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Research

Formulation Development And Characterization Of Controlled Release Tablets Of Zidovudine

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Abstract

The present study aims to develop controlled release formulation of Zidovudine to maintain constant therapeutic levels for over 12 hrs with the given drug. Gum copal, Eudragit RSPO, and Gum damar were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. From the dissolution studies it was evident that the formulation (ZDV4) showed better and desired drug release pattern i.e., 98.14 % in 12 hours. It contains the Gum copal polymer. It followed Zero order release kinetics mechanism.

Keywords: Zidovudine, Eudragit RSPO, Gum copal, Gum damar, controlled release tablets.

INTRODUCTION

Controlled release dosage form is a dosage form that release one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ. Greater attention is paid on development of oral controlled release drug delivery systems due to flexibility in designing of dosage form. A controlled release drug delivery system delivers the drug locally or systemically at a predetermined rate for a specified period of time The goal of such systems is to provide desirable delivery profiles that can achieve therapeutic plasma levels. Drug release is dependent on polymer properties, thus the application of these properties can produce well characterised and reproducible dosage forms.

Zidovudine (AZT) is a pyrimidine synthetic analogue active against human immunodeficiency virus type 1 (HIV-1). It belongs to the class of nucleoside reverse transcriptase inhibitors (NRTIs). Monotherapy with AZT is recommended only in the initial management of HIV-1 infected patients. However, combination therapy should be employed in advanced disease. AZT is used in combination therapy with lamuvidine as combivir and with lamuvidine and abacavir as trizvir. It has been demonstrated that AZT causes bone marrow suppression and can exacerbate the manifestations of anemia in HIV-positive individuals.

MATERIALS &METHODS

Zidovudine, Eudragit RSPO,Gum copal,Gum damar, MCC, PVP K30, Magnesium stearate, Talc.(procured from Sun Pharma Ltd , India)

Formulation development of Tablets

Table 1: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART								
	ZDV1	ZDV2	ZDV3	ZDV4	ZDV5	ZDV6	ZDV7	ZDV8	ZDV9
Zidovudine	100	100	100	100	100	100	100	100	100
Eudragit RSPO	60	120	180	-	-	-	-	-	-
Gum copal	-	-	-	60	120	180	-	-	-
Gum damar	-	-	-	-	-	-	60	120	180
MCC	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	10	10	10	10	10	10	10	10	10
Talc	8	8	8	8	8	8	8	8	8
Total weight	400	400	400	400	400	400	400	400	400

Procedure

1) Zidovudine and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Evaluation of Tablets

Preformulation parameters

Angle of repose

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane.

$\tan \theta = h / r$ $\tan \theta$ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Table 2: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk density

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3.

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured,

$$\text{Tap} = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is.

Carr's Index = [(tap - b) / tap] × 100

Where, b = Bulk Density

Tap = Tapped Density

Evaluation of post compression parameters for prepared Tablets

Weight variation test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness.

Thickness

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance.

Friability

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator.

% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

Procedure

900 ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C + 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals withdrawn 5 ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at 265 and 267 nm using UV-spectrophotometer.

RESULUTS & DISCUSSION

Preformulation parameters of powder blend

Table 3: Pre-formulation parameters of Core blend

Formulations	Bulk Density (gm/cm^2)	Tap Density (gm/cm^2)	Carr's Index (%)	Hausner ratio	Angle Of Repose (Ɵ)
ZDV1	0.45	0.55	18.1	1.22	26.2
ZDV2	0.47	0.55	14.5	1.17	25.4
ZDV3	0.50	0.58	13.7	1.16	26.8
ZDV4	0.46	0.55	16.3	1.19	24.8

ZDV5	0.50	0.58	13.7	1.16	24.3
ZDV6	0.47	0.55	14.5	1.17	26.3
ZDV7	0.50	0.58	13.7	1.16	26.4
ZDV8	0.41	0.50	18.6	1.21	24.3
ZDV9	0.41	0.50	18.8	1.21	28.4

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.41 to 0.50 (gm/cm^3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.50 to 0.58 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 13.7 to 18.8 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 1.16 to 1.22 indicating the powder has good flow properties.

Quality Control Parameters For tablets

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

Table 4: *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
ZDV1	399.25	5.4	0.62	5.58	97.12
ZDV2	397.10	5.9	0.48	5.25	99.81
ZDV3	398.37	4.8	0.32	5.47	97.36
ZDV4	399.65	5.7	0.49	5.16	99.32
ZDV5	395.82	4.3	0.61	5.82	98.57
ZDV6	400.2	5.8	0.25	5.65	96.87
ZDV7	398.79	4.5	0.37	5.73	99.20
ZDV8	399.28	4.6	0.18	5.19	97.56
ZDV9	399.57	5.2	0.46	5.22	99.60

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table 5: Dissolution Data of Zidovudine Tablets Prepared

TIME (hr)	CUMULATIVE PERCENT DRUG DISSOLVED								
	ZDV1	ZDV2	ZDV3	ZDV4	ZDV5	ZDV6	ZDV7	ZDV8	ZDV9
0	0	0	0	0	0	0	0	0	0
0.5	6.15	9.10	14.98	15.82	11.98	10.54	8.24	11.73	7.06
1	9.62	14.53	18.60	21.57	15.63	15.96	17.56	16.90	18.29
2	16.98	18.86	23.54	27.49	20.75	19.48	25.43	28.53	22.02
3	20.83	27.54	29.72	32.26	27.14	26.41	32.29	32.16	28.96
4	26.47	35.99	35.34	40.52	33.60	33.24	42.59	42.24	36.10
5	29.68	39.42	40.75	46.14	37.59	38.67	47.63	55.97	41.57
6	35.89	44.27	46.18	57.38	40.37	43.68	50.15	61.24	47.98
7	38.50	49.38	52.26	68.89	45.10	52.11	58.66	68.85	52.31
8	46.76	54.18	58.74	74.14	58.81	56.93	62.34	72.31	58.92
9	49.10	58.92	61.36	83.63	66.95	61.40	73.59	76.21	66.22
10	57.17	63.34	65.82	87.75	68.31	67.29	76.91	84.78	78.19
11	62.32	67.15	76.96	93.50	77.18	72.57	79.87	87.62	86.98
12	66.80	73.43	86.51	98.14	90.67	85.23	86.14	96.54	90.23

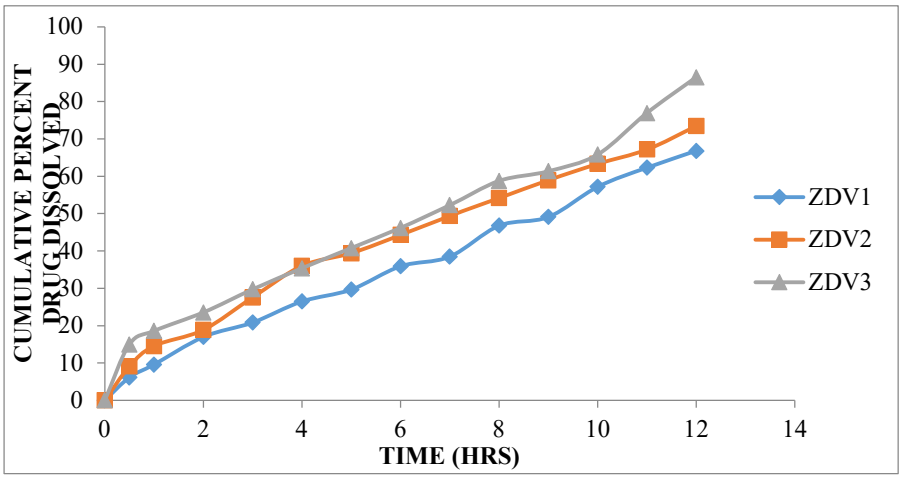

Fig 1: Dissolution profile of Zidovudine (ZDV1, ZDV2, ZDV3 formulations).

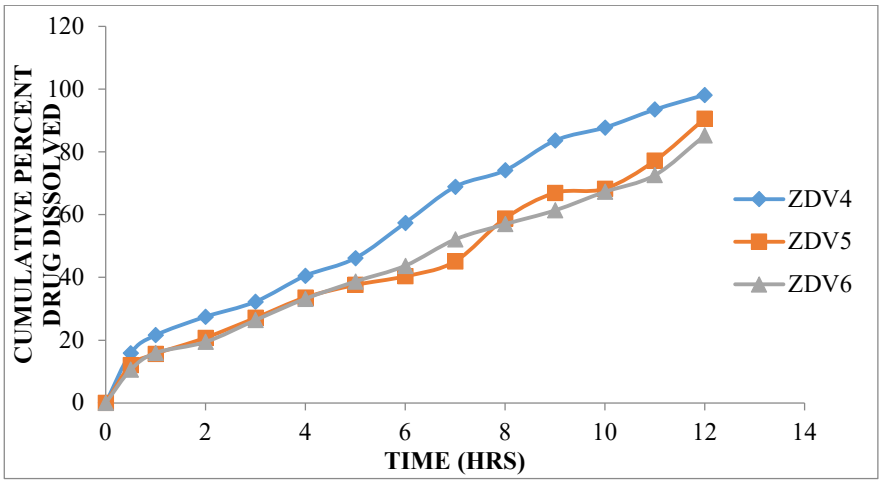

Fig 2: Dissolution profile of Zidovudine (ZDV4, ZDV5, ZDV6 formulations)

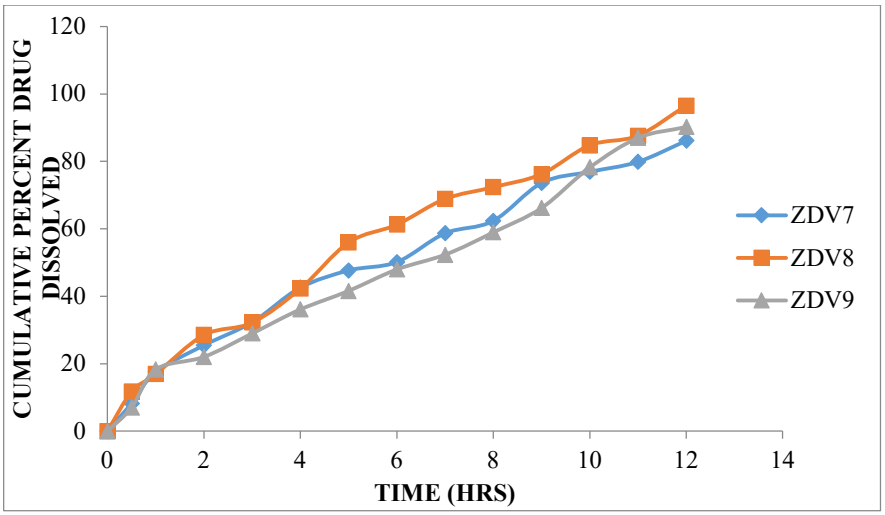

Fig 3: Dissolution profile of Zidovudine (ZDV7, ZDV8, ZDV9 formulations)

From the dissolution data it was evident that the formulations prepared with Eudragit RSPO polymer (high concentrations) were able to retard the drug release up to desired time period i.e., 12 hours.

The Formulation Containing Gum copal in 60mg Concentration Showed good retarding nature with required drug release in 12 hours i.e., 98.14 %.

Whereas the formulations prepared with Gum damar were retarded the drug release in the concentration of 120 mg (ZDV8 Formulation) showed required release pattern i.e., retarded the drug release up to 12 hours and showed maximum of 96.54 % in 12 hours with good retardation.

From the above results it was evident that the formulation ZDV4 is best formulation with desired drug release pattern extended up to 12 hours.

CONCLUSION

The present investigation was carried out for controlling the drug release up to 12 hrs. For controlling the drug release polymers used such as Eudragit RSPO, Gum copal and Gum damar. Standard graph was given that regression analysis R^2 value was 0.999 in 0.1 N HCl and 0.998 in pH 6.8 phosphate buffers. FTIR results were shown good compatibility between drug and excipients. All the pre and post compression studies such as Bulk density, Tapped density, Angle of repose, Carr's index, Hausners ratio, Weight variation, Thickness, Hardness, Drug content was found to be within limits. *In vitro* drug release studies revealed that among all formulations ZDV4 formulation was considered as optimised formulation which contains Gum copal as polymer in the concentration of 60 mg. Drug release kinetic studies were done for optimised formulation. It was followed Zero order release kinetics.

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