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Original Article

Formulation and Evaluation of Sustained Release Matrix Tablets of Zidovudine

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ABSTRACT

The objective of the present study is to develop a Sustained release matrix tablets of Zidovudine. In this present study an attempt was made to increase the therapeutic effect of Zidovudine by continuously releasing the drug up to an extended period of time by formulating the Controlled release matrix tablets. Systematic studies were conducted using different concentration of rate releasing polymer different grades of HPMC and Kollidon SR for extending the drug release up to 15 hrs. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, content uniformity, all the formulations were found within the permissible range. Finally it was concluded that: Among all the formulations (F1-F9), it was observed that formulation-9 has shown better dissolution profile. So Formulation-9 was found to be the best formulation when compared with other prepared formulations. All the polymers were used at the different concentrations in the formula, much difference were observed in the release characteristics of the SR tablets prepared. The release data were analyzed as per zero order, first order, Higuchi and Korsmeyer & Peppas models. The correlation coefficient (r2) values in the analysis of release data as per various models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from SR tablets formulated followed first order kinetics. The correlation coefficient (r2) values were higher in first order model when compared to zero order models. As per Peppas equation of F-9 shows the release exponent 'n' was found 1.748 in the case of SR indicating non-Fickian (anomalous) diffusion as the release mechanism from these tablets.

Keywords: Zidovudine, HPMC, SR tablets & Formulation.

1. INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of

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different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed. [1, 2]

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery (immediate sustained or controlled release) and the design of dosage forms (either solid dispersion or liquid) must be developed within the intrinsic characteristics of GI physiology pharmacokinetics, pharmacodynamics and formulation design is essential to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.The basic Rational for controlled drug delivery is to alter the pharmacokinetic and pharmacodynamics of pharmacological active moieties by using novel drug delivery system or by modifying the molecular structure and physiological parameters inherent in the selected route of administration. It is desirable that the duration of drug action becomes more a design property of a rate controlled dosage form and less or not at all a property of the drug molecules properties, inherent kinetics. Thus optional design of controlled release systems necessitates a thorough understanding of the pharmacokinetics and pharmacodynamics of the drugs. Zidovudine is a synthetic dideoxynucleoside antiviral agent.

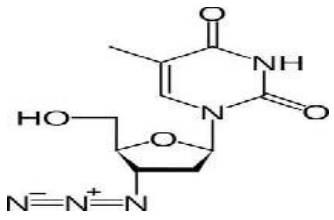

Fig 1: Stucture of Zidovudine

Physico-chemical properties

Molecular formula : C10H13N5O4

Molecular weight : 267.2413

IUPAC name : 1-[(2R, 4S, 5S)-4-azido-5-(hydroxymethyl) oxolan 2-yl]-methyl-1,2,3,tetra hydropyrimidine-2,4-dione

State : Solid

Melting point : 113-115 °C

Solubility : 20.1 mg/ml, Sparingly soluble in water, soluble in anhydrous ethanol.

Drug category : Anti-HIV Agents, Antimetabolites, Nucloeside and Nucleotide Reverse Transcriptase Inhibitors, Reverse Transcriptase Inhibitors.[3]

2. METHODOLOGY

2.1 Preformulation Study

The drug sample was evaluated for its colour and odor. Melting point of the drug sample was determined by capillary method by using melting point apparatus. The solubility of the Zidovudine was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Perkin Elmer Lambda35, double beam spectrophotometer.

2.2 Construction of Calibration Curve

Standard Stock solution

Accurately weighed 100 mg of Zidovudine sodium was dissolved in 100 ml of suitable medium (0.1N HCl and 6.8pH phosphate buffer). The resultant solutions were having concentration of 1000 µg/ml (1.1 mg/ml). 10 ml of this solution was further diluted up to 100.0 ml with 6.8pH phosphate buffer and to give a solution of Concentrations 100 µg/ml. This resultant solution is used as working stock solution for further study. Further dilutions were prepared from the same solution. [4, 5]

Preparation of calibration curve for Zidovudine

Appropriate aliquots were pipetted out from the standard stock solution in to a series of 10 ml

volumetric flasks. The volume was made up to the mark with suitable medium (0.1N HCl and 6.8pH phosphate buffer) to get a set of solutions having the concentration range of 2, 4, 6, 8 and 10 µg/ml for Zidovudine. Absorbances of the above solutions were measured at 256 and 266nm and a calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-10 µg/ml. The regression equation and correlation coefficient was determined. [6-8]

2.3 Bulk density, Tapped density, % Compressibility index & Hausners ratio

1) Apparent Bulk Density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduated measuring cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Density = Mass/Volume

2) Tapped Density: Weighed powder sample was transferred to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps (200). The tapped density was determined by the following formula.

Density = Mass/Tapped Volume

3) Percentage Compressibility (or) Carr's index (%): Based on the apparent bulk density and the tapped density, the percentage Compressibility of the bulk drug was determined by the following formula.

Carr's index (%) = [(Tapped Density-Bulk Density) / Tapped Density] X 100

Table 1: % Compressibility limits with respect to flowability

S.No	%Compressibility	Flow ability
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair
4	23-25	Poor
5	33-38	Very poor
6	More than	Very very poor

4) Housners Ratio: It indicates the flow properties of powder and is measured by the ratio of tap density to bulk density.

Hausners ratio = Tapped density/Bulk density

Table 2: Hausners ratio limits

Hausners ratio	Type of flow
< 1.25	Good flow
> 1.25	Poor flow

All these results are shown in Table.

5) Angle of Repose:

The flow property was determined by measuring the Angle of Repose. In order to determine the flow property, the Angle of Repose was determined. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where, h = height r = radius

Procedure:

- 20gms of the sample was taken
- The sample was passed through the funnel slowly to form a heap.
- The height of the powder heap formed was measured.
- The circumference formed was drawn with a pencil on the graph paper.

The radius was measured and the angle of repose was determined. This was repeated three times for a sample. [9, 10]

Table 3: Angle of repose

Flow properties	Angle of repose (θ)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	> 66

2.4 Evaluation of Tablets

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets and to monitor product quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, Friability and invitro-dissolution characters.

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size & Shape:

It can be dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness can be measured by micro-meter or by other device. Tablet thickness should be controlled within a ± 5% variation of standard value.

3. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets, different pharmacopoeia specify these weight variation tests.. These tests are primarily based on the comparison of the weight of the individual tablets (xi) of a sample of tablets with an upper and lower percentage limit of the observed sample average (x-mean). The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the latter comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. Not more than two tablets should differ in their average weight by more than percentages stated in USP. No tablet must differ by more than double the relevant percentage.

Table 4: Limits for Tablet Weight variation test

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity

The drug content of the matrix tablets was determined by standards and it meets the requirements if the amount of the active ingredient in each of 10 tested tablets lies within the range of 90% to 110% of the standard amount.

Ten tablets were weighed and taken into a mortar and crushed into fine powder. An accurately weighed portion of the powder equivalent to about 10mg of Zidovudine was transferred to 100ml volumetric flask containing 70ml of 6.8 pH phosphate buffer. It was shaken by mechanical means for 1hr then it was filtered through Watsmann filter paper (no.1) and diluted to 100ml with 6.8 pH phosphate buffer. From this resulted solution 1ml was taken, diluted to 50ml with 6.8 pH phosphate buffer and absorbance was measured against blank at 227nm. [13]

Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

A number of tablets are weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn

within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

2.5 In vitro drug release study

In vitro drug release was studied using USP II apparatus, with 900 ml of dissolution medium maintained at 37±1°C for 15 h, at 50 rpm. 0.1 N HCl (pH 1.2) was used as a dissolution medium for the first 2 h, followed by pH 6.8 phosphate buffers for further 13 h. 5ml of sample was withdrawn in different time intervels, and was replaced by an equal volume of fresh dissolution medium of same pH. Collected samples were analyzed spectrophotometrically at 256 and 266 nm, and cumulative percent drug release was calculated. The study was performed in triplicate.

Kinetic-models:

In order to describe the DS release kinetics from individual tablet formulations, the corresponding dissolution data were fitted in various kinetic dissolution models:

Zero order, first order, and Higuchi respectively.

Qt = Q0 + K0 t…….. (3)

where, Qt is the amount of drug released at time t; Q0 the amount of drug in the solution at t = 0, (usually, Q0 = 0) and K0 the zero order release constant.

logQt = logQα+ (K1 /2.303) t…….. (4)

Qα being the total amount of drug in the matrix and K1 the first order kinetic constant.

Qt = KH. t ½……. (5)

where, KH is the Higuchi rate constant.

Further, to better characterize the mechanism of drug release from matrices, dissolution data were analyzed using the equation proposed by Korsmeyer and Peppas.

Q (t-*l*) /Qα = KK (t-*l*)n……. (6)

where, Qt corresponds to the amount of drug released in time t, *l* is the lag time (*l* = 2 hours), Qα is the total amount of drug that must be released at infinite time, KK a constant comprising the structural and geometric characteristics of the tablet, and n is the release exponent indicating the type of drug release mechanism. To the determination of the exponent n, the points in the release curves where Q (t-*l*)/Qα>0.6, were only used. If n approaches to 0.5, the release mechanism can be Fickian. If n approaches to 1, the release mechanism can be zero order and on the other hand if 0.5<n<1, non-Fickian (anomalous) transport could be obtained. Anomalous (non-Fickian) transport generally refers to the drug release by the summation of both diffusion and erosion of the polymeric matrix. The criteria employed to select the ‘‘best model’’ was the one with the highest coefficient of determination (r2).

2.6 Stability studies

Selected Formulation was subjected to stability studies as per ICH guidelines.

Following conditions were used for Stability Testing.

1. 25^0C/60% RH analyzed every month for period of three months.
2. 30^0C/75% RH analyzed every month for period of three months.
3. 40^0C/75% RH analyzed every month for period of three months.

2.7 Formulation Development

S.no	Api characterisation	Results
1	Physical appearance	Zidovudine is a white crystalline solid
2	Melting point	113°c
3	Solubility	20.1 mg/ml, sparingly soluble in water, soluble in Anhydrous ethanol.
4	Bulk density	0.28 gm/ml
5	Tapped density	0.41 gm/ml
6	Carr's index/compressibility index	31.71
7	Hausner's ratio	1.46

Procedures:

The Purpose of key ingredients included in the formulation.

Table 5: Composition of Zidovudine Controlled Release Matrix Tablet

S.No.	Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)	F9 (mg)
1	Zidovudine	300	300	300	300	300	300	300	300	300
2	Kollidon-sr	25	50	---	---	---	---	---	25	25
3	Hpmc k 4 m	---	---	25	50	---	---	25	25	---
4	Hpmc k 15 m	---	---	---	---	25	50	25	---	25
5	Microcrystalline Cellulose	115	90	115	90	115	90	90	90	90
6	Pvp k-30	5	5	5	5	5	5	5	5	5
7	Magnesium stearate	3	3	3	3	3	3	3	3	3
8	Talc	2	2	2	2	2	2	2	2	2
8	Iso propyl alcohol	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s
	Total wt	450	450	450	450	450	450	450	450	450

Preparation of Formulation:

1. Drug and polymer (HPMC K1M, HPMC15M and KOLLIDON-SR combination) pass through 40 # mesh separately and then transfer it to poly bag and mix it for 3 minutes.
2. Binder (PVPK-30) dissolved in isopropyl alcohol which is used as a granulating agent.
3. Above drug-polymer blend is granulated by using binder solution.
4. Add other excipients to the above mixture. Finally add the Glidant (Magnesium Stearate) and Lubricant (Talc) to the above blend mix it for 2min.
5. Compressed the above lubricated blend by using 8mm round punches.

3. RESULTS AND DISCUSSION

3.1 Preformulation

The value of compressibility index above 25%, 15-25%, less than 15% indicates poor flowability, optimum flowability and high flowability respectively.

Table 6: List of Micromeritic Properties of Directly Compressible Powder:

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angleof repose	25.43 ±0.1	26.46 ±0.2	23.31 ±0.1	26.89±0.17	29.14 ±0.1	28.14 ±0.2	29.1 ±0.1	28.2 ±0.1	27.1± 0.4
Bulk density	0.725 ±0.3	0.734 ±0.4	0.717 ±0.2	0.724±0.28	0.96± 0.24	0.95± 0.24	0.94 ±0.2	0.92 ±0.2	0.93± 0.2
Tapped density	0.829 ±0.1	0.854 ±0.2	0.832 ±0.1	0.843±0.21	1.03± 0.27	1.03± 0.27	1.03 ±0.2	1.03 ±0.2	1.02± 0.27
%compressibility	12.54	14.05	13.82	13.63	6.89	6.81	6.88	6.84	6.85
Hausner's ratio	1.14	1.16	1.16	1.16	1.07	1.02	1.24	1.25	1.12

The construction of standard calibration curve of Zidovudine was done by using 0.1N HCl and 6.8 pH Phosphate buffer as the medium. Zidovudine was found to have the maximum absorbance at 256 and 266 nm. The standard graph of Zidovudine in 0.1N HCl & 6.8 pH Phosphate buffer was constructed by making the concentrations of 2µg/ml, 4µg/ml, 6 µg/ml, 8 µg/ml and 10 µg/ml solutions. The absorbance of solutions was examined under UV- spectrophotometer at an absorption maximum of 256 and 266 nm. The standard graph of Zidovudine was constructed by taking the absorbance on Y-axis and concentrations on X-axis.

Table 7: Standard graph of Zidovudine in 0.1N HCl at λ_{max}= 256 nm

S. No.	Concentration(µG/ML)	Absorbance
1	0	0
2	2	0.215
3	4	0.396
4	6	0.595
5	8	0.773
6	10	0.987

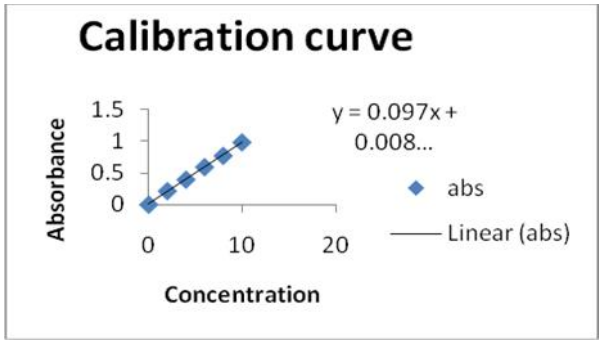

Fig 2: Standard graph of Zidovudine

3.2 Evaluation of the Prepared Tablets for Physical Parameters

All formulations were tested for Physical parameters like Hardness, thickness, Weight Variation, Friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 8: Results for Evaluation parameters of all formulations

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	250±0.4	249±0.4	249±0.7	250±0.1	249±0.3	250±0.2	249±0.9	249±0.8	250±0.1
Thickness (mm)	2.5±0.4	2.6±0.4	2.3±0.4	2.6±0.4	2.5±0.4	2.5±0.3	2.5±0.2	2.5±0.1	2.5±0.2
Hardness (kg/cm^2)	8.9±1.4	7.4±1.2	8.2±1.2	6.9±0.9	8.4±1.9	8.1±1.7	8.2±1.5	8.3±1.6	8.2±1.4
Friability	0.12% ±0.2	0.16% ±0.23	0.15% ±0.19	0.15% ±0.26	0.15% ±0.22	0.12% ±0.1	0.11% ±0.4	0.11% ±0.5	0.11% ±0.7
Content uniformity	95.01 %±0.2	96.4% ±0.4	98.7% ±0.3	98.8% ±0.2	99.8% ±0.3	99.19 %±0.2	99.18 %±0.2	99.68 %±0.2	99.88 %±0.2

In vitro Dissolution studies: The dissolution conditions used for studying the drug release from tablet of Zidovudine are:

Apparatus :USP apparatus II (Paddle)

Agitation speed (rpm) : 50rpm

Medium : 0.1N HCl and 6.8 pH Phosphate buffer

Volume : 900 ml

Temperature : 37.0 ± 0.5 C

Time : 1, 2, 4, 8, 12 and 24 hrs.

Wavelength : 256nm and 266 nm

The samples were withdrawn at predetermined time points, and were analyzed spectrophotometrically at 256nm, 266nm.

Table 9: Results of Dissolution profile for F1-F9:

Time	F1	F2	F3	F4	F5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
1	3.67	2.36	4.67	5.37	6.95	3.67	4.67	2.95	1.41
2	6.91	4.92	6.91	8.68	9.78	6.91	8.68	6.78	2.94
4	23.67	21.36	24.67	21.37	20.95	18.67	16.67	17.95	25.45
8	56.91	54.92	46.91	43.68	39.78	36.91	28.68	26.78	67.94
12	81.24	98.92	71.24	96.68	89.94	87.92	93.68	95.94	87.59
24	99.97	99.23	97.95	99.15	99.56	99.32	99.49	99.56	98.86

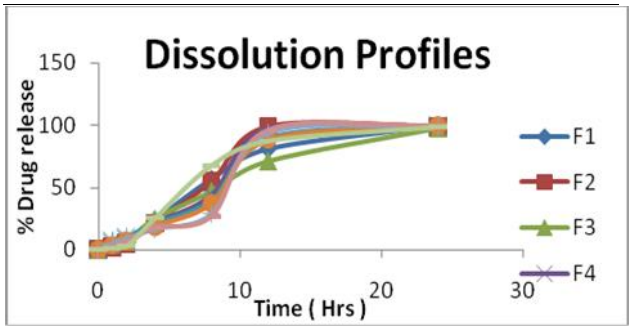

Fig 3: Dissolution Profile graph

3.3 Kinetic Models

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations. The mechanism of drug release was determined by using

Table 10: Higuchi equation

S. nome	Ti	Log t	Square root of time	%cr	%drug remaining	Log %cr	Log% drug retained	Cube root of %drug remaining
0	0	0	0	0	100	0	2	4.641589
1	1	0	1	1.41	100	0.149219	2	4.641589
2	2	0.301033	1.414214	2.94	98.22	0.468347	1.9922	4.613884
3	4	0.602066	2	25.45	76.82	1.405688	1.885474	4.251003
4	8	0.90309	2.828427	67.94	47.82	1.832126	1.67961	3.629693
5	12	1.079181	3.464102	87.59	17.06	1.942455	1.231979	2.574303
6	24	1.380211	4.898979	98.86	0.08	1.995021	-1.09691	0.430887

4. CONCLUSION

The objective of the present study is to develop a Controlled release matrix tablets of Zidovudine. In this present study an attempt was made to increase the therapeutic effect of Zidovudine by continuously releasing the drug up to an extended period of time by formulating the Controlled release matrix tablets. Systematic studies were conducted using different concentration of rate releasing polymer different grades of HPMC and Kollidon SR for extending the drug release up to 15 hrs. All the prepared systems were evaluated for the different properties. Before the preparation of tablets, preformulation studies to find out the micromeritic properties to assess flowability, compressibility properties and solubility studies. And all the formulations gave good results for above preformulation studies. Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation, content uniformity, all the formulations were found within the permissible range. Finally it was concluded that: Among all the formulations (F1-F9), it was observed that formulation-9 has shown better dissolution profile. So Formulation-9 was found to be the best formulation when compared with other prepared formulations. All the polymers were used at the different concentrations in the formula, much difference were observed in the release characteristics of the SR tablets prepared. The release data were analyzed as per zero order, first order, Higuchi and Korsmeyer & Peppas models. The correlation coefficient (r2) values in the analysis of release data as per various models are mentioned. Analysis of the release data as per zero order and first order kinetic models indicated that the drug release from SR tablets formulated followed first order kinetics. The correlation coefficient (r2) values were higher in first order model when compared to zero order models. As per Peppas equation of F-9 shows the release exponent ‘n’ was found 1.748 in the case of SR indicating non-Fickian (anomalous) diffusion as the release mechanism from these tablets**.**

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