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Newly Developed Highly Sensitive Method for the Determination of Capecitabine by Using UV-Spectroscopy

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ABSTRACT

Capecitabine is a 'pro-drug' to the cytotoxic agent 5-fluorouracil (5-FU) intended to administered orally. Capecitabine is generally used as first line monotherapy for advanced colon cancer. Simple, rapid, accurate UV spectrophotometric methods were developed in the present study and validated for the estimation of Capecitabine in bulk and its formulations as per ICH guidelines. Three solvent systems viz., 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) was tried. The results suggest that the developed method shows linearity over the range of concentration 2-24µg/ml and a correlation coefficient of 0.9999. Accuracy, precision, linearity, robustness, and ruggedness were statistically validated as per ICH guidelines for all the developed methods. The % RSD values for validated methods were found to be less than 1.5 and methods will find application in routine analysis of drug formulations containing Capecitabine.

Keywords: Capecitabine, UV-spectrophotometric, 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3).

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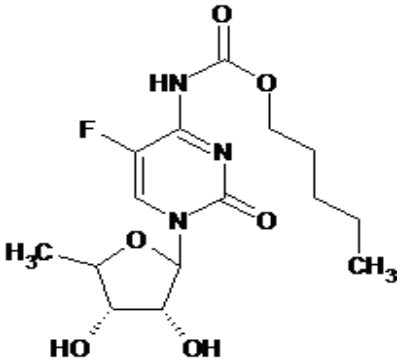
INTRODUCTION

The drug is official in the Indian Pharmacopoeia (IP). [1-2] Capecitabine ($C_{15}H_{22}FN_3O_6$) is 5-deoxy-5-fluoro-N-(pentyloxy) carbonyl]–cytidinewith molecular weight 359.35. [3-4] The synthesis of thymidine monophosphate inhibited by 5-FU, thymidine monophosphate is an active form of thymidine which is required for *de novo* synthesis of DeoxyRibo Nucleic acid (DNA).

Capecitabine is an orally administered chemotherapeutic agent used in the treatment of metastatic breast and colorectal cancers and is a prodrug of 5'-deoxy-5- fluorouridine (5'-DFUR), which is enzymatically converted to 5-fluorouracil in the tumor, where it inhibits DNA synthesis and slows growth of tumor tissue. The activation of Capecitabine follows a pathway with three enzymatic steps and two intermediary metabolites, 5'- deoxy-5-fluorocytidine (5'-DFCR) and 5'-deoxy-5- fluorouridine (5'-DFUR), to form 5-fluorouracil. Chemically it is 5'-deoxy-5-fluoro-N-[(pentyloxy) carbonyl] – cytidine (figure 1) with empirical formula $C_{15}H_{22}FN_3O_6$ and the molecular weight of 359.35 g/mol. [5]

A very few methods appeared in the literature for the assay of Capecitabine in biological fluids and

pharmaceutical formulations viz., HPLC [6-9], LC-UV [10-11], LC-MS [12], and LMS/MS [13] methods. Hence in the present work it was aimed to develop and validate accurate, precise, simple and rapid UV spectroscopic methods for the estimation of Capecitabine in bulk and its formulations as per ICH guidelines.



pentyl {1-[(3*R*,4*S*)-3,4-dihydroxy-5-methyltetrahydrofuran-2-yl]-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl}carbamate

Fig. 1: Chemical structure of Capecitabine

MATERIALS AND METHODS

Capecitabine gift sample was obtained. Procured methanol, hydrochloric acid and sodium hydroxide from S.D Fine chemicals, Mumbai and double distilled water were used throughout the experiments. The other chemicals used were of analytical grade.

METHODS

Determination of absorption maxima (λmax)

Preparation of Capecitabine standard stock solution (1000µg/ml)

About 50 mg of Capecitabine working standard weighed accurately and transferred to a 50 ml volumetric flask. To it 40 ml of 0.1N NaOH was added and was shaken for 5 minutes to dissolve and the volume was made up to 50 ml with 0.1N NaOH. Similarly a standard stock solution was prepared in 0.1N HCl and Methanol: Water (1:3) solvent systems.

Preparation of Capecitabine sample solution

Transferred aliquots of standard stock solution into a series of 10 ml volumetric flask and diluted with 0.1N NaOH to get desired concentrations. Similarly sample solutions were prepared from above stock solution. UV scanning was done for the sample solutions in the range of 200-380 nm using double beam UV Spectrophotometer and absorption maxima of Capecitabine was determined.

Determination of linearity range

Standard solutions of Capecitabine in the concentration range of 4-40µg/ml were prepared in 0.1N NaOH and absorbance was measured at 292.8nm taking the 0.1N NaOH as the blank. Similarly absorbance of Capecitabine in the concentration range of 4-40µg/ml in 0.1N HCl, and Methanol: Water (1:3) were measured at 304 nm and 300.8 nm respectively using 0.1N HCl, and Methanol: Water (1:3) solvent systems as blank.

Calibration curve

Appropriate aliquots from standard stock solutions of Capecitabine were transferred to series of 10 ml volumetric flasks. The volume was adjusted to the mark with 0.1N NaOH to obtain concentrations of 4, 8, 12, 16, 20 and 24µg/ml and the absorbance was measured at 292.8 nm. Similarly a set of same concentrations were prepared in 0.1N HCl and Methanol: Water (1:3). The absorbance was Measure at 304 nm and 300.8 nm respectively against respective solvent systems as blank. The concentration vs absorbance values were plotted and interpreted.

Accuracy Validation

The accuracy was evaluated by applying the proposed methods to the analysis formulations with known amounts of drug. The accuracy was calculated with respect to percentage of the drug recovered from the formulations.

Capecitabine standard solution preparation (for bulk)

Accurately weighed 50 mg of Capecitabine working standard was transferred to a 50 ml volumetric flask, about 40 ml of 0.1N NaOH was added to dissolve. Diluted up to the mark with 0.1N NaOH and mixed. To get desired concentrations, aliquots of stock solution were further diluted with 0.1N NaOH. Similarly standard solutions were prepared in other solvent systems viz., 0.1N HCl, Methanol: Water (1:3).

Capecitabine sample preparation (for tablets)

Accurately weighed 5 tablets were grounded in a mortar and transferred the equivalent to 50 mg of Capecitabine into a 50 ml volumetric flask. Added 40 ml of 0.1N NaOH and was shaken it for 1 h. Diluted to volume with 0.1N NaOH and the contents was mixed and filtered through 0.45µm membrane filter. Aliquots of the filtrate were transferred to 25 ml volumetric flask and diluted to volume with the 0.1N NaOH to got desired concentration. Similarly sample solutions were prepared in other solvent systems viz., 0.1N HCl, Methanol: Water (1:3). Recovery studies were carried out by adding known amount of standard drug (40% and 20%) to the sample solution. The absorbance measured and the amount was calculated from the calibration curve. The recovery percentage was calculated in terms of RSD percentage which was less than 2%.

Precision

The precision was determined by intraday and inter day observations. Repeatability was evaluated assaying 3 determinations at the same concentration (10µg/ml), during the same day, under the same experimental conditions. Intermediate precision was analyzed comparing the assays in 3 determinations at the same concentration (10µg/ml) during 3 different days. Precision (repeatability and intermediate precision) was expressed as relative standard deviation (RSD).

Sample preparation (for tablets)

Accurately weighed 5 tablets were grounded in a mortar and transferred equivalent to 50 mg of Capecitabine into a 50 ml volumetric flask, 40 ml of 0.1N NaOH was added and shaken for 1 h. Diluted to volume with 0.1N NaOH. The contents mixed and were filtered through 0.45µm membrane filter. Aliquots of

the filtrate was transferred to 25 ml volumetric flask and diluted to volume with the 0.1N NaOH to got desired concentration. Similarly sample preparations were prepared in other solvent systems viz., 0.1N HCl, Methanol: Water (1:3).

Intraday precision was determined by for three times in the same day analyzing Capecitabine (morning, afternoon, evening) at respective absorption maxima using respective solvent systems. Interday precision was determined by analyzing daily once (morning) for three days at respective absorption maxima using respective solvent systems. The percentage RSD values were calculated and it should be less than 2%.

LOD and LOQ

LOD/LOQ parameters are always useful to demonstrate that the analysis is being conducted in a region which is above the LOQ value. The LOD and LOQ were calculated based on the standard deviation of the response (y intercepts of regression lines) and the slope using three independent analytical curves, as denied by ICH.

$$\text{LOD } (\mu g/ml) = 3.3 \times \frac{\sigma}{s}$$

$$\text{LOQ } (\mu g/ml) = 10 \times \frac{\sigma}{s}$$

Where σ - Standard deviation of the response: s - Slope ratio curve.

The lowest possible concentration where the drug Capecitabine shows response was determined in all the solvent systems. The absorbance at this concentration was measured in triplicate in respective solvent systems at respective absorption maxima. The LOD/LOQ was calculated by using formulae from the data obtained.

Robustness

Robustness of the proposed methods was determined by the analysis of samples and standard solutions (10µg/ml) at different wavelengths (± 5 nm) and at different solution temperatures (refrigeration condition 2-8°C and 37°C). The stability study was performed maintaining the drug working solution in respective solvent systems for 48 h protected from light, looking for the decrease of absorbance compared with those of freshly prepared solutions to assess the stability of drug.

Appropriate concentrations of Capecitabine from bulk and formulations were prepared in respective solvent systems. Analysis was carried out at three different wavelengths (actual and ± 5 nm). Amount found was calculated at three different wavelengths in terms of percentage RSD and values were less than 2%.

Ruggedness

Ruggedness is not addressed in the ICH documents; it is a measure of reproducibility of test results under normal, expected operational conditions from analyst to analyst and instrument to instrument.

Appropriate concentrations of Capecitabine from bulk and formulations were prepared in respective solvent systems. Analysis was carried out by two different analysts and also two instruments. Amount found was calculated at three different wavelengths in terms of percentage RSD and values were less than 2%.

Table 1: Linearity range curve of Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems.

Conc. (µg/ml)	0.1N NaOH	0.1N HCl	Methanol: Water (1:3)
	Absorbance* ± SD	Absorbance* ± SD	Absorbance*± SD
4	0.0672 ± 0.0004	0.0677 ± 0.0003	0.0670 ± 0.003
8	0.118 ± 0.0021	0.123 ± 0.0021	0.124 ± 0.0022
12	0.178 ± 0.0016	0.183 ± 0.0016	0.188 ± 0.0016
16	0.237 ± 0.0010	0.242 ± 0.0010	0.243 ± 0.0011
20	0.302 ± 0.0049	0.307 ± 0.0049	0.308 ± 0.0048
24	0.362 ± 0.0020	0.368 ± 0.0020	0.369 ± 0.0021
28	0.382 ± 0.0011	0.421 ± 0.0011	0.387 ± 0.0011
32	0.412 ± 0.0032	0.441 ± 0.0032	0.412 ± 0.0032
36	0.472 ± 0.0023	0.473 ± 0.0023	0.462 ± 0.0023
40	0.512 ± 0.0033	0.511 ± 0.0033	0.489 ± 0.0023

Table 2: Calibration curve data of Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems served absorption maxima.

Conc. (µg/ml)	0.1 N NaOH	0.1 N HCl	Methanol: Water (1:3)
	Absorbance*± SD	Absorbance*± SD	Absorbance*± SD
0	0.0000 ± 0.0000	0.0000 ± 0.0000	0.0000 ± 0.0000
4	0.0622 ± 0.0012	0.0658 ± 0.0015	0.0637 ± 0.0018
8	0.1180 ± 0.0015	0.1240 ± 0.0019	0.1230 ± 0.0026
12	0.1780 ± 0.0019	0.1840 ± 0.0021	0.1830 ± 0.0029
16	0.2370 ± 0.0021	0.2470 ± 0.0024	0.2460 ± 0.0032
20	0.2970 ± 0.0026	0.3080 ± 0.0026	0.3070 ± 0.0023
24	0.3560 ± 0.0018	0.3690 ± 0.0021	0.3680 ± 0.0019

Table 3: Statistical data of calibration curve for Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems.

Parameters	0.1 N NaOH	0.1 N HCl	Methanol: Water (1:3)
λmax (nm)	292.8	304.0	300.8
Beer's range (µg/ml)	2-24 µg/ml	2-24 µg/ml	2-24 µg/ml
Molar absorptivity (mol-1cm1)	1.714×104	1.716 ×104	1.711 ×104
Best fit valves			
Slope	0.0147 ± 0.000057	0.0153 ± 0.000050	0.01531 ± 0.000076
Y-intercept when X=0.0	0.00082 ± 0.00082	0.00078 ± 0.00072	0.001714 ± 0.0011
X-intercept when Y=0.0	-0.05554	-0.05135	-0.1120
1/Slope	67.61	65.36	65.33
95% CI			
Slope	0.01464 to 0.01494	0.01517 to 0.01543	0.01511 to 0.01550
r2	0.9999	0.9999	0.9999
P valve	< 0.0001	< 0.0001	< 0.0001

RESULTS AND DISCUSSION

Simple, rapid, economic, accurate, precise and sensitive UV spectrophotometric methods were developed and validated as per ICH guideline and USP 2000 for the estimation of Capecitabine in bulk and formulations. Three different solvent systems viz., 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) was selected. The developed methods were further validated for

accuracy, precision, LOD, LOQ, specificity, robustness and ruggedness with statistical data.

Table 4: Data showing accuracy of Capecitabine (bulk) in all solvent systems.

Sample No	Concentration of Capecitabine (µg/ml)		% of recovery
	Theoritical	Experimentaly	
Method 1 0.1 N NaOH			
1	2	2	100
2	4	3.9	98.7
3	6	6	100
4	8	8.04	100.5
5	10	9.97	99.7
Method II 0.1 N HCl			
	Theoritical	Experimentaly	
1	2	2.01	100.5
2	4	4.02	100.5
3	6	5.9	99.2
4	8	8.0	100
5	10	10.2	100.2
Method III Methanol : Water (1:3)			
	Theoritical	Experimentaly	
1	2	2.02	101.1
2	4	3.9	99.4
3	6	6.03	100.5
4	8	8.04	100.5
5	10	10.06	100.6

Table 5: Data showing recovery studies of capecitabine (formulations) in all solvent systems.

Amount present in formulation (µg/ml)	Amount added		Amount recovered (µg/ml)	Mean % Recovery	RSD
	µg	%			
10	4	40	13.9	99.2 ± 1.909	1.924
	2	20	11.8	98.7 ± 1.779	1.802
Amount present in formulation (µg/ml)	**Amount added**		**Amount recovered (µg/ml)**	**Mean % Recovery**	**RSD**
	µg	**%**			
10	4	40	14.03	100.2 ± 1.808	1.824
	2	20	12.03	100.3 ± 2.219	2.102
Amount present in formulation (µg/ml)	**Amount added**		**Amount recovered (µg/ml)**	**Mean % Recovery**	**RSD**
	µg	**%**			
10	4	40	14.1	100.9 ± 2.707	1.691
	2	20	12.1	101.1 ± 3.143	1.130

Table 6: Data showing LOD/LOQ of Capecitabine in all solvent systems.

	Mean ± SD	SEM
Method I 0.1 N NaOH		
Limit of detection	0.191 ± 0.046	0.026
Limit of quantitation	0.584 ± 0.145	0.084
Method II 0.1 N HCl		
	Mean ± SD	**SEM**
Limit of detection	0.48 ± 0.047	0.027
Limit of quantitation	1.46 ± 0.148	0.084
Method III Methanol : Water (1:3)		
	Mean ± SD	**SEM**
Limit of detection	0.51 ± 0.134	0.072
Limit of quantitation	1.54 ± 0.384	0.224

The absorption maxima (λmax) with characteristic peak for capecitabine were found at 292.8 nm, 304.0 nm and 300.8 nm for 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) respectively. These absorption maxima were used to determine the linearity and it was shown linear relationship with correlation coefficient of 0.9999; 0.9999 and 0.9999 for 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) respectively in the concentration range of 2-24µg/ml. The spectra and data were shown in figure 2, 3 and table 1.

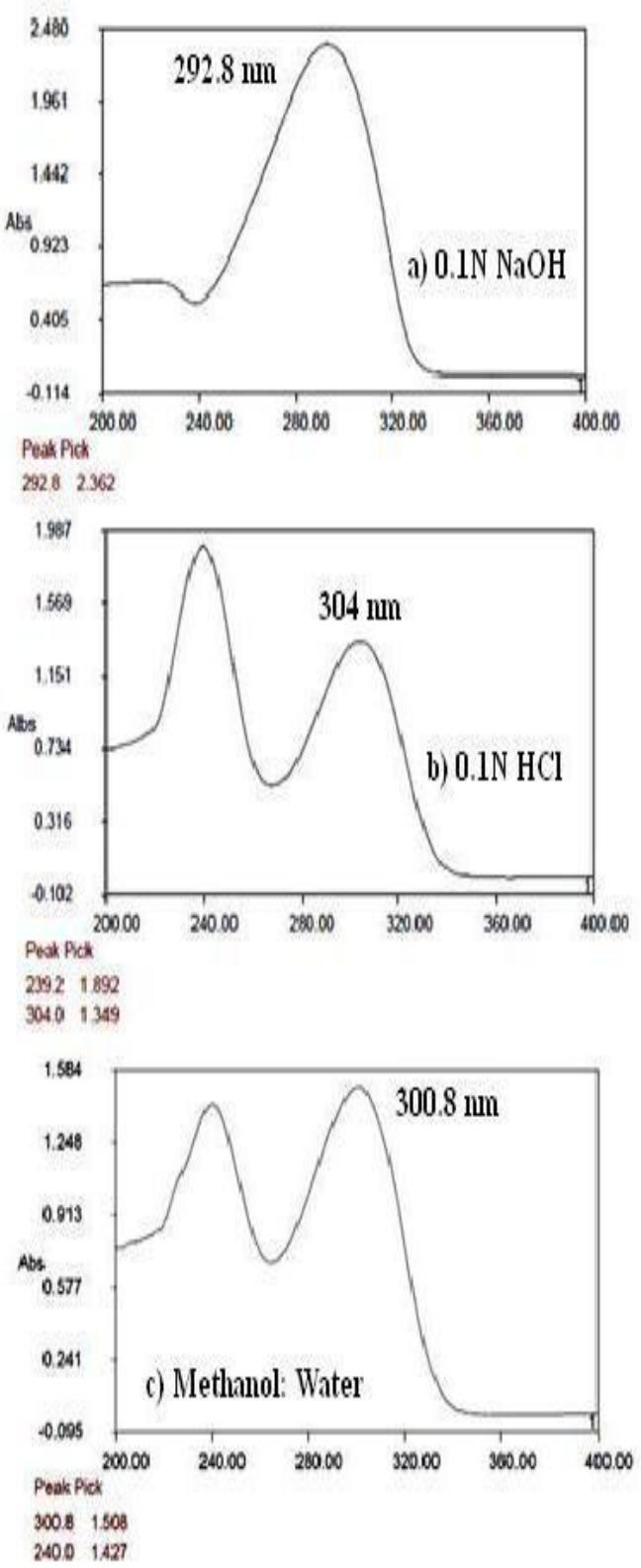


Fig. 2: Absorption maxima of Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems.

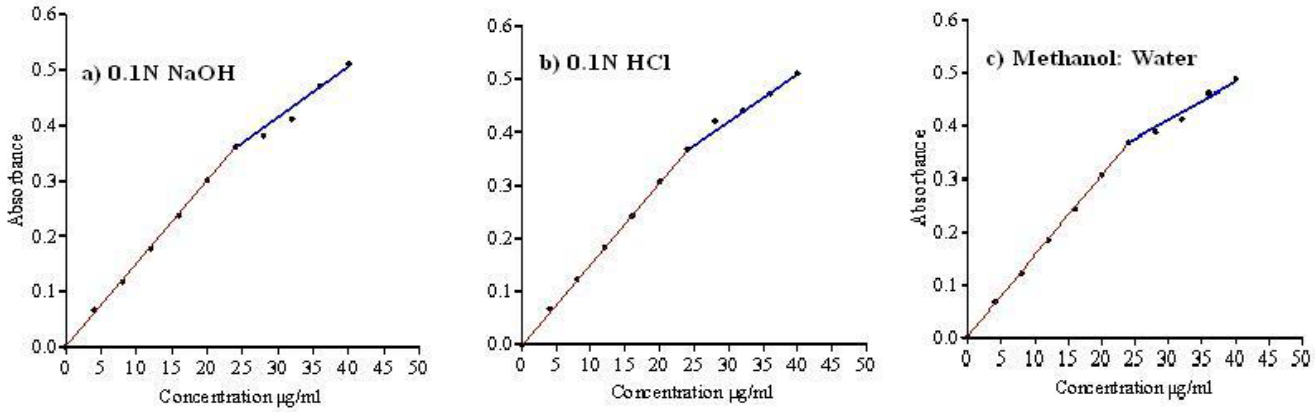


Fig. 3: Linearity range of Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems

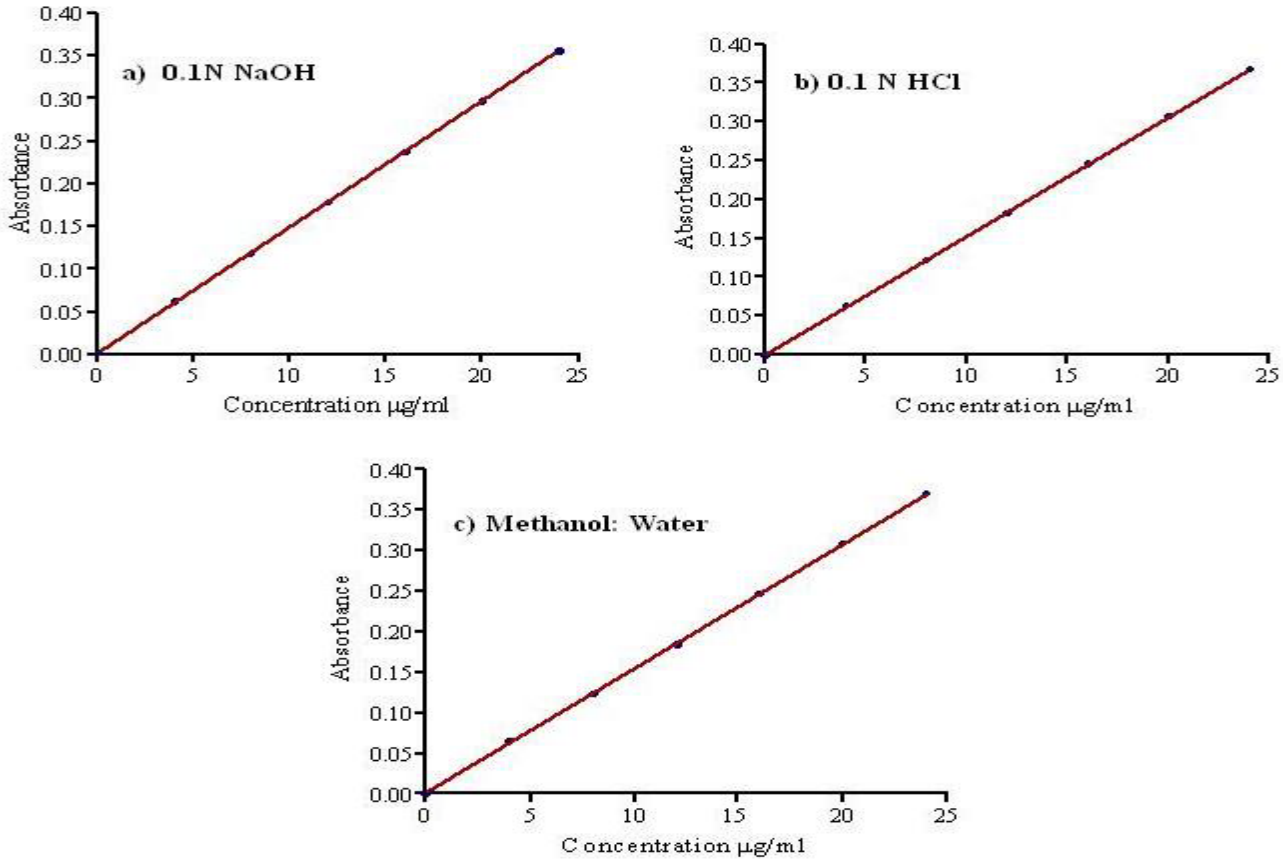


Fig. 4: Calibration curve of Capecitabine in 0.1N NaOH, 0.1N HCl and Methanol: Water (1:3) solvent systems.

Table 7: Data showing precision Intraday and Inter day trials with RSD values for Capecitabine in all solvent systems.

Trials	Label claimed (mg/tab)	Amount found (mg/tab)	% Label claimed (Mean ± SD)	SEM	RSD
Method I 0.1 N NaOH					
		50.3	100.6 ± 1.246	0.729	1.239
Day-1	50	50.2	100.4 ± 0.853	0.429	0.843
		49.5	99.0 ± 0.642	0.373	0.654
		50.1	100.2 ± 1.474	0.851	1.473
Day-2	50	49.2	98.4 ± 1.060	0.611	1.062
		49.6	99.2 ± 1.385	0.860	1.388
		50.5	101.0 ± 0.692	0.400	0.686
Day-3	50	50.01	100.02 ± 0.961	0.200	0.959
		49.7	99.4 ± 0.473	0.272	0.473
Method II 0.1 N HCl					
		50.4	100.8 ± 1.381	0.800	1.378
Day-1	50	50.3	100.6 ± 0.765	0.441	0.758
		50.2	100.4 ± 1.024	0.592	1.016
		50.4	100.8 ± 0.662	0.384	0.658
Day-2	50	50.2	100.4 ± 1.204	0.693	1.196
		50.3	100.6 ± 0.670	0.393	0.678

Intra day trials

Intra day trials

		50.2		100.4 ± 0.201		0.155	0.199
Day-3	50	49.9		99.8 ± 1.386		0.860	1.388
		49.6		99.2 ± 0.871		0.504	0.875
Method III Methanol : Water (1:3)							
		49.9		99.8 ± 0.722		0.416	0.718
Day-1	50	49.7		99.4 ± 0.791		0.458	0.796
		49.9		99.8 ± 0.792		0.458	0.803
		50.6	**Intra**	101.2 ± 1.155	**Intra**	0.665	1.156
Day-2	50	50.2	**day**	100.4 ± 1.363	**day**	0.913	1.575
		49.8	**trials**	99.6 ± 0.757	**trials**	0.437	0.760
		50.2		100.4 ±1.22		0.705	1.213
Day-3	50	49.8		99.6 ± 0.756		0.437	0.754
		49.7		99.4 ± 1.151		0.664	1.156

Table 8: Data showing robustness of Capecitabine at different wavelengths in all solvent systems.

Method	Conc. (µg/ml)	Wave length	Amount found	Mean (% ± SD)	SEM	RSD
		292	9.95	99.5 ± 0.962	0.552	0.905
Method I	10	297	8.67	86.7 ± 1.735	1.012	1.817
		287	8.7	87.0 ± 1.013	0.601	1.163
		304	9.93	99.3 ± 0.712	0.407	0.732
Method II	10	309	8.7	87.0 ± 1.507	0.928	1.720
		299	8.8	88.0 ± 1.059	0.665	1.241
		300	9.98	99.8 ± 1.241	0.721	1.256
Method III	10	305	8.34	83.4 ± 1.122	0.702	1.332
		295	8.41	84.1 ± 0.941	0.562	1.076

Table 9: Data showing ruggedness of Capecitabine by different Analysts in all solvent systems..

Method	Conc. (µg/ml)	Analyst	Amount found	Recovery ± SD	SEM	RSD
Method I	10	Analyst 1	10.01	100.1 ± 0.54	0.223	0.539
		Analyst 2	9.94	99.4 ± 0.3	0.122	0.301
Method II	10	Analyst 1	9.99	99.9 ± 0.75	0.307	0.756
		Analyst 2	10.05	100 .5 ± 0.565	0.231	0.565
Method III	10	Analyst 1	10.01	100.1 ± 0.41	0.169	0.413
		Analyst 2	9.99	99.9 ± 0.393	0.161	0.612

Table 10: Data showing ruggedness of Capecitabine by using different Instruments in all solvent systems

Method	Conc. µg/ml)	Instrument	Amount found	Recovery (± SD)	SEM	RSD
Method I	10	Instrument 1	9.92	99.2 ± 0.963	0.554	0.964
		Instrument 2	10.01	100.1 ± 0.493	0.284	0.492
Method II	10	Instrument 1	9.7	97.0 ± 0.709	0.409	0.733
		Instrument 2	9.71	97.1 ± 0.642	0.371	0.658
Method III	10	Instrument 1	9.92	99.2 ± 1.249	0.721	1.251
		Instrument 2	9.89	98.9 ± 0.600	0.346	0.610

Table 11: Robustness of capecitabine at refrigerated condition and room temperature

			Refrigerated Condition						Room Temperature					
	Trial	Label Claim (mg/tab	Amount will be found (mg/tab)		% of Label Claim Mean ± SD		SEM	RSD	Amount will be found (mg/tab)		% of Label Claim Mean ± SD		SEM	RSD
			49		98 ± 0.341		0.201	0.344	50.3		1000.6 ± 1.249		0.727	1.233
	Day-1	50	49.1		98.2 ± 0.350		0.208	0.358	50.4		100.8 ± 0.850		.424	.42
			48.8		97.6 ± 0.352		0.202	0.350	49.8		99.6 ± 0.645		.373	.654
			48.8	**Intra**	97.6 ± 0.351	**Intra**	0.201	0.350	50.,02	**Intra**	100.04 ± 1.474	**Intra**	.852	1.474
Method-I	Day-2	50	48.4	**day**	96.8 ± 0.251	**day**	0.145	0.251	49.9	**day**	99.8 ± 1.061	**day**	.611	1.062
			48.5	**trials**	99.0 ± 0.253	**trials**	0.143	0.253	49.9	**trials**	99.8 ± 1.383	**trial**	.850	1.382
			48.6		97.2 ± 0.513		0.288	0.522	50.4		100.8 ± 0.692	**s**	.400	.684
	Day-3	50	49		98.0 ± 0.251		0.145	0.253	50.03		100.06 ± 0.96		.201	0.959
			49.1		98.2 ± 0.288		0.161	0.292	49.8		99.6 ± 0.473		.273	.473
			49		98 ± 0.603		0.348	0.600	50.3		100.6 ± 1.387		.800	1.378
	Day-1	50	49		98 ± 0.452		0.260	0.449	50.2		100.4 ± 0.763		.411	.758
			49.1		98.2 ± 0.360	**Intra**	0.208	0.361	50.1		100.2 ± 1.026		.592	1.016
			49.1	**Intra**	98.2 ± 0.351	**day**	0.202	0.350	50.3	**Intra**	100.6 ± 0.665	**Intra**	.384	.658
Method-I I	Day-2	50	49.2	**day**	98.4 ± 0.451	**trials**	0.260	0.451	50.1	**day**	100.2 ± 1.201	**day**	.693	1.196
			49.1	**trials**	98.2 ± 0.360	**Intra**	0.206	0.362	50.1	**trials**	100.2 ± 0.681	**trial**	.393	.678
			49.4		98.8 ± 0.450	**day**	0.260	0.453	50.1		100.2 ± 0.200	**s**	.155	.199
	Day-3	50	49		98 ± 0.556	**trials**	0.321	0.560	49.9		99.8 ± 1.386		.860	1.388
			49.1		98.2 ± 0.360		0.20	0.363	49.8		99.6 ± 0.875		.504	0.873
			49		98 ± 0.341		0.272		50.1		100.2 ± 0.722		.416	.718
	Day-1	50	49.1		98.2 ± 0.350		0.230		49.7		99.4 ± 0.794		.458	.796
			49.2		97.6 ± 0.352	**Intra**	0.264		49.8		99.6 ± 0.793		.458	.804
			49	**Intra**	97.6 ± 0.351	**day**	0.176	0.474	50.4	**Intra**	100.8 ± 1.153	**Intra**	..665	1.156
Method-III	Day-2	50	49	**day**	96.8 ± 0.251	**trials**	0.378	0.402	50.2	**day**	100.4 ± 1.365	**day**	.913	1.575
			49.1	**trials**	99.0 ± 0.253	**Intra**	0.324	0.462	49.8	**trials**	99.6 ± 0.471	**trial**	.788	1.369
			49		97.2 ± 0.513	**day**	0.201	0.307	50.2		100.4 ± 1.22	**s**	.705	1.212
	Day-3	50	49		98.0 ± 0.251	**trials**	0.208	0.661	48.8		99.6 ± 0.757		.437	.754
			49.1		98.2 ± 0.288		0.202	0.562	49.8		99.6 ± 1.150		.664	1.1656

The proposed UV spectrophotometric methods were found to be simple, rapid, accurate, precise and economic. From the above data it was observed that all validation parameters met the predetermined acceptance criteria and validated in terms of linearity, accuracy, precision, reproducibility, robustness, and ruggedness as per the ICH guidelines. Thus it has been concluded that the proposed methods were validated for the analysis of capecitabine in bulk and its formulations.

REFERENCES

1. Brunton LL, Lazo JS, Parker KL. Goodman and Gilman: The pharmacological basis of therapeutics. Edn. 11, McGraw Hill Medical Publishing Division, 2006, pp. 1404-1405.
2. Hirsch BR, Zafar SY. Capecitabine in the management of colorectal cancer. Cancer Manag Res. 2011; 3: 79-89.
3. Walko CM, Lindley C. Capecitabine: a review. Clin Ther. 2005; 27: 23-44.
4. Milano G, Schellens JHM. Pyrimidine antimetabolites. In: Schellens JHM, McLeod HL, Newell DR. eds. Cancer Clinical Pharmacology. Oxford: University Press, 2005; pp. 51-62.
5. Indian Pharmacopoeia, 2010, 2, pp. 972-973.
6. Guichard SM, Mayer I, Jodrell DI. Simultaneous determination of capecitabine and its metabolites by HPLC and mass spectrometry for preclinical and clinical studies. J Chromatogr B. 2005; 826: 232-237.
7. Dhananjeyan MR, Liu J, Bykowski C, Trendel JA, Sarver JG, Andob H, *et al*. Rapid and simultaneous determination of capecitabine and its metabolites in mouse plasma, mouse serum, and in rabbit bile by high-performance liquid chromatography. J Chromatogr A. 2007; 1138(1-2): 101-108.
8. Farkouh A, Ettlinger D, Schueller J, Georgopoulos A, Scheithauer W, Czejka M. A rapid and simple HPLC assay for quantification of capecitabine for drug monitoring purposes. Anticancer Res. 2010; 30: 5207-5212.
9. Piorkowska E, Kaza M, Fitatiuk J, Szlaska I, Pawinski T, Rudzki PJ. Rapid and simplified HPLCUV method with on-line wavelengths switching for determination of capecitabine in human plasma. Pharmazie. 2014; 69: 500-505.
10. Reigner B, Blesch K, Weidekamm E. Clinical pharmacokinetics of capecitabine. Springer Science+, Clin Pharmacokinet. 2001; 40: 85-104.
11. Zufia L, Aldaz A, Giraldez J. Simple determination of capecitabine and its metabolites by liquid chromatography with ultraviolet detection in a single injection. J Chromatogr B. 2004; 809: 51-58.
12. Xu Y, Grem JL. Liquid chromatography–mass spectrometry method for the analysis of the anticancer agent capecitabine and its nucleoside metabolites in human plasma. J Chromatogr B. 2003; 783: 273-285.
13. Siethoff C, Orth M, Ortling A, Brendel E, Redeker WW. Simultaneous determination of capecitabine and its metabolite 5-fluorouracil by column switching and liquid chromatographic/tandem mass spectrometry. J Mass Spect. 2004; 39: 884-889.

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