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Research Article

FORMULATION AND EVALUATION OF NON EFFERVESCENT FLOATING TABLETS OF CIMETIDINE EMPLOYING OZOKERITE WAX

C. Haranath[1]*, J. Raveendra reddy[1] and N. Devanna[2]

[1]Raghavendra Institute of Pharmaceutical Education and Research, Ananthapuramu, Andhra Pradesh, India.
[2]Head of Department of Chemistry, JNTUA College of Engineering, Ananthapuramu, Andhra Pradesh, India.

ABSTRACT

Non effervescent floating tablets were prepared with different ratios of drug-wax. Water soluble channeling agent lactose was added along with Ozokerite wax in order to study the drug release. Pure drug and optimized formulation FCDO16 were subjected to the drug excipient compatibility studies using FTIR and DSC. The studies revealed that there is no interaction between the drug and excipients. Four formulations were prepared using Ozokerite wax and lactose (FCDO1-FCDO4), it was clearly observed that the drug release was only 16%, 22%, 26% and 32% respectively at the end of 12hr. Therefore in order to increase the drug release different types of superdisintegrants of different categories were chosen along with HPMC K15M as matrixing agent which protects the channels formed by lactose. Superdisintegrants gives the initial startup to the drug release. The super disintegrants acts as a swelling agent by adsorbing large amounts of aqueous fluids and swells. Among the various super disintegrants tested, reduced lag times were obtained with crospovidone, when compared to others. Complete drug release was observed by the end of 12 h for formulation FCDO16 due to the optimized concentration of Ozokerite wax and lactose. Hence the FCDO16 formulation was considered as best formulation. The drug release kinetics revealed that formulation FCDO16 follows zero order kinetics and the mechanism was nonfickian.

Kevwords: Cimetidine. Ozokerite wax. HPMCK15M. Lactose. Non effervescent tablets.

INTRODUCTION

Cimetidine (CD) was used as model drug. It is an H2-antihistaminic drug that has been widely used in treating gastric and duodenal ulceration and also in Zollinger Ellison syndrome and reflux esophagitis. It is poorly absorbed and has a short elimination half life (2 h). The objective of the present study was to develop non effervescent floating Tablets of CD in order to achieve an extended retention in the upper GIT (1-7), which may result in enhanced absorption and thereby improved bioavailability. The prepared tablets were evaluated for *in vitro* drug release and buoyancy. The effect of various formulation variables on drug release was investigated.

EXPERIMENTAL

MATERIALS

Cimetidine was obtained as gift sample from Dr. Reddy's lab, India. Ozokerite, HPMC K15M, Lactose, Magnesium Stearate and Talc were obtained from Signet chemicals, Mumbai, India.

Development of calibration curve of Cimetidine

Standard solution

Accurately weighed 50 mg of Cimetidine was dissolved in 50 ml of pH 1.2 hydrochloric acid buffer to get a solution containing 1000 µg/ml of drug.

Scanning

From the standard solution, a solution was prepared to give a concentration of 10 µg/ml in pH 1.2 hydrochloric acid buffer and UV scan was taken between the wavelengths of 200-400 nm. The spectrum is reported in the figure 1. The absorption maxima of 274 nm was selected and utilized for further studies.

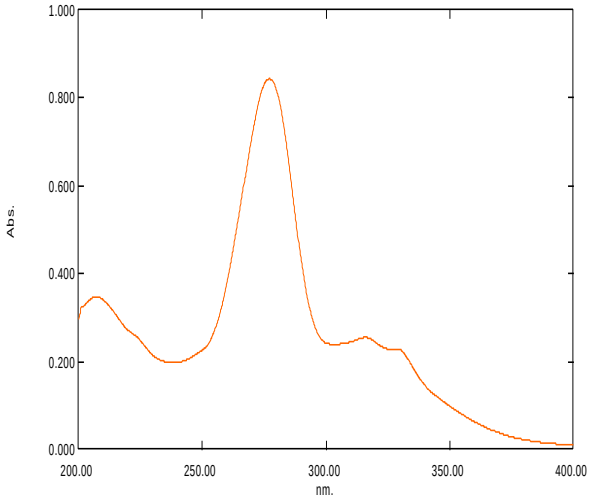


Fig. 1: UV-Spectra of Cimetidine in pH 1.2 hydrochloric acid buffer

Standard Plot

From the standard solution, a stock solution was prepared to give a concentration of 10 µg/ml in pH 1.2 Hydrochloric acid buffers. Different concentrations of Cimetidine were prepared and the absorbance of prepared solutions of Cimetidine in pH 1.2 buffer were measured at 274 nm spectrophotometrically against pH 1.2 buffer as blank. Standard plot data of Cimetidine is reported in table 1 and graph in figure 2.

Table 1: Standard plot data for cimetidine in pH 1.2 hydrochloric acid buffer

Concentration (µg/ml)	Absorbance at 274 nm (Mean ± S.D*)
1	0.247 ± 0.21
2	0.477 ± 0.36
3	0.682 ± 0.20
4	0.844± 0. 30
5	0.995 ± 0.35

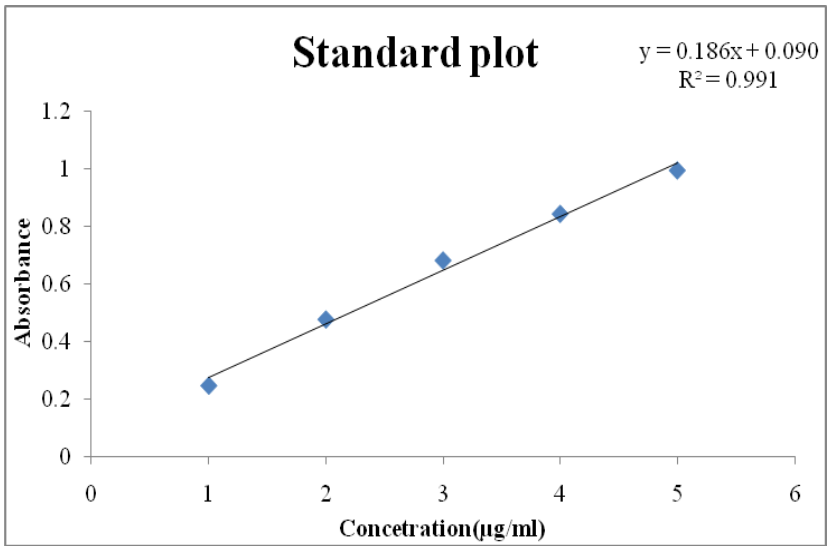


Fig. 2: Standard plot of Cimetidine

Table 2: Preformulation studies for the raw materials

Contents	Bulk density[a] (gm/ml)	Tapped density[a] (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose[a] (θ)
Cimetidine	0.426	0.624	17.84	1.26	27.46
HPMCK15M	0.498	0.554	19.56	1.11	26.32
Lactose	0.74	0.888	13.22	1.14	16.32
Magnesium stearate	0.456	0.651	15.23	1.17	26.21

PREPARATION OF FLOATING TABLETS

Preparation of Floating tablets

The Floating tablets containing CD as drug were prepared by direct compression technique (8) using Ozokerite wax as floating enhancer and HPMC as matrix former. SSG, CP and CCS as superdisintegrants were used along with lactose as chanelling agent to study the effect on drug release. The compositions of various Non effervescent (9, 10) Floating tablet formulations were given in the tables 4 and 5.

Method of Preparation

The formulations prepared are shown in tables 4 and 5 together with their compositions. The drug, diluent and other excipients were screened through # 40 and pre blended using a lab scale double cone blender. The lubricant was added and the blend was mixed again prior to compression. The tablet blends were directly compressed by using a Elite 10 station minipress with 12mm punches. All the Floating tablets prepared were further evaluated for physical parameters such as weight uniformity, hardness, friability and uniformity of drug content.

Floating lag time and floating time

The time taken by the tablet to emerge on to the surface of the liquid (floating lag time) after adding to the dissolution medium was measured using stopwatch and given in table 8.

Fourier transform infrared spectroscopy (FT-IR)

CD and optimized Floating tablet formulation FCDO16 were subjected to FT-IR spectroscopic analysis, to ascertain whether there is any interaction between the drug and other excipients used. The obtained spectra are given in figures 3, 4. Characteristic peaks of CD were compared with the peaks obtained for its Floating tablet formulation FCDO16. The data for the same is given in table 3.

Table 3: FT-IR spectral data of Cimetidine and Floating tablet formulation

Functional groups	Frequency of pure drug (cm^{-1})	Frequency of formulation FCDO16 (cm^{-1})
CN Stretching	2204	2198
C-S	690	697
N-H Stretching (2^0 Amine)	3350	3420
N-H Stretching	3200	3347
C=N Stretching	1580	1587
C=C Stretching	1450	1460

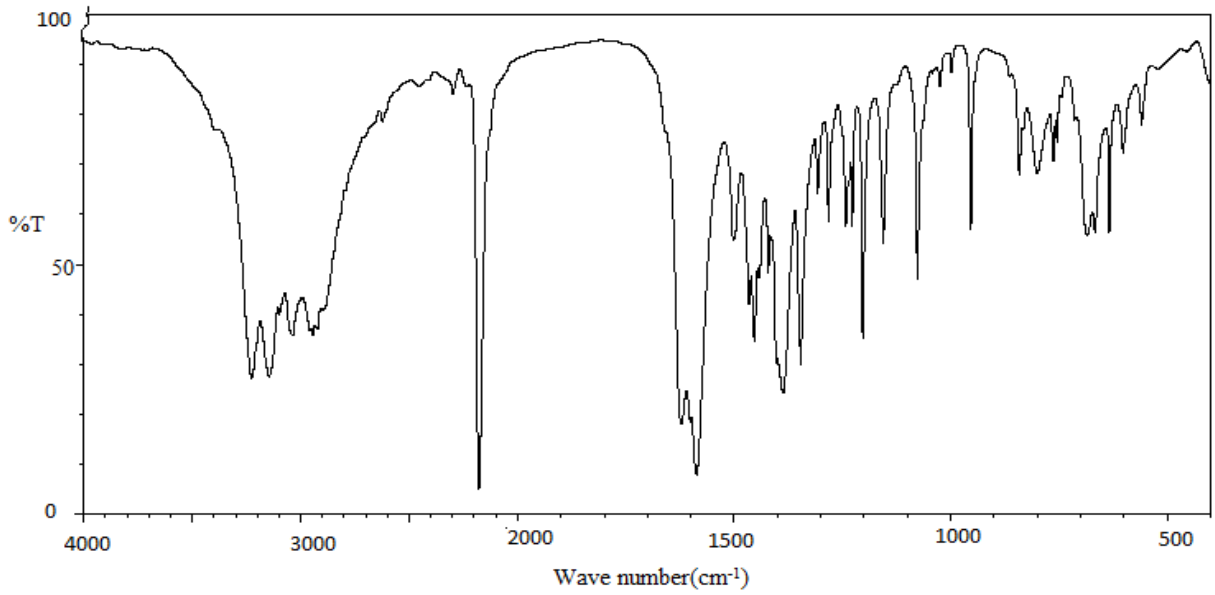


Fig. 3: FTIR of Cimetidine Pure drug

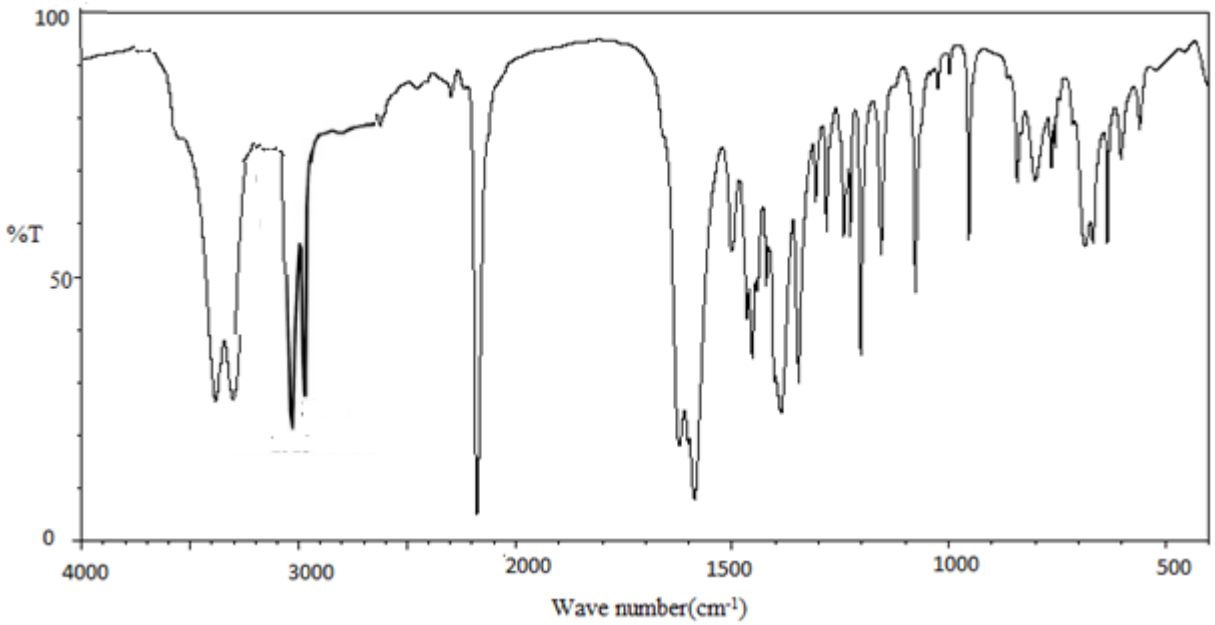
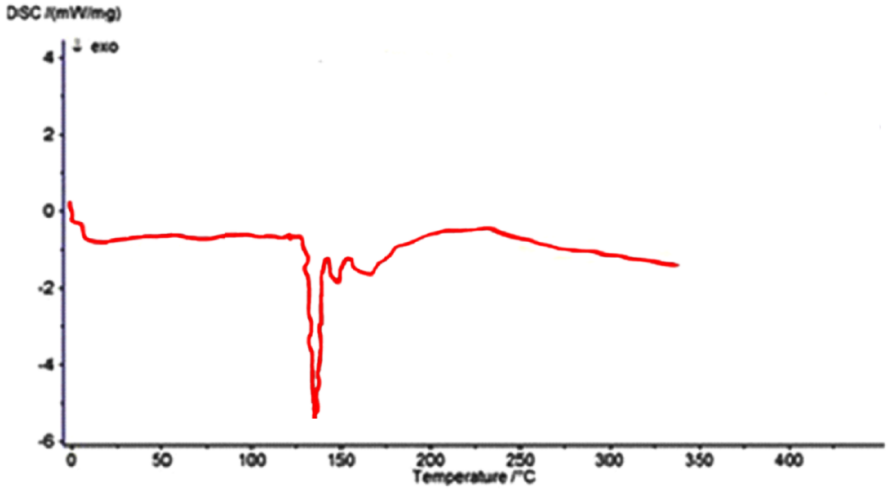


Fig. 4: FTIR of Cimetidine Optimized Formulation

Differential scanning calorimetry (DSC)

DSC studies were carried out for Cimetidine and formulation FCDO16 and the thermograms obtained are presented in figure 5. Thermogram of pure drug showed a sharp endothermic peak at 141^{o}C, which corresponds to its melting point. Floating tablet formulation FCDO16 also showed endothermic peak at 141^{o}C, which corresponds to the melting point of the drug. The evaluation of thermograms revealed no interaction between the drug and the excipients. From the thermograms shown in figure, it was evident that the melting point of Cimetidine has not changed after it was formulated as a Floating tablet.



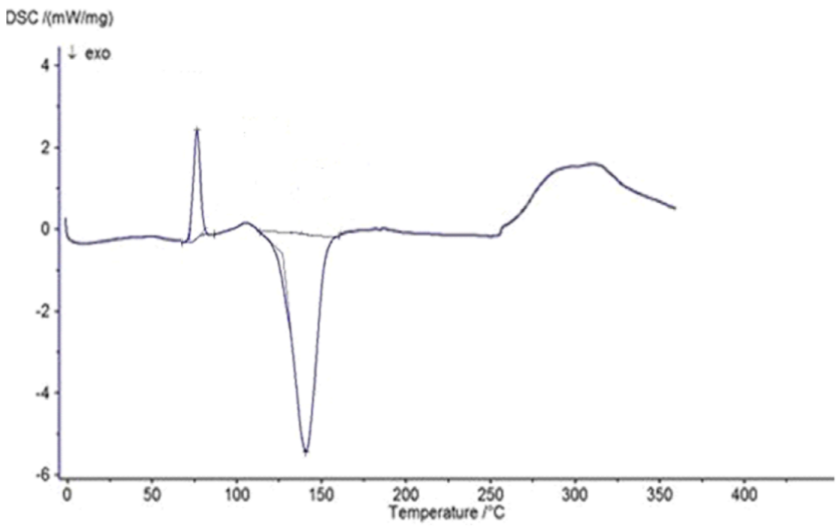


Fig. 5: DSC thermogram of pure Drug, Optimized formulation

Table 4: Composition of Cimetidine (200 mg) Floating Tablets

Ingredients [mg/tablet]	FORMULATIONS			
	FCDO1	FCDO2	FCDO3	FCDO4
Cimetidine	200	200	200	200
Ozokerite	100	75	50	25
Lactose	25	50	75	100
Magnesium stearate	5	5	5	5
Talc	5	5	5	5
Total wt of tablet (mg)	330	330	330	330

Table 5: Composition of Cimetidine (200 mg) Floating Tablets

Ingredients [mg/tablet]	FORMULATIONS											
	FCDO5	FCDO6	FCDO7	FCDO8	FCDO9	FCDO10	FCDO11	FCDO12	FCDO13	FCDO14	FCDO15	FCDO16
Cimetidine	200	200	200	200	200	200	200	200	200	200	200	200
Ozokerite	100	75	50	25	100	75	50	25	100	75	50	25
HPMC K15M	25	25	25	25	25	25	25	25	25	25	25	25
Lactose	25	50	75	100	25	50	75	100	25	50	75	100
SSG	10	10	10	10	-	-	-	-	-	-	-	-
CCS	-	-	-	-	10	10	10	10	-	-	-	-
CP	-	-	-	-	-	-	-	-	10	10	10	10
Magnesium stearate	5	5	5	5	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Total wt of tablet (mg)	370	370	370	370	370	370	370	370	370	370	370	370

Table 6: Pre compression parameters of the prepared formulations

Formulation	Bulk density[a] (gm/ml)	Tapped density[a] (gm/ml)	Compressibility index (%)	Hausner's ratio	Angle of repose[a] (θ)
FCDO1	0.45	0.53	14.32	1.17	23.46
FCDO2	0.47	0.52	14.54	1.10	22.43
FCDO3	0.46	0.54	15.31	1.17	23.35
FCDO4	0.47	0.51	14.01	1.08	25.35
FCDO5	0.46	0.55	13.33	1.19	23.35
FCDO6	0.59	0.64	14.36	1.08	22.64
FCDO7	0.49	0.52	12.23	1.06	26.40
FCDO8	0.51	0.58	13.04	1.13	23.42
FCDO9	0.53	0.59	15.23	1.11	22.47
FCDO10	0.42	0.48	14.25	1.14	23.12
FCDO11	0.49	0.55	15.10	1.12	22.33
FCDO12	0.43	0.50	11.62	1.16	26.41
FCDO13	0.54	0.60	13.43	1.11	22.42
FCDO14	0.53	0.61	14.85	1.15	25.23
FCDO15	0.55	0.60	13.85	1.09	22.34
FCDO16	0.56	0.61	13.23	1.08	24.20

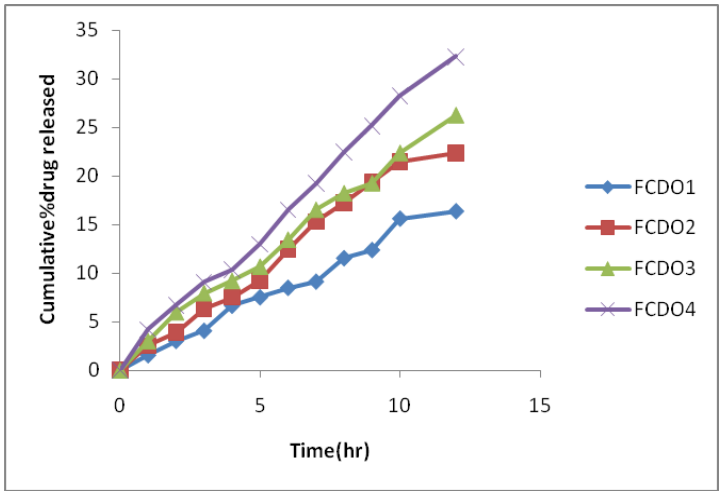
a= (n=3)

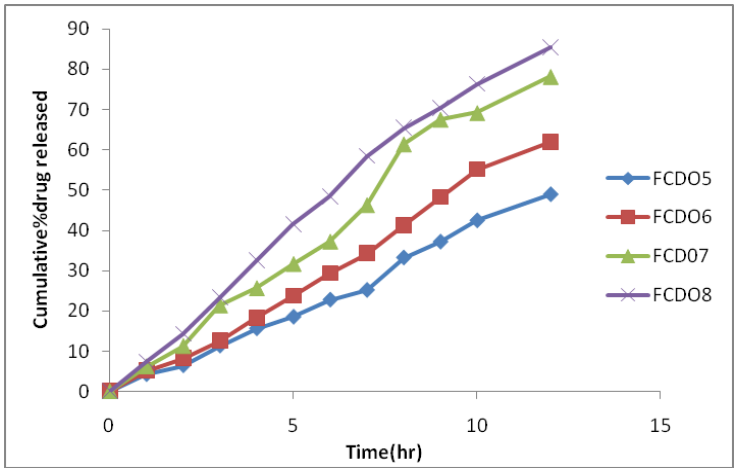
Table 7: Weight Variation, Hardness, Friability, Thickness and Drug Content of Cimetidine Floating Tablets

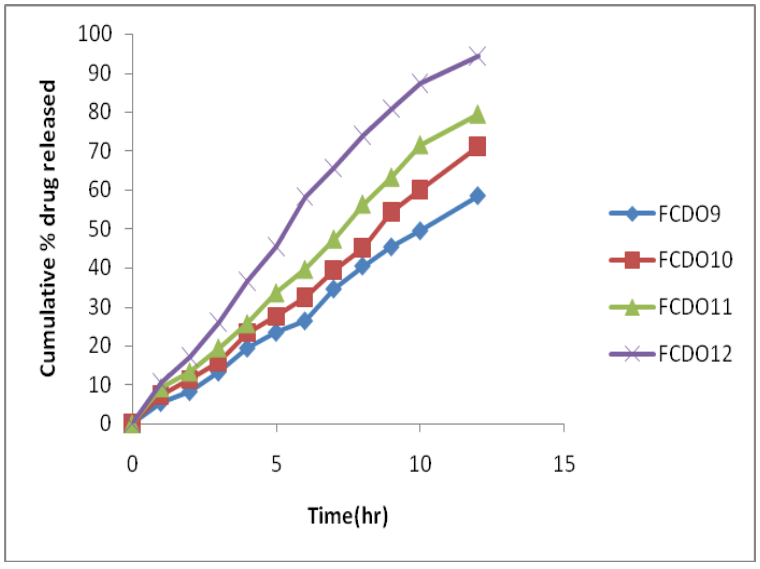
	Weight Variation	Friability (%)	Hardness (Kg/Cm^2)	Thickness (mm)	Cimetidine (%)
FCDO1	329±0.11	0.22 ± 0.61	4.9 ± 0.22	3.6	94.54 ± 0.25
FCDO2	329±0.36	0.25± 0.45	4.3 ± 0.45	3.4	95.22 ± 0.34
FCDO3	328±0.44	0.29 ± 0.36	4.2 ± 0.33	3.7	97.30 ± 0.61
FCDO4	328±0.66	0.45 ± 0.18	4.9 ± 0.44	3.6	99.25 ± 0.23
FCDO5	369±0.07	0.19 ± 0.21	4.5 ± 0.20	3.4	99.63± 0.21
FCDO6	369±0.31	0.14 ± 0.29	3.9 ± 0.23	3.5	99.12 ± 0.61
FCDO7	370±0.24	0.35 ± 0.42	4.0 ± 0.27	3.8	97.45 ± 0.22
FCDO8	370±0.51	0.49 ± 0.56	4.4± 0.45	3.7	99.19 ± 0.49
FCDO9	369±0.33	0.63± 0.07	4.6 ± 0.33	3.3	96.22 ± 0.19
FCDO10	369±0.12	0.77 ± 0.84	4.2 ± 0.47	3.3	97.30 ± 0.42
FCDO11	370±0.16	0.60 ± 0.12	4.8 ± 0.58	3.4	99.42 ± 0.17
FCDO12	369±0.43	0.18 ± 0.24	4.3± 0.61	3.2	96.37 ± 0.20
FCDO13	369±0.61	0.30 ± 0.36	4.7± 0.51	3.4	98.19 ± 0.44
FCDO14	369±0.28	0.48 ± 0.66	4.3 ± 0.25	3.5	98.33 ± 0.47
FCDO15	369±0.45	0.72 ± 0.16	4.6 ± 0.49	3.2	99.24 ± 0.39
FCDO16	370±0.16	0.23 ± 0.29	4.5 ± 0.14	3.3	99.61 ± 0.20

Table 8: Floating characteristics of Cimetidine tablets

Formulation Code	Floating lag time (sec)	Duration of floating (hrs)	Swelling Index at end of 12hr
FCDO5	292	12	23.5±0.57
FCDO6	283	12	25.37±0.36
FCDO7	279	12	27.32±0.21
FCDO8	275	12	29.25±0.49
FCDO9	254	12	33.0±0.24
FCDO10	232	12	35.3±0.27
FCDO11	225	12	38.13±0.42
FCDO12	221	12	39.2±0.51
FCDO13	190	12	46.3±0.69
FCDO14	180	12	51.21±0.23
FCDO15	169	12	52.0±0.45
FCDO16	155	12	53.22±0.51


Cumulative%drug released
Time(hr)
FCDO1
FCDO2
FCDO3
FCDO4


Cumulative%drug released
Time(hr)
FCDO5
FCDO6
FCD07
FCDO8


Cumulative % drug released
Time(hr)
FCDO9
FCDO10
FCDO11
FCDO12

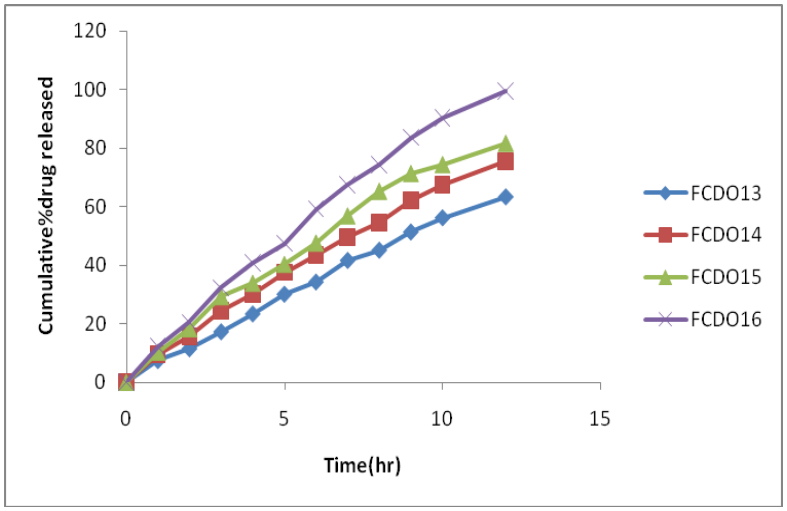
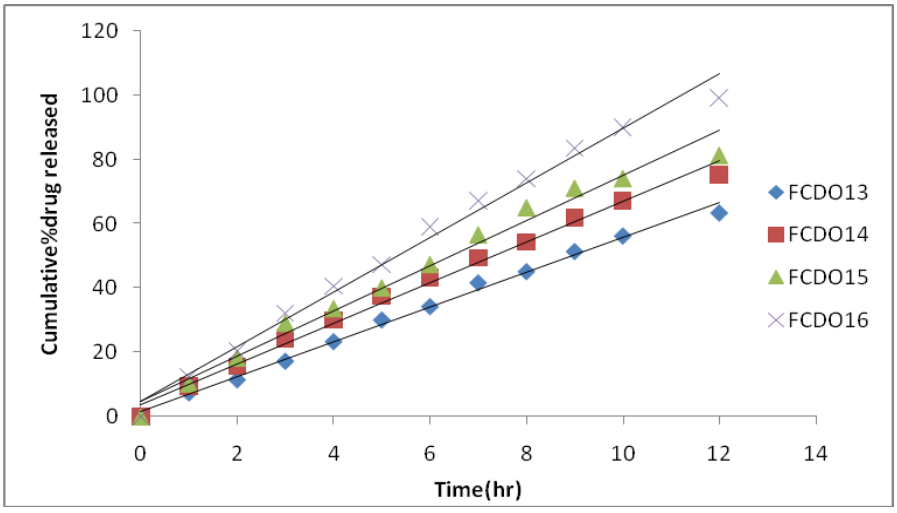
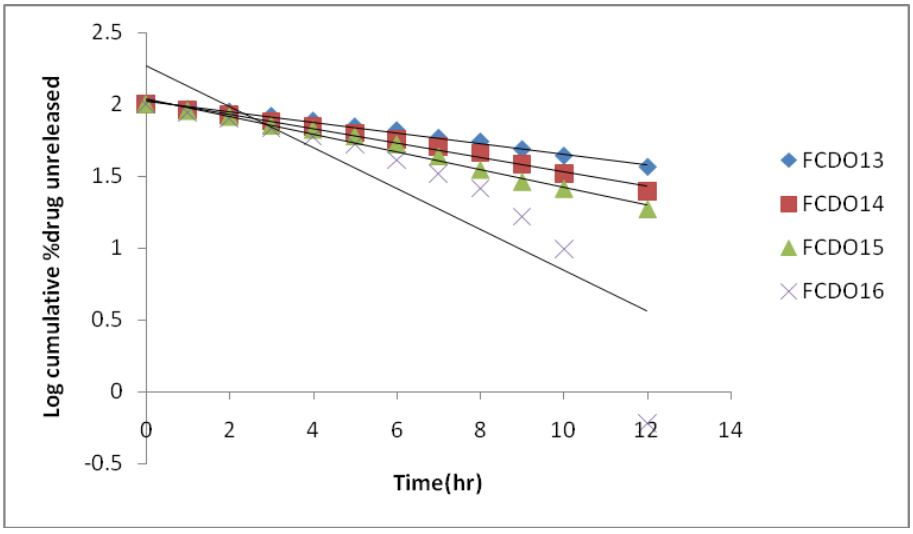
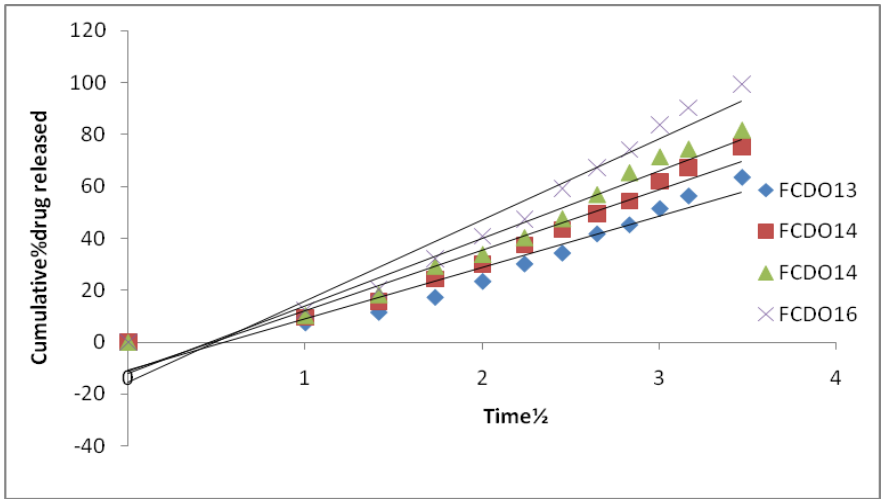


Fig. 6: Cumulative % drug released Vs Time







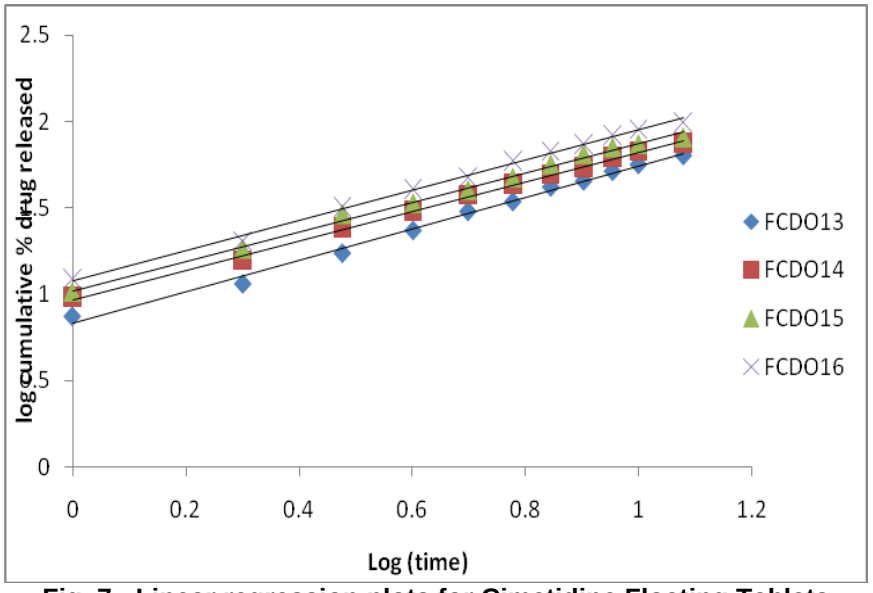


Fig. 7: Linear regression plots for Cimetidine Floating Tablets
(a) Zero order plot, (b) First order plot (c) Higuchi plot and (d) Peppas plot

Table 9: Correlation Coefficient (r^2) Values in the Analysis of Release Data of Cimetidine floating Tablets using crospovidone

Formulation	Correlation Coefficient (r^2) Values				
	Zero order	First order	Higuchi's	Peppas's	
				r^2	n
FCDO13	0.995	0.991	0.934	0.993	>0.89
FCDO14	0.992	0.985	0.95	0.998	>0.89
FCDO15	0.989	0.757	0.951	0.995	0.87
FCDO16	0.983	0.982	0.949	0.997	0.85

RESULTS AND DISCUSSION

Cimetidine non effervescent floating tablets were prepared with different ratios of drug-wax. Water soluble channeling agent lactose was added along with Ozokerite wax in order to study the drug release. Pure drug and optimized formulation FCDO16 were subjected to the drug excipient compatibility studies using FTIR and DSC. The studies revealed that there is no interaction between the drug and excipients.

Precompression parameters such as bulk density, tapped density, angle of repose, hausners ratio were performed to all the formulations and were found to be in the acceptable limits which ensure the good flow properties.

Four formulations were prepared using Ozokerite wax and lactose (FCDO1-FCDO4), it was clearly observed that the drug release was only 16%, 22%, 26% and 32% respectively at the end of 12hr. Therefore in order to increase the drug release 3 different types of superdisintegrants of different categories were chosen along with HPMC K15M as matrixing agent which protects the channels formed by lactose. Superdisintegrants gives the initial startup to the drug release. The super disintegrant acts as a swelling agent by adsorbing large amounts of aqueous fluids and swells.

The effect of type of super disintegrant on lag time is shown in Table8. Among the various super disintegrants tested, reduced lag times were obtained with crospovidone, as it exhibits high capillary activity and pronounced hydration capacity with little tendency to gel formation when compared to others. Complete drug release (99.4%) was observed by the end of 12 h for formulation FCDO16 due to the optimized concentration of Ozokerite wax and lactose. Other formulations with varying concentrations of waxes, lactose shown drug release up to 12hr but the drug release was not maximum. Hence the FCDO16 formulation was considered as best formulation. The floating lag time of optimized formulation FCDO16 was found to be 155sec and the percentage of drug release at the end of 12 hours was found to be 99.40%. The drug release kinetics revealed that formulation FCDO16 follows zero order kinetics and the mechanism was nonfickian.

CONCLUSION

The non effervescent floating tablets of Cimetidine were successfully prepared by direct compression method. Among all the formulations, FCDO16 was considered to be most promising for controlled release of Cimetidine upto 12 hours when compared with other formulations.

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