Chapter 2
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Investigating the Influence of pH on Drug Release from Zidovudine Matrices Containing Different Grades of Hydroxypropyl Methyl Cellulose

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ABSTRACT

The current study investigates the impact of a multimedia dissolution profile on the drug release of zidovudine-containing sustained-release hydrophilic matrices using a variety of hydroxypropyl methylcellulose grades. Zidovudine, the first anti-HIV drug to receive FDA approval for clinical use, is widely used to treat AIDS, either alone or in combination with other antiviral drugs. To sustain the release of the medication, matrices were created utilising a combination of several grades of HPMC, namely HPMCK4M and HPMCK15M. In-vitro multimedia dissolution studies were carried out in order to mimic the in-vivo situation. The pH/buffer is chosen based on the drug's exposure from the stomach to the intestine/colon. The research ensures that pH changes have an effect on drug dissolution and release for absorption. Matrices also provide quite regulated release of the drug zidovudine over an extended period of time.

Keywords: Multimedia; dissolution; matrices; pH.

1. INTRODUCTION

Zidovudine, the first anti-HIV drug to receive FDA approval for clinical use, is widely used to treat AIDS, either alone or in combination with other antiviral drugs. Its dose-dependent haematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability are the key limitations to its therapeutic effectiveness.It is rapidly absorbed from the gastrointestinal tract (GIT) after oral administration, reaching a peak plasma concentration of 1.2 µg/mL at 0.8 hours. It is first transformed to zidovudine triphosphate in the systemic circulation, which is pharmacologically active and suppresses HIV viral replication. Since zidovudine -triphosphate has a biological half-life of 4 hours, it must be administered often (3 to 4 times per day) to maintain therapeutic medication levels. Since zidovudine acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of zidovudine is desired for maintaining anti-AIDS effect and avoiding the strong side effects. These side effects are usually associated with excessive plasma level of zidovudine immediately after intravenous or oral administration. Zidovudine is absorbed throughout the GIT. The drug is freely soluble at any pH and hence judicious selection of release retarding excipients is necessary for achieving constant in vivo release. The most commonly used method of modulating the drug release is to include it in a matrix system [1-6].

Multimedia dissolution is to mimic the in-vivo condition by doing in-vitro test and pH/buffer selection is based on the exposure of drug from stomach to intestine/colon and to ensure the impact of pH changes on dissolution and release of drug substance for absorption [7-9]. In vitro dissolution is well established as a quality control technique to monitor the batch-to-batch quality and performance of a drug product. Dissolution is routinely used by most pharmaceutical firms to guide the development of new formulations and to monitor product quality after scale-up of batch size, and after changes in formulation, manufacturing process, equipment, and site of manufacture [10,11].

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Sustained release drug delivery system of zidovudine is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time by using different grades of Hydroxypropyl methylcellulose (HPMC) viz. HPMCK4M and HPMCK15M [12-16].

2. MATERIALS AND METHODS

Zidovudine was obtained as a gift sample and tablets were prepared by direct compression using HPMCK4M and HPMCK15M polymer combinations. Other excipients used were Magnesium stearate, Talc, MCC and dibasic calcium phosphate. The drug was analyzed by UV spectrophotometer (UV 1601 Shimadzu, Japan) at 266 nm.

3. RESULTS AND DISCUSSION

Physical properties of the tablets were found within the probable limits as shown in Table 1. The drug content was estimated from the absorbance obtained. Three tablets of zidovudine were placed into three different pH of phosphate buffer (pH2.4, pH 6.8 and pH 7.4). The USP dissolution apparatus was set at rotation 50 rpm and temperature of the assembly was set at 37°C. Absorbance was measured at 266 nm by collecting sample at different time intervals up to 12 hrs. The percentage drug release was calculated at different time intervals at different pH and shown in Table 2. The graph was plotted between percent drug release and time for different dissolution media and shown in Fig. 1.

Table 1. Physical characteristics of the tablets

FORMULATION				
HPMC K4M mg	**HPMC K15M mg**	**Weight mg Mean ± SD**	**Hardness Kg Mean ± SD**	**Friability (%)**
25	15	120 ± 1.96	5.5O ± 0.12	0.50-0.08

Table 2. Result of dissolution studies with different pH

Sr. No.	**Time hrs.**	**Absorbance (nm.)**			**% Drug release**		
		2.4	**6.8**	**7.4**	**pH2.4**	**pH6.8**	**pH7.4**
1	0.5	0.161	0.168	0.222	12.78	13.5	20.3
2	1	0.186	0.194	0.438	16.16	16.53	26.4
3	2	0.214	0.224	0.573	19.68	22.24	38.5
4	4	0.321	0.361	0.692	31.69	36.24	55.6
5	6	0.431	0.582	0.732	45.22	61.2	71.2
6	8	0.446	0.612	0.811	46.27	65.52	78.5
7	12	0.567	0.68	0.904	60.97	84.1	95.5

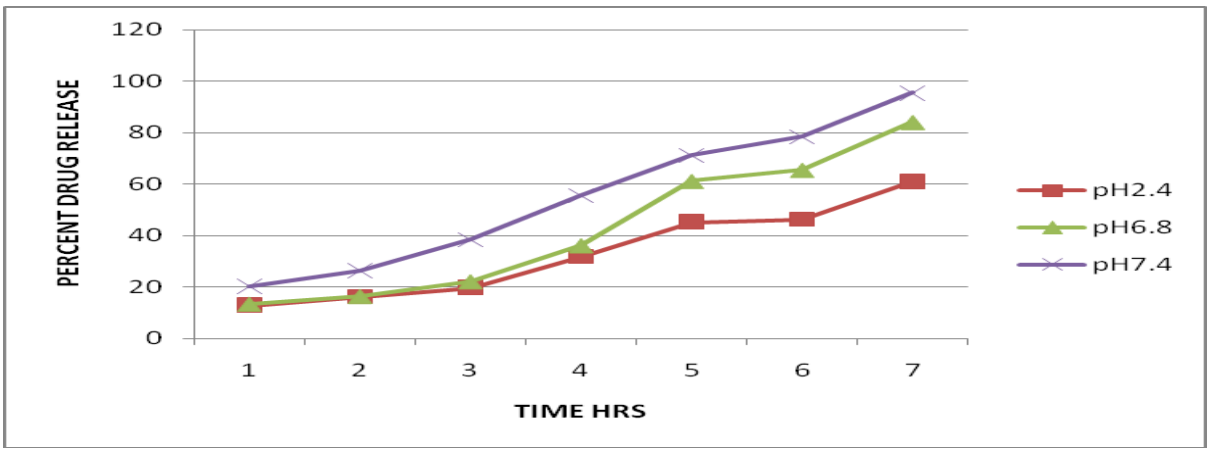

Fig. 1. Percent drug release V/s Time in different pH media

4. CONCLUSION

The release profile of zidovudine from the matrices increased continuously with time, and the amount of drug release best seen in acidic media (pH=7.4). The cumulative amount of drug release is higher at pH 7.4 than that of pH 6.8 by 11.4 % and then that of pH 2.4 by 24.53 %. This increase in drug release at higher pH can be attributed to pH dependent solubility of stavudine. As the pH increases, the solubility of zidovudine increases which might increase drug release from matrices.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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