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Research Article

Development of Capecitabine Floating Tablet Dosage Forms for Treating Stomach Cancer

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ABSTRACT

Objective: In the present research work, oral gastro retentive dosage forms (GRDFs) of capecitabine (CPC) were formulated using floating concept.

Methods: GRDFs were formulated using hydroxypropyl methyl cellulose (HPMC K4M and K15M) as drug release retardant, sodium bicarbonate (NaHCO₃) and calcium carbonate (CaCO₃) as gas generating agents, and micro crystalline cellulose (MCC), dicalcium phosphate (DCP), spray dried lactose (SDL), and pre gelatinized starch (PGS) as fillers. The tablets were prepared by direct compression method and evaluated for various parameters. The GRDFs were also characterized by Fourier-transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC).

Results and Discussion: All the formulations were subjected for pre and post compression parameters, shows all the data within the limits. The lag times of GRDFs has decreased significantly for formulations containing calcium carbonate when compared to sodium bicarbonate as gas generating agent. *In vitro* drug release studies indicate that higher polymer concentration delayed the CPC release, and the sustaining effect was in the order K4M > K15M > LVCR 100. Addition of MCC, DCP, SDL, and PGS as fillers further affected the lag time and in turn the CPC release rates.

Conclusion: The formulation (F9) containing 10%w/w HPMC K4M as the release retardant, microcrystalline cellulose as filler and 20%w/w CaCO₃ as gas generating agent fulfilled regulatory requirements in terms of percent drug release at the end of 24h.

Keywords: Capecitabine, Gastro retentive floating tablets, floating drug delivery systems, FTIR, DSC.

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INTRODUCTION

Stomach cancer or gastric cancer refers to cancer arising from any part of the stomach. Gastric cancer is fourth most common worldwide cancer, with an estimated of 934,000 new cases per year and the second most common cause of worldwide cancer deaths with an estimated 700,000 deaths annually¹. Geographically, the incidence and prevalence rates are higher in Asia, Eastern Europe and South America than in Western Europe and North America².

5-Fluorouracil (5-FU) is one of the most widely used anticancer agents in the chemotherapy of solid tumors including gastric cancer. Treatment with 5-FU infusion requires either frequent hospitalizations or the use of central venous access device, harboring potential complications.

Prodrugs of 5-FU like Tegafur and Doxifluridine have been developed to improve selectivity toward tumors than 5-FU. However, the oral administration of these drugs requires higher doses than intravenous injection due to first pass effects and moreover, adverse effects such as diarrhoea have been reported following the administration of Tegafur or Doxifluridine^{3, 4}. These factors, together with the known patient preference for oral chemotherapy generated the need for an oral anticancer agent such as capecitabine (CPC) a tumor activating oral prodrug of 5-FU which improves safety and efficacy without or with fewer side effects.

CPC (N4-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine) is an oral fluoropyrimidine carbamate prodrug and has wider and more potent spectrum of antitumor activity than other

fluoropyrimidines administered at their maximum tolerated doses when tested against the xenograft models of human breast, cervical and bladder as well as gastric cancers^{5,6}. The efficacy of CPC has been shown to be additive with Irinotecan and supradadditive with either Paclitaxel or Docetaxel and further higher antitumor activity with Trastuzumab or Bevacizumab than CPC alone⁶⁻⁸.

Human pharmacokinetic studies have also shown that after oral administration, CPC is rapidly and almost completely absorbed through the gastrointestinal wall, thus avoiding direct intestinal exposure to 5-FU⁹. CPC is considered to be bio activated into 5-FU by three enzymes. After oral administration, CPC is first metabolized by carboxyl esterase in the liver to 5'-deoxy-5-fluorocytidine (5'-DFCR), which is then converted to 5'-deoxy-5-fluorouridine (5'-DFUR) by cytidine deaminase in the liver and tumor tissue. Finally, 5'-

DFUR is converted to 5-FU by thymidine phosphorylase, which is found at much higher levels in gastric cancer tissue than in normal tissue, enabling preferential activation of the active drug, 5'-FU, at tumor site¹⁰. CPC and its metabolites, 5'-DFCR & 5'-DFUR, are not cytotoxic themselves, but become effective after conversion to 5'-FU.

However, CPC also undergoes non enzymatic hydrolysis in aqueous buffers and may convert to 5'-DFCR (Fig. 1)¹¹. CPC is well absorbed from the gastrointestinal tract (GIT); its plasma half-life is about 45-60min and these properties make CPC as an ideal candidate for developing a GRDF for treating stomach/gastric cancers. Considering the above context of principles, the present investigation was aimed at developing a once-daily oral proto-type gastro retentive dosage forms of CPC based on the floating technology.

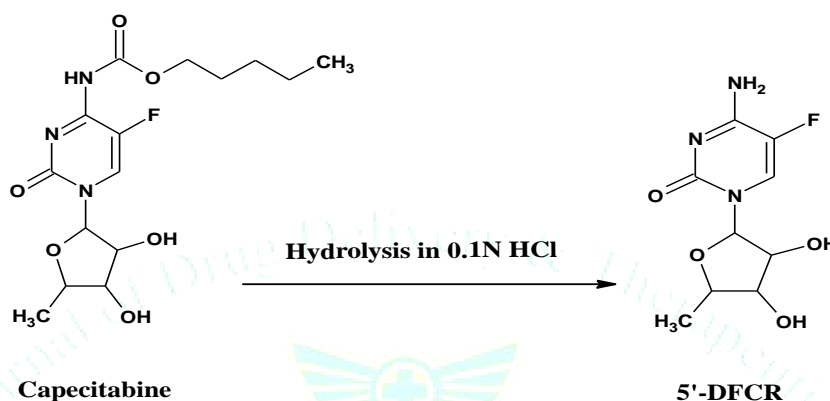


Figure 1: Acidic hydrolysis of CPC to 5'-DFCR

MATERIALS AND METHODS

Materials

Capecitabine was obtained as a gift sample from Divi's Laboratories, Hyderabad, India. HPMC K4M, HPMC K15M and HPMC LVCR 100, partially pre gelatinized starch were obtained from Colorcon Ltd, India. Sodium bicarbonate and calcium carbonate were purchased from CDH Pvt Ltd, India. Micro crystalline cellulose was obtained from FMC biopolymer, USA and spray dried lactose with maize starch was obtained from Roquette Pharma, France. Dicalcium phosphate, talc and magnesium stearate were purchased from Loba Chemie, India. All other reagents of analytical grade and all the solvents in HPLC are of HPLC grade.

HPLC Method

A reverse phase HPLC method was used for the analysis of CPC and 5'-DFCR in different samples. Chromatographic separation was performed on a Shimadzu Prominence HPLC system equipped with LC 10 AT VP binary pumps, SPD-10A VP UV Detector. LC solution software was used to collect and process the data. Mobile phase consisting of Acetonitrile: Ammonium acetate (50:50% v/v) was used and the mobile phase was filtered through nylon disc filter of 0.45µm (Millipore) and sonicated for 3min in ultrasonic bath before use. The flow rate was 1mL/min and the injection volume was 20µL. UV detection was performed at 268nm and the separation was achieved at ambient temperature. For quantitative analytical purpose, eluents were monitored at 268nm and an Apollo C₁₈ column (150mm x4.6mm, 5.0µ) was used and separation was carried out at ambient temperature with an injection volume of 20µL. The retention

times for CPC and 5'-DFCR were 1.7min and 2.5min respectively.

Stability Studies of CPC in 0.1N HCl

10mg of CPC was dissolved in 10mL of volumetric flask containing 5mL of HPLC grade water and volume was made up to with the same, to yield 1mg/mL stock solution. The stock solution was subsequently diluted with 0.1N HCl to get 20µg/mL; resulting solution was stored in an incubator at 37°C. The samples were collected at different time intervals 2, 4, 6, 8, 12, 24 & 48hrs. The samples were filtered and analyzed using the above developed HPLC method.

Drug- Excipient Compatibility Studies:

Fourier Transmittance Infrared Spectroscopy (FTIR) Studies:

The FT-IR spectra of CPC and optimized formulation i.e. F9 (containing CPC, HPMC K4M, CaCO₃, MCC, Magnesium stearate and Talc) were measured using ATR-FTIR spectrophotometer (Bruker, Germany). ATR spectra were measured over the wave number range of 4000-500cm⁻¹ at a resolution of 1.0cm⁻¹. The powder sample is simply placed onto the ATR crystal and the sample spectrum is collected.

Differential Scanning Calorimetry (DSC) Studies:

Thermal analysis of CPC alone and CPC with selected excipients like NaHCO₃, PGS, and optimized formulation i.e. F9 (containing CPC, HPMC K4M, CaCO₃, MCC, Magnesium stearate and Talc) was performed using DSC instrument (DSC 200 F3 Maia, USA). The sample was sealed in a crimped aluminium pan by application of the minimum possible pressure and heated at a rate of 10°C /min from 30-200°C under nitrogen atmosphere.

Preparation of CPC Floating Tablets:

CPC floating tablets were prepared by direct compression method (as per formulae given in Table I). 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 required amount of magnesium stearate was added and mixed for another 5min. Powder blends (for 50 tablets each) of all the above formulations were compressed on single punch tablet press (Cadmach, India) using 10mm punches (round shape) to a hardness of 4-6 kg/cm².

Table I: Composition of CPC floating tablets

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
CPC	150	150	150	150	150	150	150	150	150	150	150	150
HPMC K4M	40	60	80	100	-	-	80	60	40	40	40	40
HPMC K15M	-	-	-	-	80	-	-	-	-	-	-	-
LVCR100	-	-	-	-	-	80	-	-	-	-	-	-
MCC	126	106	86	66	86	86	86	106	126	-	-	-
PGS	-	-	-	-	-	-	-	-	-	126	-	-
SDL	-	-	-	-	-	-	-	-	-	-	126	-
DCP	-	-	-	-	-	-	-	-	-	-	-	126
NaHCO ₃	80	80	80	80	80	80	-	-	-	-	-	-
CaCO ₃	-	-	-	-	-	-	80	80	80	80	80	80
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total weight	400	400	400	400	400	400	400	400	400	400	400	400

Evaluation Parameters for Powder Blends and Compressed CPC Tablets:

Pre compression parameters of the prepared powder blend of all the formulations were determined by determining the bulk density, tapped density, compressibility index, hausner's ratio and angle of repose^{12,13}. Compressed floating tablets were characterized for weight variation ($n = 20$), hardness ($n = 6$) was measured with a Monsanto tester Campbell Electronics (India), friability ($n = 20$), with a Roche type friabilator. The drug content in each formulation was determined by triturating 5 tablets in a mortar and powder equivalent to the 20mg was added in 20mL of HPLC grade water, followed by sonication for 15min. The solution was then filtered, suitably diluted with acetonitrile: ammonium acetate (75:25% v/v) and analyzed by HPLC method.

In Vitro Drug Release Studies:

The tablets were subjected to *in vitro* drug release studies using USP-Type II (paddle) dissolution rate test apparatus (LABINDIA, DS 8000) at a temperature of $37 \pm 0.5^\circ\text{C}$ and 50rpm. 900mL of 0.1N HCl was used as the dissolution medium. 5mL aliquots of the samples were withdrawn at specific time intervals over a period of 24hrs and filtered using a 0.45 μm nylon disc filters and replaced with 5mL of fresh dissolution medium. The filtered samples were suitably diluted if necessary and analyzed for CPC & 5'-DFCR by the HPLC method as described above. The dissolution experiments were conducted in triplicate.

Drug release kinetics:

The rate and mechanism of cumulative amount of CPC & 5'-DFCR released from the prepared floating tablets were analyzed by fitting the dissolution data into the Zero-order, First-order, Higuchi and Korsmeyer-Peppas equations¹⁵⁻¹⁷.

RESULTS AND DISCUSSION

Stability Studies:

The hydrolysis of CPC to 5'-DFCR was carried out by storing stock solution of CPC in 0.1N HCl at 37°C over a period of time. Samples were removed at different time points and subjected to HPLC analysis. From the stability data it is clearly evident that CPC was rapidly hydrolyzed to 5'-DFCR under non enzymatic acidic conditions with a half-life of 0.73hrs (Fig.2)¹¹.

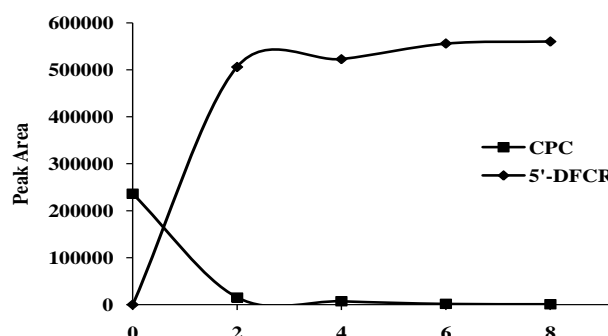


Figure 2: Stability curves of CPC in 0.1 N HCl at 37°C.

Drug - Excipient Compatibility Studies:

FTIR Studies:

FTIR studies were carried with a view to evaluate the *in situ* CPC and excipients compatibility. FTIR spectra of CPC and F9 were shown in Fig.3(A) and 3(B) respectively. Pure CPC showed characteristic IR absorption bands at 1038 cm⁻¹, 1115 cm⁻¹, 1337 cm⁻¹, 1645 cm⁻¹, 1707 cm⁻¹, 3516 cm⁻¹,

3178 cm⁻¹ indicating the presence of C-N group, C-O-C group in aromatic ring, C-F group, C=N group, C=O group, bending of N-H group, and -OH groups respectively in CPC structure. These significant bands of CPC were also present in the FTIR spectra of CPC-excipient physical mixtures. These results indicate that compatibility of CPC with the selected excipients in formulation development studies.

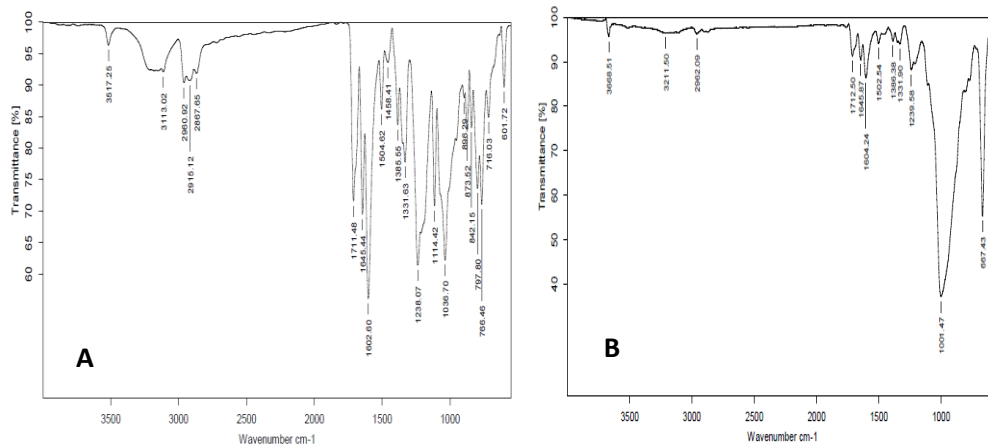


Figure 3 : FTIR spectra of CPC (A) and F9 (B)

DSC Studies:

DSC studies were also carried out to further investigate the chemical compatibility of CPC with the selected excipients. DSC thermograms of the CPC alone and CPC with the selected excipients and optimized formulation (F9) were shown in Fig.4. The CPC showed a sharp endothermic peak at around 121°C corresponding to its melting point¹⁷. The sharp

endothermic at 121°C corresponds to the melting point of CPC and was retained in all the thermograms of 1:1 w/w physical mixtures of the CPC and selected excipients like NaHCO₃, PGS and also in optimized formulation (F9). These results indicated that the CPC was compatible with all the selected excipients in the formulations and there was no chemical interaction.

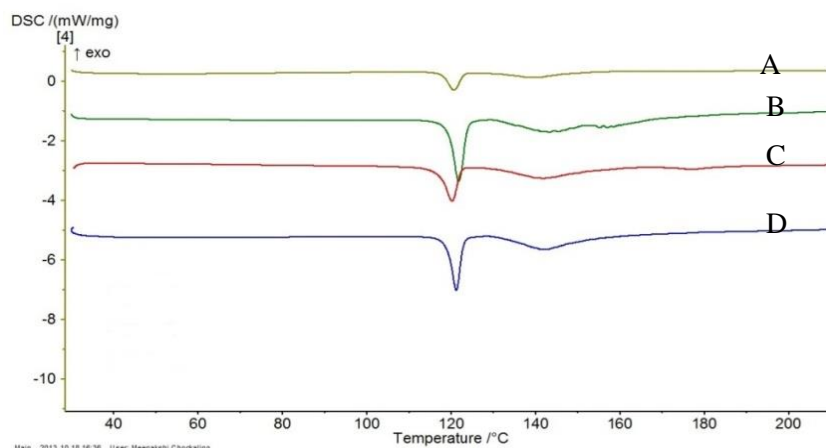


Figure 4: DSC thermo gram overlay of CPC (A), CPC-PGS (B), CPC-NaHCO₃ (C) and F9 (D)

Pre and Post Compression Parameters:

The results of various pre compression parameters (Carr's index, Hausner's ratio, and angle of repose) for powder blends of all formulations were found to be within the acceptable range and are suitable for compression to tablets using direct compression method. The compressed tablets fulfilled the official compendial requirements with regarding drug content, uniformity of weight, hardness and friability, except with F11 and F12 where reproducibility of hardness was not achieved.

In Vitro Drug Release Studies:

In the present investigation, totally 12 different formulations were formulated using swellable hydrophilic polymers like HPMC of different grades (HPMC K4M and HPMC K15M) as release retardant materials and NaHCO₃ and CaCO₃ as gas generating agents and fillers like PGS, maize starch with SDL and DCP. Cumulative percent of CPC released i.e. CPC & 5'-DFCR together with different formulations at various time intervals were calculated. The floating lag times for all the formulations were determined and that for formulations F1-

F5 containing NaHCO_3 as gas generating agent were in the range of 10-38 sec, while that were with CaCO_3 was in the range of 300-3600 sec.

Effect of Release Retardant Concentration, Viscosity and Gas Generating Agent on CPC Release:

Initial formulation studies were carried out to look in to the release retarding effect of HPMC K4M at concentration levels of 10, 15, 20, 25%w/w in F1-F4 respectively using 20%w/w NaHCO_3 as gas generating agent and MCC as filler. F1, F2, F3, F4 gave an initial burst release of $23.74 \pm 0.397\%$, 23.30 ± 0.59 , $20.15 \pm 0.08\%$ and $17.73 \pm 0.73\%$ respectively at the end of 1hr and a complete CPC release was attained at the end of 16hrs and 20hrs for F1 and F2 respectively, whereas $94.4 \pm 2.19\%$ and $91.28 \pm 0.09\%$ for F3 and F4 respectively at the end of 24hrs. In all the cases the tablets were intact and a gel layer was retained up to 24hrs. The comparative dissolution profiles of F1-F4 were shown in Fig.5 (A). From the results it can be concluded that the HPMC K4M at

concentration levels of 20%w/w and 25%w/w was able to retard the release of CPC, a water soluble drug, from floating tablets over a period of 24hrs successfully and moreover, there is no statistical significant difference between the cumulative amount of CPC released, the HPMC 20% w/w concentration was selected further to investigate the effect of HPMC viscosity on release of CPC from floating tablets.

Further studies were carried out by developing F5 with 20%w/w HPMC K15M as release retardant, gave a $15.54 \pm 0.7\%$ of initial burst release at 1hr and $97.39 \pm 0.37\%$ at end of 24hrs, tablet was intact and a gel layer remained at end of 24hrs. The comparative dissolution profile of F3 and F5 were shown in Fig. 5(B). From the results it can be concluded that the viscosity of HPMC has a little effect in the lag time values. However, the % CPC released from floating tablets was not affected and may be due to the water soluble nature of CPC. An attempt was also made with 20%w/w LVCR 100 (F6) (data was not considered) a low viscosity grade polymer however; the tablets were dissolved within 30min.

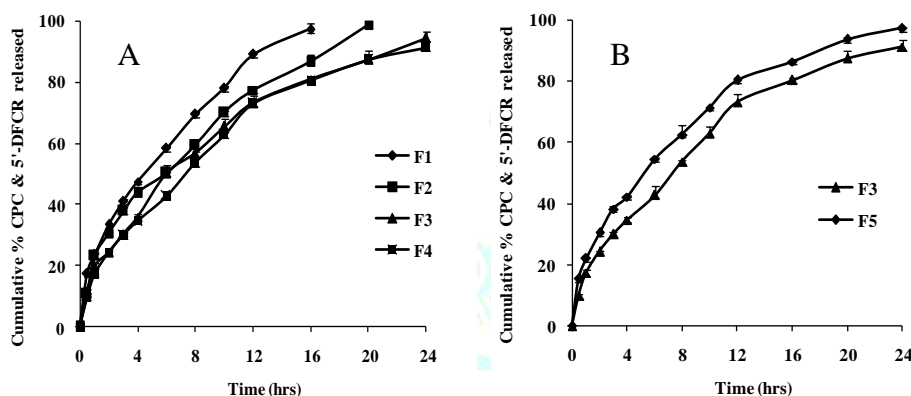


Fig.5: Comparative drug release profiles of - (A) HPMC K4M formulations at different concentrations with NaHCO_3 ; (B) formulations with different viscosities of HPMC with NaHCO_3

Even though a continuous and sustained release of CPC was observed with F3 over a period of 24hrs, reproducibility of hardness is a problem when NaHCO_3 was used as a gas generating agent. Hence, further trials were carried out by replacing NaHCO_3 with CaCO_3 at same percent levels in the formulations i.e. 20%w/w. F7- F9 were compressed with CaCO_3 as gas generating agent containing 20%w/w, 15%w/w and 10%w/w of HPMC K4M levels in floating tablets. F7, F8, F9 gave an initial burst release of $10.56 \pm 0.44\%$, $19.39 \pm 0.57\%$ and $23.0 \pm 3.73\%$ respectively at end of 1hr and $80.06 \pm 0.53\%$, $82.68 \pm 0.34\%$ and $97.12 \pm 1.26\%$ respectively at 24hrs time interval.

Overall, the CPC release was found to be inversely related to the concentration of HPMC present in the matrix structure i.e. higher the concentration the slower is CPC release from tablets. This was further confirmed by the MDT values. Moreover the increase in HPMC concentration also affected the floating lag time values i.e. lower the HPMC concentration lower the lag time values. Comparative dissolution profiles for F3 (containing NaHCO_3) and F7 were given in Fig. 6(A). The comparative dissolution profile of F7, F8 and F9 were shown Fig.6 (B).

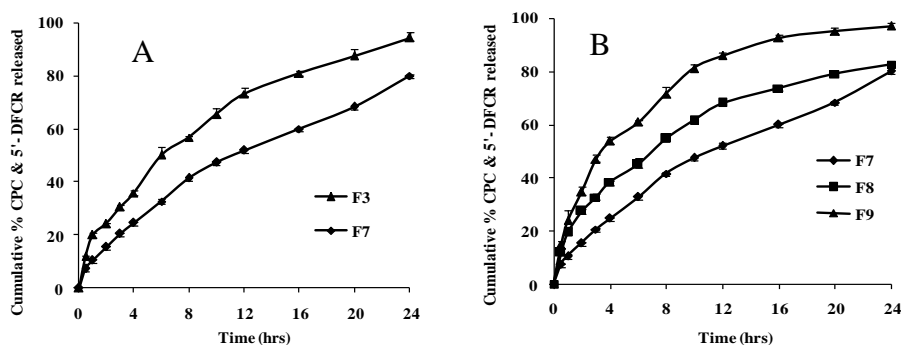


Figure 6: (A) -Comparative drug release profiles of formulations with NaHCO_3 (F3) and CaCO_3 (F7); (B) - Comparative drug release profiles of formulations with HPMC K4M at different concentrations with CaCO_3

Effect of Fillers on Lag Time Value:

Effect Fillers such as PGS (F10), SDL with maize starch (F11) and DCP (F13) on CPC release was investigated. F10 gave a CPC release of $22.70 \pm 1.02\%$ at 1hr and $99.54 \pm 0.55\%$ at the end of 24hrs. F10 though sustained the release of CPC from the floating tablets up to 24hrs; the lag time was significantly more when compared to F9 containing MCC as filler. The comparative dissolution profile for F9 and F10 is shown in Fig. 7. For F11 and F12 the reproducibility of hardness was a problem and tablets were not fulfilled the pharmacopoeial specifications.

Overall, the F9 containing 10%w/w HPMC K4M as the release retardant, MCC as filler and CaCO_3 20%w/w as gas generating agent floated within $5 \pm 0.3\text{min}$ and gave a good burst release of CPC ($23.80 \pm 3.73\%$) followed by controlled release of CPC ($97.121 \pm 1.26\%$) over a period of 24 hrs. The calculated MDT (min) value for formula F9 is 267min. F9 also fulfilled the regulatory requirements in terms of percent drug release (not less than 85% at the end of dissolution studies i.e. 24hrs)¹⁸.

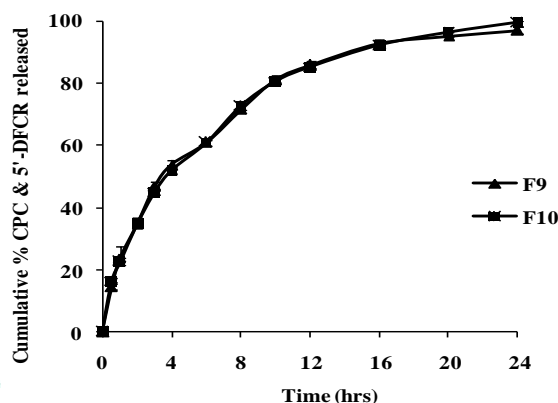


Figure 7: Comparative drug release profiles of formulations with MCC (F9) and PGS (F10)

Drug Release Kinetics and mechanism:

The results of kinetic models for CPC & 5'-DFCR release from floating tablets were shown in Table II. The coefficient of correlation (R^2) was used as an indicator of the best fitting for each of the models considered. The results reveal that all formulations best fit in the First order model. The mechanism of drug release from these tablets was found to

be diffusion, as seen from high R^2 values of the Higuchi model. The data obtained were fitted in the Korsmeyer-Peppas model in order to find out the n value. The release showed a high correlation with the Korsmeyer-Peppas model. The n value ranged from 0.45 to 0.66, which suggested that drug release from the mixture of polymers was non-Fickian diffusion controlled and was influenced by both swelling and erosion of floating tablets.

Table II: *In vitro* release kinetic parameters of CPC floating tablets

Formulation	Zero order		First order		Higuchi		Peppas		MDT (min)
	R^2	$K_0(\text{h}^{-1})$	R^2	$K_1(\text{h}^{-1})$	R^2	$K_n(\text{h}^{-1/2})$	R^2	N	
F1	0.82	3.83	0.96	0.16	0.99	24.41	0.99	0.50	377
F2	0.92	4.52	0.86	0.16	0.99	22.22	0.99	0.45	511
F3	0.91	3.74	0.98	0.11	0.95	20.21	0.96	0.49	534
F4	0.92	3.73	0.98	0.10	0.99	20.74	0.99	0.53	571
F5	0.89	3.80	0.98	0.13	0.98	20.85	0.99	0.56	517
F6	-	-	-	-	-	-	-	-	-
F7	0.96	3.14	0.98	0.06	0.98	16.59	0.99	0.66	810
F8	0.87	3.19	0.98	0.07	0.98	17.70	0.99	0.48	581
F9	0.80	3.73	0.99	0.15	0.96	19.48	0.99	0.59	267
F10	0.82	3.81	0.94	0.19	0.97	21.51	0.99	0.60	250

CONCLUSION

From the results obtained it can be concluded that, developing a once-daily oral proto-type gastro retentive dosage forms GRDFs of CPC based on the floating technology may increase the CPC pharmacotherapy as the CPC is released locally in the stomach leading to high drug concentrations at the gastric mucosa over a period of time in continuous manner thus reducing the frequency of administration. Overall, the floating tablet formulations may result in effective treatment of stomach cancer when compared to the existing immediate releasetablets.

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Conflict of Interest: No conflict of interest

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