FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF ZIDOVUDINE

SHAIK.HARUN RASHEED*[1], M.RAMA KOTAIAH[2], Y.NARASIMHA RAO[2], MULLA ARIEF[1], SILPARANI GAJAVALLI[1]

[1] Department of Pharmaceutics, BA&KR College of pharmacy, Doddavarapadu, Ongole Andhra Pradesh

[2] Department of Pharmaceutics, Donbosco College of pharmacy, Pulladi gunta, Etukuru, Guntur

ABSTRACT

Controlled release (CR) / Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The present aim is to formulate and evaluate Zidovudine Enteric coated tablets using different polymers as release retarding agent and overcome the gastric juice incompatability. The Zidovudine granules were prepared by wet Granulation method. Prepared Granules were evaluated for tests loss on drying , bulk density , tapped density , compressibility index, Hausner ratio. 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. Formulation of sustained release tablet of Zidovudine containing 20 % of Ethyl cellulose Std 100p, diluents MCC and with binder Povidone i.e formulation batch F6 can be taken as an ideal or optimized formulation of Enteric coated sustained release tablets for 12 hour release as it full fills all the requirements for sustained release tablet.

KEY WORDS: Enteric Coated Tablets, Zidovudine, Sustained release tablets, Ethocel, Eudragit L100.

1.INTRODUCTION

The tablet coating is perhaps one of the oldest pharmaceutical process still in existence .It offers many benefits namely improving the aesthetic quality of the dosage form, masking unpleasant odour or taste, easing ingestion, improving product stability and modify the release characteristics of the drug (Durriya,2008). Controlled release (CR) / Sustained release (SR) technology has rapidly emerged over the past three decades as a new interdisciplinary science that offers novel approaches to the delivery of bioactive agents into the systemic circulation for a prolonged period at a predetermined rate. The choice of drug to be delivered, clinical needs and drug pharmacokinetics are some of the important considerations in the development of CR / SR formulations, in addition to the relationship between the rates of drug release from the delivery system to the maximum achievable rate of drug absorption in to the systemic circulation. The therapeutic advantages of CR / SR systems over the conventional dosage forms have been amply documented in the literature. One of the important advantages is the reduced dosing frequency, thereby improving patient compliance and therapeutic efficacy. In order to be divisible, a CR / SR dosage form must not loose its release characteristics upon division to avoid dose dumping.

Although a variety of dosage forms have been developed for the preparation of oral CR / SR formulations, they broadly fall into two categories: single unit dosage forms and multiple (multiparticulate) dosage forms.

Modified release delivery systems may be divided conveniently in to four categories.

A) Delayed release (Enteric coated drug delivery system)
B) Sustained release
   i) Controlled release
   ii) Extended release
C) Site specific targeting
D) Receptor targeting

DELAYED -ACTION AND ENTERIC COATED TABLETS

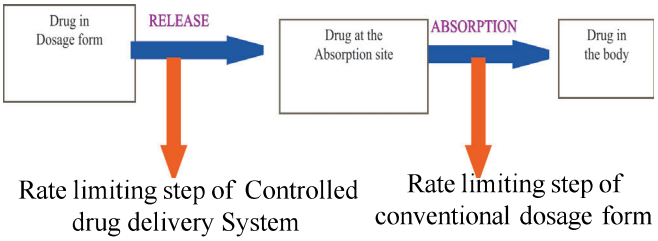
The delayed-action tablet dosage form is intended to release a drug after some time delay, or after the tablet has passed through one part of the GI tract into another. The enteric coated tablet is the most

***Adress for correspondence**
E-mail: shaikharunrasheed@gmail.com, mrk.pharma@gmail.com
Phone No: 09949722492, 09985909940.

common example of a delayed-action tablet product. All enteric coated tablets (which remain intact in the stomach but quickly release in the upper intestine) are a type of delayed-action tablet. Not all delayed – action tablets are enteric or are intended to produce the enteric effect.

Cellulose acetate phthalate has the longest history of use as an enteric coating. More recently, polyvinyl acetate phthalate and hydroxypropyl methylcellulose phthalate have come into use. All three polymers have the common feature of containing the dicarboxylic acid, phthallic acid, in partially esterified form. These polymers, being acid esters, are insoluble in gastric media that have a pH of up to about 4; they are intended to hydrate and begin dissolving as the tablets leave the stomach, enter the duodenum (pH of 4 to 6) and move further along the small intestine, where the pH increases to a range of 7 to 8. The primary mechanism by which these polymers lose their film integrity, thereby admitting intestinal fluid and releasing drug, is ionization of the residual carboxyl groups on the chain and subsequent hydration. The presence of esterase in the intestinal fluid that break down ester linkages of the polymer chains may also play some role, as may surface activity effects of bile salts and other components in bile that enter the upper small intestine via the bile duct.

Enteric coating is one method of reducing or elimination irritation from such drugs. There are other drugs that if released in the stomach may produce nausea and vomiting. The low pH of the stomach destroys others drugs (for example, erythromycin) and hence enteric coating may be necessary to bring the drug through that environment to the more neutral intestinal contents. Yet another reason for enteric coating may be the desire to release the drug undiluted and in the highest concentration possible within the intestine (Examples are intestinal antibacterial or antiseptic agents and intestinal vermifuges). As in the case of repeat-action and other controlled-release dosage forms, the influence of altering the release profile of the drug on total drug bioavailability, distribution and pharmacokinetics must be investigated.



Zidovudine chemically known as 3-Azido3-azoxy thymidine was the first drug approved for the treatment of Aids and HIV infection. Zidovudine is Thymidine analogue (Yarchoan,1988). It is phosphorylated in the body to zidovudine Triphosphate which is the active form that inhibits HIV replication (Mitsuya,1990). Zidovudine inhibits the key enzyme reverse transcriptase.

2.MATERIALS AND METHODS

Zidovudine was obtained as a gift sample from Aurobindo labs Ltd, Hyderabad (Andhra Pradesh), Ethocel was purchased from National scientific products, Mumbai. All the chemicals were AR grade.

EXPERIMENTAL

Formulation Of Zidovudine Enteric Coated Sustained Release Tablets

Accurately weigh requires quantity of Zidovudine and sifted through #40 mesh. Ethylcellulose, Microcrystalline cellulose, povidone were passed through #40 mesh and added to the above granular material and blended for 5 min and prepare damp mass and finally pass through #24 mesh and allow the granules at 40ÚC.Magnesium stearate and aerosil were passed through 60#and added to the above blended material. Compress the blend into tablets with punch size of 20 x 7mm rod shaped (Table No. 2).

EVALUATION OF GRANULES (Reddy,2003)

Angle Of Repose:

The angle of repose of granules were determined by funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted just touches the apex of the heap of the granules. The granules were allowed to flow through the funnelfreely on to the surface. The diameter of the powder cone was measured& angle of repose was calculated using the following equation (Table No. 4).

Tan è = h/r, Where h and r are the height and radius of the powder cone.

Bulk Density:

Both loose bulk density & tapped bulk density were determined. A quantity of 2 gram of Powder from each formula, previously lightly shaken for the break of any agglomerates formed, was introduced into a 10 ml of measuring cylinder.After the initial volume was observed, the cylinder was allowed to falldownits own weight from the hard surface from a height of 2.5cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. LBD & TBD were calculated using the following formulas (Table No. 4).

LBD: Weight of the powder/Volume of the packing
TBB: Weight of the powder/Tapped volume of the packing

Compressability Index:

The comperssability index of the granules wes determinedby Carr's compressability index.

Carrs index (%) = [(TBD-LBD) * 100] / TBD

Where LBD: Weight of the powder/Volume of the packing

TBD: Weight of the powder/Tapped volume of the packing (Table No. 4)

Coating Of Tablets

Preparation of coating solution: Take required quantity of isopropyl alcohol stir with propeller stirrer to form vortex. Add quantity of Eudragit in vortex stir for 25 mins. Maintain the solution without air bubbles then use the solution for coating. Tablets are taken in a coating pan and coating have done. Quantity of tablets to be coated is 100 Tab (Table No.3).

EVALUATION OF TABLETS (Pue,1993; Judmaier,1994)

Thickness:

The thickness of the tablet was measured by using thickness guage (Mitutoyo). Six tablets from each batch were used and average values were calculated (Table No. 5).

Weight Variation:

20 tablets from each batch were weighed using an electronic balance and the test was performed according to official method. The USP limit for weight variation in case of tablet weight between 161.72 and 167.25 mg that is 6.5% (Table No. 5).

Hardness & Friability:

For each formulation that hardness of 6 tablets were determined using tablet hardness testers. The friability of 20 tablets were determined using roche fibrilator. The limit for Friability is NMT 1% (Table No. 5).

In Vitro Release Studies (The United states pharmacopoeia,2004)

Dissolution studies were performed using USP standard dissolution apparatus at 37 ± 0.5ºC Using one tablet at a time in a vessel. The basket was immersed in 900ml of dissolution medium and rotated at 50 rpm. The dissolution Media used was initially 0.01N Hcl up to 2hrs.

During the test 10ml of the sample was withdrawn at specific time intervals 1, 2, 4, 6, 8, 10, 12 hrs after each withdrawal, same volume of fresh dissolution medium was added to maintained sink conditions. Different aliquots were suitably diluted. The absorbance was measured in the UV spectrophotometer at ë max 265nm (Table No. 6).

3.RESULTS AND DISCUSSION

The Enteric coated sustained release tablet of Zidovudine were prepared by wet granulation method, They were evaluated for weight variation, drug content, friability, hardness and thickness for all batches (F1 to F9).

No significant difference was observed in the weight of individual tablets from the average weight. The data of uniformity of content indicated that tablets of all batches had drug content within pharmacopoeia limits. The hardness of tablets of all batches are in acceptable limits, which shows in the literature. All the formulation showed % friability less than 1% that indicates ability of tablets of withstands shocks, which may encounter. No significant difference was observed in the thickness of individual tablet from the average weight.

The release of Zidovudine from enteric coated sustained release tablet of various formulations varied according to the ratio and degree of the polymer. In case of formulation F1 shows the 91% of drug release with in 8hrs, In case of Formulation F2 shows maximum release of 96% in 8hrs only.

In case of tablet of F3 containing shows the 95% of drug release with in 10hrs and Formulation F4 containing shows maximum release in 10hrs only, In case of tablet of F5 shows the 92% of drug release with in 10hrs and Formulation F6 containing Drug & Ethyl cellulose Std 100FP 20%, povidone, MCC, shows accurate results that is drug release up to 12hrs. In case of Formulation F7 shows maximum release in 10hrs only and Formulation F8 shows maximum release in 10hrs only, In case of Formulation F9 shows maximum release in 10hrs only (Table No. 6) (Figure No 1). In case of tablet of F6 containing Drug & Ethyl cellulose Std 100FP 20%, povidone, MCC, shows accurate results that is drug release up to 12hrs.

4.CONCLUSION

Series of Experiments were performed during preformulation studies to select suitable excipient. Combination of different excipient in various compositions were used to formulate Zidovudine enteric coated tablet. Evaluation experiments such as weight variation, drug content, friability, hardness, thickness and

dissolution profile were performed and found the results were satisfactory.Dissolution of all 9 batches of Zidovudine enteric coated tablet were carried out and found that shows accurate results that is drug release of 99.28 % up to 12hrs.

Table No.1: Standard Curve Of Zidovudine

S.NO.	Concentration (µg /ml)	Absorbance
1	0	0
2	20	0.228
3	40	0.428
4	60	0.612
5	80	0.842
6	100	1.028

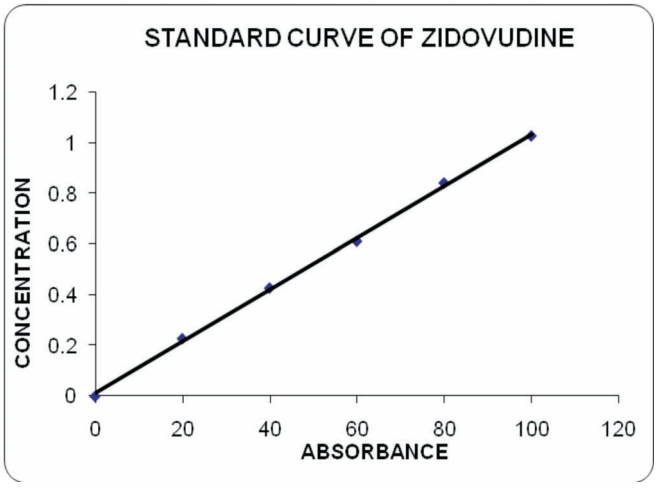


Table No.2: Formulation Of Tablets

S. No	INGREDIENTS	Quantity per Tab (mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Zidovudine	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. 3: Coating solution contents

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

Coating parameters:

Atomization Air	2 kg/cm²
Pan RPM	5
Inlet temperature	65 °C
Exhaust temperature	48-50 °C

Table No. 4: Physical Characterization of all formulation Blends

B.No	Bulk density	Tapped density	Loss on Drying in %	Compressibility Index %	Hausner Ratio	Angle of Repose
F1	0.49	0.57	1.1 ± 0.010	12.8	1.19	28°.3"
F2	0.44	0.56	1.0 ± 0.09	13.6	1.13	26°.1"
F3	0.47	0.53	1.2 ± 0.015	12.2	1.16	26°.8"
F4	0.50	0.59	1.4 ± 0.016	13.1	1.15	26°.2"
F5	0.51	0.59	1.4 ± 0.013	14.9	1.12	27°.4"
F6	0.49	0.61	1.7 ± 0.016	15.1	1.19	28°.6"
F7	0.48	0.55	0.9 ± 0.021	12.5	1.17	23°.9"
F8	0.46	0.62	2.1 ± 0.014	13.9	1.15	25°.9"
F9	0.50	0.58	1.6 ± 0.016	14.2	1.20	27°.5"

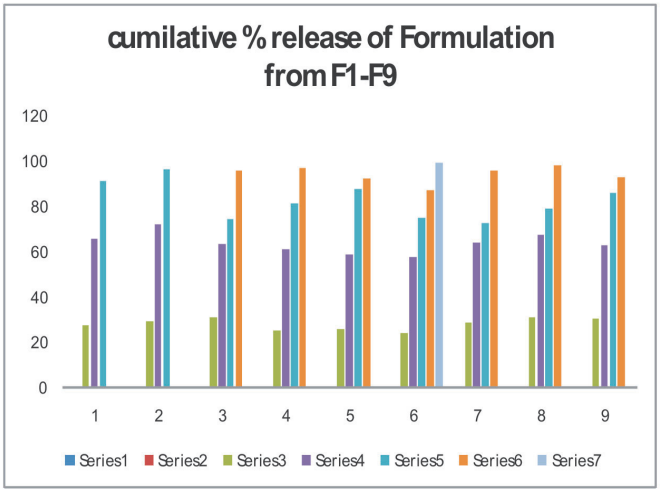
Physical evaluation study report

S.No	B.No.	Weight variation (%) ±5	Hardness (kg/cm²)	Thickness (mm)	Friability (%)	Assay (%)
1	F1	164.45	7.6	4.16	0.15	93.3
2	F2	162.45	7.5	4.19	0.28	96.8
3	F3	166.39	7.7	4.21	0.32	97.6
4	F4	163.47	7.4	4.19	0.40	98.5
5	F5	161.72	7.5	4.12	0.41	98.6
6	F6	163.75	7.4	4.13	0.39	99.5
7	F7	164.42	7.5	4.14	0.36	98.6
8	F8	162.75	7.5	4.20	0.41	99.8
9	F9	167.25	7.7	4.13	0.45	100.1

Table No. 6: Comparative Dissolution study of Formulations F1 to F9

Time in hours	% Cumulative Drug release								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0
4	27.55	29.65	31.12	25.61	25.85	24.17	28.92	31.29	30.48
6	65.65	72.26	63.56	61.2	59.13	57.65	63.98	67.44	62.98
8	91.28	96.23	74.54	81.54	87.65	75.28	72.41	78.86	85.95
10	-	-	95.85	96.91	92.23	86.89	95.62	97.91	92.69
12	-	-	-	-	-	99.28	-	-	-

FIGURE 1: Cumulative % release of All formulations from F1-F9



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