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DESIGN AND EVALUATION OF SUSTAIN RELEASE MATRIX TABLET OF ZIDOVUDINE BY USING COMBINATIONS OF DIFFERENT POLYMER

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ABSTRACT

The matrix system is one of the intricate approaches for the preparation of the sustained release dosage forms. formulation of matrix tablet has gained immense popularity now a day because it has the advantage of simple processing and low cost of fabrication. formulated oral sustained release matrix tablets of zidovudine in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Matrix tablet of zidovudine were formulated by wet granulation method using 5% PVP K-90 paste as the binder talc and magnesium stearates as lubricants. The present study was carried out to develop and evaluate the matrix tablets of zidovudine containing HPMC, XG, GG as release modifying polymer. The physicochemical compatibility of the drug with polymers was established through FTIR spectroscopy. Zidovudine sustained release matrix tablets were prepared successfully by wet granulation using HPMC K100M, GG and XG as polymers in different proportion, to retard the release and achieve required dissolution profile. Therefore it was concluded that HPMCK100M and EC in the ratio of 1:1 (F-5) is suitable for the formulating matrix system of zidovudine. Drug release kinetics of F-5 formulation correspond best to Higuchi model and drug release mechanism as per n-value of Korsmeyer & Peppas (Power law) followed non-Fickian diffusion, that means water diffusion and polymer rearrangement had an essential role in the drug release. results of the current study were indicated, a promising potential of the zidovudine matrix system as an alternative to the conventional dosage form. Since the polymer and the drugs were found to be compatible and the release mechanism is

characterized, there is a great scope for the formulation of this anti-HIV drug as a matrix system.

KEYWORDS: Zero order kinetics, Higuchi model, zidovudine, non- Fickian, PVP K-90.

1. INTRODUCTION

Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians alike. The goal of any drug-delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve promptly and then maintain the desired drug concentration. Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. Sustained release systems are those, which achieves slow release of drug over an extended period of time and in this system drug is initially made available to the body in amount to cause the desired pharmacological response. Controlled release system These system release drug at predetermine or programmed rate and provide plasma concentration that remain invariant with time.

1.1 Advantages of sustained release drug delivery system

- Improved Patient Compliance less frequent
- Dosing (by reducing number of doses).Reduced night time dosing. Reduced patient care time
- Decreased local and systemic side effects
- Reduced gastrointestinal irritation and other dose related side effects
- Improved efficiency in the treatment optimized therapy4. More uniform blood concentration. Reduction in fluctuation in drug level
- Cure or control of condition more promptly

1.2 Matrix system

The matrix system is one of the complicated approaches for the preparation of the sustained release dosage forms. In actual practice direct compression of drug, retardant material, additives are done to form a tablet in which drug particles are embedded in the matrix core of the retardant. Dry or wet granulation technique may also be employed for the preparation of this type tablets. Among the different strategies mentioned above to prolong the drug action, formulation of matrix tablet has gained immense popularity now a day because it has the advantage of simple processing and low cost of fabrication. To define matrix, it is necessary

to know the characters that differentiate it from other sustained release dosage forms. Hence the following must be considered. The chemical nature of support (generally, the support are formed by polymeric network) (Reddy et al., 2003; Jain et al., 2005).

- The physical state of drug (dispersed under molecular or particulate form or both).
- The matrix shape and alteration in volume as a function of time.
- The route of administration (oral administration remains the most widely used but other routes are adaptable).
- The release kinetic model.

1.2.1 Classification of matrix system

A. Mineral matrix

- Drug retained in the support.
- Drug adsorbed on the support.

B. Lipidic matrix

- Deliver by diffusion.
- Deliver by surface erosion.

C.Hydrophilic matrix

- Un-limited swelling, deliver by diffusion.
- Limited swelling controlled delivery through swelling.

D. Inert matrix

- Controlled delivery by diffusion.

E. Biodegradable matrix

- Non-Lipidic.

1.2.2 Advantages of matrix system

- Easy to manufacture.
- Versatile, effective and low cost.
- Can be made to release high molecular weight compounds.
- Their capacity to incorporate active principle is large, which suits them to delivery of large dosage (Vyas et al., 2002).

2. OBJECTIVE

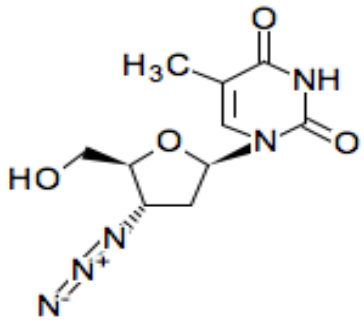
To carry out preformulation study and drug-excipient compatibility study. To study the effect of different polymers in the formulation. To develop stable and efficacious formulation of sustained release tablet. To prepare sustained release tablet of zidovudine. Increase the release time of formulated drug. Development of a zidovudine sustained release matrix tablet formulation would be a significant advantage for patient compliance accompanied by minimization of the drug side effects as a result of reduction in the drug blood concentration fluctuations, especially in long-term therapy.

Methods of preparation

- Types of polymers and excipients
- Polymer to polymer ratio
- Dissolution medium
- Various evaluation parameters and techniques

3. DRUG PROFILE

3.1 Zidovudine: A di-deoxynucleoside compound in which the 3'-hydroxy group on the sugar moiety has been replaced by an azido group. This modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chains. The compound is a potent inhibitor of HIV replication, acting as a chain-terminator of viral DNA during reverse transcription. It improves immunologic function, partially reverses the HIV-induced neurological dysfunction, and improves certain other clinical abnormalities associated with AIDS. Its principal toxic effect is dose-dependent suppression of bone marrow, resulting in anemia and leukopenia.



3.2 Mechanism of action

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido (-N3) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP),

by the sequential action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3′- OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

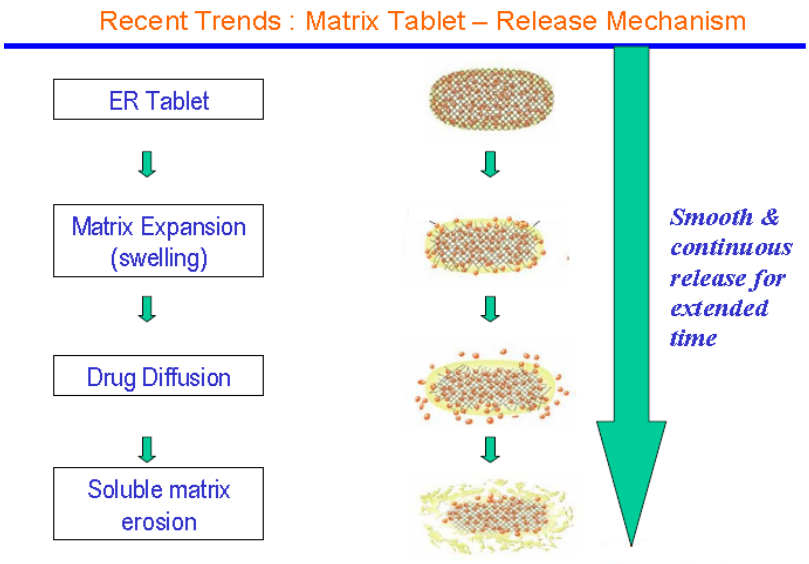


Figure 1.2: Mechanism of drug release from Matrix system.

4. Pharmacodynamics/Kinetics

- **Absorption**- Rapid and nearly complete absorption from the gastrointestinal tract following oral administration; however, because of first-pass metabolism, systemic bioavailability of zidovudine capsules and solution is approximately 65% (range, 52 to 75%). Bioavailability in neonates up to 14 days of age is approximately 89%, and it decreases to approximately 61% and 65% in neonates over 14 days of age and children 3 months to 12 years, respectively. Administration with a high-fat meal may decrease the rate and extent of absorption.
- **Metabolism-** Hepatic Metabolism by glucuronide conjugation to major, inactive metabolite, 3′-azido-3′-deoxy-5′- O-beta-D-gluco pyranuronosyl thymidine.

Table 4.1: Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients.

Parameter	Mean SD(except where noted)
Oral bioavailability (%)	64 ±10
Apparent volume of distribution (L/kg)	1.6 ±0.6
Plasma protein binding (%)	<38
Systemic clearance (L/h/kg)	1.6 ±0.6
Renal clearance (L/h/kg)	0.34 ±0.05
Elimination half-life (h)	0.5 to 3

Table 4.2: Methocel grades, their viscosities and application.

Grade	Viscosity	Application
E4M	4000	sustained release, medicated gel, thickening agent
E4MCR	4000	Sustained release
E10M	10,000	Sustained release
E10MCR	10,000	Sustained release
F4M	4000	Eye drops, Suspending agent
K4M	4000	Sustained release, Suspending agent
K15M	15,000	Sustained release
K15MCR	15,000	Sustained release
K100M	100,000	Sustained release
K100MCR	100,000	Sustained release

5.1 Materials used

Table 5.1: The materials used in the preformulation studies.

S. No.	Material used	Manufacturers
1.	Zidovudine	Alembic Ltd., Vadodara
2.	HPMC K100M	Oxford Laboratory, Mumbai
3.	Xantham gum	Central Drug house, New Delhi
4.	Guar gum	Central Drug house, New Delhi
5.	Magnesium stearate	Central Drug house, New Delhi
6.	Talc	Oxford Laboratory, Mumbai

5.2 Equipment's used

Table 5.2: List of Equipment's and their manufacturers.

S. No.	Equipment's/Instr-uments	Manufacturers
1.	Digital melting point apparatus	Jyoti Scientific Ind. Gwalior (M.P)
2.	Digital weighing balance	Jyoti Scientific Ind. Gwalior (M.P)
3.	Digital pH meter	M Kow Optics, Delhi
4.	PC based double beam UV-Spectrophotometer 2202	Systronics, Vadodara
5.	Hardness tester (Pfizer)	Jyoti Scientific Ind. Gwalior (M.P)
6.	Friability test apparatus	Jyoti Scientific Ind. Gwalior (M.P)
7.	Dissolution apparatus	Electrolab, Delhi
8.	Thickness tester (Vernier caliper)	Jyoti Scientific Ind. Gwalior (M.P)

5.3 Preformulation studies

5.3.1 Identification of drug

- **Organoleptic characteristics**
- **Colour:** A small quantity of zidovudine powder was taken in butter paper and viewed at well-illuminated place.
- **Taste and odour*:*** Very less quantity of zidovudine was used to get taste with the help of tongue as well as smelled to get the order.
- **Melting point determination:** The Melting point was determined by the capillary method using Digital Melting point apparatus. The capillary tube was fused and filled by pressing the open end gently into pure drug sample and packed by tapping the bottom of the capillary on a hard surface so that the drug packed down into the bottom of the tube. When the drug was packed into the bottom of the tube, the tube was placed into the slot of the apparatus, the apparatus was started and the temperature was noted at which the drug melt.
- **Confirmation of λ_{max}:** Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCl in 10 ml of volumetric flask and prepare suitable dilution. The spectrum of this solution was run in 200-400 nm range in UV/Vis. Spectrophotometer.
- **FT-IR analysis**: The FT-IR analysis of the zidovudine was carried out for qualitative compound identification. The FT-IR spectrum for pure drug was carried out by KBr disc method, the spectrum was recorded in the range of 4000 cm^{-1} and 450cm^{-1}.

5.3.2 Determination of solubility of drug by visual observation

A fixed amount of drug was taken, and then distilled water was added and observed the solubility visually. The same procedure was followed for 0.1 N HCl, pH 7.4 Phosphate buffer.

5.3.3 Preparation of standard curve of zidovudine

- **Preparation of stock solution in distilled water**

100 mg of zidovudine was accurately weighed and transferred to a 100 ml volumetric flask. Then distilled water was added to dissolve the drug completely. The volume was made up to 100 ml with Distilled water. The solution resulted is ≈1000 µg/ml. Then 10

Ml of this solution is transferred to another 100 ml volumetric flask to obtain solution of 100 µg/ml served as stock.

- **Preparation of dilutions from stock solution**

From this stock solution 0.2, 0.4, 0.6, 0.8, 1.0 ml was pipette out in 10 ml calibrated volumetric flask and dilution was made with distilled water to obtain 2, 4, 6, 8, 10 µg/ml solutions.

Same procedure was followed for 0.1 N HCl and pH 7.4 Phosphate buffer.

5.3.4 Flow property of granule (Ali et al., 2007)

- **Angle of repose:** The angle of repose was determined by fixed funnel method. A funnel was kept vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom is closed and 5gm of sample powder is filled in funnel. Then funnel was opened to release the powder on the paper to form a smooth conical heap. The height and radius of the heap was measured and the angle of repose was calculated by using the following formula.

$$\theta = \tan^{-1} h/r$$

Where, θ = Angle of repose, h = Height of heap and r = radius

Table 5.3: Relationship between Angle of Repose (θ) and flow properties.

Angle of repose(θ)	Flow property
< 25°	Excellent
25-30^0	Good
35-40^0	Passable
> 40^0	Very poor

- **Bulk density:** A known amount of drug was transferred into a 25 ml measuring cylinder, carefully level the powder without compacting and measure the bulk volume. The bulk density was determined by using the formula-

Bulk Density = weight of drug / bulk volume

- **Tapped density** Tapped density was determined by digital bulk density apparatus.A known amount of drug was transferred into the measuring cylinder and tapped up to 100 times and measures the tapped volume. The Tapped density was determined by using the formula:

Tapped Density = weight of drug / tapped volume

- **Compressibility Index**: Compressibility index was determined by the following formula:

Compressibility Index = [Tapped density – Bulk density / Tapped density] x100

Table 5.4: Practical consideration of compressibility Index.

% Compressibility Index	Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very -Very poor

- **Hausner's ratio**: Hausner's ratio was determined by the following formula:

Hausner's ratio = Bulk Density / Tapped Density

Table 5.5: Practical consideration of hausner's ratio.

Hausner's Ratio	Flow
< 1.25	Good
>1.25	Poor
1.25-1.5	Addition of glidant needed

Table 5.6: Formulation design for the sustained release matrix tablet of zidovudine.

S. No.	Ingredients (Quantity in mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8
1	Zidovudine	300	300	300	300	300	300	300	300
2	HPMC K100 M	210	-	-	70	150	60	150	-
3	Xantham gum	-	210	-	70	60	150	-	150
4	Guar gum	-	-	210	70	-	-	60	60
5	Magnesium Stearate	6	6	6	6	6	6	6	6
6	Talc	4	4	4	4	4	4	4	4
	Total Wt. (mg.)	520	520	520	520	520	520	520	520

5.4.1 Preparation of zidovudine matrix tablet

Matrix tablet of zidovudine were formulated by wet granulation method using 5% PVP K-90 paste as the binder talc and magnesium stearates as lubricants. The composition of different formulation used in the study is given in Table 6.6. The powders were mixed and granulated with 5% PVP K-90 paste. The wet mass passed through a mesh number 08. The obtained wet granules were dried at 50^0C for 2 hours. The dried granules were passed through mesh no. 16 superimposed on mesh no. 36, and these granules lubricated with the mixture of talc and magnesium stearates, finally these granules were compressed into tablets of each 520 mg using 8 station tablet punching machine. The tablets were compressed to a hardness of 5 to 7 kg/cm^2.

5.5 Evaluation of tablet

All the prepared Sustained release tablets were evaluated for following official and unofficial parameters.

- Weight variation
- Friability test
- Hardness.
- Thickness and diameter.
- *In-Vitro* Dissolution Studies (Banker et al., 2002; Liberman et al., 1999; Remington et al., 1998).

5.5.1 Weight variation

The weight variation test would be a satisfactory method of determining the drug content uniformity. I.P. procedure for uniformity of weight was followed, 20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance (DJ Series Shinko). The average weight of one tablet was determined from the collective weight.

Table 5.7: Specification as per IP.

Average weight of tablets (mg)	Percentage deviation
80 or less	10
80 – 250	7.5
more than 250	5

5.5.2 Friability test

The test was done by using Roche friabilator .10 tablets were taken and carefully dedusted prior to testing. The tablets were weighed accurately, and placed the tablets in the drum. The drum was rotated 100 times, and after that the tablets were removed. Removed loose dust from the tablets as before, and accurately weigh.

The % loss was determined by using following formula:

$$\% \text{ weight Loss} = [\text{Initial Weight} - \text{Final Weight} / \text{Initial Weight}] \times 100$$

A maximum loss of mass not greater than 1.0 % is considered acceptable.

5.5.3 Hardness

Tablet hardness was determined by using a tablet Pfizer Tester. Mean hardness of 5 tablets from each formulation batch was determined.

5.5.4 Thickness and diameter

The thickness and diameter of tablets was determined by using Vernier Caliper. Mean thickness and diameter of 5 tablets from each formulation batch was determined.

5.5.5 *In - Vitro* dissolution studies

In-Vitro dissolution study was carried out using USP II apparatus in 900 ml of 0.1N HCl (pH 1.2) at 50 rpm. The temperature of the dissolution medium was kept at 37± 0.5^{o}C. 5 ml of sample solution was withdrawn at specified interval of time. The absorbance of the withdrawn samples was measured at λ_{max} 267.2 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of zidovudine prepared in 0.1N HCl at λ_{max} 267.2 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

5.6 Mathematical models (Liberman et al., 2008; Gibaldiet al., 2001)

- **Zero order kinetics**

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation;

$$Q_t = Q_o + k_o t$$

Where, Q_t= amount of drug released in time‘t’, Q_o= initial amount of drug in the solution, k_t= zero order release constant.

The pharmaceutical dosage forms following this profile, release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a pharmacological prolonged action. This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage form, as in the case of some transdermal system, as well as matrix tablets with low soluble drugs coated form, osmotic systems, etc.

- **First order kinetics**

The application of this model to drug dissolution studies was first proposed by Gibaldi and Feldman (1967). The following relation can express this model:

$$\text{Log } Q_t = \text{Log } Q_o + k_t t/2.303$$

Where, Q_t= amount of drug released in time‘t’, Q_o= initial amount of drug in the solution, k_t= first order release constant.

The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in porous matrices release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminishes.

Higuchi model

Higuchi (1961, 1963) developed several theoretical models to study the release of water soluble drugs incorporated in semisolid and/or solid matrixes. Simplified Higuchi model can be expressed by following equation:

$$f_t = k_H t^{1/2}$$

Where, k_H= Higuchi diffusion constant, f_t= fraction of drug dissolved in time't'.

Higuchi describes drug release as a diffusion process based in the Fick's law, square root time dependent. This relation can be used to describe the drug dissolution from several types modified release pharmaceutical dosage forms, as in the case of some transdermal systems and matrix tablets with water soluble drugs.

- **Korsmeyer-Peppas model**

Korsmeyer et al., (1983) developed a simple, semi empirical model, relating exponentially the drug release to the elapsed time (t);

$$f_t = at^n$$

Where, a = constant incorporating structural and geometric characteristics of the drug dosage form, n = release exponent, $f_t = M_t/M_\infty$ = fraction release of drug.

6. CONCLUSION

The sustained release system includes any drug delivery system that achieves slow and extended release of drug over an extended period of time. The present study was carried out to develop and evaluate the matrix tablets of zidovudine containing HPMC, XG, GG as release modifying polymer. The physicochemical compatibility of the drug with polymers was established through *FTIR* spectroscopy. The study was indicated that the drug have good compatibility with polymers. The data generated from *in-vitro* studies showed, the drug release from matrices containing HPMCK100M and XG alone not sustained the release of drug 10-12 hr. GG retard the release but release is not proper. When HPMC K100M and XG are taken in combination the retard the release for 10-12 hr. the release was based on diffusion and erosion. Therefore, XG, GG and HPMCK100M can be used to modify release

rate of zidovudinein matrix tablets. The results of *in-vitro* drug release studies in simulated GI fluids was showed that matrix tablets containing 1:1 ratio of HPMCK100M and XG (F-5) are able to control the release of water-solublezidovudine. Therefore it was concluded that HPMCK100M and EC in the ratio of 1:1 (F-5) is suitable for the formulating matrix system of zidovudine. Drug release kinetics of F-5 formulation correspond best to Higuchi model and drug release mechanism as per n-value of Korsmeyer & Peppas (Power law) followed non-Fickian diffusion, that means water diffusion and polymer rearrangement had an essential role in the drug release. No significant difference was observed in the release profile of optimized matrix formulation, indicating that the manufacturing process employed was reliable and reproducible. Also release kinetics unaltered on storage and there were no changes in the tablets characteristics, suggesting that zidovudinewas stable in the designed matrices. Thus, results of the current study were indicated, a promising potential of the zidovudine matrix system as an alternative to the conventional dosage form. Since the polymer and the drugs were found to be compatible and the release mechanism is characterized, there is a great scope for the formulation of this anti-HIV drug as a matrix system.

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