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FORMULATION OF COLON TARGETED PRESS COATED TABLETS OF CAPECITABINE BY USING NATURAL POLYMERS AND ITS *IN-VITRO* EVALUATION.

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ABSTRACT

The aim of the present work was to formulate and evaluate colon targeted drug delivery system (CTDDS) of capecitabine tablets using natural polymers such as Guar gum, Xanthan gum and Psyllium husk alone in combination with HPMC K-100. Tablet was prepared by press coated method. The basic idea behind the dosage form is to target the organ that is colorectal cancer and maintain lag time. To investigate effect of coating design on lag time and drug release from directly compressed tablet. The compatibility of drug and optimized formulation were determined by differential scanning calorimeter, FTIR spectroscopy and X-ray diffraction patterns. The pre-compression evaluation of coating material like angle of repose, bulk density, tapped density, Hauser's ratio, flow property and also post-compression studies of core and coat tablet for hardness, thickness, friability, weight variation studies. It was observed that the increasing or decreasing concentration of polymer blend had affected on the drug release. As we increases the concentrations of polymer blend the lag time increases & vice versa. The results of *in-vitro* drug release studies showed that formulation (F2) has better drug release after 6 hrs. Lag time.

KEYWORDS: Capecitabine, CTDDS, Press coated tablets and In-vitro study.

INTRODUCTION

According to the World Health Organization more than 70% of all cancer deaths occurred in countries with low and middle income, and deaths from cancer worldwide are projected to

continue to rise to over 11 million in 2030 (WHO 2011). Colorectal cancer is the third most common cancer in men (663,000 cases, 10.0% of the total cancers) and the second in women (570,000 cases, 9.4% of the total cases) worldwide.[1] Cancer is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths per year. All types of cancers have been reported in Indian population including the cancers of skin, lungs, breast, rectum, stomach, prostate, liver, cervix, oesophagus, bladder, blood, mouth etc.[2] Most frequently observed cancers in Indian population are of lungs, breast, colon, rectum, stomach and liver.[3, 4, 5] The colon and rectum form the large intestine, which is the last portion of the digestive system. Colon is susceptible to many diseases like ulcerative colitis, carcinoma, constipation, inflammatory bowel disease, colorectal cancer etc. Cancer that starts in the cells that line the inside of the colon (the longest part of the large intestine) and rectum (the last few inches of the large intestine before the anus) are called colorectal cancers. Those diseases are poorly managed by the conventional delivery of drug, for treatment of these diseases needs to be developing colon targeted drug delivery system.[6]

Absorption and degradation of the active ingredient in the upper part of GIT is the major problem, the conventional tablet dosage form provides minimal amount of drug in the colon with undesirable adverse effect due to variation in the transit time. Hence, to target the drug directly to the site of action in the colon, there is need to develop colon targeted drug delivery systems that will enhance the therapeutic drug level, increases the bioavailability of active medicament and reduce the dose of drug. By maintaining lag time target to the organ is latest approach of drug delivery to the colon.[7, 8]

In compression coated tablets drug present in inner core, surrounded by outer layer which contain polymer and other excipients. The inner core tablet is made by pure drug Capecitabine (140mg). Outer coat degraded only in the colonic region. "Capecitabine is a chemotherapy drug used to treat different cancers including breast, colon, and rectal cancers". The dose of Capecitabine is 150-500 mg daily by mouth.[9]

MATERIAL AND METHODS

Materials and chemicals

Capecitabine was obtained as a gift sample from Naprod Life Sciences Pvt. Ltd Mumbai.

Guar gum, Xanthan gum, HPMC K 100, Micro Crystalline cellulose (MCC), Cross-Carmellose Sodium (CCS), Talc and Magnesium Stearate was obtained from Loba-Chemical

Pvt. Ltd. Mumbai. Psullim Husk was obtained from Bagwan Ayurvedic Medical Store, Karad (Satara, India).

Method- Preparation of Capecitabine tablets

A] Pre-compression parameters[10, 11]

Evaluation of Pre-compression parameters like Angle of repose, Bulk density, Tapped density, Hauser's ratio and Carr's index was performed.

B] Drug and Excipients Study[14,15,16]

The drug-excipients interaction study was carried out by using Infrared Spectroscopy (FTIR) to check purity of drug and drug-excipients interaction. Differential scanning calorimetric (DSC) study was carried to check melting point and compatibility. The X-ray diffractometer was carried to check the physical nature of drug and excipients.

C] Preparation of core tablets by direct compression.

The core tablets of capecitabine for compression coating were prepared by direct compression technique. Each core tablet consisted of 140 mg capecitabine 5 mg Cross carmellose-sodium and 5 mg magnesium stearate. The mixture was compressed into tablets using KBr press with an applied pressure 0.5 tons for 1min. Using 8mm round flat, plain punch. The prepared core tablets were tested for the post-compression studies like weight Variation, hardness, friability, Thickness, drug content and *in-vitro* drug release characteristics.

D] Compression coating of Capecitabine core tablets.

The coating materials of Guar gum, Xanthan gum, Psyllium husk alone mixture of these in combination with HPMC K-100, micro crystalline cellulose and talc were used to prepare coats. Half the amount of compression coating material was placed in the die cavity followed by carefully centring the core tablet and addition of the remaining coat weight. The coating material was then compressed around the core tablets using KBr press at an applied pressure of 4 tons using 13mm round, flat, plain punch. The prepared coated tablets were tested for the post-compression studies like weight Variation, hardness, friability, Thickness, drug content and *in-vitro* drug release characteristics.

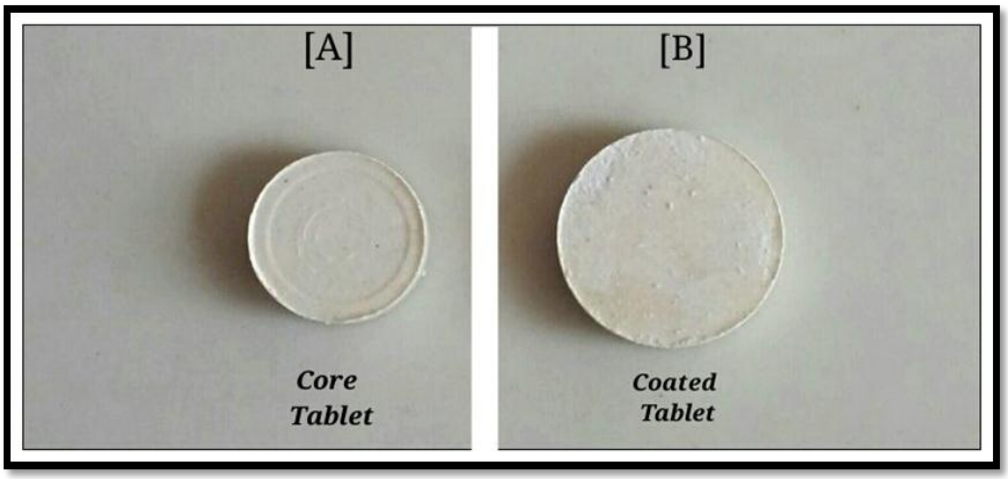

Figure 1: (A) Core tablet and (B) Coated tablet.

[A] Core tablet: (Capecitabine, Cross-Carmellose Sodium and Magnesium Stearate).

[B] Coated tablet: (Core tablet coated with Polymer like Guar gum/ Xanthan gum/ Psyllium husk in combination with HPMC K100, MCC and Talc.)

E] Evaluation of core and Coated Tablets.[12, 13]

Evaluation of post-compression parameters of core and coated tablets by Weight variation, thickness, Hardness, Friability, and *in-vitro* dissolution was evaluated.

F] *In-vitro* Dissolution for press-coated tablets

In –vitro dissolution studies of Colon targeted drug delivery system was done with the USP II (Paddle) dissolution apparatus at 50 rpm. For first 2hr. dissolution medias-acidic buffer 1.2 and buffer 6.8 for next 5hr. Medium is maintained at 37±0.5 °C. A 5ml of sample was manually withdrawn at specific time intervals and replaced with 5 ml of fresh medium and maintain the sink condition. The samples were analysed at 303nm using a UV spectrophotometer.[17]

G] Stability Studies

The stability study of optimized formulation was subjected for one month according to ICH guidelines at 40±2^{0}C/ 75±5% RH. The optimized formulations were packed in aluminium foil in tightly closed container.[18]

Table 1: Formulation of Capecitabine Colon Targeted tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Capecitabine	140	140	140	140	140	140	140	140	140
CCS	5	5	5	5	5	5	5	5	5
Guar gum	40	60	80	-	-	-	-	-	-
Xanthan Gum	-	-	-	40	60	80	-	-	-
Psullim Husk	-	-	-	-	-	-	100	125	150
HPMC K100	20	20	20	20	20	20	20	20	20
MCC	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Talc	5	5	5	5	5	5	5	5	5
Mg. Stearate	5	5	5	5	5	5	5	5	5
Total	450	450	450	450	450	450	450	450	450

RESULTS AND DISCUSSION

A] Evaluation of Pre-compression parameters

The powder characteristics are the most important prior to formulation studies. These basic measurements evaluation of the powder have been used to develop and monitor the manufacturing of many successful formulations.

Table 2: Powder characteristics of Capecitabine.

Formulation	Angle of Repose (θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)
F1	26.32±0.53	0.660±0.002	0.788±0.009	1.137±0.021	14.53±0.084
F2	25.12±0.72	0.669±0.005	0.740±0.011	1.136±0.001	12.09±0.324
F3	26.89±0.92	0.617±0.004	0.720±0.003	1.134±0.022	13.24±1.202
F4	27.89±0.94	0.634±0.012	0.757±0.006	1.130±0.019	11.99±0.327
F5	25.62±0.80	0.669±0.005	0.722±0.008	1.135±0.009	11.62±0.562
F6	27.21±0.082	0.652±0.006	0.742±0.002	1.170±0.002	11.89±0.169
F7	26.58±0.098	0.645±0.002	0.728±0.005	1.150±0.013	11.29±1.739
F8	24.78±0.72	0.654±0.011	0.750±0.003	1.131±0.003	12.16±0.926
F9	27.22±0.69	0.646±0.024	0.735±0.006	1.127±0.001	11.93±0.233

(n=3±SD)

B] Drug-Excipient Interaction Study by DSC Thermogram.[14]

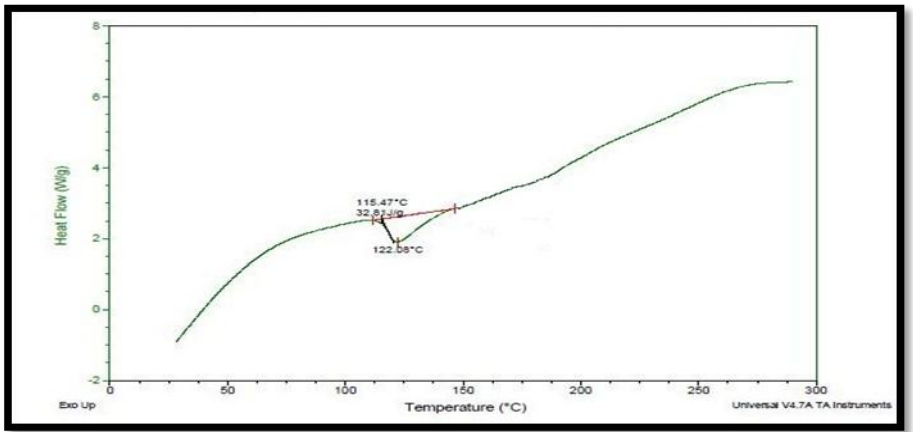

Figure 2: DSC of Capecitabine.

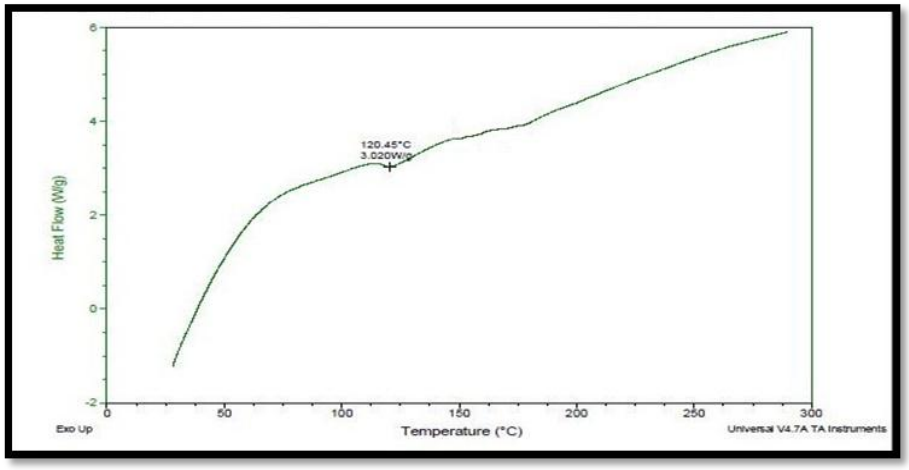

Figure 3: DSC of formulation F2.

From the above DSC spectra's it was observed that the characteristic of pure drug (Capecitabine) and Physical mixture shows a sharp endothermic peak at 122.08^0C and 120.45^0 respectively.

C] FTIR Spectrum Studies.[15]

FTIR studies were carried with a view to drug and excipient/s compatibility. Figure 4 and 5 shows the IR spectra of pure capecitabine and formulation F2. Pure Capecitabine showed characteristic IR absorption bands at 1114 cm-1 indicating the presence of C-N group, 796 cm-1 indicates the bending of C-H group, 1037 cm-1 indicates the presence of C-O-C stretching, 1238 cm-1 indicates the presence of C-F group, 1710 cm-1 indicates the presence of stretching of C=O group, 1604 cm-1 indicates the presence of bending of N-H group, 3109 cm-1 indicates the presence -OH group.

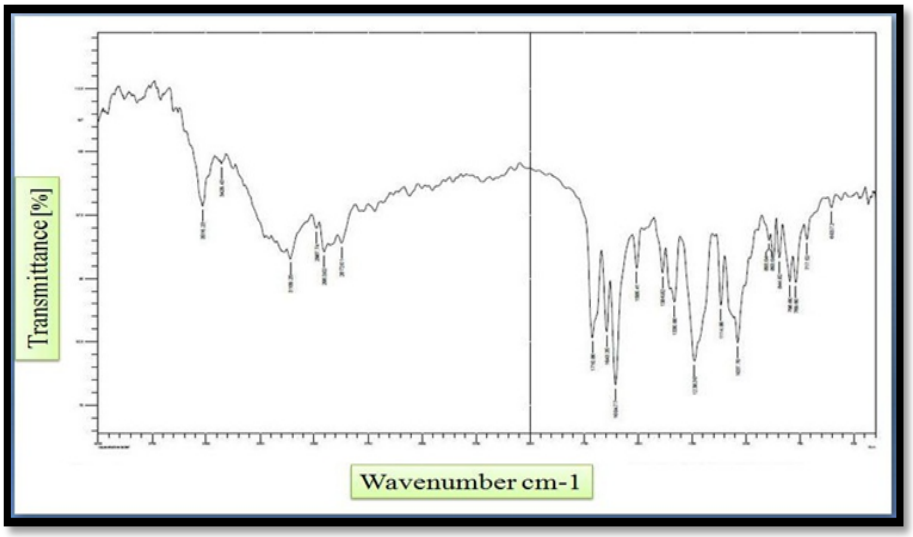

Figure 4: FTIR Spectrograph of CAPECITABINE pure.

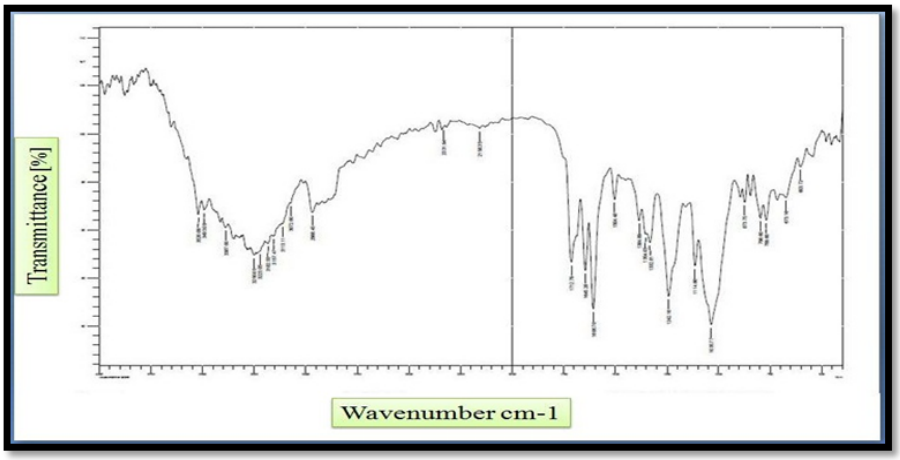

Figure 5: FTIR Spectrograph of formulation F2.

D] Drug-Excipient Physical Nature Study by XRD.[16]

The XRD patterns of the pure drug and final formulation are shown in following figures. The XRD scan of Pure Capecitabine showed intense peaks at 2θ of 20° and formulation F2 Showed intense peak at 2θ of 21° that indicated the crystalline nature of the drug.

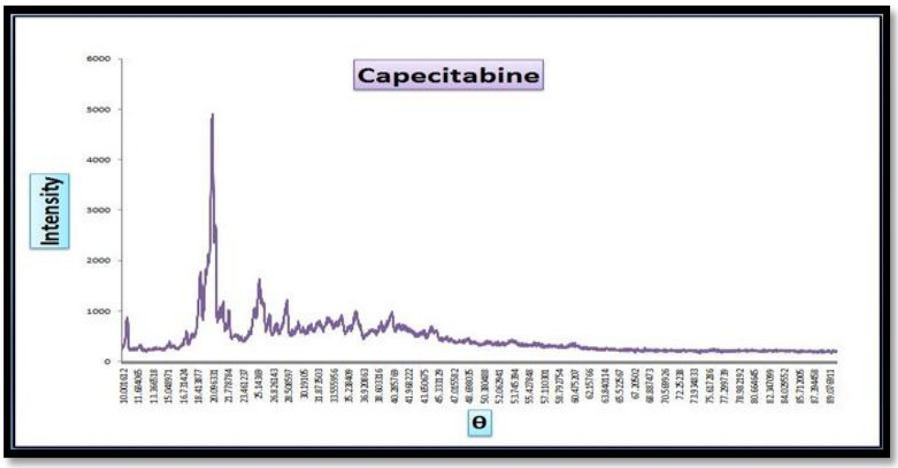

Figure 6: PXRD Pattern of Capecitabine.

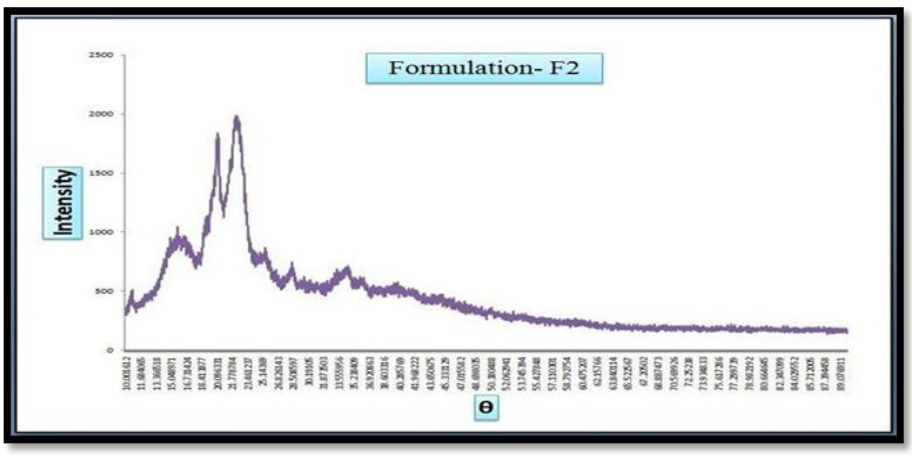

Figure 7: PXRD Pattern of Formulation F2.

E] Evaluation of Capecitabine Core Tablets

The Capecitabine core tablets were prepared by direct compression method. The tablet from each batches were evaluated for Average weight, Hardness, Friability and Thickness results are reported in Table 3. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RDS < 1%). The tablet hardness varied from 2.2±0.42 to 2.8±0.18. The tablet thickness were found to range from 2.4±0.14 mm to 2.6±0.21 mm, The tablets passed the friability test, as all the batches were within the pharmacopeial limit (F < 1%)

Table 3: Post-compression parameters for Core tablet.

Formulations	Wt. Variation (mg)	Hardness (kg/cm2)	Friability (%)	Thickness (mm)
F1	149±0.53	2.2±0.42	0.59	2.4±0.14
F2	150±0.26	2.6±0.14	0.55	2.6±0.21
F3	150±0.64	2.5±0.25	0.4	2.5±0.16
F4	150±0.45	2.8±0.18	0.62	2.5±0.05
F5	150±0.35	2.5±0.09	0.54	2.6±0.02
F6	149±0.76	2.6±0.14	0.62	2.5±0.01
F7	150±0.19	2.5±0.21	0.57	2.5±0.07
F8	150±0.12	2.4±0.32	0.4	2.6±0.14
F9	152±0.82	2.5±0.13	0.54	2.5±0.02

(n=3±SD)

F] In Vitro Dissolution Study for Core tablet

The dissolution of Capecitabine core tablet was constructed in pH 6.8 Phosphate buffer at 303nm using UV visible spectroscopy. Solution containing 5-30µg/ml of Capecitabine in pH 6.8 Phosphate buffer. Figure 5 shows the dissolution of Capecitabine core tablet.

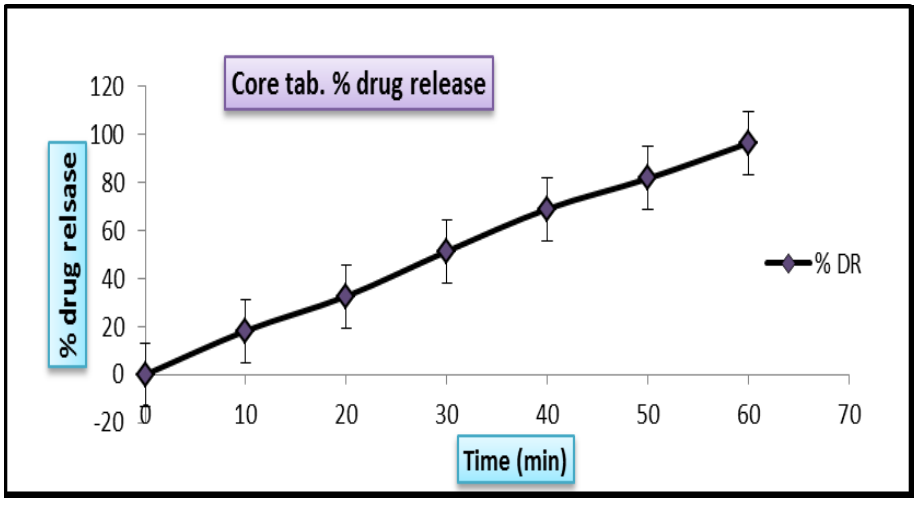

Figure 8: Dissolution of CPB Core tablet in pH 6.8 Phosphate buffer.

G] Evaluation of Capecitabine Coated Tablets

The Capecitabine Coated tablets were prepared by direct compression method. The tablet from each batches were evaluated for Average weight, Hardness, Friability, Thickness and Drug content and result are reported in Table 4. The tablets showed good weight uniformity as indicated by the low value of Relative Standard Deviation (RDS < 1%), the tablet hardness varied from 5.6 ±0.13 to 6.4 ±0.25. The tablet thickness were found to range from 3.81±0.21 mm to 4.01±0.14 mm, The Drug content uniformity of the tablet was found to in range 97.08±0.86 to 99.05±0.07 of the value. The tablets passed the friability test, as all the batches were within the pharmacopeial limit (F < 1%).

Table 4: Physicochemical evaluation of Capecitabine Coated Tablets

Formulation	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Thickness (mm)	Drug Content (%)
F1	449±0.15	5.8±0.32	0.56	3.92±0.24	98.71±0.02
F2	450±0.46	5.9±0.21	0.57	3.89±0.02	98.75±0.07
F3	450±0.14	6.3±0.42	0.62	3.81±0.21	97.7±0.08
F4	452±0.34	5.6±0.13	0.58	3.94±0.16	98.15±0.04
F5	450±0.12	6.1±0.14	0.62	4.01±0.14	98.67±0.32
F6	450±0.19	5.7±0.14	0.59	3.69±0.02	99.05±0.07
F7	452±0.61	6.4±0.25	0.62	3.95±0.01	97.08±0.86
F8	450±0.76	6.2±0.18	0.62	3.9±0.012	97.63±0.28
F9	449±0.35	5.9±0.09	0.56	3.92±0.05	98.43±0.65

(n=3±SD)

H] In-vitro Dissolution Study

- **In-vitro Dissolution Study Of Capecitabine on various concentrations of Guar gum and HPMC K100.**

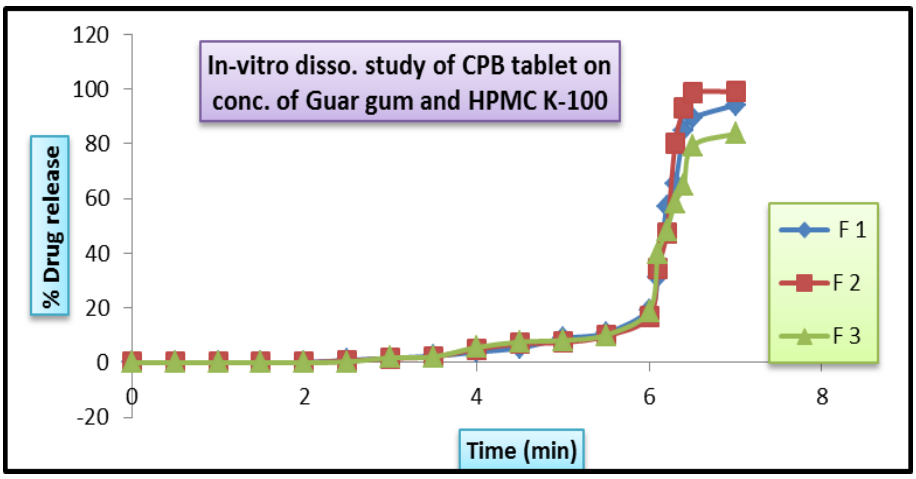

Figure 9: %Drug release of formulations F1, F2 and F3.

At the end of 7hr, the mean % drug release of batches F1, F2 and F3 was found to be 94.3±0.65 %, 99.18±1.54% and 83.78± 2.84% respectively.

As the concentration of polymer blend increased, drug release was decreased and vice versa. Higher concentration of HPMC would reduce the free water volume and increase the viscosity of the coat causing a reduction in the polymer leaching and subsequent reduction in drug releases shown in figure 6. Based on these results the batch F2 was optimized for further study.

➢ **In-vitro Dissolution Study Of Capecitabine on various concentrations of Xanthan gum and HPMC K100.**

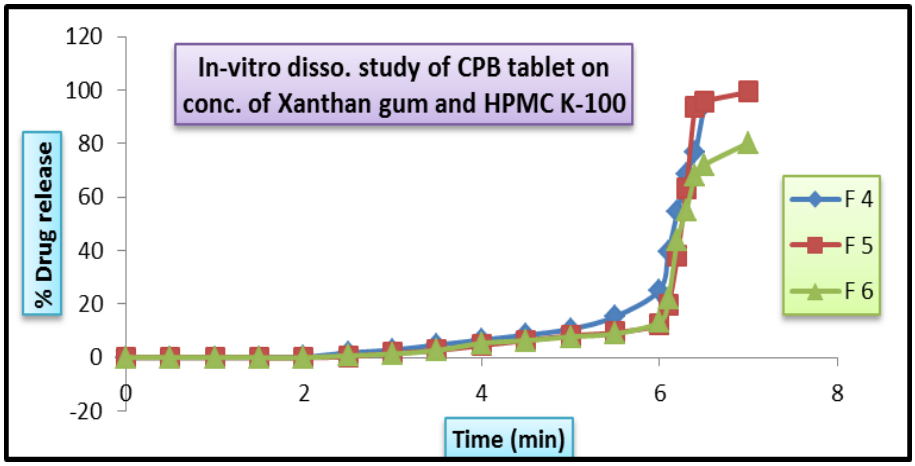

Figure 10: %Drug release of formulations F4, F5 and F6.

At the end of 7hr, the mean % drug release of batches F5, F6 was found to be 99.27±2.16% and 80.27±1.34% respectively. The batch F4 shows 94.24±2.31% drug release at the time of 6:50 as shown in figure 7. Due to lower concentrations of xanthan gum and HPMC K-100 the tablet was completely dissolved. Based on these results the F5 batch gives satisfactory results in *in-vitro* dissolution study.

➢ **In-vitro Dissolution Study Of Capecitabine on various concentrations of Psyllium husk and HPMC K100.**

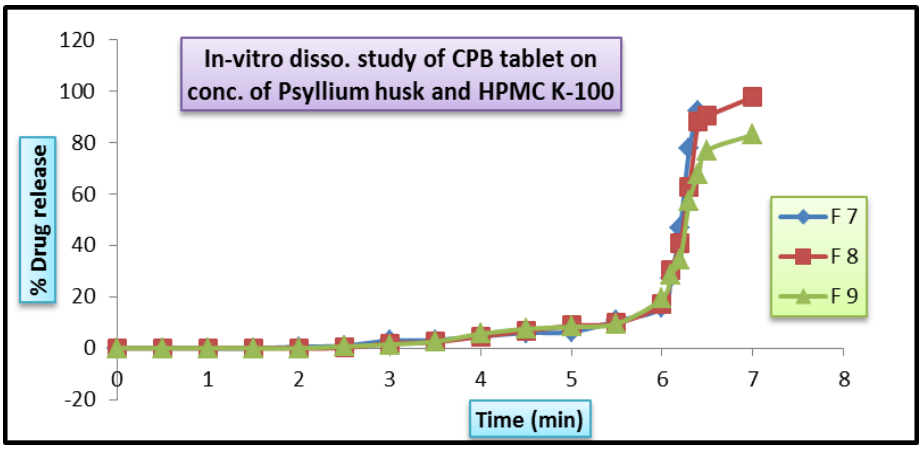

Figure 11: %Drug release of formulations F7, F8 and F9.

At the end of 7hr, the mean % drug release of batches F8 and F9 was found to be 97.65±2.94 % and 82.98±1.98% respectively. The batch F7 shows 92.02±1.98% drug release at the time of 6:40 as shown in figure 8. Due to lower concentrations of HPMC and Psyllium husk the tablet was completely dissolved. Based on these results the batch F8 gives satisfactory results in *in-vitro* dissolution study.

At the end of 7hr, the mean % drug release of batch F2 gives better results 99.18±1.54. Based on these results of batch F2 were used for comparisons of stability studies.

I] Stability studies

The optimized formulation F2 was subjected to stability studies at 40 ± 2^0C/75 ± 5 % RH for one month. The results show that after analyzing tablet there was no change in case of physical and chemical properties. No significant differences in the dissolution study. Comparison of drug release profile of formulations before and after stability the formulations found to be stable throughout the study period.

CONCLUSION

Drug excipient compatibility studies were carried out by FTIR and DSC which showed that Guar gum and HPMC were compatible with Capecitabine and thus suitable for the formulations of Capecitabine colon targeted tablets. From XRD it was concluded that reduction in peak intensity of physical mixture shows crystalline nature.

Colon targeted drug delivery system of Capecitabine compression coated tablet was formulated and evaluated successfully by using different natural polymer such as Guar gum, Xanthan gum and Psyllium husk alone in combination with HPMC.

The *in-vitro* dissolution studies were performed for all the formulations, by using 0.1N HCL solution and 6.8 phosphate buffers at 37^0 C. It was concluded that the increasing or decreasing concentration of polymer blend had affected on the drug release. As we increases the concentrations of polymer blend the lag time increases & vice versa.

Based on *in-vitro* drug release study, it was concluded that compression coated tablets with combination of Guar gum and HPMC system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 6 hr. and could produce a successful drug targeting to the colon with minimal amount released in the stomach and small intestine. From

stability study, it was concluded that there were no any significant changes observed in tablet characterisation after stability study.

REFERENCES

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN. 2008. Int J Cancer., 2010; 127: 2893–917.
2. Imran Ali, Waseem A. Wani and Kishwar Saleem. Cancer Scenario in India with Future Perspectives. Cancer Therapy, 2011; 8: 56-70.
3. Nandakumar A. Consolidated report of the population based cancer registries. National Cancer Registry Programme. Indian Council of Medical Research. New Delhi, India, 1990-96.
4. Rao DN, Ganesh B. Estimate of cancer incidence in India in 1991. Indian J Cancer., 1998; 35: 10-8.
5. Murthy NS, Mathew A. Cancer epidemiology, prevention and control., 2004; 4-25.
6. Chithaluru K, Tadikonda R. Formulation and Evaluation of Microbially triggered compression coated tablets of Ketorolac Tromethiamine. Der Pharmacia Lettre., 2011; 3(4): 29-39.
7. Philip AK, Philip B. Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches. Oman Medical Journal 2010. 2010; 25(2): 1-9.
8. Asian journal of pharmaceutics, 2008; 141-145.
9. Hans-Joachim Schmoll, Dirk Arnold, Update on Capecitabine in Colorectal Cancer, The Oncologist., 2006; 11: 1003–1009.
10. Chein YW. Controlled and modulated release drug delivery system, *Encyclopedia of Pharmaceutical Technology*, 1990; 281–313.
11. International pharmacopoeia, 2006; 968.
12. Chein, YW. Potential Developments and new approaches in Oral controlled release drug delivery systems, *IJCP*, 1983; 294-1330.
13. Lachman L, Liberman HA, Kanig J, Lordi NG, Theory and practice of industrial pharmacy,sustained release dosage forms. 3rd Edn, *Bombay, Varghese Publishing House,* 1991; 453-454.
14. Chatwal GR, Anand SK. Instrumental Methods of Chemical Analysis. 5thed. Himalaya Publishing House., 2002; 2: 747.
15. Chatwal GR, Anand SK, Instrumental Methods of Chemical Analysis. 5th ed. Himalaya Publishing House., 2002; 2: 29.

16. Ashwin B. Kuchekar, Atmaram P. Pawar, screening of factors using plackett burman design in the preparation of capecitabine-loaded nano polymeric micelles, International Journal of Pharmacy and Pharmaceutical Sciences, 2014; 6(5): 489-496.
17. Ilango KB, Manisha M, Brinda P. Investigation of Colon Specificity of Novel Polysaccharide okra Mucilage-Film Coated With Enteric Materials. Int. J. of Pharma and Bio Sci., 2012; 3(2): 53-62.
18. ICH Q1A (R2) Stability testing guidelines: Stability Testing of new drug substances and products.[online]. [Cited 2008 Nov 10]; Available from:URL:http://www.tga.health.gov.au/docs/ pdf/euguide/inch/273699r2en.pdf.