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Development and Evaluation of Capecitabine Tablets by Core in Cup Method for Pulsatile Delivery

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Abstract

The role of Chronotherapeutics in colon cancer management Instead, it tends to be higher in the early morning hours and lower in the evening hours. The main objective of the present studies reported here was to investigate whether cup in core compression coating could be used to produce tablets providing maximum in-vitro drug release 6 to 8 hours after an evening dose taken at approximately 10:00 pm. The basic idea behind the dosage form development is to investigate effect of coating design on lag time and drug release from directly compressed time-controlled release tablet. The aim of the present study was to design time controlled tablet of capecitabine as Chrono-modulated drug delivery system by compression coating. Formulation design involves coating polymer blend ratio (5% and7.5%, 5% & 7.5%, 5% & 7.5% 5% & 7.5%, 2%, 2%) of Cross Carmellose Sodium, Sodium Starch Glycolate and Cross Povidone, Megnesium stearate which were exploited for their drug release at only one direction ability. The effect of different weight ratio of combination of permeable polymers and gellable polymer, different particle size of Non aqueous polymer in outer shell polymers blend were studied on the drug release behaviour of the time controlled tablet formulation. Coating materials blend were evaluated for micromeritic properties like flow properties, compressibility index, Hausner's ratio and also evaluated the tablet for hardness, thickness, friability, weight variation, water uptake studies. The obtained results showed the capability of the system in delaying drug release for a programmable period of time to attain drug release 6 to 8 hours after an evening dose taken at approximately 10:00 pm according to a time-dependent approach.

Keywords: Compressed coated tablet; Colon cancer, Core in cup Method, Capecitabine and Chrono modulated Drug Delivery.

Contents

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1. Introduction

1.1. Introduction of Circadian Rhythm and Chronotherapy

Circadian rhythms are self-sustaining endogenous oscillations that occur with a period of about 24 hrs. The term circadian is derived from the Latin circa means "about" and dies which can be defined as "a day". Normally circadian rhythms are synchronised according to internal biologic clocks related to the sleeping cycle our circadian rhythm regulates many body functions in human body like metabolism, physiologic behaviour and sleep and hormone production. There are number of conditions which show circadian rhythm pattern and advantage could be taken by timing and adjusting the administration of drugs according to circadian rhythm of the disease. Coordination of Biologic rhythm and medical treatment is called chronotherapy while chronotherapeutics is the discipline concerned with the delivery of drugs according to inheriting activities of a disease over a certain period of time. Chronotherapy is most benefit patients suffer from allergic rhinitis, rheumatoid arthritis, asthma cancer cardio vascular diseases and peptic ulcer diseases [1, 2].

1.1.1. Introduction of Pressed Coating

The press-coated delayed release tablets will be formulated with polymeric coating that is an instance of breaking. The press-coated tablet for pulsatile delivery consists of rapid release core tablet of drug and rapid release of hydrophilic or hydrophobic or synthetic or natural polymers and super disintegrates for modified drug delivery. These including increased patient acceptance, selective pharmacological action to minimise side effects. Pressed coating systems have more therapeutic efficacy. To reach peak plasma concentration we need controlled drug delivery systems and that peak plasma levels within therapeutic range [1, 2]. Pressed pulsatile systems of drug release does not allow for appropriate plasma drug level balance. Dose dependent side effects may cause by 1st order drug releases. Constant quantity of drug to be released over an extended period of time resulting in uniform and sustained drug delivery is should ideally exhibit zero-order drug release kinetics [5, 6].

1.2. Pulsatile Drug Delivery Systems

New trends in drug discovery and development

In this century, the pharmaceutical industry is caught between pressure to keep prices down and the increasing cost of successful drug discovery and development. The average cost and time for the development of a new chemical entity are much higher (app $500 million and 10-12 years) than those required to develop a novel drug delivery system (NDDS or Chr DSS) ($20-$50 million and 3 to 4 years). In the form of an NDDS or ChrDDs, an existing drug molecule can get a new life thereby increasing its market value and competitiveness and extending patent life.**2**

These dosage forms offer many advantages such as:

- Nearly constant drug levels at the site of action.
- Avoidance of undesirable side effects.
- Reduced dose and
- Improved patient compliance.

Diseases targeted for pulsatile technology Diseases presently targeted for chronopharmaceutical formulations are those for which there are enough scientific backgrounds to justify PDDS- compared to the conventional drug administration approach. They include: hypercholesterolemia, asthma, cancer, duodenal ulcer, arthritis, diabetes, neurological disorders, cardiovascular diseases (e.g. hypertension and acute myocardial infarction) and colonic delivery.

2. Materials and Methods

2.1. Materials

Capecitabine received from Chandra labs (hyd), MCC was obtained from Degussa India Pvt. Ltd., Mumbai L.R, Cross povidone, sodium starch glycolate and Cross carmellose Sodium was received from S.D. Fine Chem. Ltd., Mumbai. L.R, HPMC and Ethyle Cellulose was obtained from L.R. Sisco Research Lab.Pvt. Mumbai.

2.2. Methods

a. Free formulation studies:

In these studies such as Tapp density, bulk density and angle of repose etc.

2.3. Formulation Development

Formulation of core tablets by direct compression:

The inner core tablets were prepared by using direct compression method. As shown in Table powder mixtures of Capecitabine, Micro rystalline cellulose (MCC), Cross-carmellose sodium (Ac-Di-Sol), SSG, Crospovidone, ingredients were dry blended for 20 min. Followed by addition of Magnesium Stearate. The mixtures were then further blended for 10 min., 200mg of resultant powder blend was manually compressed using KBr hydraulic press at a pressure of 1 ton, with an 8mm punch and die to obtain the core tablet.

2.3.1. Preparation of press-coated tablets:

The core tablets were press-coated with 400mg of mixed blend/granules as given in Table. 200mg of barrier layer material was weighed and transferred into a 12mm die then the core tablet was placed manually at the centre. The remaining 200mg of the barrier layer materiel was added into the die and compressed at a pressure of 5 tons for 3min using KBr hydraulic press.

2.4. Evaluation of Coated Tablets

Evaluation of rapid release core (RRCT) and press-coated tablets of Capecitabine tablet Weight variation, thick ness, Hard ness, Friability, disintegration and Dissolution are performed.

Disintegration time:

LABINDIA DT 1000 USP disintegration test apparatus. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1 litre beaker containing Distilled water at 37°C ± 1°C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

***In-vitro* Dissolution methods for press-coated tablets:**

In –vitro Dissolution studies of Pulsatile delivery systems was done with the conventional paddle method of press coated tablets were performed at 37 ± 0.5 °C using Distilled water in USP II paddle method at 50 rpm. 5 ml of filtered aliquot was manually withdrawn at pre-determined time intervals and replaced with 5 ml of fresh Distilled water medium maintained at the same temperature. The samples were analysed at 242nm using a UV spectrophotometer. The lag time and percentage release was determined of the each formulation.

2.5. Stability Studies:

The stability study of the formulations was carried out according to ICH guidelines at 40 ± 2o C/75 ± 5 % RH for one month by storing the samples in stability chamber (Lab-care, Mumbai).The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

Table 2.1: Composition of core tablets

S.No	Ingradients	F1	F2	F3	F4	F5	F6	F7	F8
1	Capecitabine (mg)	150	150	150	150	150	150	150	150
2	Cross- Carmellose Sodium	7.5%	-	-	10%	-	-	12.5%	15%
3	Sodium Starch Glycolate	-	7.5%	-	-	10%	-	-	-
4	Cross povidone	-	-	7.5%	-	-	10%	-	-
5	Magnesium stearate	1%	1%	1%	1%	1%	1%	1%	1%
6	Micro crystalline cellulose	QS	QS	QS	QS	QS	QS	QS	QS
	Total wt. (mg)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**

3. Results and Discussion

3.1. Results

3.1.1. Standard Calibration Curve for Capecitabine

Analytical Methods for the Estimation of Capecitabine:

a. Determination of λ_{max} for Capecitabine:

On the basis of preliminary identification test, it was concluded that the drug complied the preliminary identification. From the scanning of drug, it was concluded that the drug had λ max of 242 nm [16].

Table 3.1: Calibration curve data of CAPECITABINE in Distilled water

S. No	Concentration (µg/ml)	Absorbance (nm)
1	0	0
2	4	0.311
3	6	0.467
4	8	0.605
5	10	0.839

Table 3.2: Composition of Press coat tablets

Press coat	F^C1	F^C2	F^C3	F^C4	F^C5	F^C6
HPMC (mg)	30	40	50	30	40	50
EC (mg)	200	200	200	250	250	250
Total wt. (mg)	**230**	**240**	**250**	**280**	**290**	**300**

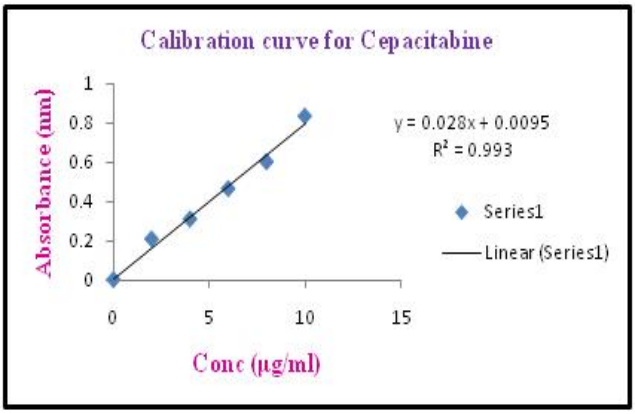

Figure 3.1: Calibration curve of CAPECITABINE in Distilled water

3.1.2. Pre Formulation Parameters

Table : 3.3 Physical Evaluation Parameters for CORE Tablets

Formulations	Angle of Repose (θ)	Loose Bulk Density (g/cc)	Tapped Density (g/cc)	% Compressibility	Hausner'sratio	Flow property
F1	22.6±0.15	0.45±0.045	0.52±0.07	13.4±0.6	1.15±0.05	Very good
F2	24.9±0.15	0.44±0.45	0.52±0.07	15.3±0.6	1.18±0.05	Very good
F3	21.2±0.14	0.45±0.46	0.51±0.06	11.7±0.5	1.13±0.04	Very good
F4	22.5±0.14	0.44±0.44	0.50±0.04	12.0±0.7	1.13±0.06	Very good
F5	21.6±0.15	0.45±0.04	0.52±0.05	13.6±0.6	1.15±0.06	Very good
F6	22.6±0.15	0.43±0.04	0.50±0.06	14.0±0.8	1.16±0.05	Very good

Table: 3.4 Post compression parameters for CORE tablets

S.No	Physical parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	**Weight (mg)**	200	200	198	200	199	202	200	200	198
2	**Hardness (Kg/cm^2)**	4.6	4.5	4.8	4.5	4.5	4.5	4.5	4.8	4.6
3	**Thickness (mm)**	2.4	2.6	2.5	2.5	2.5	2.6	2.5	2.5	2.6
4	**Friability %**	0.4	0.55	0.62	0.54	0.62	0.57	0.4	0.54	0.54
5	**Disintegration time**	2.3 min	3.3 min	28 sec	2.5 min	2.5 min	29 sec	2.3 min	3.4 min	29 sec

3.1.3. Drug content

Ten tablets were weighed individually; these were placed in a mortar and powdered with a pestle. Accurately weighed powder sample equivalent to 20 mg of CPC was transferred into a 20 ml volumetric flask and made up to volume with distilled water. The solution was then filtered, suitably diluted with distilled water and absorbance was measured at 303 nm using Elico SL150 UV-Visible Spectrophotometer (Elico Ltd., Hyderabad).

Table 3.5: Dissolution studies for CORE tablet

Time (min)	Cumulative % Drug Release							
	F1	F2	F3	F4	F5	F6	F7	F8
5	43.49	21.19	43.07	61.71	19.07	44.78	8.21	9.37
10	68.35	45.71	60.21	74.78	20.78	62.78	13.51	12.24
15	70.28	56.66	64.07	87.21	27.42	70.49	13.53	12.29
20	71.14	70.49	69.42	89.57	39.21	77.35	28.56	19.76
30	88.28	81.64	83.35	92.78	51.21	84.42	33.56	22.76
45	89.14	83.57	87.64	95.64	63.64	88.28	43.59	25.89
60	91.92	87.64	89.57	99.28	64.07	91.49	51.77	42.91

Observation:
From the above dissolution study optimized core formulation is **F4**. F7 & F8 formulations are increased % of Disintegrant (CCS) but these are after observation not increasing %Drug release. The super disintegrants increasing their % they will act as fillers.

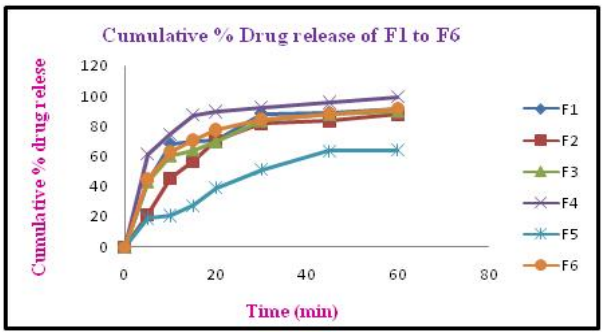

Figure 3.2: Dissolution graph for core formulations F1-F6

Observation: Based on the drug release within the required time period **F4** was optimized and further formulated for press coating.

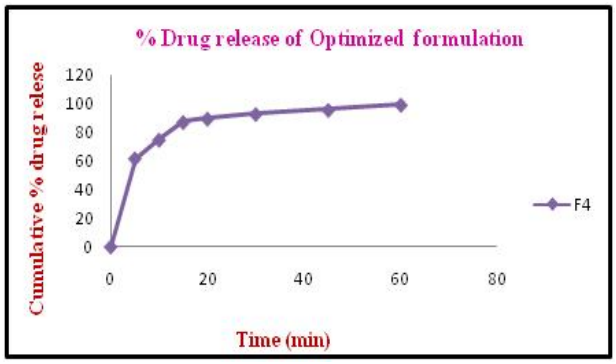

Figure 3.3: Graph for % Drug release of Optimized formulation

Table 3.6: Evaluation Parameters for Press Coated Tablets

S.No	Physical parameter	$1F^C4$	$2F^C4$	$3F^C4$	$4F^C4$	$5F^C4$
1	Weight (mg)	499	500	500	502	499
2	Hardness (Kg/cm^2)	5.5	5.2	6.2	5.2	6.3
3	Thickness (mm)	2.5	2.6	2.4	2.4	2.5
4	Friability %	0.56	0.55	0.62	0.54	0.62
5	Drug content%	99	99	98	99	98

3.1.4. Post compression evaluation parameters:

Table 3.7: Dissolution data for press coated tablets

Time (hrs.)	Cumulative % Drug Release				
	$1F^{C}4$	$2F^{C}4$	$3F^{C}4$	$4F^{C}4$	$5F^{C}4$
1	**1.11**	0.77	3.94	2.01	12.35
2	**1.67**	2.42	4.19	8.59	15.65
3	**1.90**	9.29	5.58	14.25	18.28
4	**2.05**	13.88	5.99	19.56	22.36
5	**2.65**	16.45	87.65	28.65	38.54
6	**9.29**	19.04	88.33	86.86	91.29
7	**28.35**	59.76	98.06	97.52	92.52
8	**97.85**	60.45	98.78	98.75	95.78
9	**99.89**	68.02	99.69	99.28	99.25
10	**99.94**	77.08	99.78	99.42	99.27

From the above core formulations **$1F^{C}4$** was selected for press coat by using different polymers like HPMC, Ethyl cellulose in different ratios among which 1part of HPMC and 5parts of Ethyl cellulose was optimized 99.94% of drug release at 10 hours.

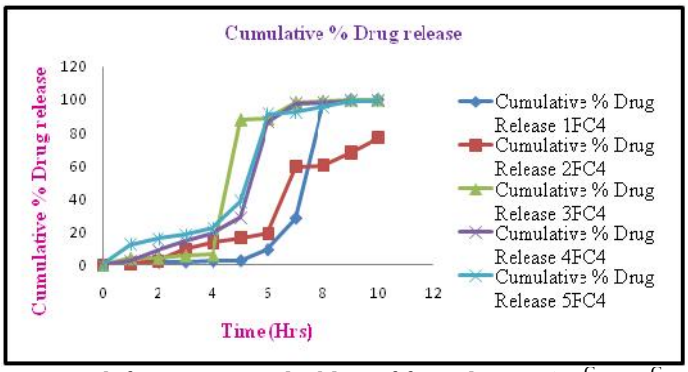

Figure 3.4: Dissolution graph for press coated tablets of formulations ($1F^{C}4$, $2F^{C}4$, $3F^{C}4$, $4F^{C}4$, $5F^{C}4$).

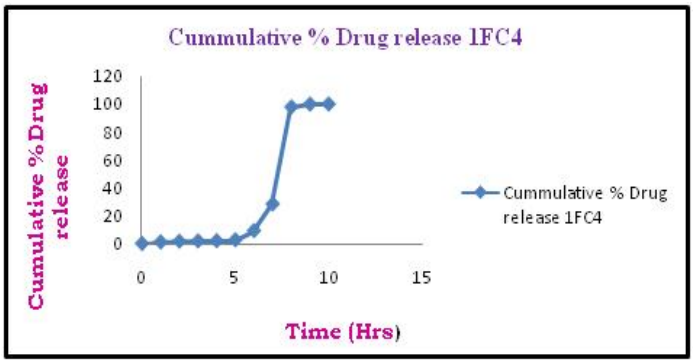

Figure 3.5: Dissolution graph for press coated tablets of formulation $1F^{C}4$

Figure 3.6

A. At the time of cap is opening for drug release.
B. Cap is totally disappearing for drug release.
C. Complete drug release.

3.1.5. FTIR studies:

FTIR studies were carried with a view to evaluate the *in situ* drug and excipient/s compatibility. Figure 3.8 &3.9 shows the IR spectra of pure CPC and CPC with different excipients. Pure CPC showed characteristic IR absorption bands at 1038 cm-1 indicating the presence of C-N group, 1115 cm-1 indicates the presence of C-O-C group in aromatic ring, 1337 cm-1 indicates the presence of C-F group, 1645 cm-1 indicates the presence C=N group, 1707 cm-1 indicates the presence of stretching of C=O group, 3516 cm-1 indicates the presence of bending of N-H group, 3178 cm-1 indicates the presence -OH group.

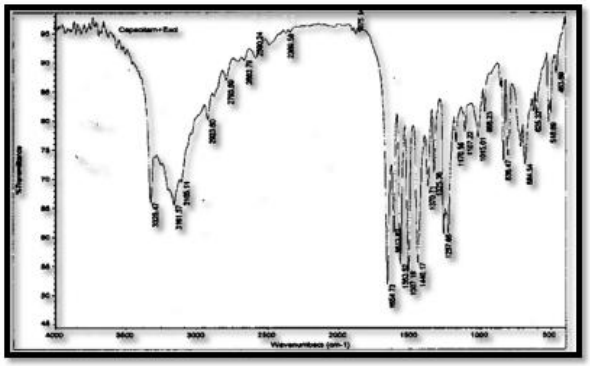

Figure 3.8: FTIR Spectrograph of CAPECITABINE pure

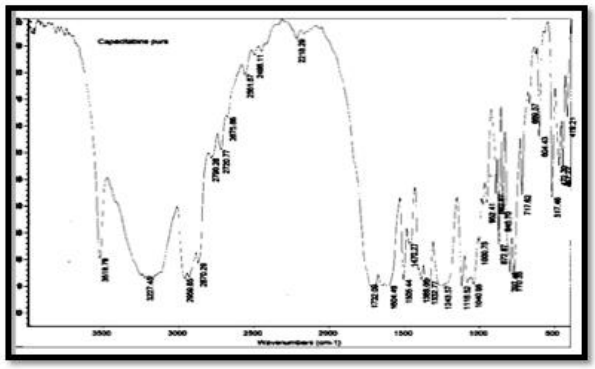

Figure 3.9: FTIR Spectrograph of CAPECITABINE with Exepients

4. Conclusion

A coated PDDS for Capecitabine to mimic the circadian rhythm of the disease by releasing the drug at desired time (based on at the time of symptoms). The system was found to be satisfactory in terms of release of the drug after a predetermined lag time of 6 h and thus the dosage forms can be taken at bedtime so that the content will be released in the morning hours i.e. at the time of symptoms. The release of drug was rapid and complete after the lag time. Lag time can be controlled by adjusting the percent weight gain as well as the super disintegrant concentration.

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