively). The permeability of propranolol, metoprolol and imipramine was reduced by using FaSIF to 64–72% compared with that measured using HBSS. This effect was enhanced by using FESIF, with a reduction in permeability to 19–22% compared with that measured using HBSS. No effect of the donor matrix on the permeability of digoxin was observed. The findings with FaSIF are consistent with those reported previously (Ingels et al 2004). With FeSIF the effects on drug permeability observed when using FaSIF were enhanced, and can be attributed to increased micellar encapsulation of drug in bile salt:lecithin mixed micelles reducing free drug concentration. The FaSIF and FeSIF provide the opportunity to perform experiments under more physiological conditions than standard transport medium. However, the relevance in vivo of the effects on permeability measured in vitro requires further investigation.

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