Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(1):320-328

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Development of modified release tablet dosage forms of capecitabine for better therapeutic efficacy

Seetha Sunkara, Deekonda Sravanthi, Karna Male Maheswari, Shaik Salma and Buchi N. Nalluri*

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, AP, INDIA

ABSTRACT

The aim of the present investigation was to develop a once-daily modified release (MR) matrix tablet formulations of Capecitabine (CPC), an anti-cancer drug, using Hydroxy Propyl Methyl Cellulose (HPMC K4M & HPMC K15M) as drug release retardant. The tablets were prepared by direct compression process and evaluated for various physico-chemical/mechanical parameters. Among the two grades of HPMC used, K15M was selected as release retardant based on viscosity in controlling the CPC release during dissolution. The effect of different fillers like microcrystalline cellulose (MCC, Avicel PH 105), Spray Dried Lactose (SDL), Pre Gelatinized Starch (PGS), Di Calcium Phosphate (DCP) on CPC release was also studied and the percent release at the end of dissolution is in the order of SDL > Avicel PH 105 > DCP > PGS. The formulation containing 10% (w/w) of HPMC K15M and MCC (Avicel PH 105) as filler gave a complete and controlled release of CPC over a period of 24h (94.4 ± 1.76 %). The dissolution data was also evaluated for drug release kinetics and mechanisms.

Keywords: Modified release (MR) matrix tablets; Capecitabine (CPC); HPMC; Fillers and *In vitro* dissolution studies.

INTRODUCTION

The development of oral MR dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the commercially successful controlled release dosage forms [1]. The most important variable in hydrophilic matrix systems is the rate at which the drug substance is released and the release of drug is controlled by the formation of a hydro-gel layer around the matrix following exposure to aqueous fluid [2]. Overall, the basic goal of the controlled release therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non toxic for an extended period of time [3].

Capecitabine (CPC) is an orally-administered chemotherapeutic agent used in the treatment of metastatic breast, stomach, pancreas and colorectal cancers [4]. CPC is fluoropyrimidine carbamate pro-drug of 5- fluorouracil (5-FU) and its absorption is higher than 5-FU [5]. CPC is selectively tumor-activated to its cytotoxic moiety, 5-FU, by thymidine phosphorylase, an enzyme found in higher concentrations in many tumors compared to normal tissues or plasma, where it inhibits DNA synthesis and slows the growth of tumour tissue. The tumour-preferential activation of CPC reduces systemic exposure to 5-FU and potentially improves safety and efficacy [6]. Presently, CPC is marketed as immediate release (IR) tablets (150, 500mg) and in the existing type of dosage form (as an IR tablet) poor patient compliance and exposure to high doses of drug may be anticipated and MR dosage forms are needed for better therapeutic efficacy and patient compliance. CPC is well absorbed from the gastrointestinal tract, and its plasma half-life is about 45-60 min and all these properties make it an ideal drug candidate for development into MR dosage forms [7]. So far, no reports were published on MR dosage forms of CPC based on the matrix tablet technology. However, some patents were published [8] and also a report on the chitosan hydrogel micro spheres of

CPC were published [9]. Hence, the aim of this present investigation is to develop a once-daily oral MR matrix tablets of CPC based on the matrix tablet technology using hydrophilic cellulose ether polymers.

EXPERIMENTAL SECTION

Capecitabine was obtained from Divi's Laboratories, Hyderabad, India as a gift sample. Hydroxy Propyl Methyl Cellulose K4M was obtained from Colorcon, India. Hydroxy Propyl Methyl Cellulose K15M was obtained from Colorcon, India. Partially pre Gelatinized Starch was obtained from Rouette Pharma, France. Spray Dried Lactose with maize starch was obtained from Rouette Pharma, France. Dicalcium Phosphate was obtained from Finar, Mumbai, India. Microcrystalline Cellulose PH 101 and PH 105 were obtained from FMC Biopolymers, USA. Talc was obtained from Loba Chemie, India. Magnesium stearate was obtained from Loba Chemie, India. All other reagents used were of analytical grade.

FTIR Studies:
The FT-IR spectra of pure drug and CPC with different excipients like HPMC K 4 M, HPMC K 15 M, Avicel PH 105, Avicel PH 101, SDL, PGS, DCP, Magnesium stearate and talc was measured using ATR-FTIR spectrophotometer (Bruker, Germany). ATR spectra were measured over the wave number range of 500-4000cm^{-1} at a resolution of 1.0 cm^{-1}. The powder sample is simply placed onto the ATR crystal and the sample spectrum is collected.

Preparation of CPC MR Tablets by direct compression Technique:
CPC MR Matrix tablets were prepared by direct compression method, as per formulae given in Table 1. HPMC (K4M, K15 M) was used as release retardant materials. Sufficient quantities of MCC (Avicel PH 101 and PH 105), pre gelatinized starch, maize starch, spray dried lactose and Di-Calcium Phosphate were used to raise the bulk volume of the tablets to a targeted weight of 400mg each. Talc and magnesium stearate at 0.5% w/w levels were used as glidant/lubricant.

All the ingredients were passed through sieve # 80 before mixing. Initially drug and polymers were mixed thoroughly and then required quantities of fillers were added and finally the blend was mixed with talc and mixed thoroughly for 5min in a poly bag and then added the required amount of magnesium stearate and mixed for another 5 min. Powder blends (for 50 tablets each) of all the above formulations were compressed on single punch tablet press (Cadmach, India) using 10 mm punches (round shape) to a hardness of 4-6 kg/cm^2.

TABLE 1: Composition of MR CPC Matrix Tablets

S.No.	Ingredients (mg/tab)	Formulations								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	CPC	150	150	150	150	150	150	150	150	150
2	HPMC K4M	100	100	60	40	-	-	-	-	-
3	HPMC K15M	-	-	-	-	40	100	40	40	40
4	Avicel PH-105	146	-	186	206	206	146	-	-	-
5	Avicel PH-101	-	146	-	-	-	-	-	-	-
6	Spray Dried Lactose	-	-	-	-	-	-	206	-	-
7	PreGelatinisedStarch	-	-	-	-	-	-	-	206	-
8	DiCalciumPhosphate	-	-	-	-	-	-	-	-	206
9	Magnesium Stearate	2	2	2	2	2	2	2	2	2
10	Talc	2	2	2	2	2	2	2	2	2
	Total weight	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**	**400**

Evaluation of Pre compression Parameters of the powder blend:
Pre compression parameters of the prepared powder blend of all the formulations were studied by determining the Bulk density, Tapped density, Compressibility Index, Hausner's ratio and Angle of repose [10].

Evaluation of post Compression parameters of MR CPC tablets:
The compressed MR CPC tablets were subjected to various physical tests which include hardness, friability, weight variation and drug content uniformity [11].

Hardness
The hardness of the tablets was measured with a Monsanto hardness tester (M/s Campbell Electronics, model EIC-66, India). The results reported were average of 6 tablets for each formulation.

Friability

For each formulation 10 tablets were weighed, placed in Friabilator (M/S Campbell Electronics, India) and were subjected to 100 rotations in 4min. The tablets were reweighed and friability was calculated by the following formula: $Friability = \frac{W_2 - W_1}{W_1} \times 100$

Where W_1 is the initial weight and W_2 is the final weight of the tablets.

Weight variation

The individual and total weight of 20 tablets from each batch was determined. Percentage deviation of the individual weights from the average weights was calculated.

Drug content

Ten tablets were weighed individually; these were placed in a mortar and powdered with a pestle. Accurately weighed powder sample equivalent to 20 mg of CPC was transferred into a 20 ml volumetric flask and made up to volume with distilled water. The contents of the volumetric flask were sonicated for 15 min in-order to extract the drug into distilled water. The solution was then filtered, suitably diluted with distilled water and absorbance was measured at 240 nm using Elico SL150 UV-Visible Spectrophotometer (Elico Ltd., Hyderabad). The estimation was carried out in triplicate.

***In-vitro* drug release studies:**

In-vitro dissolution studies of MR CPC tablet formulations prepared were carried in 900 mL of distilled water as dissolution medium using USP XXI type II (Paddle method) Dissolution Rate Test Apparatus (LABINDIA, DS 8000) at 50 rpm. The temperature was maintained constant at 37±0.5°C. At regular time intervals, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 240 nm for CPC against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve. The dissolution experiments were conducted in triplicate.

Release kinetics and mechanism

In order to describe the kinetics of the release process of CPC, various equations were used such as the zero-order rate equation, which describes the systems where the release rate is independent of the concentration of the dissolved species [12]. The first-order equation describes the release from systems where dissolution rate is dependent on the concentration of the dissolving species [13]. The Higuchi square root equation, describes the release from systems where the solid drug is dispersed in an insoluble matrix and the rate of drug release is related to the rate of drug diffusion [14]. Two factors, however, diminish the applicability of Higuchi's equation to matrix system. This model fails to allow for the influence of swelling of the matrix upon hydration and gradual erosion of the matrix. Therefore, the dissolution data were also fitted according to the Peppas equation, which is often used to describe the drug release from polymeric system [15].

$$Mt/M\infty = K\, t^n$$

Where $Mt/M\infty$ is the fractional drug release at time t; K is a constant incorporating the properties of the macromolecular polymeric system and the drug and n is a kinetic constant which depends on and is used to describe the transport mechanism. The value of n for a tablet, n=0.45 for Fickian (Case I) release, > 0.45 but < 0.89 for Non Fickian (anomalous) release and 0.89 for case II (zero-order) release and > 0.89 for super case II type of release. Equation one was used to calculate the n values and to identify the drug release mechanism of drug.

Due to the differences in drug release kinetics, the Peppas constant 'k', though is one of the measures of release rate, should not be used for comparison. Therefore, to characterize the drug release rate in different formulations, mean dissolution time (MDT) was calculated from dissolution data using the formula:

$$MDT = (n/n+1) \times k^{-1/n}$$

Where n is the release exponent and k is the Peppas constant [16]. MDT value is used to characterize the drug release rate from the dosage form and the retarding efficacy of the polymer. A higher value of MDT indicates a higher drug retarding ability of the polymer and vice-versa [17].

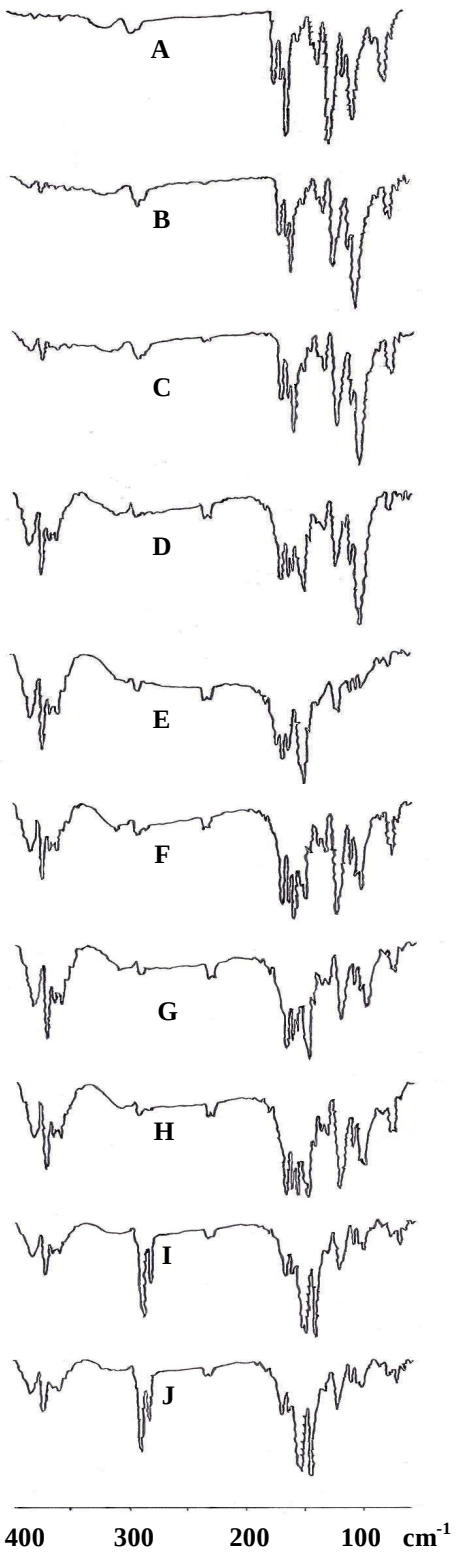

FIGURE 1: FTIR spectrum of CPC (A), CPC-HPMCK4M (B), CPC –HPMCK15M (C), CPC-Avicel PH 105 (D), CPC-Avicel PH 101(E), CPC-SDL (F), CPC-PGS (G), CPC-DCP (H), CPC-Magnesium Stearate (I), CPC-Talc

RESULTS AND DISCUSSION

FTIR studies:

FTIR studies were carried with a view to evaluate the *in situ* drug and excipient/s compatibility. Figure 1 shows the IR spectra of pure CPC and CPC with different excipients. Pure CPC showed characteristic IR absorption bands at 1038 cm^{-1} indicating the presence of C-N group, 1115 cm^{-1} indicates the presence of C-O-C group in aromatic ring, 1337 cm^{-1} indicates the presence of C-F group, 1645 cm^{-1} indicates the presence C=N group, 1707 cm^{-1} indicates the presence of stretching of C=O group, 3516 cm^{-1} indicates the presence of bending of N-H group, 3178 cm^{-1} indicates the presence -OH group. From the result, these prominent peaks of drug were also present in the IR spectra of physical mixtures of drug with various excipients. Thus, revealing compatibility of the selected drug with excipients.

Determination of pre and post compression parameters:

The results of various pre compression parameters are given in Table 2. These results indicate that the powder blends of all formulations can be suitable to prepare tablets by direct compression technique. The compressed tablets fulfilled the official compendia requirements regarding drug content, uniformity of weight, hardness and friability. The results are given in Table 3.

TABLE 2: Pre Compression Parameters of the Powder blends

Powder Blend	Bulk density(g/ml)	Tapped density(g/ml)	Carr's index (%)	Hausner's ratio	Angle of Repose(°)
F1	0.252	0.336	14.3	1.33	28.6
F2	0.257	0.331	18.7	1.31	27.5
F3	0.243	0.328	15.3	1.28	27.9
F4	0.258	0.359	16.8	1.25	29.8
F5	0.233	0.319	11.6	1.16	26.5
F6	0.262	0.345	13.5	1.21	28.1
F7	0.249	0.342	20.7	1.37	30.5
F8	0.256	0.353	22.9	1.37	34.2
F9	0.249	0.348	21.2	1.38	31.1

TABLE 3: Post Compression Parameters of MR CPC Tablets

Formulation	Drug content (mg/tab)	Weight variation (Mean ± SD)	Hardness (kg/cm^2)	Friability (% wt loss)
F1	149.2 ± 0.198	398 ± 2.4	5	0.62
F2	149.8 ± 0.199	398 ± 3.2	5	0.52
F3	151.4 ± 0.201	399 ± 1.2	5	0.56
F4	150.3 ± 0.200	401 ± 2.3	5.5	0.41
F5	149.4 ± 0.199	397 ± 3.2	5	0.69
F6	150.6 ± 0.200	402 ± 2.1	5	0.52
F7	149.2 ± 0.198	398 ± 2.9	5	0.57
F8	150.5 ± 0.200	403 ± 2.1	5	0.34
F9	149.5 ± 0.199	397 ± 1.6	4.5	0.49

***In-vitro* drug release studies:**

All the tablet formulations were subjected to *in vitro* drug release studies using distilled water as dissolution medium, in order to assess drug release profiles including release kinetics and drug release mechanisms from tablets. In the present investigation, swellable polymer like HPMC of viscosity grades K4M, K15 M were used to retard the CPC release from the MR tablets. The dissolution profiles of the formulations (F1-F9) clearly indicated a controlled release pattern over a period of 8-24 h. This controlled release of CPC from the tablets is because of release retardant material, HPMC, and it swells upon contact with dissolution medium and a gel layer forms on tablet surface. This gel layer retards further uptake of fluid and subsequent CPC release.

Effect of MPMC concentration and viscosity on CPC release:

Initial formulation studies were carried out to look into the release retarding effect of HPMC K4M at a level of 25%w/w in the formulations (F1 and F2) using AVICEL PH 105 and 101 as fillers.

Formulation F1 containing MCC (Avicel PH 105) as a filler has given a CPC release of 90.46 ± 0.40% at the end of 24 h. The calculated MDT for formulation F1 is 650 min (Table 4). In the case of formulation F2, (Avicel PH 101 as filler) gave a CPC release of 89.77 ± 0.99 % at the end of 24 h. The calculated MDT for formulation F2 is 662 min (Table 4). The initial % CPC release at 1 hr time point is 13.27 ± 1.29% for F1 and 12.80 ± 1.65% for F2 formulations and there is no significant difference in the values. However, based on the data from pre compression parameters (Table 2), Avicel PH 105 was selected as filler in further formulation studies. The comparative

dissolution profiles were shown in Figure 2. Overall, from these results HPMC K4M was able to retard the CPC, a water soluble drug, release from MR tablets over a period of 24h.

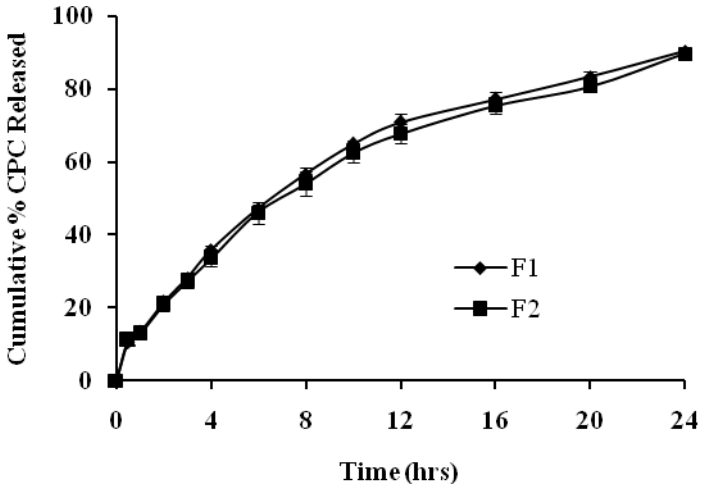

FIGURE 2: Comparative dissoltion profile of Formulation F1 & F2

Further studies were carried out to enhance the initial burst release of CPC from the MR tablets by lowering release retardant HPMC K4M concentration. Formulation F3, 15% w/w HPMC K4M, with Avicel PH 105 as a filler gave 22.12 ± 2.21% initial burst release of CPC at 1h and 92.36 ± 1.91% at the end of 24 h. The calculated MDT for formulation F3 is 559 min (Table 4). In case of formulation F4, the polymer (HPMC K4 M) concentration was further reduced to 10%w/w with the same filler and gave 35.19 ± 0.33% initial burst release of CPC at 1 h and 95.52 ± 0.33% at the end of 24h.

Further studies were carried out by developing formulation F5 with 10%w/w HPMC K15M, Avicel PH 105 as a filler in order to compare the effect of viscosity of HPMC on the CPC release from the MR tablets. A 24.27 ± 0.35% of initial burst release at 1h and 94.41 ± 1.76 % at the end of 24 h were observed. The Comparative dissolution profiles of formulations F4 and F5 were shown in Figure 3. Interestingly CPC release at the end of 24h was not much affected by the HPMC viscosity but the initial burst release of CPC at 1h for formulation F4 is higher than F5. However, the tablet integrity and gel strength were maintained with 10%w/w HPMC K15M when compared to 10%w/w HPMC K4M.

The calculated MDT values for formulation F4 (HPMC K4M 10%w/w) is 487 min, whereas, for formulation F5 (HPMC K15M 10%w/w) is 516 min (Table 4). Based on the MDT values it can be further confirmed that HPMC K15M retarded the CPC release well when compared with formulation F4 containing HPMC K4M.

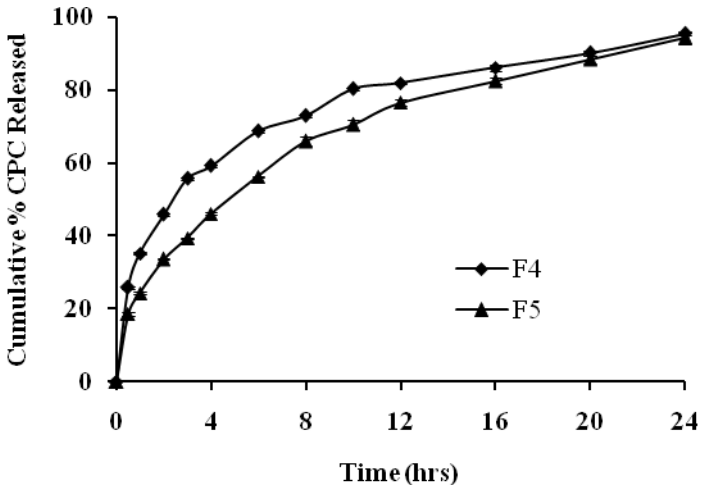

FIGURE 3: Comparative dissoltion profile of Formulation F4 & F5

Since, CPC is a water soluble drug, in formulation F6 the HPMC K15M concentration was further increased to 25%w/w to control the drug release for a prolonged period of time and with MCC (Avicel PH 105) as a filler it gave CPC release of 87.56 ± 1.24% and tablets were intact and a gel layer was remained even at the end of the 24 h. The calculated MDT for the formula F6 (HPMC K15M 25%w/w) is 686 min (Table 4). This MDT is significantly higher when compared to formulation F5 containing 10% w/w of HPMC K15M.The comparative dissolution profiles of F5 and F6 were shown in Figure 4.

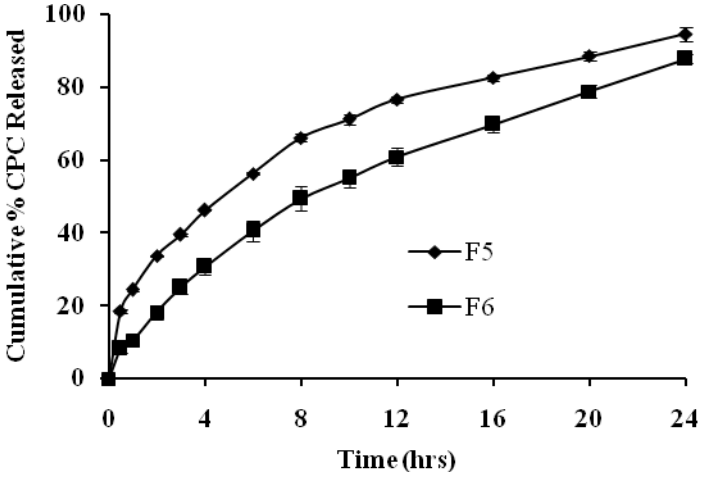

FIGURE 4 : Comparative dissoltion profile of Formulation F5 & F6

Overall, the release of CPC was found to be inversely related to the viscosity grade of HPMC present in the matrix structure i.e., higher the viscosity grade slower is the CPC release from the matrix tablets. The retarding ability of the HPMC matrices is in the order of HPMC K15M > HPMC K4M. The concentration of the polymer in the formulation also affected the CPC release from the matrix tablets i.e., higher the concentration of the polymer slower is the CPC release. From the results obtained as above, further formulation studies HPMC K15M was selected as release retardant material at a concentration of 10%w/w.

Effect of fillers on CPC release from MR tablets:

Diluents fill out the size of a tablet or capsule, making it practical to produce and convenient for the consumer to use. By increasing the bulk volume, the fillers make it possible for the final product to have the proper volume for patient handling. Diluents slightly affect the drug release from a dosage form especially in MR dosage forms. Fillers such as, PGS, maize starch with spray dried lactose (SDL) and Di Calcium Phosphate (DCP) were used in the further studies to formulate MR tablets and their effect on CPC release was investigated. All the formulations were prepared with 10%w/w HPMC K15M as the release retardant.

Formulation F7 with SDL (spray Dried Lactose) a water soluble filler gave complete CPC release at the end of 8 h and the tablets were completely dissolved. This could be due to the large particle size and water soluble nature of SDL and thereby making the channels in gel matrix. These results were further confirmed by the low MDT value (444 min) obtained with this formulation (Table 4).

With formulation F8 containing PGS (pre gelatinized starch) water insoluble filler, the CPC release was 75.9 ± 0.36% at the end of 24 h. Tablets were intact and gel layer was remained at the end of 24 h. These results were further confirmed by the MDT value of 869 min which is significantly higher when compared to all other fillers and also all other formulations (Table 4). Formulation F9 with DCP (Di-calcium phosphate) as filler, the CPC release was 79.9 ± 1.37% at the end of 24 h. The slower drug release with DCP is may be due to the hydrophobic nature of DCP which results in the decreased penetration of the dissolution medium towards the matrix core. These results were further confirmed by the MDT value of 754 min (Table 4). The Comparative dissolution profiles were shown in Figure 5.

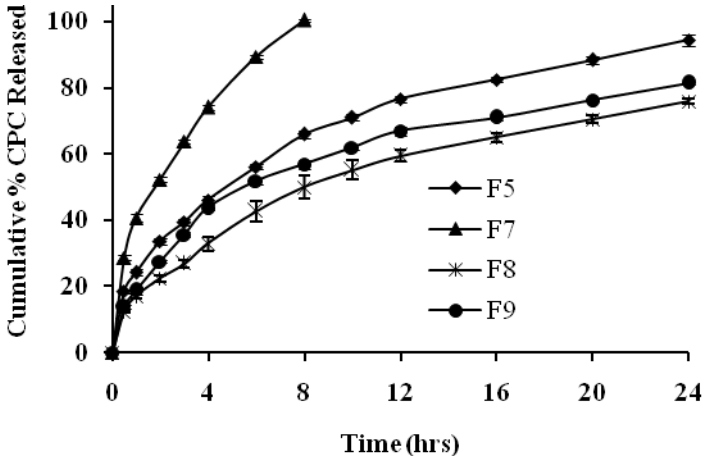

FIGURE 5 : Comparative dissolution profiles of different fillers

Overall, as supported by MDT values the effect of fillers on the CPC release is in the order of SDL > MCC (Avicel PH 105) > DCP > PGS with HPMC K15M 10% w/w as the release retardant.

Drug Release Kinetics and mechanism:

The R^2 values for F1-F9 obtained with first order plots were found to be superior when compared to the R^2 values obtained with zero order plots**.** These results indicated that the CPC release from F1-F9 followed first order kinetics. The Higuchi square root model showed higher correlation coefficient values (0.926-0.997) and diffusion is the release mechanism for CPC from tablets. The graphs of **LogQ_t/Q *versus* Logt** showed a linear relationship with R^2 values ranged from 0.981-0.998 and 'n' values from 0.430-0.643. The formulations F4, F5 and F7 showed values of n < 0.45, indicating Fickian diffusion is the drug release mechanism. The formulations F1, F2, F3, F6, F8 and F9 showed values of n >0.45 but < 0.89, indicating anomalous transport as the release mechanism which includes both swelling and erosion. The results are given in Table 4.

TABLE 4 : *In vitro* Drug Release Kinetic Data

Formulation	Zero order		First order		Higuchi		Peppas		MDT (min)
	R^2	$K_0(h^{-1})$	R^2	$K_1(h^{-1})$	R^2	$K_H(h^{-1/2})$	R^2	'n'	
F1	0.918	3.63	0.994	0.089	0.992	19.67	0.990	0.618	650 ± 6.3
F2	0.892	3.58	0.986	0.087	0.984	19.61	0.981	0.640	662 ± 5.9
F3	0.875	3.34	0.982	0.092	0.992	18.54	0.998	0.473	559 ± 5.7
F4	0.730	3.08	0.966	0.110	0.926	18.09	0.996	0.430	487 ± 7.8
F5	0.800	3.29	0.977	0.103	0.963	18.79	0.982	0.450	516 ± 5.7
F6	0.942	3.42	0.986	0.075	0.995	18.32	0.998	0.622	686 ± 5.3
F7	0.888	11.06	0.908	0.502	0.997	35.25	0.992	0.446	444 ± 6.9
F8	0.885	2.90	0.974	0.055	0.990	15.97	0.993	0.643	869 ± 7.5
F9	0.829	3.00	0.958	0.064	0.974	16.96	0.996	0.512	754 ± 6.5

CONCLUSION

The present study was carried out to develop once-daily oral MR matrix tablets of CPC based on the matrix tablet technology using HPMC as release rate retardant. The formulation F5 containing HPMC K 15 M (10% w/w) as release retardant and Avicel PH 105 as filler showed good flow properties, mechanical properties and good initial burst release of CPC (24.27 ± 0.35%) and maintained integrity of the tablet and controlled the release of CPC over a period of 24 h (94.4 ± 1.76%). This formulation also fulfilled the regulatory requirements in terms of percent drug release (not less than 85% at the end of dissolution studies i.e. 24 h). Drug release kinetics of the optimized

formulation F5 followed first order kinetics and the mechanism was governed by diffusion process as indicated by both the Higuchi and power law equations.

Acknowledgements
The authors are thankful to the Divi's Laboratories for providing Capecitabine sample and Siddhartha Academy of General and Technical Education, Vijayawada, for providing necessary facilities to carry out this research work.

REFERENCES

[1] LV Robles; AME Campos. *Eur J Pharm Biopharm*., **1997**, 43, 173-178.
[2] J Balasubramaniam; MT Kumar; G Srinivas. *Ind j pharm sci*., **2005**, 67, 414-421**.**
[3] S Bhansali; R Massodi. *J of association of physicians of India*., **2005,** 53, 441-445.
[4] G Milano; JHM Schellens. Pyrimidine antimetabolites, In: JHM Schellens; HL McLeod. Newell DR eds. *Cancer Clinical Pharmacology*. Oxford: University Press., **2005**, 51– 62.
[5] Merck Index- *An Encyclopedia of Chemicals, Drugs and Biologicals.;* 13thedition, **2001**, 1759.
[6] J Schuller; J Cassidy; E Dumont; B Roos; S Durston; L Banken; M Utoh; K Mori; E Weidekamm; B Reigner. *Cancer Chemother Pharmacol.*, **2000**, 45, 291–297.
[7] B Reigner. Effect of food on the pharmacokinetics of capecitabine and its metabolites following oral administration in cancer patients. *Clin cancer Res.*, **1998**, 4, 941-948.
[8] L Gary; AJ Scott. Modified release components comprising a fluorocytidine derivative for the treatment of cancer. US 2007/0122481 A1., **2007**.
[9] AA Sunil; MA Tejraj. *Int. J of Pharm.*, **2006**, 324, 103-115.
[10] L Lachman; AL Herbert; LK Joseph. **1987**, 296-300.
[11] The United State Pharmacopoeia, USP30-NF-25, Asian edition. M Rockville, United State Pharmacopoeial Convention Inc., **2007**, 643-645.
[12] CS Brazel; NA Peppas. *Eur. J. Pharm. Biopharm.*, **2000**, 49, 47-58.
[13] H Lapidus; Ng Lordi. *J Pharm. Sci.*, **1966**, 55, 840-843.
[14] T Higuchi. *J Pharm. Sci* ., **1963**, 52, 1145-1148.
[15] RW Korsmeyer; R Gurny; E Doelker; P Buri; NA Peppas. *Int. J Pharm*., **1983**, 15, 25-35.
[16] JE Mockel; BC Lippold. *Pharm Res*., **1993**, 10, 1066-1070.
[17] AM Hamzah; AA Othman; AK Reem; KS Ashok; M Anwar. *Acta Poloniae Pharm. - Drug Res.*, **2010**, 67, 93-97.