

Formulation and Evaluation of Extended Release Capecitabine Loaded Pellets

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ABSTRACT

Capecitabine is a well known orally-administered anticancer agent utilized in the treatment of colorectal cancer and metastatic breast cancer. The present study reveals the development and evaluation of an extended release Capecitabine loaded pellets. The Capecitabine loaded pellets were prepared by using a layering process followed by Wurster Process and made it extended release using Ethylcellulose (EC), Polyvinyl Pyrrolidone (PVP-K30) and Kollicoat SR 30D coating. The prepared extended release pellets were characterized by FTIR, SEM, DSC and XRD studies. The extended-release pellets also evaluated for particle size and shape, yields, moisture content, drug content, mechanical crushing strength, and micrometric properties. The surface of the uncured beads was found to be uniform and smooth and no crystals were visible. The DSC and XRD study revealed the compatibility of the drug and the polymers. The prepared pellets were showed the good characteristics in term of various parameters and release the drug from the formulation for the prolonged period of time for up to 10.3 h.

Keywords: Pellets, Capecitabine, Extended released, Ethyl cellulose, Kollidon SR, Kollicoat SR30D, PVP- K30.

INTRODUCTION

Capecitabine is mostly used as an anticancer drug used in different types of cancer. It has a short elimination half-life of 0.5 to 1 h. The frequent dosing of the Capecitabine made it a good candidate for the released of the drug for the extended period of time^{1,2}. Multiple unit pellets system with matrix pellet used generally in extended release formulations. These pellets are coated with polymers. Currently, more importance is being set on the improvement of extended-release dosage forms in preference to single unit systems³. Pellets are small particles, good flowability, and spherical particulate prepared by compression of powder or granules^{4,5}. The pellets having of small in size, usually about 0.5-1.5 mm in size, and are intended for oral administration. It consists of a small unit and posses some derived characteristics created by agglomeration of fine powder with different binder solution⁶. The various polymer such as PVA, Kollidon SR, EC was selected for the formulation of Extended released tablets of Capecitanib. The extended released pellets were initially geared up by layering and followed by coating with the hydrophobic polymers.

MATERIALS AND METHODS

Materials

Capecitabine was received as a gift sample from USV Private Limited, B.S.D. Marg, Gavandi, Mumbai. The polyvinyl Alcohol, Kollidon SR, Ethylcellulose were purchased from Loba Chemie, Mumbai and chemicals,

solvents were purchased from SD fine chemicals, Mumbai. All other materials used are of Analytical grade.

Method of Preparation of drug layering solution

Ethanol: Water (95:5) was placed into a suitable vessel and ethylcellulose was added to it at room temperature and stirred well to get a clear solution. To the above povidone (PVPK30) and acetyl triethyl citrate were added gradually with continuous mixing to dissolve completely. After this Capecitabine was added slowly to form a uniform dispersion. After the formation of uniform dispersion, talc was added immediately with continuous stirring. The above solution was passed through #40 sieve. Sugar spheres were loaded into Wurster column and the process started with present parameters to adjust the fluidization. The dispersion was sprayed onto sugar spheres at an inlet temperature of $60 \pm 10^\circ\text{C}$ and bed temperature of $40 \pm 5^\circ\text{C}$ then spray rate increased slowly to optimum rate. The drug-layered pellets were dried for a minimum 15 min with low fluidization at a bed temperature of $40 \pm 5^\circ\text{C}$ and weight gain was checked. The drug-layered pellets were passed initially through #20 sieve and the twins retained on the sieve were removed. Again it was passed through #30 sieve and the passed drug layered pellets were discarded⁷.

The extended-release coating on drug layered pellets

Extended-release coating solution in which polymer concentration 1:7 ratio was prepared and weight build up was noted. In brief; required quantity of ethanol was transferred into a suitable vessel at room temperature to that extended release coating solution and triethyl citrate

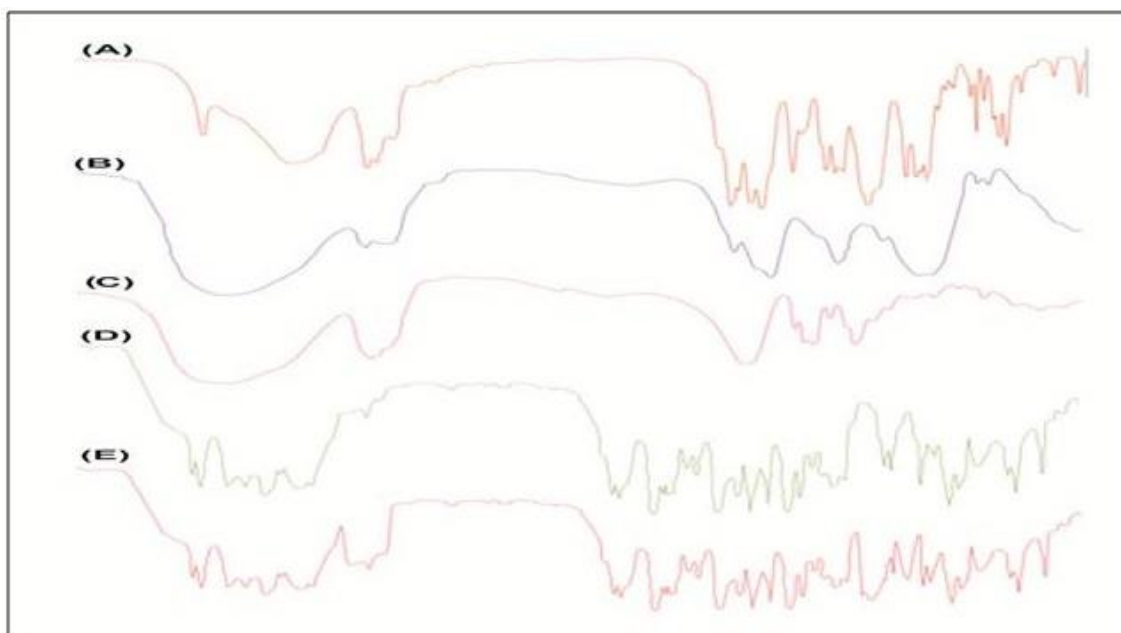


Figure 1: FT-IR spectra of A) Pure Capecitabine B) Ethyl Cellulose C) PVP K30 D) Kollicoat SR 30 D and E) Formulation.

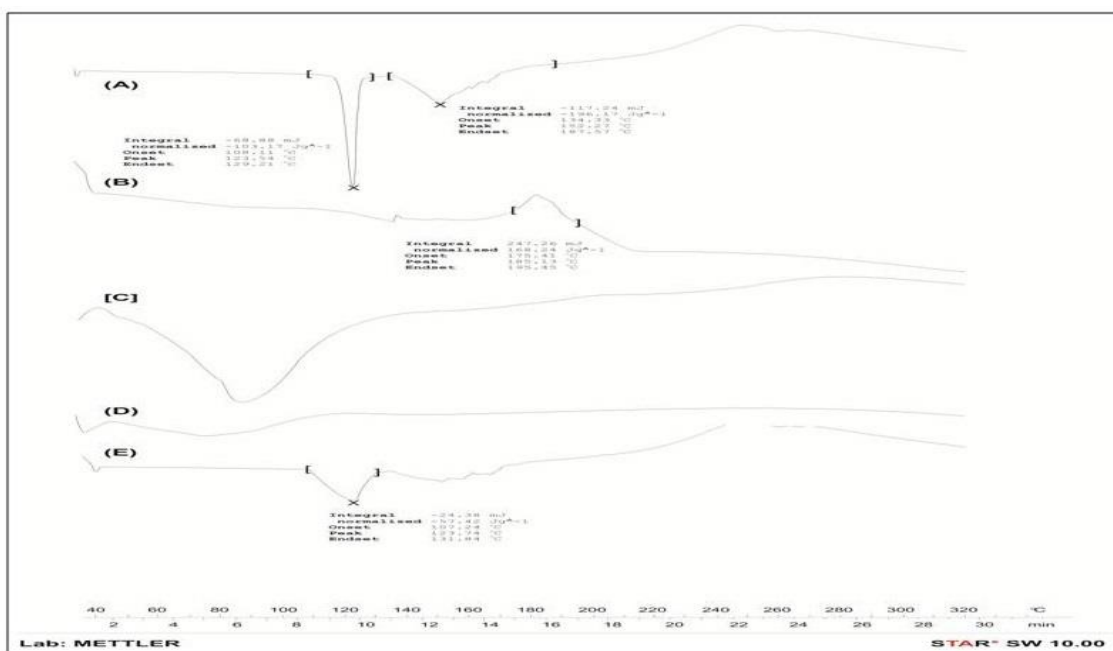


Figure 2: DSC thermograph of (A): Capecitabine, (B): Ethylcellulose, (C): PVP K30, (D): Kollicoat SR30D and (E): Formulation.

was added gradually with continuous mixing until it dissolved at 45°C completely. The drug-layered pellets were loaded into Wurster column and the process started with present parameters to adjust the fluidization. The solution was sprinkled onto drug layered pellets at an inlet temperature of $60 \pm 10^{\circ}\text{C}$ and bed temperature of $40 \pm 5^{\circ}\text{C}$ then spray rate increased slowly to optimum rate. The extended release coated pellets were dried for not less than 30 min with low fluidization at a bed temperature of $40 \pm 5^{\circ}\text{C}$ and weight build-up was checked, the extended release coated pellets were passed initially through #20 sieve and the twins remain on the sieve were removed.

Again it was passed through #30 sieve and the passed drug layered pellets were discarded⁸.

Characterization of Capecitabine Pellets

Fourier Transform Infrared spectroscopy (FT-IR)

FT-IR spectra of Capecitabine, Ethylcellulose, Kollidon, and prepared pellets were obtained using an FT-IR spectrometer (8400 S, Shimadzu Corporation, Japan). The spectra were scanned over a wavenumber range of $4000 - 600 \text{ cm}^{-1}$ at 40 scans per spectrum⁹.

Scanning Electron Microscopy (SEM)

Morphological examination of the surface of pellets was carried out using a Scanning Electron Microscopy EOL

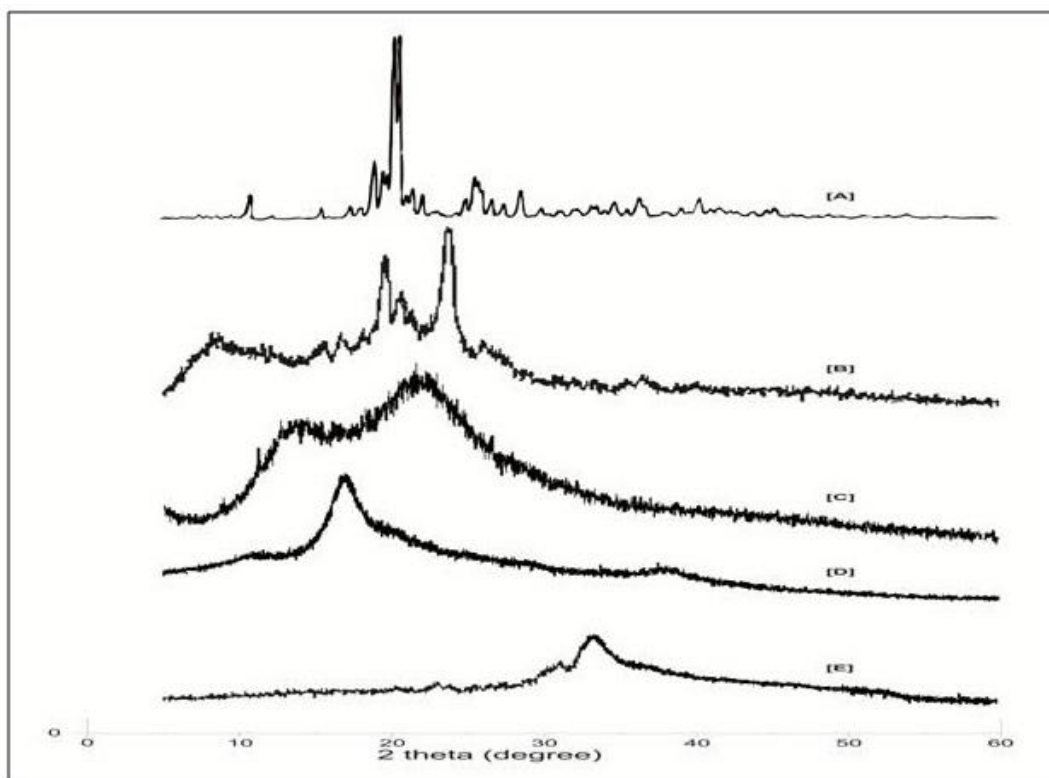


Figure 3: X-ray diffraction patterns of (A): Capecitabine, (B): Ethylcellulose, (C)PVP K30, (D): KollicoatSR30D and (E) Formulation.

Table 1: Micromeritic evaluation parameters, Residual moisture content, and drug content of optimized extended release pellets.

Evaluation Parameter	Capecitabine pellets \pm S.D
Mean Pellet Size i.e. Diameter, d (0.9) (μm)	1208.7 \pm 46.684
Usable yield (% theoretical)	92.417 \pm 3.56
Sphericity and shape analysis (pellips)	1.0763 \pm 0.0842
Abrasion resistance (% friability)	< 1%
Porosity (%)	37.067 \pm 7.2067
Mechanical crushing force i.e. Crushing Strength (N)	4.708 \pm 0.6014
Bulk density (g/cm^3)	0.4855 \pm 0.0417
Tapped density (g/cm^3)	0.6303 \pm 0.0375
Carr's index (% compressibility)	22.9731 \pm 0.4679
Hausner's ratio (RH)	1.2982 \pm 0.4936
Residual moisture content i.e. Water Content (%)	1.07 \pm 0.1411
Drug content (%)	97.5 \pm 1.2188

JSM (JEOL 6100, Japan). The particles were observed microscopically at an accelerating voltage of 5.0 kV¹⁰.

Differential Scanning Calorimetry (DSC)

DSC thermograms of drug and the pellets were obtained using differential scanning calorimeter (Mettler Toledo 821e, Mettler Toledo) operated with Stare software (version 9.01). 1-2 mg samples were analyzed in hermetically-sealed, pin-holed aluminum crucibles¹¹.

X-ray Diffraction

The X-ray diffraction spectra of drug and polymer were collected using a D/max-gamma B X-ray diffractometer (Rigaku, Japan). The patterns with 2θ ranging from 5° to 60° were collected using a scan rate and step of $10^\circ/\text{min}$ and 0.02° , respectively⁹.

Mean Pellet Size

Pellets size distribution (span) was carried out by Malvern Mastersizer (Malvern 2000, Malvern Instruments, UK). Estimations were done in triplicate. 50th percentile diameter of the cumulative particle size distribution was considered as mean pellet size¹².

Usable yield (% theoretical)

The usable yield of the pellets was determined by sieve analysis, utilizing a sieve shaker (EMS-8, Electrolab, India) furnished with (600-2360 μm) sieves for 5 min at an adequacy of 2 mm. Estimated yield of pellets was dependent on the pellet fraction between sieve 14/22 and displayed as the percent of total pellet weight. This size fraction was used for all further measurements¹³.

% Yield

$$\% \text{ Yield} = \frac{\text{Weight of pellet}}{\text{Weight of Polymer} + \text{Weight of Drug}} \times 100$$

Sphericity and shape analysis

The spherical shape of the pellets was estimated by using image analysis system. Photomicrographs of pellets were taken with a digital camera linked with a stereo microscope system a stereomicroscope Leica S4E (Germany). The captured images were analyzed using image analysis software (AnalySIS, Soft Imaging System, Germany). Approximately 50 pellets were analyzed from each batch.

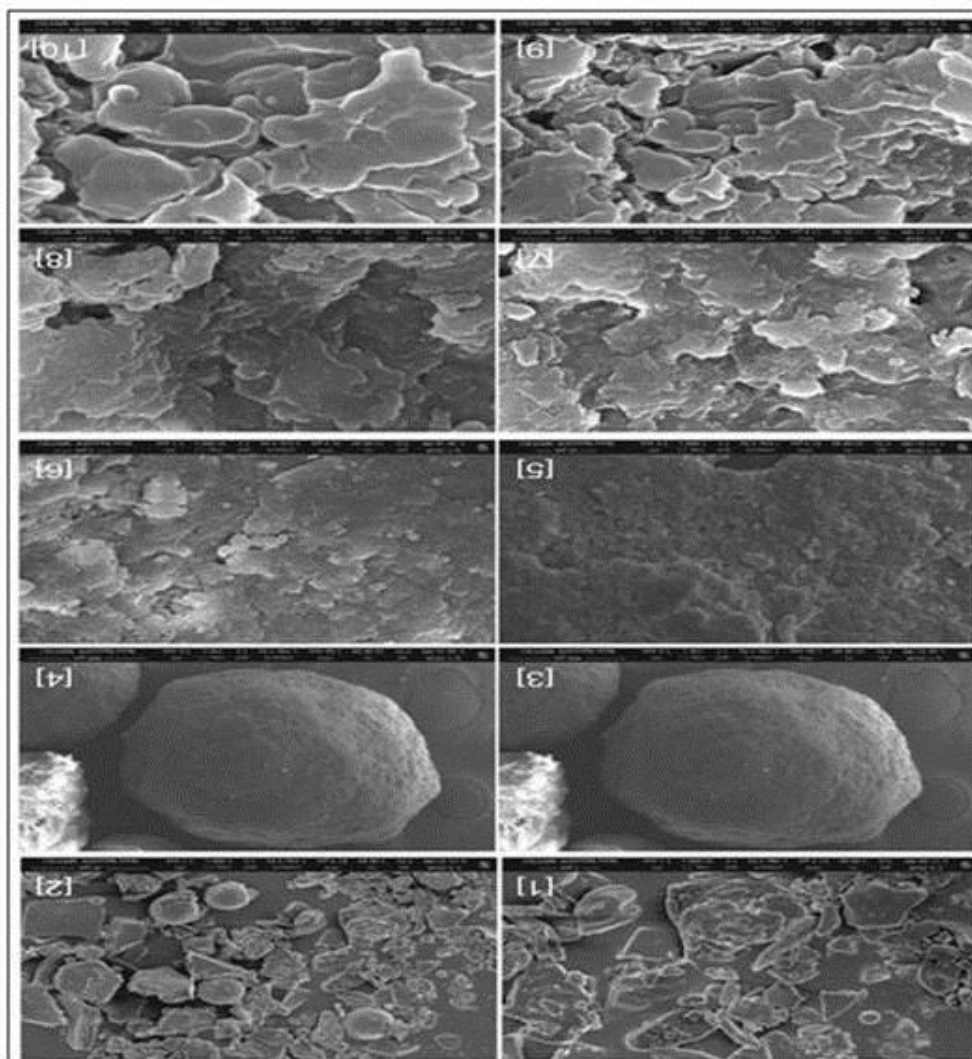


Figure 4: SEM images of Capecitabine (1&2) and pellets surface with different magnifications at various magnification.

The shape of each individual pellet was characterized as pelliaps¹⁴.

$$Pelliaps = \frac{P}{\pi \times dmax}$$

Where,

P is the perimeter

max is the maximum diameter of the pellet, calculated directly by using image analysis software.

Abrasion resistance (friability)

The friability of the uncoated pellets (#14/ 22 fraction) was determined. Weighed amount pellets were placed in the drum to perform the test along with 24 steel balls (diameter about 2 mm) in a Roche friabilator for four minutes having 25 revolutions/min and then sieved through a #22 sieve. The percent weight loss was then calculated. Each batch was analyzed in triplicate¹⁵.

Porosity

Pellet porosity was calculated using the following equation, for percent effective porosity

$$\% \varepsilon = [(\rho_t - \rho_b) / \rho_b] \times 100$$

Where,

ε = effective porosity, ρ_t = true density and ρ_b = bulk density. The true density of the prepared pellets was determined using Helium pycnometry (Smart Pycno 30, Smart Instruments, Mumbai)¹⁶.

Mechanical crushing force

20 pellets from the Modal size fraction of each formulation were estimated for their diametral crushing force using a tablet strength tester (EH 01, Electrolab, India)^{14,17}.

Densities

The bulk density and tapped density was determined using bulk density test apparatus. From bulk and tapped densities Carr's index and Hausner's ratio were determined using the following formulae^{10,14,18}.

Carr's index (% compressibility)

$$= [(\rho_t - \rho_b) / \rho_t] \times 100$$

Hausner's ratio = ρ_t / ρ_b

Where, ρ_b is bulk density and ρ_t is tapped density

Residual moisture content

Residual moisture content present in the pellets subsequent to drying was estimated by utilizing Karl Fischer titrator (Systronics Universal titrator 353, India), USP Method I.

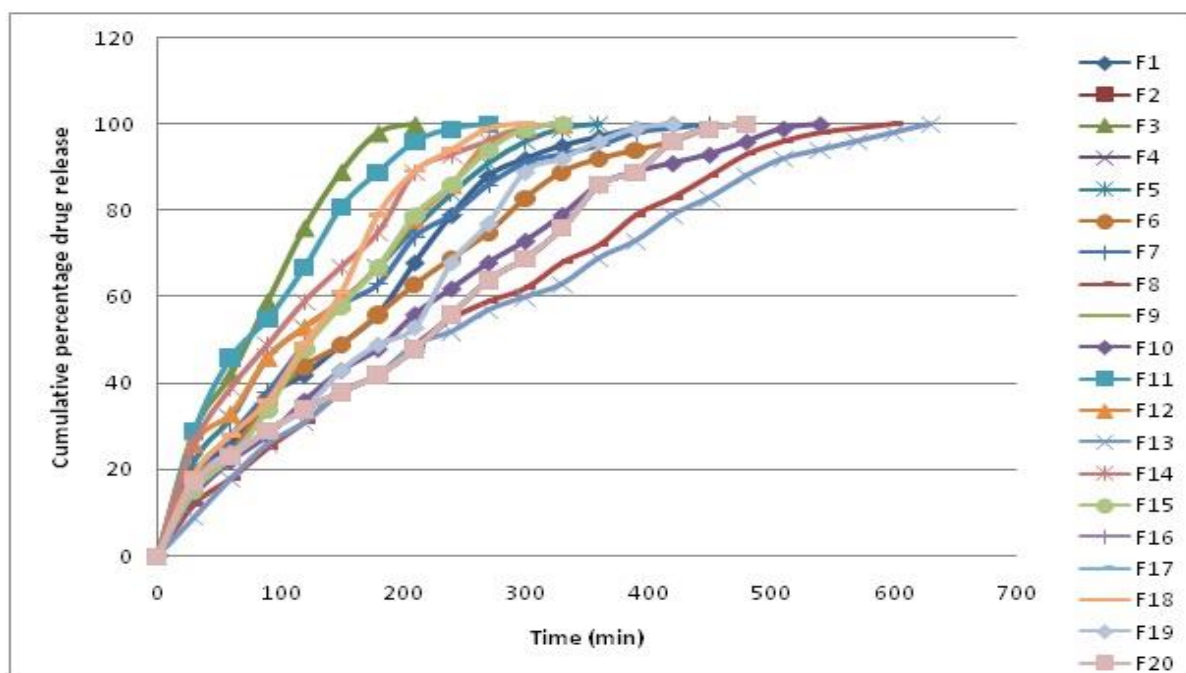


Figure 5: In-vitro drug release studies of formulations (F1 to F20).

Table. 2: Formulation and variables of Capecitabine Pellets.

Formulation	Independent Variable			Dependable Variables		
	Triethyl citrate (%)	Coating Level (%)	Curing Time (h)	Mean Dissolution Time (min)	Entrapment Efficiency (%)	Friability (%)
F1	0.98	15.00	6.50	150	73.42	1.24
F2	3.50	15.00	6.50	205	94.7	0.07
F3	3.50	6.59	6.50	77	78.23	1.57
F4	3.50	15.00	6.50	205	94.7	0.07
F5	2.00	10.00	3.00	127	68.95	0.88
F6	2.00	20.00	3.00	168	86.4	0.09
F7	3.50	15.00	0.61	144	56.23	1.02
F8	3.50	23.41	6.50	234	98.65	0.02
F9	3.50	15.00	6.50	205	94.7	0.07
F10	5.00	20.00	3.00	200	91.24	0.16
F11	2.00	20.00	10.00	86	47.24	0.66
F12	2.00	10.00	10.00	122	49.35	0.84
F13	6.02	15.00	6.50	249	96.23	0.08
F14	5.00	20.00	10.00	107	68.24	0.55
F15	3.50	15.00	12.39	134	58.32	1.88
F16	3.50	15.00	6.50	205	94.7	0.07
F17	3.50	15.00	6.50	205	94.7	0.07
F18	5.00	10.00	10.00	118	62.35	0.25
F19	5.00	10.00	3.00	174	73.25	1.02
F20	3.50	15.00	6.50	205	94.7	0.07

The titrator was pre-calibrated and standardized with disodium tartrate. 250 mg of pellets were weighed accurately and immediately positioned in the moisture analyzer for titration with Karl Fischer reagent¹⁹.

Drug content

The Capecitabine pellets were assayed as per US pharmacopoeial method, using HPLC. The exact amount of pellets were weighed, triturated and dissolved in a suitable solvent. The solution was suitably diluted and the concentration was estimated using HPLC²⁰.

Dissolution testing

Dissolution testing was performed according to United States Pharmacopeia (USP) monograph using a type 2 (paddle) dissolution apparatus (Erweka, Heusenstamm, Germany) at 37° C, stirred at 50 rpm and phosphate buffer of pH 7.4 as a medium. The Samples were withdrawn at the specific interval were filtrated using a 0.45-µm filter and subsequently analyzed on an HPLC system equipped with a UV/VIS detector. The dissolution test was

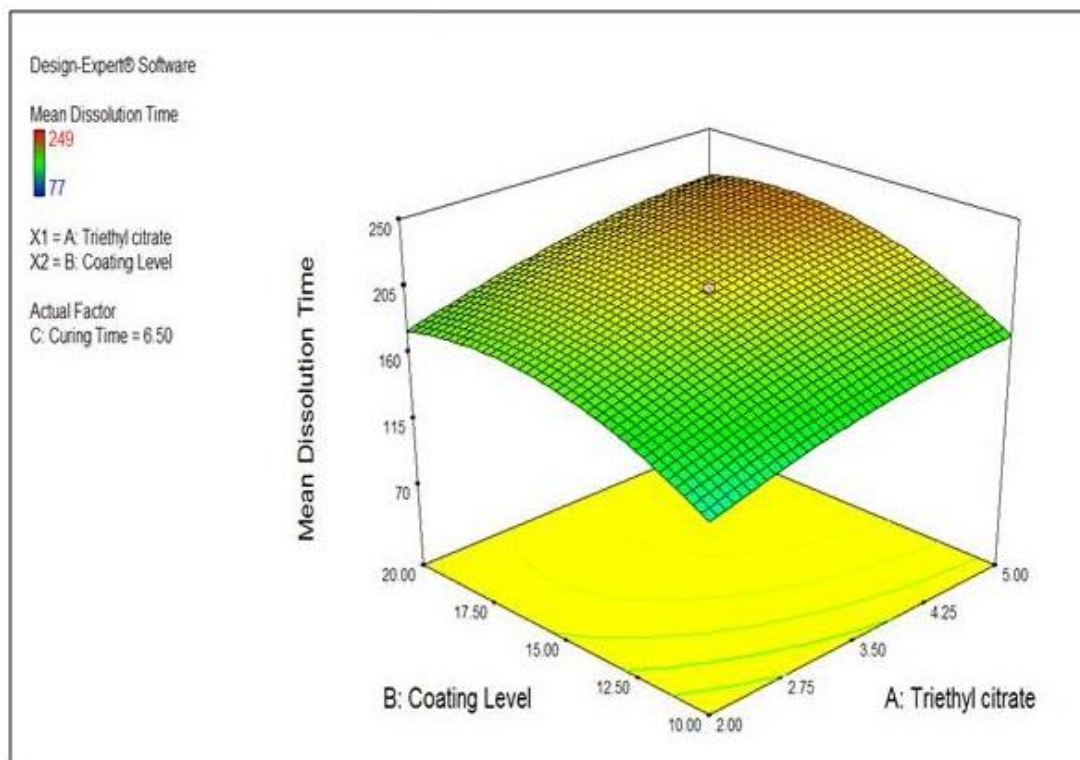


Figure 6: Response surface graph for Mean dissolution time with the amount of triethyl citrate, coating level and curing time

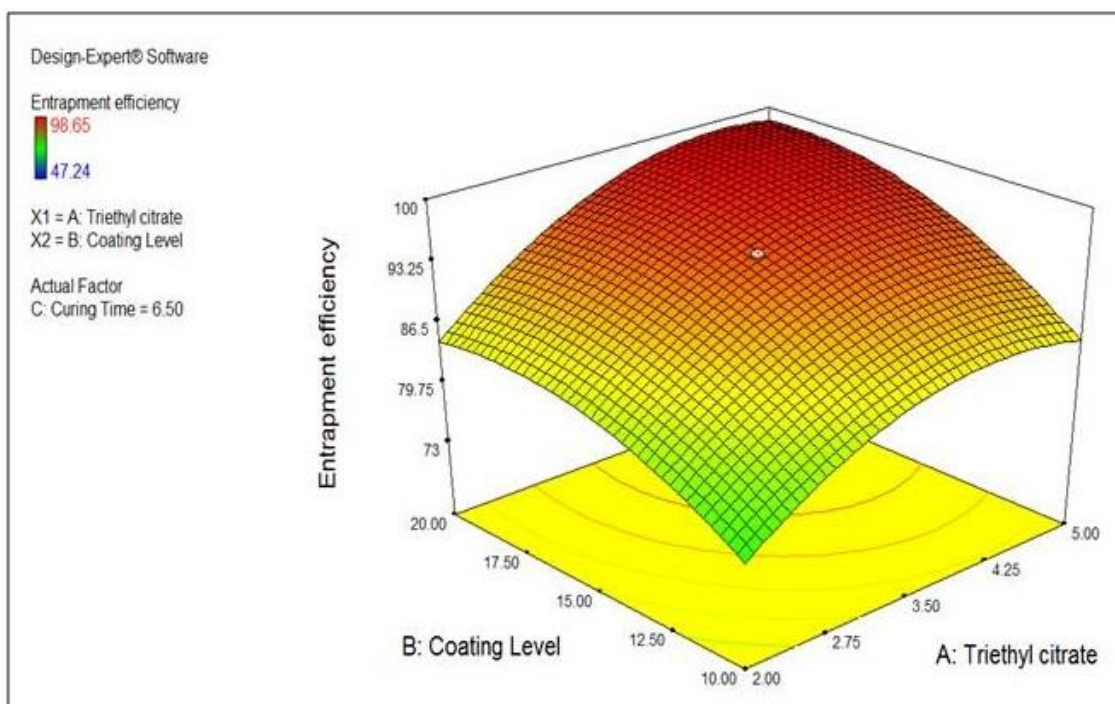


Figure 7: Response surface graph for Entrapment efficiency with amount of triethyl citrate, coating level and curing time

continued to 100% dissolution or until a constant dissolution percentage²¹.
Statistical analysis of the data and validation of the optimization model

The independent variables i.e. Triethyl citrate (%), Coating level (%), Curing times (h) of pellet obtained by using Fluidized bed processing technique against dependent variables i.e. Mean dissolution time (min), Entrapment efficiency (%) and Friability (%) was studied. Central

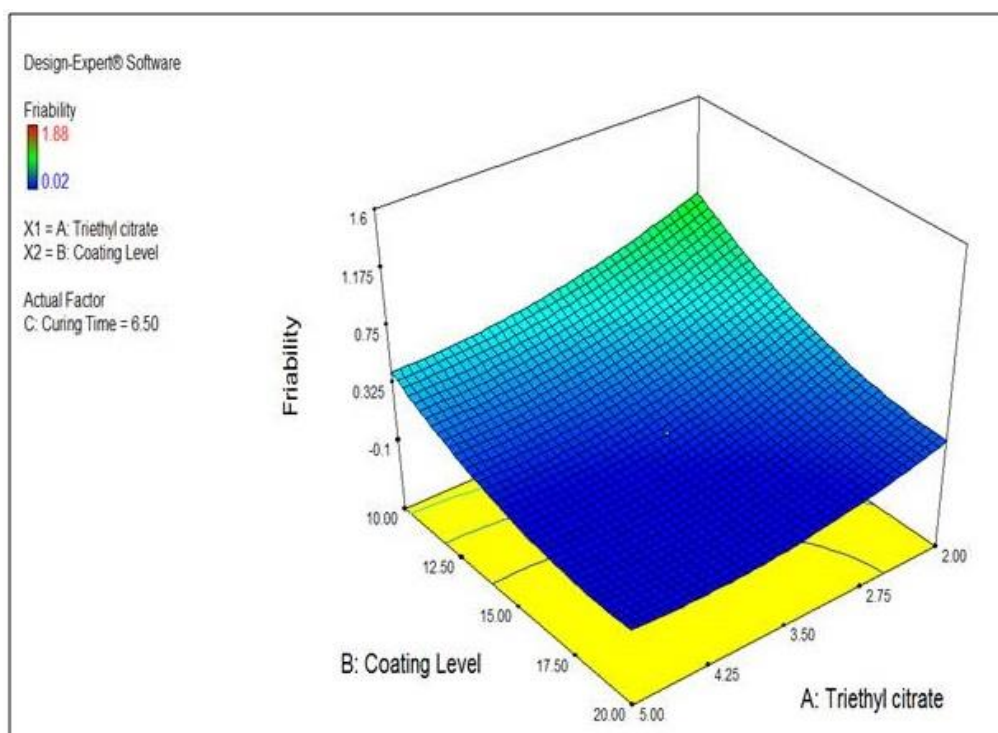


Figure 8: Response surface graph for Friability with the amount of triethyl citrate, coating level and curing time.

Table 3: The experimental and predicted values for all the eight responses (Y1 to Y3) along with percentage prediction error* observed for optimum formulation (A) and random formulation (B and C).

Response	A (5,17.18,4.37)#			B (4.99, 17.02, 4.44)#			C (4.12, 15.99, 7.21)#		
	Experimental value	Predicted Value	% PE*	Experimental Value	Predicted value	% PE*	Experimental Value	Predicted value	% PE*
Mean	232.16	232.42	0.20	231.58	231.99	0.25	209.38	209.64	0.10
Dissolution time			1			3			4
Entrapment efficiency	95.60	95.61	0.37	95.68	95.72	0.14	95.66	95.70	0.09
Friability	0.02	0.02	0	0.02	0.02	0	0.02	0.02	0

Table 4: Assay stability samples of Capecitabine extended release pellets at 1 M, 2M, 3 M and 6 M.

Assay (%)		40°C ± 2°C/75% RH ± 5%		At room temperature	
		HDPE	Alu. Strip	HDPE	Alu. Strip
		1M	99.63	100.11	98.24
2M	98.23	99.24	99.64	99.47	
3M	100.05	99.84	100.34	99.08	
6M	99.68	100.48	99.87	100.74	

Composite Design with quadratic and 2FI as a design model for response surface category was selected for optimization purpose.

Stability studies

The extended release pellets prepared were subjected to stability studies. The pellets were filled into empty hard gelatine capsule shells and were stored in tightly closed HDPE (high-density polyethylene) containers and in the aluminum pack. The stability studies were carried out as per ICH guidelines (ICH, 2003). The accelerated stability conditions were 40°C ± 2°C/75% RH ± 5%. The stability samples were analyzed interval such as 1, 2, 3 and 6 M.

The drug content and drug release of these pellets was performed as per the methods described earlier. To ensure the equivalence in release profile of the stability samples with that of initial samples, the fit factor, f2, was calculated. The optimized Capecitabine extended release pellets were exposed to accelerated stability studies (40°C ± 2°C/75% RH ± 5%) for 6 months. Stability of Capecitabine extended release pellets was also studied at room temperature for 6M. The samples were withdrawn from both the stability conditions at 1 M, 2 M, 3 M and 6 M. The samples were analyzed for their drug content and dissolution profile²².

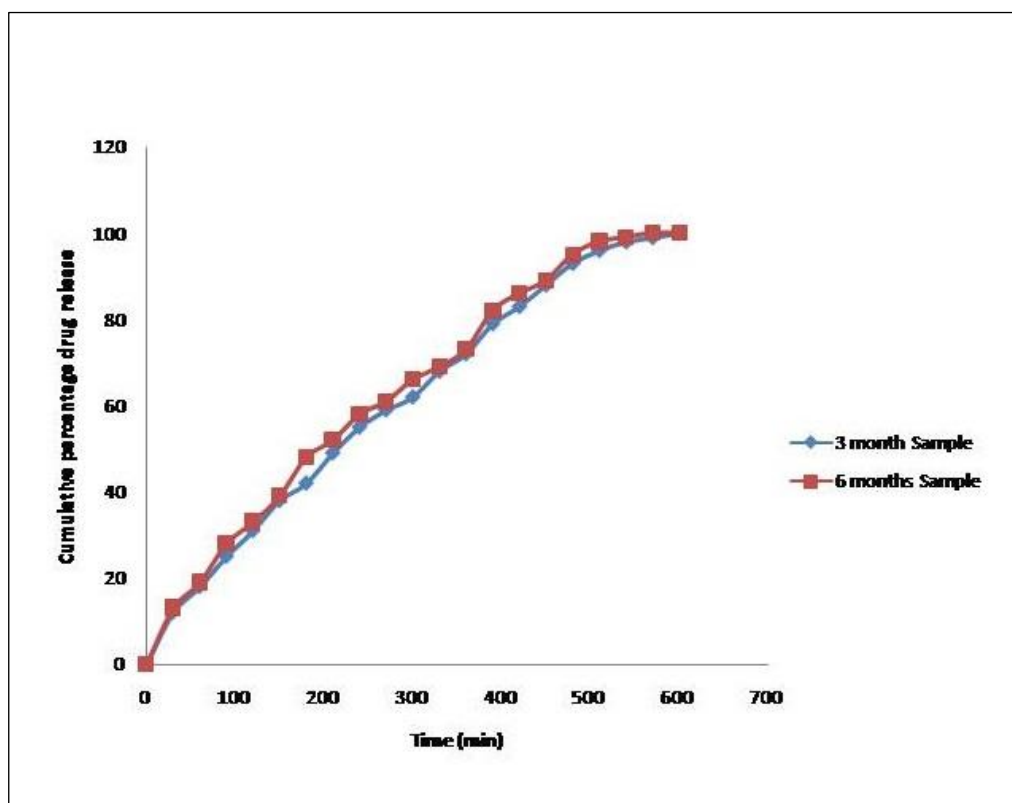


Figure 9: Dissolution profile of initial, 3 M and 6 M stability sample of Capecitabine extended release pellets.

A pharmacokinetic study in rats

Male Wistar rats (220 to 250 gm) were used for this study. The study was conducted at P. E. Society's, Modern College of Pharmacy, Nigdi, Pune, Maharashtra, India after getting the Ethical Committee Approval. (Approval No. MCP/IAEC/197/2017)

Isolated Perfused Rat Livers (IPRL) Experiments

Male Rats have very low activity of cytidine deaminase, isolated perfused rat livers (IPRL) and healthy rats were used as simple models to evaluate the primary process of CAP activation. New metabolites of CAP were observed. A nonsystemic glucuronide of 5-DFCR (5-DFCR-G) has been detected in liver and bile. Rats were randomly divided into two groups, each containing six. They were treated with 80 mg/kg B.W. of CAP and optimized pellets, were sequentially anesthetized per at 2, 4, 6, 8, 10, 12 h. The abdomen was then opened and the whole blood was collected. The bloodless liver was excised and immersed in liquid nitrogen, then maintained at -80°C until PCA extractions were performed²³⁻²⁵.

Perchloric Acid (PCA) extractions

The liver was weighed (13.6 ± 1.2 g), dipped in liquid nitrogen, grind and converted into powder, and sequentially extracted with cold and hot 1 M perchloric acid (PCA) by using the method of Wain and Staats (1973). The acid-soluble (AS) and acid-insoluble (AI) fractions thus obtained were lyophilized to dryness and stored at -80°C until analysis. The lyophilized materials were resuspended in a known volume of water containing 30 mM EDTA close to 3 ml and centrifuged immediately. The pH of the supernatant was adjusted to 5.5²⁶.

Statistical analysis

Data were analyzed by One-way ANOVA of variance followed by Bonferroni's multiple pair comparison tests. The differences in T_{max} among the groups were tested by Kruskal-Wallis test and Dunn's multiple pair comparison tests.

RESULT

FT-IR analysis of Capecitabine pellets

The chemical compatibility between Capecitabine and other formulation components (excipients) was ensured using an FT-IR study. Results showed that all characteristic peaks of pure Capecitabine (A) were observed in FT-IR spectra of formulation (E) as shown in Figure 1.

Differential scanning calorimetry

The DSC spectra of Capecitabine showed two endothermic peaks, a peak at 123.54°C , which almost related to the melting point of Capecitabine ($118-121^{\circ}\text{C}$) and the other at 152.27°C is due to thermal composition (Figure 2). DSC curves of ethyl cellulose (EC) gives a small endothermic peak before exothermic peak which determines Glass transition temperature (T_g). The T_g of EC without plasticizer (unmodified) was at 140°C , which means that below this temperature the restricted movements of polymer segments do not support a quick migration through the film. Applying 5–10% w/w of plasticizer the T_g can be lowered to $50-60^{\circ}\text{C}$. The T_g value of EC free films without plasticizer is 140°C .

X-ray powder diffraction

XRD pattern of Capecitabine in Figure 3 showed that, the drug was crystalline in nature, which shows the characteristic peaks with intensity at 2θ of $10.64-10.74$,

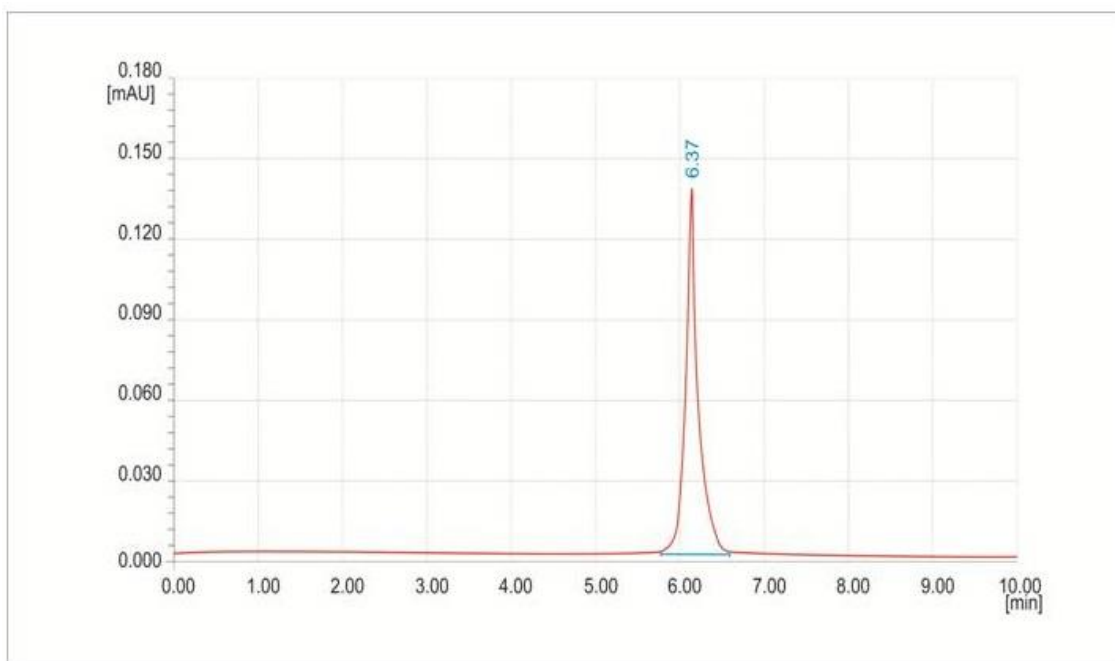


Figure 10: HPLC chromatograms of the purified of 5-DFCR.

Table 5: Pharmacokinetic parameters of Pure Capecitabine 90% confidence intervals (CI) following oral administration of Optimized pellets.

Sample	T _{max} (h)	C _{max} (ng/mL)	AUC _{0-last} (ng.h/mL)	AUC _{0-inf} (ng.h/mL)	MRT _{0-t}	T _{1/2} (h)
Pure Capecitabine	1.37	412 ± 42	1625 ± 745	1745 ± 245	4.9 ± 1.2	3.4 ± 1.5
Optimized pellet	8.81	13.4 ± 6.1	117 ± 14.7	147 ± 19.1	9.3 ± 2.1	8.3 ± 2.8

15.14–15.5, 16.92–17.4, 18.4–21.20, 21.57, 22.90, and 24.32 and other minor peaks up to 30°. XRD pattern of ethyl cellulose showed three characteristic peaks at 2θ-18.9°, 20.4° and 24.8° which corresponded to the crystallographic plane of crystals. PVP K30 is observed to show minor XRD peaks at 2θ = 12.74°, 13.32° and 22.74° respectively, which is reliable with data in the previous report.

Scanning Electron Microscopy

Scanning electron microscopy was utilized to exemplify the surface morphology of the pellets. The photographs were obtained at various magnification and the results are shown in Figure 4.

Micromeritic and another parameter

The values of flow properties and other parameters shown in Table 1. The flow properties, density, compressibility, porosity, crushing strength and other properties of the pellets were studied.

Kinetic study

Dissolution data were fitted in various kinetic models to know the mechanism of drug release. (Table 2). The correlation coefficient (R^2) was used as an indicator for best fitting, in which all formulation regression values were between (R^2) = 0.997 to 0.999 Korsmeyer-Peppas with lag.

Mean Dissolution Time

Correlation of Mean dissolution time (Table 3) with the amount of triethyl citrate (0.327), coating level (0.354) and

curing time (-0.315) was shown in Figure 5. Amount of triethyl citrate (0.327), coating level (0.354) shows a positive correlation as curing time (-0.315) shows a negative correlation as given in Table 2.

ANOVA proposed for the scheme is as follows. In this case B² and C² significant model terms shown in Figure 6.

Mean Dissolution Time

$$= +205.79 + 19.22 * A + 20.80 * B - 18.51 * C + 1.25 * A * B - 7.75 * A * C - 14.25 * B * C - 7.11 * A^2 - 22.66 * B^2 - 28.50 * C^2$$

Entrapment efficiency

Correlation of Entrapment efficiency with amount of triethyl citrate (0.291), coating level (0.262) and curing time (-0.318) was shown in table 3. Amount of triethyl citrate (0.291), coating level (0.262) shows positive correlation as curing time (-0.318) shows negative correlation given in Table 2.

ANOVA proposed for the scheme is as follows. In this case, A, B, C, A², C² are significant model terms shown in Figure 7.

Entrapment efficiency

$$= +94.94 + 5.97 * A + 5.39 * B - 6.53 * C + 1.07 * A * B + 3.11 * A * C - 3.96 * B * C - 5.05 * A^2 - 3.77 * B^2 - 14.79 * C^2$$

Friability

Correlation of Friability (Figure. 3) with the amount of triethyl citrate (-0.264), coating level (-0.447) and curing time (0.173). Amount of triethyl citrate (-0.264), coating

level (-0.447) shows a negative correlation as curing time (0.173) shows a positive correlation.

ANOVA proposed for the scheme is as follows. In this case B, C² are significant model terms shown in Figure 8.

$$\begin{aligned} \text{Friability} &= \\ +0.085-0.18 & * A-0.30 & * B+0.12 & * \\ C+0.051 & * A * B-0.11 & * A * C \\ +0.22 & * B * C+0.11 & * A^2+0.16 & * B^2+0.39 \\ & * C^2 \end{aligned}$$

*Percent prediction error (PE) was calculated using the formula (Experimental Value – Predicted Value) / Experimental Value x 100.

The values represented in the brackets are the amount of triethyl citrate in % w/w, coating level in % w/w and the curing time in hours, respectively for A, B and C formulations.

Stability Study

The drug content of the Capecitabine extended release pellets on stability ranged from 98.23-100.74%. An almost constant drug content within pharmacopoeial limits (95% - 105% w/w) indicates that, Capecitabine extended release pellets are stable till 6 Month at room temperature and at accelerated stability conditions given Figure 9 and Table 4.

Isolation and Purification of 5-DFCR-G.

Prior HPLC analysis liver AS extract (3 ml) samples pooled and subjected to a cleaning procedure. Then an equal volume of dichloromethane was added; after extraction, the aqueous phases were collected and reextracted with ethyl acetate. The aqueous phases were then lyophilized. The dry residues were diluted in 400 µl of H₂O and then placed at the top of a 10 cm-length glass column of 0.8-cm diameter. Elution of the column was carried out by water (5 ml fractions) and then by a water-methanol(80:20 v/v) mixture (6:1 ml fractions). Fraction 8 contained the 5-DFCR. Fractions 8 were used for further fine purification by HPLC with a Waters2960 Alliance chromatographic system (Waters, Milford, MA) under the following conditions: column, C18 ProntoSIL (250 X 4 mm i.d., 50 µm particle size; Bischoff Chromatography, Leonberg, Germany) maintained at 35°C; mobile phase, mixture of acetonitrile/water with 0.1% trifluoroacetic acid (TFA) in 5:95 ratio for the first 8.5 min and then in 90:10 ratio for 3 min to wash out the column; flow rate, 1.0 ml/min; detection, UV absorbance at 280nm with a diode array detector (Waters 996). Collection of the major peak at a retention time (RT) of 6.3 min was done shown in Figure 10.

Pharmacokinetic data analysis

The area under curve from 0 to 12 h (AUC 0→12h) and mean residence time (MRT) were estimated using non-compartmental analysis (WinNonlin 2.1, Pharsight Corp., Mountain View, CA). The maximal concentration of the drug (C_{max}) and the time to reach maximum concentration (T_{max}) was directly obtained from data. Pure Capecitabine showed T_{max} 1.37 hr with C_{max} 412 ± 42 ng/mL and optimized pellets of Capecitabine showed T_{max} 8.81 hr with C_{max} 13.4 ± 6.1 ng/mL. T_{1/2} pellets were found 8.3 ± 2.8 hr given in Table 5.

DISCUSSION

The present research work was involved in the formulation and evaluation of extended-release Capecitabine loaded pellets. Formulated Capecitabine pellets was evaluated for various physical parameters.

The FT-IR spectra of the pure drug, polymers and formulation were recorded to check the compatibility of drug and polymers. The characteristic pick of Capecitabine seen in the spectra of formulation without any significant change in the position. This shows that there was no chemical interaction between Capecitabine and polymers. The surface of the uncured pellets was uniform and smooth and no crystals were visible. There was no evidence of drug partition on the surface thereby uniform coating results. From the SEM micrographs, it can be inveterate that there were no perceptible macroscopic changes in the surface morphologies of the film-coated pellets as a result of curing. Basically, the curing process which improves polymer-chain inter-diffusion in the coating, which “fill up” small cracks and pores. SEM photomicrographs of the cured pellets didn't show any sign of the presence of drug crystals on the surfaces of the film coated pellets. In this manner, the higher release rates did not rely upon the partitioning of the drug into the film coating. DSC studies showed that, less intense peak observed at the melting range of temperature range of Capecitabine in the formulation which is evidence that there was no crystalline drug material in the formulation. It indicates that, crystallinity of drug have considerably reduced in pellet formulation. The DSC studies, which measure the heat gain or loss from chemical or physical changes within a sample as a function of temperature, no shifting of melting endotherm of the drug was conclusive of no incompatibility of drug with any of the excipients. The XRD pattern of pellets demonstrates that most of the characteristic peaks of the drug were abridged in intensity. A distinct halo pattern and absence of principal diffraction peaks characteristic of a crystalline drug in XRPD profile of pellets confirmed that the drug molecularly dispersed in the polymer matrix and the pellets so formed were homogeneous, amorphous solid solution system; supporting the predictions of thermal analysis¹². The Capecitabine pellets were obtained posses spherical shape and mean diameter size 1208 um. The friability of pellets was in the specific range indicate the good mechanical strength and pellets size distribution (span)¹⁶.

The value of Carr's index and Hausner's ratio indicates the passable floability of pellets for filling into capsule. This may be due to the spherical nature of the pellets. Overall, the Capecitabine pellets prepared by fluidized bed coater showed the improved micromeritic as well as other properties such as pellets size distribution (span)⁹.

The slow release of Capecitabine can be attributed to the insoluble PVAc component of Kollidon SR that forms an inert hydrophobic matrix after hydration. The increasing length of the diffusion pathway over time is responsible for the ER of Capecitabine. Pellets were coated with Kollicoat SR 30 D, containing different levels of triethyl citrate, a water-soluble plasticizer. The drug release was very rapid at a low level of triethyl citrate (i.e. 10 % w/w of polymer).

This plasticizer concentration was insufficient to reduce the least film formation temperature below the coating temperature, which was a prerequisite for coalescence. At intermediate plasticizer levels, the beads resulted in a decrease in the drug release. Batch 13 showed 100% drug release in 10.3 h when the curing time is 6.5 h, the coating level is 13.41 and concentration of triethyl citrate is 6.02 %. One more interesting observation in this study is that, gradual change in the shape of the release profile with increasing curing times. It can be concluded from that, the coating property of Kollicoat SR30D of the Capecitabine extended release pellets is not affected on stability. To assess change in release profile statistically, similarity factor (f_2) was calculated. Similarity factor is essentially a quantitative method, which reflects the differences between the two release curves. The f_2 or similarity factor of Capecitabine extended release pellets was found to be > 90 for all the stability samples with respect to their initial release profile.

CONCLUSION

The Capecitabine pellets were prepared using different polymers such as ethyl cellulose, PVP-K30 and Kollicoat SR30D without any toxic solvent. The Capecitabine pellets extended the drug release for the period of 10.3 h. Kollidon SR induced the most prominent ER effect. This slow release of Capecitabine can be attributed to the insoluble PVAc component of Kollidon SR that forms an inert hydrophobic matrix after hydration. The increasing length of the diffusion pathway over time is responsible for the ER of Capecitabine. It was concluded that the Batch 13 showed 100% drug release in 10.3 h when the curing time is 6.5 h, the coating level is 13.41 and concentration of triethyl citrate is 6.02 %.

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