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Research Article

Development and characterization of anti-hiv drug (zudovudine) controlled release matrix tablets

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ABSTRACT

The aim of the present work is to Develop and Characterize controlled release of Zidovudine matrix tablets used for treatment of HIV infection. Development of CR Zidovudine is proposed considering the adverse event profile and high fluctuation index of Zidovudine observed with IR dosage forms. In the present work, attempts were made to formulate and evaluate controlled release of matrix tablets of Zidovudine. Zidovudine was subjected to Preformulation studies; based on the results obtained Zidovudine controlled release tablets were successfully formulated. Formulations prepared by wet granulation using HPMC and carbopol 934 as control release polymers and 5% W/W of povidone in isopropyl alcohol as binder solution have showed desired in vitro release. Set of trials were formulated for which Zidovudine evaluated parameters (bulk density, tapped density, compressibility index, Hausner's ratio, weight, thickness, and hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 6.8 phosphate buffer. From the results of the in vitro study it appears that the release of the Zidovudine was significantly influenced by the characteristics of the polymer used.

Keywords: Zidovudine, polymers, wet granulation technique, in vitro drug release studies, zero order kinetics.

INTRODUCTION[1,2,3,4]

Oral drug deliveryproducts, such as tablets and capsules, are formulated to release the active drug immediately after oral administration, to obtain rapid and complete systemic drug absorption. Such immediate-release products result in relatively rapid drug absorption and onset of accompanying Pharmacodynamic effects. However, after absorption of the drug from the dosage form is complete, plasma drug concentrations decline according to the drug's pharmacokinetic profile. Eventually, plasma drug concentrations fall below the minimum effective plasma concentration (MEC), resulting in loss of therapeutic activity. Before this point is reached, another dose is usually given if a sustained therapeutic effect is desired. An alternative to administering another dose is to use a dosage form that will provide sustained drug release, and therefore maintain plasma drug concentrations, beyond what is typically seen using immediate-release dosage forms.[1]

The term modified-release drug productis used to describe products that alter the timing and/or the rate of release of the drug substance. so several types of modified-release drug products are recognized:

1. *Extended-release drug products*. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products.

2. *Delayed-release drug products*. A dosage form that releases a discrete portion or portions of drug, at a time or at times other than promptly after administration,Enteric-coated dosage forms are the most common delayed-release products.

3. *Targeted-release drug products*. A dosage form that releases drug at or near the intended physiologic site of

action. Targeted-release dosage forms may have either immediate- or extended-release characteristics.

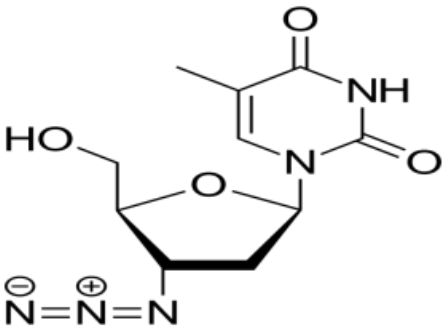
Oral controlled release drug delivery systems

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects.[2,3]

Characteristics of drugs suitable for formulation as Sustained Release Products

1. Exhibit moderate rates of absorption and excretion.
2. Uniform absorption throughout the gastrointestinal tract.
3. Administered in relatively small doses.
4. Possess good margin of safety.
5. Used for treatment of chronic therapy.

DRUG PROFILE: Zidovudine,
Category: Anti HIV drug
Structural formula:



Molecular structure of Zidovudine

Solubility: Zidovudine is soluble in organic solvents like ethanol, DMSO, and dimethyl formamide (DMF)
Melting point: 113 ^{0}C - 115^{0}C, Molecular formula: $C_{10}H_{13}N_5O$, Molecular weight: 267.24 g/mol

MATERIALS AND EQUIPMENTS

List of equipments

S.NO	EQUIPMENT	MANUFACTURER
1.	Electronic Balance	Mettler Tolido&Sartorius
2.	Compression Machine	Rimetek mini press-II
3.	Mechanical Sieve Shaker	Retsch , Germany
4.	Tap Density Tester	Electrolab, Mumbai
5.	Disintegration Tester	Electrolab, Mumbai
6.	Hardness Tester	Pfizer
7.	Friabilator	Electrolab, Hyd
8.	Thickness Tester	Sams Techno Mumbai
9.	Dissolution Apparatus USP II	Lab India, Disso 8000

List of materials and suppliers

S.NO	MATERIALS	SUPPLIER
1.	Zidovudine	SD Fine chemicals
2.	HPMC k_{4M}	SD Fine chemicals
3.	Carbopol 934	SD Fine chemicals
4.	Microcrystalline cellulose	SD Fine chemicals
5.	Povidone	SD Fine chemicals
6.	Magnesium Stearate	SD Fine chemicals
7.	Talc	SD Fine chemicals

METHODOLOGY

Preformulation Studies: (Methods ofAPI Characterization)
Physical properties: The color odour, tasteof the drug were recorded using descriptive terminology.

Solubility studies: Solubility study of Zidovudine was performed in Water, methanol, ethanol, 0.1 N HCl, pH 6.8 phosphate buffer and pH 6.8 phosphate buffer
Determination of melting point: Melting point of Zidovudine was determined by capillary method.

Pre compression parameters, Flow property studies, Angle of repose

Procedure: Weighed quantity of the drug was passed through a funnel kept at a height 2 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius the base of the conical pile, and the height of pile were measured and the angle of repose was calculated using the formula:

$$\tan\theta = h/r$$

Where: h=height of the pile, r=radius of the base of the conical pile, θ=angle of repose

Bulk density and Tapped density

Weighed quantity of the Zidovudine was transferred into 100 ml measuring cylinder without significant mechanical stresses during transfer. The volume occupied by the drug was measured, and then subjected to 500, 750, 1250 taps in the tap density tester (electro lab USP II), the blend was subjected to 500, 750.taps respectively then the percentage variation in volume was calculated, if it is more than 2 then the blend has to be subjected for 1250 taps and the percentage variation in volume has to be calculated.

Drug excipient compatibility studies

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Preparation of standard curve of Zidovudine:

Preparation of 0.1 N HCL: 8.5 ml of concentrated Hcl dissolve in 1000 ml of distilled water.

Preparation of standard curve of Zidovudine in 0.1 N HCL : For the standard graph, Zidovudine 10 mg was accurately weighed and dissolved in 10ml of 0.1 N HCL. From the stock solution (1mg/ml), different concentration of Zidovudine viz, 10, 20, 30, 40, 50 mcg/ml were prepared and made up to volume with distilled water. The absorbance's, which were found, are given in Table No. and the graph plotted of concentration Vs absorbance is shown in Fig no.

Preparation of 6.8 phosphate buffer: 28.80 gm of Disodium hydrogen phosphate and 11.45 gm of potassium dihydrogen phosphate in 1000 ml of water.

Preparation of standard curve of Zidovudine in 6.8 pH; For the standard graph, Zidovudine 10 mg was accurately weighed and dissolved in 10ml of 6.8 phosphate buffer. From the stock solution (1mg/ml), different concentration of Zidovudine viz, 10, 20, 30, 40, 50 mcg/ml were prepared and made up to volume with distilled water.

Table 1: Formulation of sustained release tablets of Zidovudine

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Zidovudine	100	100	100	100	100	100	100	100
HPMC K_4M	25	50	75	100	125	150	175	200
Carbopol 934	-	15	30	45	60	75	100	125
Povidone	10	10	10	10	10	10	10	10
Microcrystalline cellulose	360	320	280	240	200	160	210	60
Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Total wt	500	500	500	500	500	500	500	500

Preparation method

Different tablet formulations were prepared by wet granulation method. The formulations are composed of polymers HPMC K_4M,and carbopol 934. All powders were passed through 100-mesh sieve.

The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. Solution of PVP K30 added to the above mixture for making dump mass. Dump mass was passed through sieve no.40 and dried the granules for 2 hrs at 50^o c. The resulting granules were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated granules were compressed using 10mm punch (single punch tablet machine) in to tablets. Compression pressure was adjusted during tableting of each formula to get the tablet hardness in the range of 5 to 7 Kg/cm$^{3.}$ The total weight of tablet was kept at 500 mg.

Post compression parameters are:Weight variation: Thickness Hardness Friability: Content Uniformity were observed

Mechanism of drug release

The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and Koresmeyer Peppas model, The obtained regression co-efficient (which neared 0.999) was used to understand the release pattern of the drug from the controlled release tablets.

Stability studies

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile

The prepared Matrix tablets of Zidovudine were placed on plastic tubes containing desiccant and stored at ambient

conditions, such as at room temperature, 40±2°c and refrigerator 2-8°c for a period of 3 months.

RESULTS AND DISCUSSIONS

Preparation of standard curve of Zidovudine

Standard curve of Zidovudine was determined by plotting absorbance V/s concentration at nm. Using solution prepared in ethanol, buffer pH 1.2, pH 6.8 at nm. And it follows the Beer's law. The results were shown in Table no. 2 to 4 and Fig. 6 to 8.

EVALUATION STUDIES

Pre compression Parameters: Evaluation of granules:

Table2: Results of Pre compression parameters of tablets

F. No	Bulk density	Tappeddensity	Compressibility index	Hausner ratio	Angle of repose (0)
F1	0.620	0.711	12.79	1.14	30^0
F2	0.627	0.715	12.30	1.14	31^0
F3	0.619	0.725	14.62	1.17	32^0
F4	0.628	0.723	13.13	1.15	35^0
F5	0.624	0.728	14.28	1.16	30^0
F6	0.626	0.729	14.12	1.16	31^0
F7	0.619	0.725	14.62	1.17	29^0
F8	0.621	0.728	14.69	1.17	30^0

Table-: Results of Evaluation parameters of tablets

B. NO.	WEIGHT VARIATION (MG)*	THICKNESS (MM)*	HARDNESS (KG/CM^2)*	FRIABILITY (%)	DRUG CONTENT (%)
F1	500	3.20	6.82	0.45	95.85
F2	499	3.19	6.62	0.44	97.42
F3	500	3.17	6.82	0.41	96.78
F4	498	3.23	6.75	0.50	97.82
F5	500	3.31	6.61	0.49	98.98
F6	499	3.28	6.65	0.51	97.80
F7	501	3.20	6.59	0.49	95.86
F8	500	3.21	6.58	0.50	97.53

In-vitro Dissolution Study

Kinetic modeling of drug release

All the Eight formulation of prepared matrix tablets of Zidovudine were subjected to in vitro release studies these studies were carried out using dissolution apparatus.The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time. The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation)
5. (Percentage retained) $1^{/3}$ Vs time (Hixson –Crowell Erosion Equation)

Table 3: Drug Release Kinetics of Formulation F6

TIME	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	1	1	100	2
1	35.82	4.89	1.38	1.55	64.68	1.80
2	45.25	6.92	1.68	1.65	54.75	1.73
3	52.89	8.48	1.85	1.72	47.11	1.67
4	68.87	8.71	1.88	1.83	31.13	1.49
5	77.91	10.95	2.07	1.89	22.01	1.34
6	88.83	12	2.15	1.90	11.17	1.04
7	96.62	12.96	2.22	1.94	1.05	0.24
8	98.62	14.39	2.82	1.99	1.38	0.139

The values of invitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix, Peppas and Hixson-Crowell were depicted.

Regression values are higher with Zero order release kinetics. Therefore all the Zidovudine tablets Zero order release kinetics. Therefore all the Zidovudine tablets follow first order release kinetics.

Table4: Regression equations of Zidovudine tablets F6

Film code	In vitro release in phosphate buffer P^H 7.4 Regression values			
	Zero order	First order	Higuchi Plot	Kross mayerpeppas
F_6	0.957	0.817	0.973	0.968

The table indicates that r^2 values are higher for Higuchi's model compared for all the tablets. Hence Zidovudine release from all the films followed diffusion rate controlled mechanism.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-3 after 3 months. Parameters quantified at various time intervals were shown;

Table 5: Results of stability studies of optimized formulation F-6

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-6	25^0C/60%RH % Release	98.62	98.60	98.54	98.51	Not less than 85 %
F-6	30^0C/75% RH % Release	98.62	98.58	98.51	98.49	Not less than 85 %
F-6	40^0C/75% RH % Release	98.62	98.56	98.52	98.45	Not less than 85 %

CONCLUSION

In the present work, attempts were made to formulate and evaluate controlled release Zidovudine matrix tablets. Zidovudine was subjected to preformulation studies based on the results obtained Zidovudine controlled release tablets were successfully formulated.Formulations prepared by wet granulation using HPMC and carbopol 934 as control release polymers and 5% W/W of povidone in isopropyl alcohol as binder solution have showed desired in vitro release. Set of trials were formulated for which physical parameters (bulk density, tapped density, compressibility index, hausner's ratio, weight, thickness, hardness) were found to lie within the specifications. Dissolution study was performed in USP type II apparatus at 100 RPM in 0.1 HCL for 2 hours followed by pH 6.8 phosphate buffer upto 24hr.From the results of the in vitro study it appears that the release of the Zidovudine was significantly influenced by the characteristics of the polymer used.

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