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Trichotomous gastric retention of amorphous capecitabine: An attempt to overcome pharmacokinetic gap

Yuvraj Singh, Meenakshi Singh, Jay Gopal Meher, Vivek K. Pawar, Manish K. Chourasia *

Pharmaceutics Division, CSIR-Central Drug Research Institute, Lucknow 226031, India

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ABSTRACT

Capecitabine (CAP) is an oral drug of choice for treatment of colorectal cancer. But its short plasma half-life limits clinical utility and the usually prescribed dosing regimen results in significant periods of therapeutically irrelevant concentration. To overcome this pharmacokinetic void a trichotomous gastroretentive (TRGDDS) system made up of CAP housed in xanthan gum microparticles (CXGMP) has been developed for extending CAP's gastric residence time thereby prolonging the subsequent elimination. TRGDDS was evaluated for particle size ($243 \pm 25\,\mu m$), surface morphology (porous) entrapment efficiency ($87.72 \pm 7.31\%$), buoyancy ($86.32 \pm 2.3\%$), mucoadhesiveness ($88 \pm 4.3\%$), swelling index (80.37 ± 4.65). X-ray diffraction (XRD) and differential scanning calorimetry (DSC) of CXGMP suggested CAP had been rendered amorphous, a property which unconventionally slows its dissolution. Significant control was offered by CXGMP compared to crystalline CAP in terms of drug release. Pharmacokinetic studies in Wistar rat further revealed that CXGMP increased the MRT (three times), elimination half-life (roughly 4 fold) and AUC (1.44 folds) of CAP at a dose of 5 mg/kg in comparison to CAP solution of same strength. Conclusively the employment of TRGDDS had extended the duration for which CAP stayed in the rodent model, providing evidence for potentially obtaining a more efficacious dosing regimen in actual disease models.

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1. Introduction

Capecitabine (CAP) is an orally administered fluoropyrimidine carbamic acid derivative used for treatment of colorectal cancer (Venturini, 2002) which is one of the most commonly diagnosed cancers in the world (Chaurasia et al., 2006). Colorectal cancer is a resultant of unabated cell growth in parts of large intestine, or in appendix. Colon cancer starts in lining of the bowel and if left unchecked, can grow into the muscle layers underneath, and then through the bowel wall. Tumor that are confined within the wall of the colon are often curable with surgery, while cancer that has undergone metastasis is untreatable and management then focuses on extending the person's life *via* chemotherapy and improving quality of life. CAP is used as a first line treatment of colorectal cancer and is commercially available as an immediate release tablet (Xeloda®, Roche). Following oral administration CAP undergoes rapid and extensive absorption. Once inside portal circulation, CAP is quickly converted to 5-fluorouracil (5-FU) *via* a tri-step enzymatic process. Subsequently, 5-FU is eliminated rapidly and is untraceable in systemic circulation after approximately 6 h (Reigner et al., 2001). It can be envisaged that the clinically accepted twice daily dosing roster (morning–evening split) of CAP results in an intermittent dosing pattern which creates two windows of approximately 6 h out of 24 h, during which relevant concentration of drug is absent from the body.

Even the simplistic paradigm of developing a single unit controlled release tablet of CAP is not a straight-forward solution for this delinquent proposition as tablets are plagued with issues of premature gastric expulsion (Pawar et al., 2011). Additionally, the high dosing requirement of CAP warrants that it occupies almost 80% of the tablet weight (500 mg out of total 625 mg of Xeloda®), with remnant occupied by the excipients. Given the standard regimen of up to 1250 mg/m^2 CAP daily (Midgley and Kerr, 2009), it is easy to comprehend from a patient standpoint that little room exists for utilizing the traditional release retarding excipients, as it would result in either an escalation in size or number of tablets. Therefore in order to truly translate the concept of maintaining 5-FU concentrations obtained after infusing 5-FU *via* an oral plan of CAP, an extended release oral dosage form, devoid of gastric residence issues is merited.

* Corresponding author at: Pharmaceutics Division, CSIR-Central Drug Research Institute Sector 10, Jankipuram Extension, Lucknow, UP 226031, India. Tel.: +91 522 2612411 18; fax: +91 522 2623405.
E-mail address: manish_chourasia@cdri.res.in (M.K. Chourasia).

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Gastroretentive technology can circumvent drawbacks associated with drugs like CAP through various principles including floating, mucoadhesion, swelling and/or dual working systems. The long retention of drug at absorptive locations with control on drug release by these systems implies that drug appears slowly in systemic circulation, thereby getting slowly eliminated also. The current manuscript deals with the development of a trichotomous gastroretentive drug delivery system (TGRDDS) and takes one step forward in the field of gastroretentive technology.

The novel multiparticulate TGRDDS utilizes simultaneous application of three gastroretentive principles (floating, swelling and mucoadhesion) for prolonged systemic delivery of CAP. Systems based on floating principle alone rely on presence of substantial gastric volume to exhibit floating capabilities (Awasthi et al., 2012) whereas those working on isolated mucoadhesive principle, often do not adhere to gastric epithelia due to strong peristalsis (Pawar et al., 2012). Xanthan gum (XG), a useful pharmaceutical excipient which has both swelling and mucoadhesive character, if employed in formulation, is expected to accord excellent mucoadhesivity and swellability (relatable to floating ability) to the TGRDDS (Patel and Patel, 2007; Rowe et al., 2006; Singh et al., 2008; Talukdar and Kinget, 1995). The probability of gastric retention is thus greatly increased in TGRDDS when these two mechanisms act in sync. Mucoadhesion and swelling are two inbred features of XG; the third dimension of our intended formulation becomes overt after incorporation of pore former. Porous systems float immediately after administration and exclude the concept of lag time further augmenting the floating ability of system (Pawar et al., 2011). The system would technologically ensure that the dosage form stays in the stomach for an extended period of time so that CAP is slowly distributed amongst the gastric fluids and moves with the gastric flux, getting absorbed at locations where it is most suitable.

It is well established that using a multiparticulate system prevents the risk of dose dumping or premature gastric expulsion (Awasthi et al., 2012), however we wish to simultaneously exploit an auxiliary feature excavated by the probable physical state morphism in CAP induced by TGRDDS. In a recent study Meulenaar et al. (2013) reported counterintuitive dissolution behavior of amorphous CAP and exploited it to slow the release of drug (Meulenaar et al., 2014). The TRGDDS like other multiparticulates would be expected to render the inherently crystalline CAP into an amorphous state (Jeong et al., 2005; Serajuddin, 1999) executing added control on its dissolution and subsequent systemic appearance. The end result would be a three pronged gastric retention device, which would control release of CAP at two distinct levels, ultimately resulting in favourable modulation of its pharmacokinetic profile. To substantiate this hypothesis XG based microparticles of CAP were prepared, optimized and characterized for size, swelling index, drug content, powder X-ray diffraction (XRD) pattern, drug-polymer interaction *via* differential scanning calorimetry (DSC), drug release, *in-vitro* floating capability, *ex-vivo* and *in-vitro* mucoadhesion testing and *in-vivo* pharmacokinetic behavior.

2. Materials and methods

CAP was obtained as a kind gift sample from Fresenius Kabi, Oncology Ltd., Gurgaon, Haryana, India and used as provided. Edible soybean oil (SO) was bought locally from the market. XG from *Xanthomonas campestris*, Span80, gluteraldehyde, $NaHCO_3$, conc.H_2SO_4,*n*-hexane, glacial acetic acid, HPLC grade solvents and dialysis tubing (molecular weight cut off 12 KDa) were procured from Sigma–Aldrich, MO, USA. Millipore Direct Q® 3UV water was used in all the studies.

2.1. Preparation of XG microparticles (XGMP)

XG microparticles were prepared by water-in-oil (w/o) emulsification crosslinking technique with CAP (CXGMP) or without CAP (Jain et al., 2004). Initially an aqueous dispersion containing required amount of CAP, XG and $NaHCO_3$ (Table 1) was prepared and left for complete drug solubilisation. This aqueous homogenate was added drop wise to soybean oil (25 mL) being stirred mechanically (500–750 rpm). The oil phase was supplemented with span 80 (1–5% w/v), to ensure emulsification. After 30 min, concentrated sulfuric acid (500 μL) and gluteraldehyde (50 μL) were added to the emulsion, under continued stirring. The entire operation was carried out at elevated temperature (40–60 °C). After stipulated time period (3–5 h) developed particles were filtered and washed repeatedly with hexane and dried overnight in an oven. Various processing and formulation variables were varied to arrive at the optimized formulation. For comparative evaluation non porous XGMP were also prepared similarly, but without the addition of $NaHCO_3$.

2.2. Determination of particle size and distribution

Samples for particle size measurement were prepared by suspending the CXGMP in *n*-hexane by bath-sonication for 5 min and concentration of the suspension was adjusted to 3% w/v. Particle size and distribution was determined using Malvern MasterSizer 2000 (Malvern Instruments Ltd., Malvern Worcestershire, UK).

2.3. Surface morphology

The surface morphology was examined using scanning electron microscope (EVO-50, ZEISS, United Kingdom). The samples for SEM were prepared by mounting the CXGMP on a double adhesive tape straddled to an aluminium stub and sputter coated with a gold-palladium alloy under an argon atmosphere using a high vacuum evaporator (SC7640 Polaron Sputter Coater) to minimize surface charging. Microparticles were imaged using a 5 kV accelerating

Table 1
Physicochemical characteristics of various formulations obtained during optimization. Data are represented ± s.d. where number of sample equals 3.

Code	CAP (mg)	XG (w/v) (%)	CAP: XG	Span 80 (v/v) (%)	$NaHCO_3$ (mg)	Mean particle size (μm)	%Entrapment efficiency	%Drug loading	%Buoyancy	%Swelling index	%Mucoadhesiveness
F1	25	0.8	1:3.2	1	25	243 ± 25	87.72 ± 7.31	14.62 ± 4.87	86.32 ± 2.3	80.37 ± 4.65	88 ± 4.3
F2	25	0.8	1: 3.2	5	50	120 ± 31	79.16 ± 1.94	11.31 ± 1.10	91 ± 3.6	82.17 ± 2.54	85.7 ± 1.3
F3	25	0.7	1:2.8	1	35	245 ± 15	83.25 ± 2.89	13.88 ± 1.92	82.96 ± 1.5	78.85 ± 4.32	81.72 ± 2.1
F4	25	0.6	1:2.4	3	10	175 ± 17	84.23 ± 1.85	18.31 ± 1.6	68.60 ± 3.3	75.3 ± 3.27	70 ± 5.2
F5	25	0.5	1:2	2	15	202 ± 21	80.22 ± 2.25	18.23 ± 2.04	75.06 ± 4.8	64.21 ± 3.21	68.10 ± 1.4
F6	25	0.5	1:2	4	20	160 ± 32	78.26 ± 8.23	17.01 ± 7.15	73.1 ± 1.3	66.35 ± 1.34	62.31 ± 3.7
F7	25	0.7	1:2.8	2	10	195 ± 10	85.81 ± 3.98	17.16 ± 3.18	79.26 ± 4.3	77.63 ± 3.24	66.87 ± 4.1
F8	25	0.6	1:2.4	5	50	110 ± 19	84.22 ± 2.65	13.58 ± 1.70	75 ± 2.9	72.04 ± 1.43	71.8 ± 2.1

Mean ± s.d. (n = 3).

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