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FORMULATION AND EVALUATION OF CIMETIDINE PRESS COATED TABLETS FOR CHRONOTHERAPEUTIC DRUG DELIVERY

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Abstract:

Since early times daily rhythms in plants and animals have been observed. The leaves of certain plants opened during day and closed at night, showing a clear rhythmicity. Circadian rhythms of behaviour in mammals are known to be robust and precise. The efficacy and toxicity of many drugs vary depending upon the relationship between the dosing schedule and the 24 hour rhythms of biochemical, physiological and behavioural processes. Also several drugs cause alterations to 24 hours rhythms leading to illness and altered homeostatic regulation. The alteration of biological rhythm is a new concept of adverse effects, which can be minimized by optimizing the dosing schedule.They are predictable resonating dynamic systems whom require different amounts of drug at predictably different time within circadian cycle which will maximize desired and minimize undesired drug effects.The aim of the work was to prepare and evaluate of cimetidine press coated tablets for chronotherapeutic drug delivery.

Keywords: *Cimetidine, Press coating , Chronotherapeutic, Drug Delivery*

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INTRODUCTION:

The role of Chronotherapeutic in gastric ulcer management is based on the recognition that ulceration does not remain constant throughout the day. Instead, it tends to be higher in the afternoon and evening hours and lower in the morning hours. The widespread use of ambulatory ulcer monitoring has been instrumental in revealing this pattern of variation, which is mediated by the body's diurnal circadian rhythms, the "internal clock" exhibited by all mammals that regulates patterns of physiologic changes throughout the day. One of the primary functions of the changes in physiologic responses is the arousal propensity in the morning and the sleep requirement after an awake period[1-2].

A dry-coated tablet was recently renewed as a novel system to deliver a drug in a pulsatile way, at predetermined times following oral administration. This novel system is not only rate-controlled but is also time controlled. The dry- coated tablets were prepared by a direct compression method. This compression method eliminates the time-consuming and complicated coating or granulation processes and also improves the stability of the drug by protecting it from moisture[3-4].

The purpose of this study was to develop press coated tablets for chronopharmaceutical drug delivery of Cimetidine. The oral press coated tablet was developed to achieve the time-controlled disintegrating of erodible function with a distinct predetermined lag time. Press-coated tablet containing Cimetidine and other excipients in the inner core was formulated with an outer of permeable polymers Eudragit S-100 and Eudragit L-100.

MATERIALS AND METHODS:

Cimetidine, (Zydus, Mumbai)
Crospovidone, (Molychem, Mumbai).
Microcrystalline Cellulose, (Yarrow Chemicals, Mumbai)
Talc, (Molychem, Mumbai)
Magnesium Stearate, (Molychem, Mumbai)
Eudragit S-100, (Yarrow Chemicals, Mumbai)
Eudragit L-100, (Yarrow Chemicals, Mumbai)

Methods:

Precompression Parameters of Coating Powder Blend and Core Tablet Powder Blend:

Coating powder blend and core tablet powder blend were evaluated for various pre compression parameters such as bulk density, tapped density, angle of repose and compressibility index.

Characterization of Core Tablets:

- **Bulk Density[5]**:

Bulk density (g/cc) was determined by three tap method in a graduated cylinder.

$$\textbf{Bulk Density} = \frac{\textbf{Bulk Volume of the Powder}}{\textbf{Mass of the Powder}}$$

- **Tapped Density[6]**:

Tapped is achieved by mechanically tapping a measuring culinder containing a powder sample.

$$\textbf{Tapped Density} = \frac{\textbf{Mass of Powder}}{\textbf{Tapped Volume of Powder}}$$

- **Angle of Repose[7]**:

Angle of repose was measured by fixed funnel method.

$$\textbf{Tan}\theta = \frac{\textbf{h}}{\textbf{r}}$$

- **Compressibility Index[8]**:

Compressibility index(CI) was determined by measuring the initial volume (V_o) and final volume (V) after hundred tappings of a sample in a measuring cylinder. CI was calculated using equation.

$$\textbf{Compressibility Index(CI)} = \frac{\textbf{vo} - \textbf{v}}{\textbf{vo}} X100$$

- **Drug Content of Core Tablets:**

Tablets were finely powdered and quantity of powder equivalent to 10mg of Cimetidine was accurately weighed and transferred to volumetric flask containing 100ml Phosphate Buffer (pH6.8) and mixed thoroughly. One millilitre of filtrate with suitable dilution was estimated for Cimetidine content at 218nm using Double Beam Spectrophotometer (Analytical Techos T60 UV Double Beam Spectrophotometer, Mumbai).

Preparation of Cimetidine Core Tablets:

The inner core tablet was prepared by direct compression method. The powder mixture of Cimetidine (API), Crospovidone (super disintegrant), Microcrystalline Cellulose (Diluent), Talc (Glidant), Magnesium Stearate (Lubricant) was further blended for 10 minutes. The resulting powder mixture was then compressed into tablets (average tablet weight 350mg) using a Rotary Tablet Machine (Shakthi Pharma TEC.PVT.Ltd.) equipped with 6mm flat punch. The core tablets were evaluated for hardness, weight variation, friability and drug content. The core compositions for one tablet are reported in table 1.

Table No. 1: Core Compositions with Varying Concentrations

Ingredients (mg/tablet)	F1 (mg)	F2 (mg)
Cimetidine	200	200
Crospovidone	17.5	35
Microcrystalline Cellulose	118.5	101
Talc	7	7
Magnesium Stearate	7	7
Total Weight(mg)	350	350

Table No. 2 : Coat Compositions with Varying Concentrations

S.No	Formulations		Coating Material(150mg)	Percent Ratio	Amount Used in Upper and Lower Shell(Mg)
	Code	Coretablet			
1	CD1	F2	Eudragit L-100:Eudragit S-100	100:0	100
2	CD2	F2	Eudragit L-100:Eudragit S-100	75:25	100
3	CD3	F2	Eudragit L-100:Eudragit S-100	50:50	100
4	CD4	F2	Eudragit L-100:Eudragit S-100	25:75	100
5	CD5	F2	Eudragit L-100:Eudragit S-100	0:100	100

Preparation of Press Coated Tablets:
The compositions of the coated materials are given in the table. 2. All the powder mixtures were previously passed through the sieve no. 44. 150mg of the powder mixture was used for the upper hand and lower shell. The press coating of tablets was performed using a rotary tablet machine (Shakthi Pharma TEC.PVT.Ltd. Tablet press). A half amount of the powder was filled into the die to make a powder bed, in the centre of which core tablet was placed manually. Then, the remaining half of the coating material filled in the die, and the contents were compressed under a sufficient compression force, using a flat punch 10mm in diameter.

Evaluation of Core and Press Coated Tablets:

The above core and press coated tablets were evaluated for physical properties like weight variation, hardness, friability.

Hardness:
The hardness of the tablet was determined using a Monsanto Hardness Tester. It is expressed in kg/cm^2.

Friability:
The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage. Ten tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for 4mins. The tablets were weighed again (W_{final}). The % Friability was then calculated by:

$$F = \frac{Winitial - Wfinal}{Wfinal} X\ 100$$

Weight Variation:
Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets less than 250mg is 5.0%.

***In-vitro* Dissolution Studies of Core and Press Coated Tablets:**
The dissolution test for core tablet was performed in triplicate using a Eight-Station USP II (Paddle) Apparatus (Model-Electro Lab, India) at 370c ±0.50c and 100rpm speed. The dissolution studies were carried out in HCl buffer upto 2 hours. At every five minutes interval samples of 5ml were withdrawn from dissolution medium and replaced with fresh medium.

Assayed for the amount of Cimetidine released by a Spectrophotometer (Analytical Techos T60 UV Double Beam Spectrophotometer, Mumbai) at a wavelength of 218nm for HCl buffer. The amounts of drug present in the samples were calculated with the help of appropriate calibration curve constructed from references standard.

RESULTS AND DISCUSSION:

Precompression Parameters of Core Tablets and Coated Material Powder Blend:
Core tablets and coated material powder blend were evaluated for angle of repose, bulk density, tapped density and compressibility index. The values for angle of repose and compressibility index were found to be good correlation indicating that all formulations possess good flow property and compressibility.

Table No. 3: Precompression Parameters of Core Tablet Material Powder Blend.

Formulation	Bulk Density gm/Cm3	Tapped Density	Compressibility Index	Angle of Repose
F1	0.513±0.015	0.615±0.001	15.53±2.19	18.79±0.83
F2	0.446±0.073	0.546±0.019	18.47±2.84	14.67±1.17

Table No 4: Precompression Parameters of Coated Material Powder Blend.

Formulation	Bulk Density gm/Cm3	Tapped Density	Compressibility Index	Angle of Repose
CD1	0.523±0.019	0.772±0.013	16.79±3.47	20.41±1.28
CD2	0.519±0.015	0.617±0.015	15.57±2.19	23.63±1.15
CD3	0.473±0.002	0.537±0.005	12.16±2.17	27.37±0.36
CD4	0.426±0.015	0.456±0.014	7.853±2.47	24.57±0.26
CD5	0.365±0.006	0.437±0.011	15.96±1.65	20.27±0.73

Characterization of Core and Press Coated Tablets:
The core tablets were subjected for weight variation, hardness, friability and percentage drug contents. Weight variation and hardness were found to be within acceptable limit. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. Drug content of core tablets were observed within the range 50-99.0%. The press coated tablets were subjected for weight variation, diameter, hardness and friability. Weight variation and hardness were found to be within acceptable limit (shown in table no. 5 and 6).

Table No. 5: Characterization of Core Tablets

S.No.	Formulation	Weight Variation (Mg)	Hardness (Kg/Cm^3)	Friability (Percent Loss of Weight)	Percent Drug Content
1	F1	99.54±0.37	4.36±0.55	0.15±0.015	98.68±0.72
2	F2	99.75±0.031	4.00±0.03	0.17±0.013	99.25±0.35

Table No. 6: Characterization of Press-Coated Tablets

S.No.	Formulation	Weight Variation	Hardness (Kg/Cm^3)	Friability (Percent Loss of Weight)
1	CD1	294.65±3.55	3.85±0.287	0.11±0.013
2	CD2	295.74±3.48	2.46±0.279	0.13±0.015
3	CD3	298.49±2.59	4.37±0.283	0.14±0.017
4	CD4	298.81±2.37	2.38±0.212	0.16±0.014
5	CD5	298.89±2.04	1.17±0.52	0.17±0.015

***In -Vitro* Dissolution Studies of Core Tablets**:
The effect of crospovidone level on drug release profile from uncoated tablet (formulation F1 and F2) was determined. As amount of crospovidone increases from formulation F1 to F2; the formulation containing highest amount (10%) of crospovidone (F2) showed fast disintegration.

***In-Vitro* Dissolution Studies of Press Coated Tablets:**
Formulations CD1 to CD5 (fig 2) showed increase in lag time and decrease in Cimetidine release rate with increase in weight ratio of Eudragit S-100. When Eudragit L-100, the viscosity of this mixture increases as the ratio increased. Upon contact with dissolution medium, it formed a gel like structure. But due to presence of Eudragit L-100 in greater amount in CD1 the gel formed is not capable enough to hold drug for long time, instead started to erode and allow dissolution medium to penetrate into the core tablet and there was bursting effect. In the case CD2, the lag time was 8 hours, after 8 hours there was sudden release of large quantity of drug, which can show therapeutic effect at the time at which the blood pressure in the patients will be increased. In the case of CD3, CD4 and CD5, the lag time was more than 10 hours, and they were not appropriate for Chronotherapeutic drug delivery. Therefore Eudragit L-100: Eudragit S-100 in the ratio of 75:25 is ideal for the Chronotherapeutic drug delivery with appropriate lag time and complete release of drug within 10 hours.

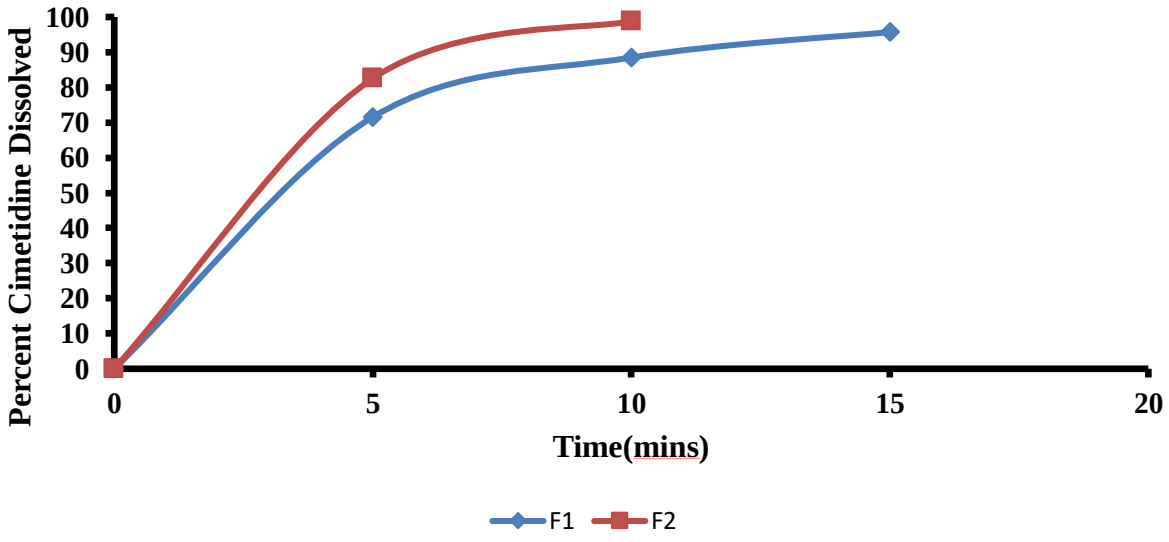

Fig: 1 Dissolution Profiles of Core Tablets (F1,F2)

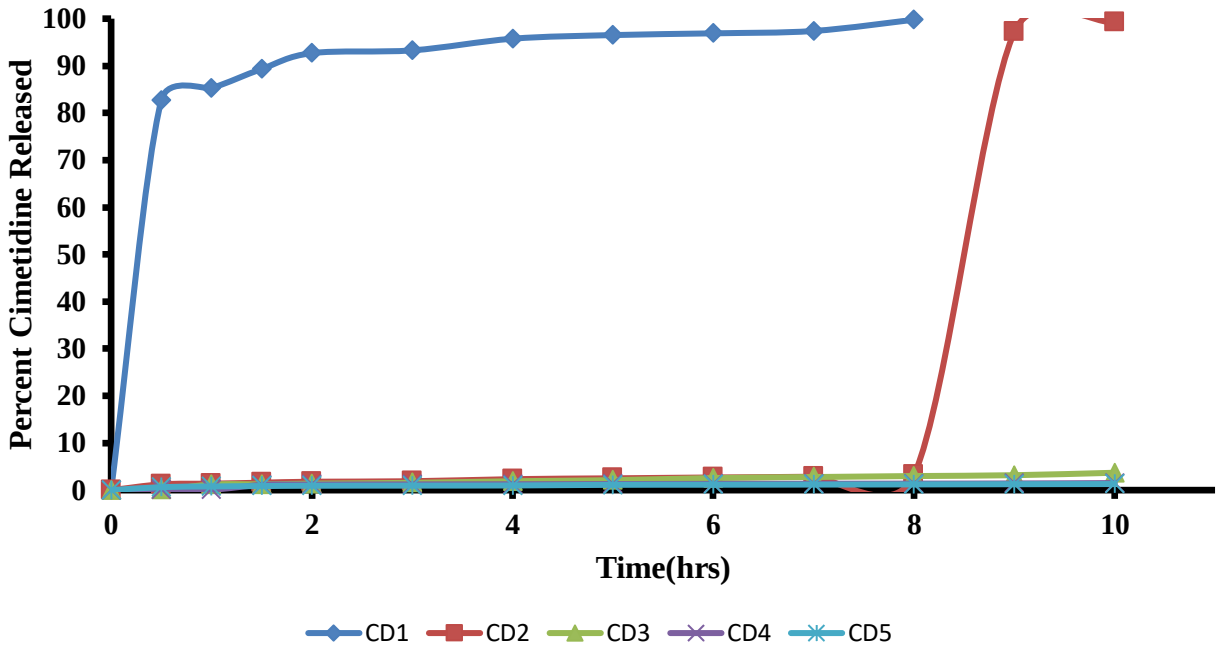

Fig: 2 Release Profiles of Press Coated Tablets (CD1-CD5)

CONCLUSION:

Press coated tablets of Cimetidine utilizing Eudragit L-100, Eudragit S-100 in the ratio of 75:25 displayed timed release dissolution i.e., a lag phase was observed in the dissolution profile and the drug was released rapidly after complete erosion of the outer coating. Therefore, Eudragit L-100 and Eudragit S-100 in the ratio of 75:25 can be used for press coating of the cimetidine chronotherapeutic timed release tablets.

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