International Journal of Pharmaceutical Research and Development (IJPRD)
Platform for Pharmaceutical Researches & Ideas
www.ijprd.com

DESIGN AND EVALUATION OF ETHOCEL COATED ENTERIC SUSTAINED RELEASE FORMULATIONS OF ZALCITABINE

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ABSTRACT

The project was undertaken with an aim to formulate and evaluate Zalcitabine Enteric coated sustained release tablet using different polymers as release retarding agent and to overcome the gastric juice incompatibility. Preformulation study was done initially and the results were directed for the further course of formulation. Based on preformulation studies, different batches of Zalcitabine were prepared using selected excipients. Granules were evaluated for tests such as loss on drying, bulk density, tapped density, compressibility index, and Hausner ratio before tablet punching. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables.

The results attained shows that the formulation of sustained release tablet of Zalcitabine (formulation batch F6) containing 20 % of Ethyl cellulose Std 100 P, MCC and povidone, is an ideal formulation of Enteric coated sustained release tablets for 12 hour release as it fulfills all the requirements of a sustained release tablet.

KEYWORDS : *Ethocel Std100 FP, Ethocel Med 70P, Ethocel Med 50P, Zalcitabine.*

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INTRODUCTION

An ideal drug delivery system should be able to deliver an adequate amount of drug for an extended period of time for its optimum therapeutic activity[1,2,3,6]. Most drugs are inherently not long lasting in the body and require multiple daily dosing to achieve the desired blood concentration to produce therapeutic activity[1,3,5,7].

To overcome such problems greater attention has been focused on sustained release drug delivery system[9]. Conventional dosage form has to be administered several times to produce therapeutic efficacy, which yields fluctuations in plasma level[4,8,11]. Repetitive dosing of drug causes poor compliance among the patients. Sustained release formulations can be utilized to avoid repetitive dosing of drugs in a day[9,10,11].

Few drugs like Zalcitabine were found to be incompatible with gastric juice and hence to overcome this incompatibility the drug is coated with the enteric coat. And also drug concentrations could be possibly controlled within the narrow therapeutic range by the use of sustained release systems, which will minimize the severity of side effects[18].

Since the drug has biological half-life of 2hrs, the administration of drug 6 times per day for acute and sub-acute conditions, the bioavailability attained is 35-54[18]. The objective of the present study is to develop competitive enteric sustained release tablets of Zalcitabine, by wet granulation method using different polymers and to study the effect of polymers on their release pattern.

MATERIALS AND METHODS

Materials

Zalcitabine was a gift sample from Dr.Reddy's Laboratories Ltd, Hyderabad, Ethocel Std 100FP, Ethocel Med 70P and Ethocel Med 50P were purchased from Dr.Reddy's Laboratories Ltd. All other chemicals or ingredients used in this study were either analytical or pharmaceutical grade.

Methods

The Enteric coated sustained release tablet of Zalcitabine was prepared by wet granulation method, using various concentrations of Ethocel Std100FP, Ethocel Ethocel Med 70P, Ethocel Med50P (Table 1).Ethyl cellulose, Microcrystalline cellulose, povidone were passed through #40 mesh and added to the above granular material and blended for 5 min and prepared to a damp mass and finally passed through #24 mesh and allowed to dry at 40˚C, Magnesium stearate and aerosil were passed through #60 mesh and added to the above blended material. The blend was compressed into tablets with punch size of 20 x 7mm. Tablets were taken in a coating pan and coating has been performed.

Formulation of Zalcitabine Enteric Coated Sustained release tablets

Table No.1: Composition of all Formulations F1-F9.

S.No	INGREDIENTS	Quantity per Tab (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zalcitabine	100	100	100	100	100	100	100	100	100
2.	Ethocel Std 100FP	-	-	-	16	24	32	-	-	-
3.	Ethocel Med 70P	16	24	32	-	-	-	-	-	-
4.	Ethocel Med 50P	-	-	-	-	-	-	16	24	32
5.	MCC	26	18	10	26	18	10	26	18	10
6.	Povidone	10	10	10	10	10	10	10	10	10
7.	Aerosil	6	6	6	6	6	6	6	6	6
8.	Mg Stearate	2	2	2	2	2	2	2	2	2

Table No. 2. Coating solution contents

INGREDIENTS	%USED
Eudragit L100	20%
Diethylpthalate (to polymer)	6%
Isopropyl alcohol	q.s.

Evaluation of Matrix Tablets

Dimensions

The dimensions (diameter and thickness) were determined to lie within ± 0.01 mm by using digital vernier calipers.

Hardness

The hardness of the tablets was determined by using Monsanto type hardness tester. For adequate mechanical stability 4-5 kgs/tablet hardness is required. Determinations were made in triplicate.

Uniformity of weight

In each batch all tablets were in uniform weight and the weight variation has lied within the limits. The weights determined by using digital weighing balance (Shimadzu) found to be within ±1mg. And the weight control was based on a sample of 20 tablets.

Friability

The friability of the tablets was measured by Roche friabilator (Campbell Electronics, Mumbai, India). Tablets of known weight (Wo) were rotated for fixed revolutions (100 revolutions) and reweighed to determine the weight loss. Loss in weight of tablet was measured by % friability and calculated by using the equation,

$$F (\%) = [1-Wo/W] X100$$

Determination of drug content

Three tablets were powdered and the weight equivalent to one tablet (160mg) was transferred to 100ml volumetric flask containing distilled water. For ensuring complete solubility sonication was done for 30 min. Solution was suitably diluted and the absorbance was determined by UV-Visible spectrophotometer at 248nm.

Drug Excipient Compatibility Studies

To study the Zalcitabine compatibility with different formulation excipients Differential scanning calorimetry (DSC) was performed. DSC studies were conducted on samples of Zalcitabine pure drug, solid admixture of DS+Ethocel Std 100FP, DS+Ethocel Med70P, DS+Etocel 50P.

These studies were performed using a DSC (diamond, Mettler star). Indium/zinc standards were used to calibrate the temperature and enthalpy scale. Accurately weighed 5-6 mg samples were hermetically sealed in aluminum pans and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C and inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

In vitro drug release studies

In vitro drug release studies of matrix tablets was performed in eight-station USP XXII type1 dissolution test apparatus(Electro lab TDT-08, India) at 37°C (± 0.5°C), 100 rpm speed in 900mL of distilled water. 5ml samples were taken by filtration at predetermined time intervals and after each sampling the volume of dissolution medium was replaced with 5ml of fresh distilled water. The absorbance of samples was measured at 248nm using UV-Visible double beam spectrophotometer (Elico SL 164 India) and cumulative percentage drug release was calculated.

Determination of Theoretical Release profile & Similarity factor

The theoretical release profile of a drug is constructed to check whether the formulations are releasing the drug similar to the predicted profile. Theoretical release profile of a drug is plotted on basis of the loading dose and the drug availability rate [12].

$$D_t = \text{Dose } [1+0.693 \times t / t_{½}]$$

D_t = Total dose of drug; Dose = dose of the immediate release part. (13.26), t = time (hrs) during which the sustained release desired (12hrs),

t ½ = halflife of the drug (3 hrs).

The dissolution similarity was assessed by f2 similarity factor[13].

$$f_2 = 50 \times \log \{[(1+1/n) \sum (R_t - T_t)^2]^{-0.5} \times 100 \}$$

Where, n = number of sample points, R_t=Percent of marketed product (or) theoretical release profile, T_t=Percent of test formulations release observed.

Accelerated Stability studies

Optimized formulations were packed in blister and stored in ICH certified stability chambers maintained at 40°C and 75% RH for three months. The tablets were withdrawn periodically

and evaluated for friability, hardness, drug content and in vitro release studies.

Mechanism of drug release

To know the mechanism of drug release from these formulations the data was treated according to first order[14] (log cumulative percentage of drug remaining vs time) higuchi's[15] (cumulative % drug release vs square root of time) and korsmeyer et al's[16] (log cumulative % drug release vs log time) equations along with zero order[17] (cumulative amount drug release vs. time).Korsmeyer and Peppas model was fitted into the following equation[17.]

$$M_t / M_\infty = K.t^n$$

M_t / M_∞ is the fraction of drug released is equal to the release constant, t= release time, n=diffusion exponent If n = 0.89, the release is zero order. If n = 0.45, the release is Fickian diffusion. If 0.45 < n < 0.89, the release is anomalous diffusion or non fickian diffusion (Swellable & Cylindrical Matrix).

Accelerated stability studies

As it is important to determine the stability for all the pharmaceutical dosage forms, an accelerated stability study was performed after optimization of the formulation. This will include storage at both normal and exaggerated temperature conditions, with the necessary extrapolations to ensure the product will remain over its designed shelf life and provide medication for absorption at the same rate as when originally formulated. The design of the formal stability studies for the drug product was based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance

Ten tablets were individually wrapped using aluminum foil and packed in amber colored screw cap bottle and put at specified condition in incubator for 2 months. After two months, tablets were evaluated for content uniformity and in vitro drug release.

RESULT AND DISCUSSION

Physicochemical Properties of Compressed Tablets

Table-3 indicates the results of physicochemical properties (hardness, thickness, weight variation, friability and assay) of compressed matrix tablets. Tablet thickness was in the range of 4.12 to 4.210 mm; and hardness, 7.4 - 7.7Kg/cm^2. Tablet friability and weight variation of all the tablet batches were in the range of 0.15 to 0.45% and 160 to 165% respectively. The formulated tablets of all batches showed low weight variations and uniform drug content (>100%) and satisfactory. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in house specifications for weight variation, drug content, hardness and friability.

TABLE 3: Physical Properties of Compressed Tablets

S.No	Formulation Batches	Weight variation (%) ±5	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
1	Formulation-1	162.25	7.6	4.16	0.15	93.3
2	Formulation-2	160.65	7.5	4.19	0.28	96.8
3	Formulation-3	164.19	7.7	4.21	0.32	97.6
4	Formulation-4	161.27	7.4	4.19	0.40	98.5
5	Formulation-5	159.92	7.5	4.12	0.41	98.6
6	Formulation-6	161.85	7.4	4.13	0.39	99.5
7	Formulation-7	162.42	7.5	4.14	0.36	98.6
8	Formulation-8	160.95	7.5	4.20	0.41	99.8
9	Formulation-9	165.15	7.7	4.13	0.45	100.1

** All values represent mean ± SD, n = 20, * All values represent mean ± SD, n = 6*

Drug-excipient compatibility studies

Drug was mixed with excipients in different ratios. These mixtures were kept in a 2 ml glass vial and exposed to 25ºC, 55% RH; 30ºC, 60% RH for 2 months. After 60 days no changes observed from compatibility study, so the selected excipients were found to be suitable for formulation and also the Fig .1 shows the incompatibility between the drug and excipients.

Table No. 4: Drug and Excipients compatibility Study

S.No	Drug+excipient	Initial colour	Storage Conditions	
			25°C/55% RH	30°C/60% RH
			End of 60 days	End of 60 days
1.	D+Ethylcellulose	White to dull White powder	White to dull White powder	White to dull White powder
2.	D+MCC	White to dull White powder	White to dull White powder	White to dull White powder
3.	D+Povidone	White to dull White powder	White to dull White powder	White to dull White powder
4.	D+Aerosil	White to dull White powder	White to dull White powder	White to dull White powder
5.	D+Eudrajit	White to dull White powder	White to dull White powder	White to dull White powder
6.	D+Diethylpthalate	White to dull White powder	White to dull White powder	White to dull White powder
7.	D+Mg Stearate	White to dull White powder	White to dull White powder	White to dull White powder

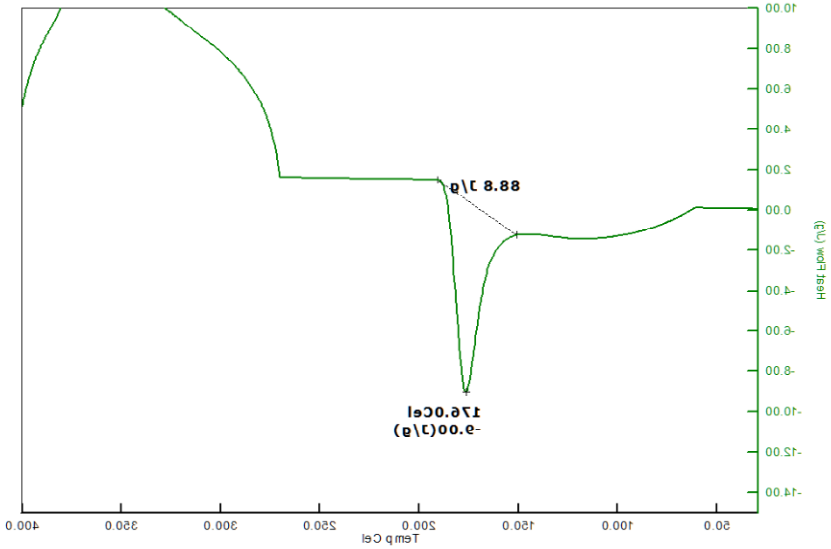

Fig .1. DSC Graph of Zalcitabine Pure Drug

In Vitro drug release studies

The release of Zalcitabine from enteric coated sustained release tablet of various formulations varied according to the ratio and degree of the polymer used. The formulation F1, containing Drug, 10% Ethyl cellulose Med 70p, with povidone and MCC showed 91% drug release with in 8hrs, whereas the Formulation F2 containing Drug, 15%Ethyl cellulose Med 70 P with povidone, MCC showed maximum release in 8hrs only. In case

of formulation F3 containing Drug, 20% Ethyl cellulose Med 70p, with povidone and MCC showed the 95% of drug release with in 10hrs. In case of Formulation F4 containing Drug, 10%Ethyl cellulose Std 100 P with povidone, MCC shows maximum release in 10hrs. In case of formulation F5 containing Drug, 15% Ethyl cellulose Std 100 P, with povidone and MCC showed the 96% of drug release with in 10hrs. In case of Formulation F6 containing Drug, Ethyl cellulose Std 100FP 20%, povidone, MCC, showed accurate results that is drug release up to 12hrs. In case of Formulation F7 containing Drug, 10%Ethyl cellulose Med 50 P with povidone, MCC showed maximum release in 10hrs. In case of Formulation F8 containing Drug, 15%Ethyl cellulose Med 50 P with povidone, MCC showed maximum release in 10hrs. In case of Formulation F9 containing Drug, 12%Ethyl cellulose Med 50 P with povidone, MCC showed maximum release in 10hrs. In case of tablet of F6 containing Drug & Ethyl cellulose Std 100FP 20%, povidone, MCC, showed accurate results, i.e. drug release up to 12hrs. No significant changes were observed in Formulation-6 in the stability studies to all physical tests, assay and dissolution test.

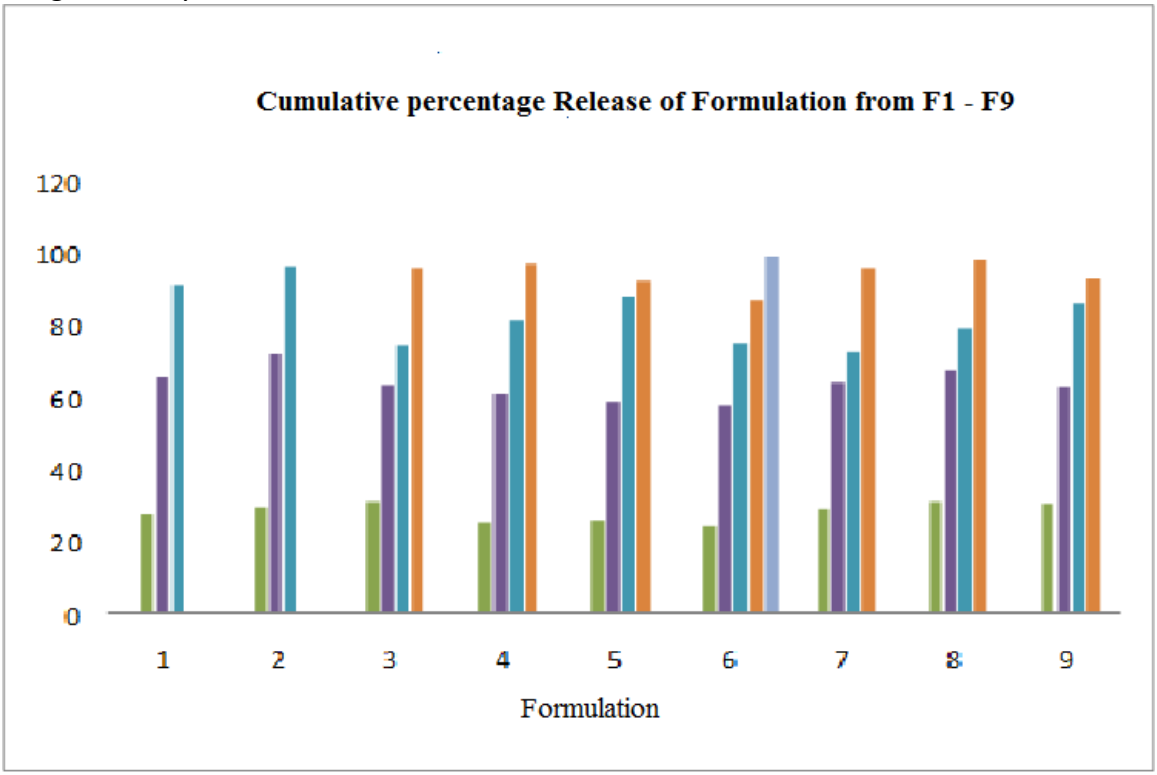

Fig: 2: Cumulative % drug release of all formulations F1-F9

The results of kinetic analysis of the dissolution data, dissolution efficiency (DE_{12}) theoretical release and similarity factor values of all the formulations were shown in Table-3. DE_{12} at the end of 12h was found to be 80.1-98.4%. The drug release data of all tablet formulations did not fit satisfactorily with zero order, first order and higuchi models but showed a good fit to the korsmeyer-peppas mode and some degree with Higuchi model. From the regression coefficients, the plots indicate that the highest linearity is achieved from Higuchi model followed by first order and zero order. The value of the release exponent 'n' for the various matrices ranged from 0.44-0.57, indicating that the release mechanism was Fickian release and totally based on diffusion. The diffusion is related to the transport of a drug from the dosage matrix into the in vitro dissolution medium. As gradient varies, the distance for diffusion increases. The similarity factor values of F2, F6 were 77.8, 76.8, which suggests that their dissolution profiles were similar to the theoretical release.

Table 5. Correlation coefficient (R^2) and release exponent (n) values for different kinetic models, f2 factor and theoretical release.

Code	Zero order	First Order	Higuchi's	Korsmeyer	Peppas 'n'	f2 values	Time in hrs to be released	% release
F1	0.8502	0.962	0.9812	0.9730	0.58	52.95	0	0
F2	0.9192	0.971	0.9935	0.9951	0.48	77.02	1	26.52
F3	0.8502	0.910	0.9105	0.9658	0.52	65.04	2	33.2
F4	0.9118	0.950	0.9915	0.9924	0.54	62.23	4	46.56
F5	0.8073	0.886	0.9579	0.9614	0.44	68.42	6	59.92
F6	0.9334	0.967	0.9989	0.9979	0.48	76.82	8	73.28
F7	0.9226	0.992	0.9986	0.9985	0.57	64.08	10	86.64
F8	0.8502	0.962	0.9835	0.973	0.47	61.12	12	100
F9	0.9294	0.990	0.998	0.9975	0.53	72.25		
F10	0.9214	0.984	0.994	0.9959	0.54	72.25		
F11	0.9237	0.992	0.9919	0.9926	0.54	69.41		
F12	0.9222	0.960	0.9912	0.9939	0.52	64.2		

Accelerated stability studies

After the optimization of the formulation the stability has been evaluated. Table 6, 7 & 8, shows the physical parameters, drug content after two months and the dissolution rate.

Table No.6: Physical evaluation report after Stability study

Formulation	Weight variation (%)	Hardness (kg/cm²)	Thickness (mm)
Formulation-6	162.65	7.2	4.26

Table No. 7: The drug content results of stability study after two months are:

Time	Drug Content (%)
Initial	99.50
One month	99.25
Two month	98.84

Table No. 8: Dissolution study of Formulation-6 after stability study

Dissolution Medium	Time (hrs)	Cumulative % Drug release	
		Initial	After Two months
0.1N HCl	0	0	0
	2	0	0
6.8 pH Buffer	4	25.56	24.82
	6	54.25	57.29
	8	68.31	66.86
	10	80.16	78.87
	12	98.35	98.24

The tests performed above did not vary much with the data attained before the stability study.

CONCLUSION

The project was undertaken with an aim to formulate and evaluate Zalcitabine Enteric coated sustained release tablet using different polymers as release retarding agent and overcome the gastric juice incompatibility. Preformulation study was done initially and results were directed for the further course of formulation. Based on preformulation studies different formulation batches of Zalcitabine were prepared using selected excipients. Granules were evaluated for loss on drying, bulk density, tapped density, compressibility index, Hausner ratio before punching the tablet. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables.

From the above results, it was found that Zalcitabine (formulation batch F6) containing 20 % of Ethyl cellulose Std 100 P, MCC and Povidone is an ideal formulation and a perfect sustained release tablet with the in vitro drug release for 12 hours.

ACKNOWLEDGEMENT

The authors are thankful to the management of Hindu college of Pharmacy for providing the facilities necessary for the current research.

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