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ORIGINAL ARTICLE

A phase 0 clinical trial of novel candidate extended-release formulations of capecitabine

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Abstract
Purpose To examine the pharmacokinetic (PK) profile of several candidate extended-release (ER) formulations of capecitabine in patients.
Methods In a phase 0 clinical study, PK profiles of several oral candidate ER formulations of capecitabine were compared to the PK profile of capecitabine after administration of the commercially available immediate-release (IR) tablet. A single dose of 1000 mg IR formulation (two 500 mg tablets) was administered on day 1, and a single dose of a 1000 mg candidate ER formulation of capecitabine (two 500 mg tablets) was administered on day 2. Candidate ER formulations of capecitabine differed with regard to the amount of the ER excipient (Kollidon® SR) in tablet matrix (0–5 % w/w) and coating (0–12 mg/cm^2).
Results PK profiles of nine different candidate ER formulations were examined. The tablet coating seemed the main determinant for ER of capecitabine and tablet integrity. Average (±standard deviation) AUC_{0-2h}, relative to AUC_{0-2h} after oral administration of the IR tablet, were 43.3 % (±34.9 %) and 1.2 % (±1.2 %) for candidate ER formulations coated with 3 and 6 mg/cm^2, respectively. Corresponding AUC_{0-last} were 93.6 % (±40.2 %) and 44.0 % (±5.4 %).
Conclusion Modulation of capecitabine release in patients can be accomplished by varying tablet coating content. Proof of principle was demonstrated for candidate ER formulations with coating content of 3 mg/cm^2.

Keywords Cancer · Capecitabine · Extended release · Phase 0 · Pharmacokinetics

Introduction

Capecitabine is an orally available pre-prodrug of 5-fluorouracil (5-FU) that is used for treatment of colorectal, gastric and breast cancer. The recommended dosing schedule of capecitabine is 1250 mg/m^2 twice daily on day 1–14 of a 21-day cycle [1, 2]. Currently commercially available capecitabine formulations are immediate-release (IR) tablets. After oral administration of these tablets, capecitabine is rapidly and almost completely absorbed. Capecitabine is subsequently converted to 5-FU through a three-step enzymatic cascade. Time to maximum plasma concentration (t_{max}) of capecitabine and 5-FU is approximately 1–1.5 h with high and variable peak concentrations [3, 4]. Average elimination half-life of both compounds is less than 1 h [3–5]. Approximately 80 % percent of formed 5-FU is catabolized to inactive metabolites by the enzyme dihydropyrimidine dehydrogenase (DPD) [5], while only a small fraction of 5-FU is anabolized to active metabolites that inhibit cell proliferation through inhibition of thymidylate synthase (TS) and misincorporation in DNA and RNA [6, 7].

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Capecitabine and 5-FU are undetectable in plasma approximately 6 h after oral intake [3, 4]. As a consequence, a gap in exposure to capecitabine and 5-FU of approximately 6 h is expected within every dosing interval according to the twice daily administration schedule of the currently available IR capecitabine.

Approximately 10–30 % of patients who are treated with capecitabine will develop severe (≥National Cancer Institute Common Toxicity Criteria grade 3) toxicity and treatment-related death is observed in approximately 0.5–1 % of patients [8–10]. The treatment-induced toxicity is poorly predictable and seriously limits the clinical application of capecitabine.

Previously, tolerability, but also efficacy, of 5-FU continuous infusion was shown to be superior to 5-FU bolus administration [11]. Currently available IR formulations of capecitabine lead to short lasting 5-FU exposure, which resembles the PK profile of 5-FU after intravenous bolus infusion. In view of this, a more continuous exposure to capecitabine might reduce toxicity and improve efficacy and thus improve the clinical applicability of capecitabine.

Extended-release (ER) formulations may overcome the exposure gap of IR capecitabine formulations. Previously, we reported slow dissolution behavior of amorphous capecitabine compared to crystalline capecitabine [12]. A prototype ER tablet formulation was developed with amorphous capecitabine [13]. This prototype ER tablet contained a co-spray dried (CoSD) mixture of capecitabine and the ER excipient Kollidon® SR (98 % capecitabine/2 % Kollidon® SR, w/w). Based on in vitro–in vivo correlation modeling, it was estimated that this prototype formulation would lead to 12 h of continuous exposure to capecitabine after oral administration in patients [13]. In addition, several other candidate ER formulations of capecitabine were developed that contained 500 mg amorphous capecitabine, but differed with respect to the content of Kollidon® SR in the CoSD mixture. To further modulate capecitabine dissolution, candidate ER tablets were also coated with Kollidon® SR with variable coating thicknesses. These candidate ER formulations of capecitabine were all available for clinical testing.

A phase 0 clinical study design is attractive for early evaluation of pharmacokinetics (PK) of novel drugs or formulations [14]. The current phase 0 study was performed to investigate the candidate ER formulations of capecitabine to allow rapid selection of the most promising formulation for further clinical development. The primary objective of this study was to examine the PK of these candidate ER formulations of capecitabine in comparison with the original IR formulation of capecitabine.

Materials and methods

Patient selection

Patients aged ≥18 years with advanced solid tumors, World Health Organization (WHO) performance status of ≤2, a life expectancy of at least 3 months and adequate bone marrow, hepatic and renal function were eligible for enrollment. Relevant exclusion criteria were known DPD deficiency, as demonstrated by a *DPYD*2A* genetic mutation, bowel obstructions or motility disorder that might influence the absorption of capecitabine. Patients provided written informed consent before study enrollment. The study was approved by the independent Medical Ethics Committee of The Netherlands Cancer Institute and was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and registered in the Dutch Trial Registry (http://www.trialregister.nl, study identifier: NTR3647).

Candidate ER formulations of capecitabine

Capecitabine was CoSD with Kollidon® SR as previously described [13]. The content of Kollidon® SR in the CoSD mixture was variable: 0, 1, 2, 3, 4 or 5 % (w/w). All candidate ER formulations contained 500 mg of capecitabine. Magnesium stearate and silica colloidalis anhydrica were added to the CoSD powder of capecitabine and Kollidon® SR before tableting. Tableting of candidate ER formulations of capecitabine was previously described [13].

Candidate ER tablets were coated with Kollidon® SR that was dissolved in a mixture of acetone: isopropanol (1:1, v/v) at ambient temperature. Talcum was dispersed in this mixture for manufacturing purposes. Using a pan-coating procedure, the mixture of Kollidon® SR and talcum (2:1, w/w) was applied on the tablet surfaces with variable amounts, leading to final coating contents of 0, 3, 6, 9 and 12 mg/cm^2.

In total, 30 different candidate ER formulations containing 500 mg of capecitabine with 0–5 % (w/w) Kollidon® SR within tablet matrix and coating contents of 0–12 mg/cm^2 were available for clinical testing in this phase 0 study. In addition, a capecitabine formulation with 500 mg of crystalline capecitabine was produced with a coating content of 6 mg/cm^2. Production of the candidate ER formulations of capecitabine was performed under good manufacturing practice (GMP) conditions.

Study design

This was a single-center, open-label, pharmacological crossover study in which the PK profile of different oral

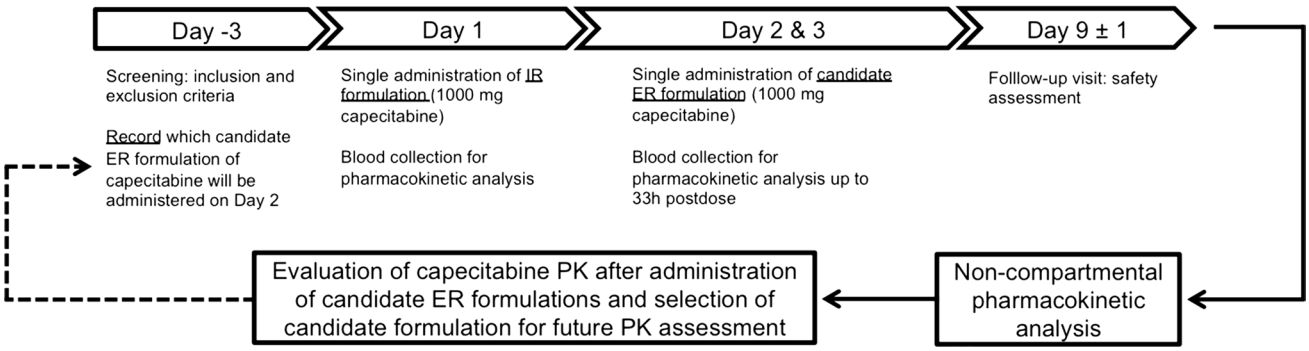

Fig. 1 Phase 0 clinical study design. *IR* immediate-release, *ER* extended-release, *PK* pharmacokinetic

ER formulations of capecitabine was compared to the PK profile of IR capecitabine (Xeloda®). Patients were hospitalized during three consecutive days. On the first day, patients received a single dose of 1000 mg IR capecitabine (two tablets of 500 mg) at approximately 9:00 h. On the second day, patients received a single dose of 1000 mg of one candidate ER formulation of capecitabine (two tablets of 500 mg) at approximately 9:00 h. Patients fasted overnight before intake of the study medication and were not allowed to eat and drink (except a small amount of water <50 mL) up to 1 h after drug intake to prevent interference of food on capecitabine absorption. Blood samples for PK analysis were collected just before and after oral administration of IR capecitabine and of a candidate ER formulation of capecitabine. A follow-up visit was planned on day 9 of the study for examination of preliminary safety. Toxicity was scored according to the Common Terminology Criteria for Adverse Events version 4.03. Only one candidate ER formulation was tested in each patient. The study design is illustrated in Fig. 1.

Based on obtained PK data from previously tested ER formulations and before enrollment of a subsequent patient, a decision was made which candidate ER formulation to apply next for in clinical examination.

Predefined criteria for adequate ER of capecitabine were (a) mean area under the capecitabine plasma concentration–time curve (AUC) to the last quantifiable observation ($AUC_{0–last}$) was ≥50 % of the mean $AUC_{0–last}$ of capecitabine after intake of the same dose of IR capecitabine and (b) mean AUC of capecitabine up to 2 h ($AUC_{0–2h}$) that was <50 % of that of IR capecitabine. The number of candidate ER formulations to be examined was limited to 12. Each tested formulation was administered to a minimum of one and up to a maximum of three patients, except for one candidate ER formulation. Extension of administration up to a maximum of six patients was allowed for one formulation.

Pharmacokinetic analyses

Peripheral blood was collected at baseline and after oral administration of 1000 mg IR capecitabine and after 1000 mg of a candidate capecitabine ER formulation (Fig. 1). Samples were collected at baseline and at 0.5, 1, 1.5, 2, 3, 4, 6, 12 and 24 h after drug administration. After intake of a candidate capecitabine ER formulation, an additional blood sample was collected 33 h postdose.

Blood samples were collected in lithium-heparinized tubes, gently mixed and directly placed on ice, followed by centrifugation at 1500 g for 10 min at 4 °C. Plasma was isolated and stored at −70 °C until analysis. Capecitabine and its metabolites 5′-deoxy-5-fluorocytidine (dFCR), 5′-deoxy-5-fluorouridine (dFUR), 5-fluorouracil (5-FU) and fluoro-β-alanine (FBAL) were quantified using liquid chromatography with tandem mass spectrometric detection (LC–MS/MS) [15].

Non-compartmental PK analyses and descriptive statistics were performed with R version 3.1.2 [16]. A previously validated R script was used for non-compartmental PK analyses. Primary endpoints were relative $AUC_{0–last}$ and $AUC_{0–2h}$ of capecitabine, which were expressed by individual estimates of $AUC_{0–last}$ and $AUC_{0–2h}$ after intake of a candidate ER formulation as a percentage of the values after intake of IR capecitabine. Maximum plasma concentrations (C_{max}) and t_{max} were also extracted from the data.

Results

A total of 15 patients were enrolled into this phase 0 study, of which 13 patients were evaluable for PK analyses (Supplementary Table 1). Two patients withdrew from the study due to decline in clinical status.

Table 1 Characteristics of the tested candidate extended-release formulations of capecitabine

Formulation	Coating content (mg/cm^2)	Kollidon® SR in tablet matrix (%, w/w)[b]	Number of patients
A	0	5	3
B	3	5	2
C	3	4	2
D	3	0	1
E	6	5	1
F	6	0	1
G[a]	6	0	1
H	9	5	1
I	12	5	1

All formulations contained 500 mg of capecitabine and differed with respect to tablet coating content and proportion of Kollidon® SR in co-spray dried powder that was used for tableting

[a] Contains crystalline instead of amorphous capecitabine

[b] Percent of Kollidon® SR in co-spray dried powder with capecitabine

Pharmacokinetic results

Characteristics of candidate ER formulations of capecitabine that were examined are reported in Table 1. Coating content of the candidate ER formulations showed to be rate limiting for extended release of capecitabine in patients (Fig. 2). The results did not suggest that the content of Kollidon® SR in the CoSD powder significantly contributed to ER of capecitabine in patients. Therefore, it was decided to pool the PK data of the candidate ER formulations of capecitabine based on tablet coating content. The corresponding PK data of the different tested formulations are given in Table 2.

Formulation A (5 % Kollidon® SR within the tablet matrix without coating) was the first tested candidate ER formulation of capecitabine. The observed PK profile of formulation A (upper left panel of Fig. 2b) was similar to the pattern observed after intake of IR capecitabine (Fig. 2a). Formulation I, containing the highest tested tablet coating content (12 mg/cm^2), was selected next for PK examination. Administration of this formulation, however,

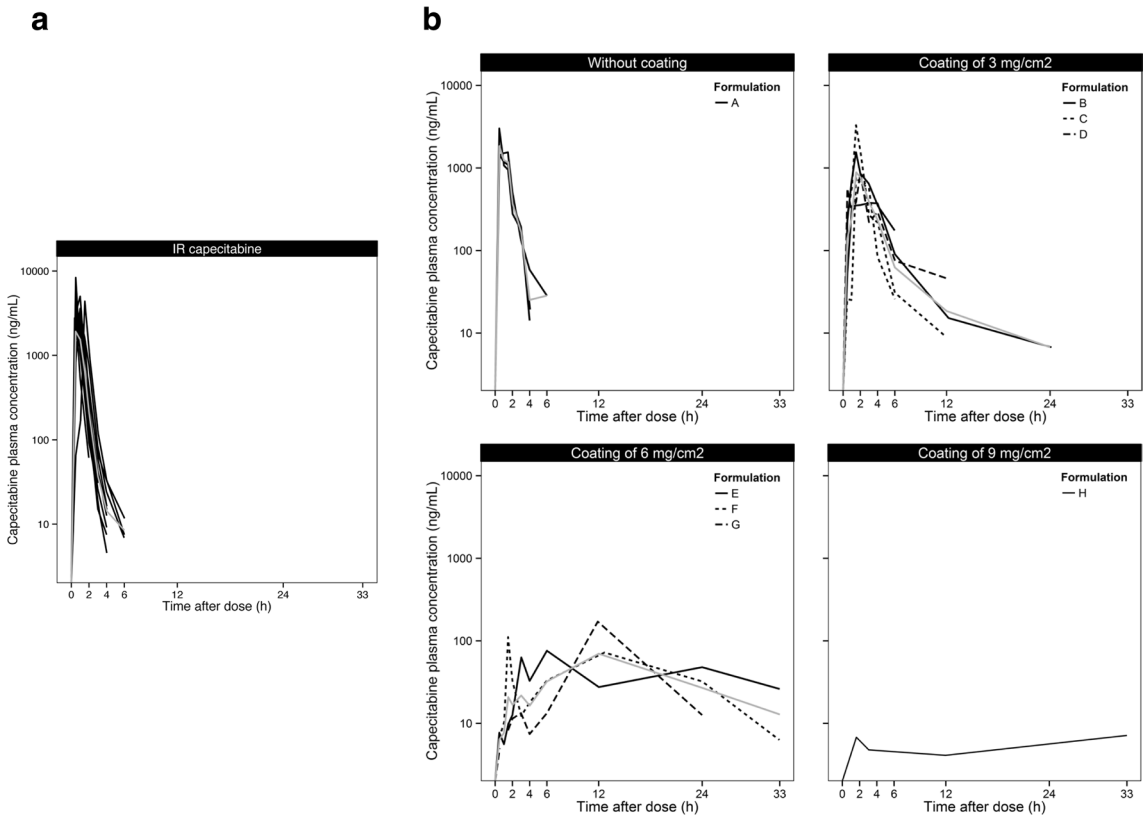

Fig. 2 Log plasma concentration of capecitabine versus time after administration of 1000 mg IR capecitabine (**a**) and 1000 mg candidate ER formulation of capecitabine (**b**). Pharmacokinetic profiles of candidate ER formulations were grouped by coating content and formulation code. A total of 13 patients were evaluable for pharmacokinetic analyses. Pharmacokinetic profiles of individual patients are shown in *black*. *Gray lines* represent average capecitabine plasma exposure. *IR* immediate-release, *ER* extended-release

Table 2 Pharmacokinetic parameters for capecitabine after oral administration of IR capecitabine and candidate ER formulations

IR capecitabine		Candidate ER formulations of capecitabine			
		Tablet coating 0 mg/cm^2	Tablet coating 3 mg/cm^2	Tablet coating 6 mg/cm^2	Tablet coating 9 mg/cm^2
Parameter	Mean ± SD ($N = 13$)	Mean ± SD ($N = 3$)	Mean ± SD ($N = 5$)	Mean ± SD ($N = 3$)	Estimate ($N = 1$)
$AUC_{0–last}$ (µg*h/mL)	3.20 ± 0.96	2.73 ± 0.32	2.67 ± 0.94	1.43 ± 0.25	0.17
Relative $AUC_{0–last}$ (%)[a]	N/A	107 ± 20.0	93.6 ± 40.2	44.0 ± 5.4	3.4
$AUC_{0–2h}$ (µg*h/mL)	3.00 ± 0.93	2.33 ± 0.32	1.17 ± 0.83	0.03 ± 0.03	0.01
Relative $AUC_{0–2h}$ (%)[a]	N/A	95.8 ± 16.6	43.3 ± 34.9	1.2 ± 1.2	0.1
C_{max} (µg/mL)	3.80 ± 1.64	2.00 ± 0.87	1.38 ± 1.16	0.12 ± 0.05	0.01
t_{max} (h)	0.72 ± 0.35	0.82 ± 0.57	1.92 ± 0.69	6.50 ± 5.22	33

Pharmacokinetic results for candidate ER formulations are grouped according on tablet coating content. Capecitabine could not be detected in plasma after administration of the candidate ER formulation with coating content of 12 mg/cm^2 (Formulation I)

$AUC_{0–last}$ area under the plasma concentration–time curve up to last observation, $AUC_{0–2h}$ area under the plasma concentration–time curve up to 2 h postdose, C_{max} maximum plasma concentration, t_{max} time to reach maximum plasma concentration, *SD* standard deviation, *IR* immediate-release, *ER* extended-release, *N/A* not applicable, *N* number of patients

[a] Relative $AUC_{0–last}$ and $AUC_{0–2h}$ were normalized to corresponding estimates for IR capecitabine

did not lead to any detectable levels of capecitabine in plasma.

The relative $AUC_{0–2h}$ and $AUC_{0–last}$ for candidate ER formulations of capecitabine with coating contents of 3 mg/cm^2 were on average (± SD) 43.3 % (± 34.9 %) and 93.6 % (± 40.2 %), respectively.

The relative $AUC_{0–2h}$ for formulations with a coating content of 6 mg/cm^2 was on average (± SD) 1.2 % (± 1.2 %). Of the examined candidate ER formulations coated with 6 mg/cm^2, the tablet matrices contained 5 % Kollidon® SR (formulation E), 0 % Kollidon® SR (formulation F) or consisted of crystalline capecitabine (formulation G). As shown, these candidate ER formulations lead to exposure of capecitabine up to 33 h (lower left panel of Fig. 2b). Differences with respect to the content of Kollidon® SR in the tablet matrix or the use of crystalline instead of amorphous capecitabine did not influence the PK profile of capecitabine. The average relative $AUC_{0–last}$ for formulations with coating content of 6 mg/cm^2 was below 50 %.

The candidate ER formulation with coating content of 9 mg/cm^2 resulted in relatively low capecitabine exposure.

The PK results of capecitabine metabolites were in agreement with the findings from the PK profiles of capecitabine (Supplementary Table 2). Based on the available PK results, it was found that coating content was crucial for ER release of capecitabine in patients. Examination of other candidate ER formulations would most probably not lead to other insights and was therefore considered unnecessary.

Average $AUC_{0–2h}$ and $AUC_{0–last}$ of tablet formulations with 3 mg/cm^2 met predefined criteria for ER of capecitabine. However, these results were influenced by a single observation of 104 % for $AUC_{0–2h}$ of one out of two patients exposed to formulation C, which indicated immediate release of capecitabine. Altogether, proof of concept was demonstrated for candidate ER formulations for capecitabine with coating content of 3 mg/cm^2.

Preliminary tolerability

Adverse events that were possibly, probably or definitely related to study treatment were grade 1 diarrhea in one patient, grade 2 diarrhea in one patient and grade 3 fatigue in one patient.

Discussion

This is, to our knowledge, the first report that describes the applicability of a phase 0 trial design for development and optimization of an oral extended-release formulation in oncology. Within one year, this trial design enabled rapid examination of pharmacokinetics of nine candidate ER formulations of capecitabine in patients.

The availability of multiple candidate ER formulations of capecitabine allowed for a PK-driven study approach. The candidate ER formulation to apply in the next included patient was chosen based on PK results obtained by the patient previously treated in the study. A major advantage of this approach is that candidate ER formulations can be selected based on actual clinical data. This was especially important since the first tested candidate ER formulation, which was selected based on in vitro dissolution data, did

not show any ER properties in humans. This implies poor predictability of the in vitro dissolution test for in vivo absorption behavior.

Results of this study suggest that prolonged exposure to capecitabine in patients can be achieved with candidate ER formulations of capecitabine. Particularly, coating content of the candidate ER formulations seems to be essential for slow release of capecitabine. Results do not suggest that the content of Kollidon® SR in the CoSD powder significantly contributed to in vivo ER of capecitabine. Therefore, release of capecitabine from candidate ER formulations seems to be rate-limited by the tablet coating thickness. The uncoated candidate formulation with 5 % Kollidon® SR in the CoSD powder resulted in immediate release of capecitabine. However, in vitro examination of a prototype with only 2 % Kollidon® SR in the CoSD powder showed capecitabine release for up to 12 h [13].

Application of tablet coating seems to be crucial to prevent disintegration of the tested candidate formulations and to maintain ER characteristics. It appears that candidate ER formulations with coating content of 3, 6, 9 and 12 mg/cm^2 have unique PK profiles. On average, formulations with coating content of 3 mg/cm^2 seem to fulfill predefined criteria of adequate ER of capecitabine. However, immediate release of capecitabine was observed in one patient after oral administration of formulation C, which might be explained by an incomplete coverage of the whole tablet with this relative thin coating, resulting in rapid disintegration of the tablet. Tablet coating content of 12 mg/cm^2 prevents the candidate ER formulation from disintegration at all. Although a coating of 12 mg/cm^2, but also 9 mg/cm^2, provides formulation robustness, coating thickness seems too high for significant release of capecitabine.

Candidate ER formulations with coating content of 6 mg/cm^2 provide continuous capecitabine exposure for over 24 h, with acceptable relative $AUC_{0–2h}$ but with rather low relative $AUC_{0–last}$. The findings also suggest that amorphous capecitabine, which showed slow dissolution in vitro compared to crystalline capecitabine [12], is not important for slow dissolution of capecitabine in patients. Results from the study point out that ER of capecitabine can be achieved by modulation of tablet coating content and that subtle deviations in coating content highly affect capecitabine release and plasma exposure.

The use of amorphous capecitabine requires that tablets are stored in the refrigerator or freezer to ensure physical stability [12, 13]. For this reason, the use of crystalline capecitabine, which is physically stable at ambient temperatures and therefore more convenient, is considered for the future ER formulation of capecitabine. Kollidon® SR will be omitted from the tablet matrix, since the presence of this excipient in the tablet matrix did not attribute to ER of capecitabine in patients.

A reproducible coating process is crucial for the manufacturing of the subsequent ER formulation of capecitabine. Optimization of critical tablet coating parameters, such as pan speed, coating time and temperature during the coating process, is required to improve tablet coating reproducibility and robustness.

Others have also described development of extended-release formulations of capecitabine. Agnihotri et al. developed capecitabine-loaded hydrogel microsphere that showed slow release of capecitabine in vitro [17]. Singh et al. developed a prototype mucoadhesive cum floating gastroretentive system containing amorphous capecitabine that showed extended release of capecitabine in rats [18]. However, no data are available describing the translation of their concepts to the clinical situation.

Diarrhea and fatigue are common side effects after administration of capecitabine [8]. Preliminary observed toxicity after a single oral dose of study drug administered was mild and did not require intervention or special attention. A clinical phase I dose escalation study is needed to further evaluate the safety of ER capecitabine treatment and to determine the maximum tolerated dose and preliminary efficacy.

In conclusion, a unique and innovative study was performed with the goal to accelerate the development of an ER formulation of capecitabine. The PK profiles of nine different candidate formulations for ER of capecitabine were examined in patients within a short period of time. Modulation of capecitabine release can be accomplished by varying tablet coating content and proof of principle was demonstrated for candidate ER formulations with coating content of 3 mg/cm^2.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Schellens JHM (2007) Capecitabine. Oncologist 12:152–155. doi:10.1634/theoncologist.12-2-152
2. Midgley R, Kerr DJ (2009) Capecitabine: have we got the dose right? Nat Clin Pract Oncol 6:17–24. doi:10.1038/ncponc1240
3. Budman DR, Meropol NJ, Reigner B et al (1998) Preliminary studies of a novel oral fluoropyrimidine carbamate: capecitabine. J Clin Oncol 16:1795–1802
4. Mackean M, Planting A, Twelves C et al (1998) Phase I and pharmacologic study of intermittent twice-daily oral therapy with capecitabine in patients with advanced and/or metastatic cancer. J Clin Oncol 16:2977–2985
5. Reigner B, Blesch K, Weidekamm E (2001) Clinical pharmacokinetics of capecitabine. Clin Pharmacokinet 40:85–104

6. de Bono JS, Twelves CJ (2001) The oral fluorinated pyrimidines. Investig New Drugs 19:41–59
7. Wilson PM, Danenberg PV, Johnston PG et al (2014) Standing the test of time: targeting thymidylate biosynthesis in cancer therapy. Nat Rev Clin Oncol 11:282–298. doi:10.1038/nrclinonc.2014.51
8. Twelves C, Wong A, Nowacki MP et al (2005) Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med 352:2696–2704. doi:10.1056/NEJMoa043116
9. Scheithauer W, McKendrick J, Begbie S et al (2003) Oral capecitabine as an alternative to iv 5-fluorouracil-based adjuvant therapy for colon cancer: safety results of a randomized, phase III trial. Ann Oncol 14:1735–1743. doi:10.1093/annonc/mdg500
10. Mikhail SE, Sun JF, Marshall JL (2010) Safety of capecitabine: a review. Expert Opin Drug Saf 9:831–841. doi:10.1517/14740338.2010.511610
11. Meta-analysis Group In Cancer (1998) Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 16:301–308
12. Meulenaar J, Beijnen JH, Schellens JHM, Nuijen B (2013) Slow dissolution behaviour of amorphous capecitabine. Int J Pharm 441:213–217. doi:10.1016/j.ijpharm.2012.11.041
13. Meulenaar J, Keizer RJ, Beijnen JH et al (2013) Development of an extended-release formulation of capecitabine making use of in vitro-in vivo correlation modelling. J Pharm Sci. doi:10.1002/jps.23779
14. Marchetti S, Schellens JHM (2007) The impact of FDA and EMEA guidelines on drug development in relation to phase 0 trials. Br J Cancer 97:577–581. doi:10.1038/sj.bjc.6603925
15. Deenen MJ, Rosing H, Hillebrand MJ et al (2013) Quantitative determination of capecitabine and its six metabolites in human plasma using liquid chromatography coupled to electrospray tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 913–914:30–40. doi:10.1016/j.jchromb.2012.11.033
16. R Development Core Team (2008) R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna
17. Agnihotri SA, Aminabhavi TM (2006) Novel interpenetrating network chitosan-poly(ethylene oxide-g-acrylamide) hydrogel microspheres for the controlled release of capecitabine. Int J Pharm 324:103–115. doi:10.1016/j.ijpharm.2006.05.061
18. Singh Y, Singh M, Meher JG et al (2014) Trichotomous gastric retention of amorphous capecitabine: an attempt to overcome pharmacokinetic gap. Int J Pharm 478:811–821. doi:10.1016/j.ijpharm.2014.11.055