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Comparative evaluation of zidovudine tablets formulated using natural and semi synthetic binder

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Abstract

Zidovudine is an anti-retroviral drug used in the treatment of AIDS/HIV. Zidovudine tablets were prepared by wet granulation technique using two different binding agents such as hydroxypropylmethylcellulose (semi synthetic binder) and acacia (Natural binder). Formulated tablets were evaluated for hardness, friability, disintegration and weight variation. In vitro release study of the tablets formulated using HPMC shows slow release of drug when compared to tablet with acacia and marketed formulation. Mechanism of release of drug was found to be anomalous type (diffusion followed by erosion) for all the tablet formulations.

Keywords: Zidovudine, AIDS, Acacia, HPMC, Hausner ratio, Higuchi model

Introduction

"AIDS is an epidemic disease; a potentially preventable, deadly infection for which there is no cure, no vaccine, and it is not under control" (National Commission on AIDS 1993).

Human Immunodeficiency Virus (HIV) is a retrovirus that causes irreversible destruction of the immune system, leading to the occurrence of opportunistic infections and malignancies. Attempts were being made to eradicate HIV, it was found that eradication of HIV is highly unlikely, and effective anti-retroviral therapy is required on a long-term basis to maintain viral suppression and reduce disease progression. In HIV-1-infected patients, highly active anti-retroviral therapies (HAART) have been used both to reduce viral load in plasma to undetectable levels, and to increase the number of CD4 cells in the majority of infected individuals.

Zidovudine (AZT), the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of AZT is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 h. It is also rapidly metabolized to the inactive glucuronide with a mean elimination half-life ($t_{1/2}$) of 1 h, thus necessitating frequent administration of large doses (200 mg every 4 h) to maintain therapeutic drug level. Orally administered ZDV reported to have plasma concentrations below optimal anti-retroviral concentrations (1μm) for more than half of the dosing interval. (Balis et al. 1989). It is crucial to maintain the systemic drug concentration within the therapeutic level throughout the treatment course.

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The purpose of the study is to formulate AZT tablets using release retarding excipients from natural and semi synthetic source for maintaining optimal anti-retroviral concentrations to minimize the drug resistance. In this investigation the changes that occur during granulation and tablet dissolution with respect to the addition of binding agents were also studied.

Materials and methods

Materials

Zidovudine was a gift sample from Aurobindo Ltd., India. hydroxypropylmethylcellulose (HPMC) and acacia were procured from Himedia chemicals, India. Zidovir marketed tablet from Cipla, India. All other chemicals used in the study were of analytical grade.

Preparation of the Tablets by wet granulation technique

Tablets were prepared using a natural binder (acacia) and a semi synthetic binder (HPMC). AZT (200 mg) was dry blended with appropriate quantity of excipients and wet massing of powder blend was done using gelatin solution. The wet mass was subjected to coarse screening using a suitable sieve (No. 18) and semi dried at dried at 500 ± 50°C for 15 min. Dried granules were again passed through sieve No. 25. The granule mixture was blended with appropriate quantity of magnesium stearate, talc and compressed using semi automatic single punch tableting machine (Rimek mini press - I). The formulation ingredients of two different batches are summarized in Table 1.

Table 1. Composition of tablet formulations F1 and F2 (for 50 tablets)

Ingredients	F1 (g)	F2 (g)
Zidovudine	10	10
(HPMC)	1	-
Acacia	-	1
Gelatin	0.5	0.5
Magnesium stearate	0.1	0.1
Talc	0.1	0.1

Evaluation of granules

Angle of repose:

Flow properties of the granules were evaluated by determining the angle of repose and compressibility index. Static angle of repose was measured according to the fixed funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and the angle of repose was calculated. It is the angle produced between the heap of the pile and base (Khan et al. 2007).

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

where θ = angle of repose; h = height of heap; r = radius of pile.

Bulk density:

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk volume (Vb) and weight of the powder (M) was determined (Khan et al. 2007).

$$\rho b = (M / V_b)$$

where M = weight of powder; V_b = bulk volume

Tapped density:

The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured (Khan et al. 2007).

$$\rho t = (M / V_t)$$

where M = weight of powder; V_t= volume after tapping

Compressibility index

The simplest way of measurement of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility index (Khan et al. 2007).

$$I = [(V_b - V_t) / V_b] \times 100$$

where V_b = bulk volume; V_t = tapped volume

Hausner ratio

Hausner ratio is an indirect method to determine granule powder flow property (Khan et al 2007). It is a very important parameter to be measured since it affects the mass of uniformity of the dose.

$$\text{Hausner ratio} = (\rho t / \rho d)$$

where ρt = tapped density; ρd = bulk density

Dispersibility index

10 g of granule was weighed and dropped from total height of 610 mm on to a watch glass (diameter 102 mm) through a hollow cylinder (330 X 102 mm) placed vertically 102 mm above the watch glass. The drop point is approximately 178 mm vertically above the top of the cylinder. Material landing in watch glass is weighed. Any loss of granules is due to result of dispersion (Subrahmaniyam 2002).

$$\text{Dispersibility (\%)} = [\text{weight of powder in watch glass / Initial weight}] \text{ X } 100$$

Characterization of tablets

The properties of compressed tablets, such as hardness, friability, weight variation and disintegration were determined using reported procedure. Hardness was determined using Pfizer hardness tester. Friability was determined using friability testing apparatus. Weight variation and disintegration were performed according to IP procedure.

In vitro dissolution studies

The dissolution study was carried out in 0.1 N HCl using USP-II dissolution test apparatus employing paddle stirrer. Six tablets was taken from each formulation and placed inside the 900 ml dissolution medium and speed of the paddle was set at 100 rpm. 5 mL of the samples were withdrawn at a time interval of 5 min. and replaced with same quantity of 0.1 N HCl. Samples were analyzed for drug content at 267 nm using UV double beam spectrophotometer (Shimadzu, model UV 1650 PC, Kyoto, Japan).

Drug release kinetics

To analyze the mechanism of drug release rate kinetics of the dosage form, the data obtained were fitted into Higuchi model, zero order, first order (Higuchi 1963) and Korsmeyer - Peppas (Peppas 1985).

Result and Discussion

Evaluation of granules

Formulation of proper powder blend is the key factor in the production of a tablet dosage form. Formulated powder blend of two different formulations (F1 and F2) were evaluated for angle of repose, bulk density, tapped density, Compressibility index, Dispersibility index and Hausner ratio. Angle of repose for granules with HPMC was less than 25° which shows the excellent flow property of the

granules and granules with acacia were between 30-40° shows passable flow property. Bulk density was found to be between 0.42-0.44 g/cc and tapped density values were between 0.47-0.50 g/cc for the granules. Percentage compressibility was found to be < 15% for both the granules which shows excellent flow property. Hausner's ratio for both the granules was < 1.25 g/cc which further supports the excellent flow property nature of the granules (Table 2).

Table 2. Evaluation of granules

Parameters	F1	F2
Angle of repose	24°11 ± 0.32	35°11 ± 0.28
Bulk density (g/cc)	0.42 ± 0.02	0.44 ± 0.03
Tapped density (g/cc)	0.47 ± 0.01	0.5 ± 0.02
Compressibility index (%)	15 ± 1.21	11.1 ± 1.64
Hausner ratio (g/cc)	1.175 ± 0.12	1.136 ± 0.16
Dispersibility index (%)	78 ± 1.2	86.5 ± 0.9

All values are mean ±S.D for n=3

Evaluation of Tablets

The tablets with different binding agents were subjected to various evaluation tests such as hardness, weight variation, friability and disintegration according to procedure specified in *Indian Pharmacopoeia*. Hardness of the tablets formulated with HPMC was between 6.3-6.9 kg/cm^2 and for tablet with Acacia; it was 5.4-6.2 kg/cm^2. The weight variation was found to be below 7.5% which is the acceptable variations as per I.P. specifications. Friability below 1 % was an indication of good mechanical resistance of the tablets (0.1%). Disintegration time was 45 min and 20 min for F1 and F2 respectively (Table 3). The results of Percentage weight variation, hardness and friability confirms with the official standard for tablets.

Table 3. Evaluation of tablets

Parameters	Formulation F1	Formulation F2
Hardness(kg/cm^2)	6.6 ± 0.3	5.8 ± 0.4
Friability (%)	0.04 ± 0.02	0.08 ± 0.01
Weight variation (%)	Below 7.5	Below 7.5
Disintegration Time(min)	45 ± 5	20 ± 3

In vitro dissolution studies

In vitro drug release was determined for the formulated tablets and it was compared with marketed formulation. Figure 1 shows the effect of different binding agents (HPMC and Acacia) on release rate of Zidovudine tablets. The drug release was slower from tablets containing HPMC when compared with that of tablets containing Acacia. Marketed formulation shows higher rate of drug release in 30 min. Tablet containing HPMC and Acacia shows 26.1% and 76.5% release in 30 min respectively. But the

marketed formulation shows 97.8% in 30 min. The slow *in vitro* dissolution of formulation F1 may be due to the strong rigid complex formed by HPMC with drug.

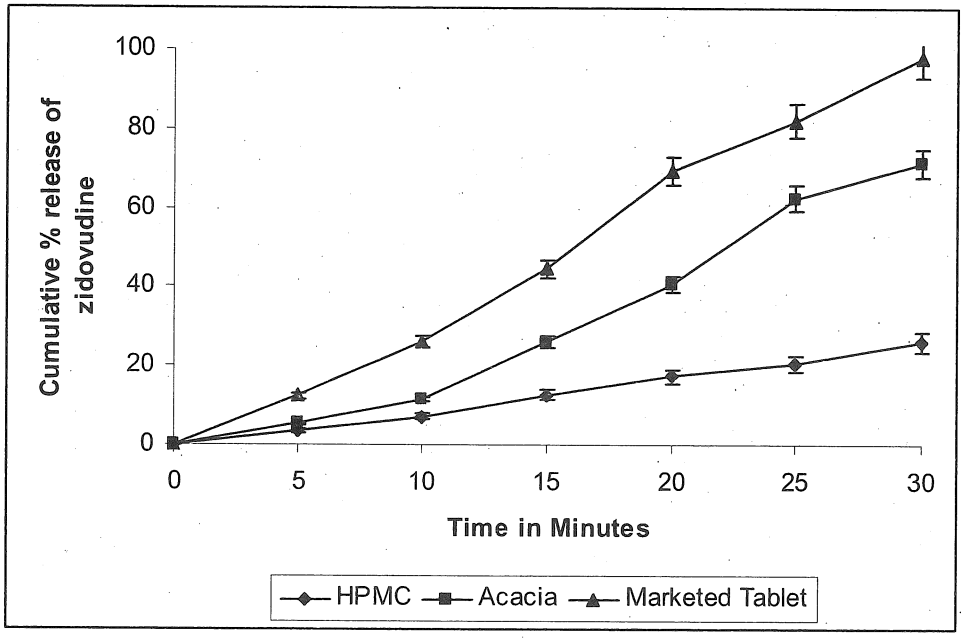

Figure 1. Comparative *in vitro* release profile of zidovudine marketed tablets and tablets formulated with binders hydroxypropylmethylcellulose and acacia

Release kinetics

Tablets formulated with Acacia and marketed formulation exhibits zero order kinetics and tablet with HPMC shows first order release kinetics. The release mechanism for all the tablets was found to anomalous type (diffusion followed by erosion) (Table 4).

Table 4. Determination of order of release of zidovudine tablets

Formulation	Higuchi	Korsermayer-Peppas	Zero order	First order	Release mechanism
F1 (HPMC)	0.9997	1.287	0.9996	0.9999	Anomalous type
F2 (Acacia)	0.9987	1.803	1.0	0.9984	Anomalous type
Marketed formulation	0.9911	1.405	0.9964	0.9805	Anomalous type

Comparative evaluation of granules and tablets compressed using two different binding agents was studied. Granules prepared using HPMC shows excellent flow property and acceptable compressibility when compared to granules prepared with acacia. Tablet with HPMC controls the release of drug and make the formulation buoyant. Bioavailability study in animals has to be carried out to justify the optimal drug concentration existing between the dosing intervals in disease state.

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