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FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF ZIDOVUDINE

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ABSTRACT

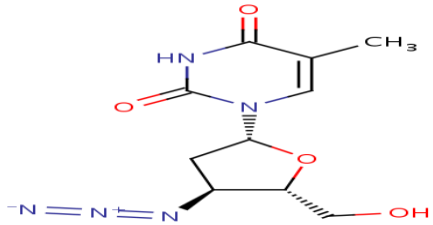
Zidovudine is considered a good candidate for incorporation in a gastro-retentive dosage form due to its high solubility in the stomach medium compared with its solubility in the small intestine medium. As its solubility decreases with increase in pH, it would be more beneficial to retain the drug in stomach (acidic environment) for prolonged duration so as to achieve maximum absorption and bioavailability. Zidovudine is the first approved compound for the treatment of aids; however the limitation for the therapeutic effectiveness of zidovudine is its dose-dependent toxicity, short biological half-life and poor bioavailability. The present research work, an attempt has been made to develop the zidovudine gastro-retentive dosage form for controlled release.

Keywords: Zidovudine, Gastro-retentive dosage, Controlled release.

INTRODUCTION

Zidovudine is a thymidine analogue, which differ structurally from thymidine in that zidovudine contains a 3'-azide rather than a 3'-hydroxyl group. Zidovudine is belong to the class of nucleoside reverse transcriptase inhibitor, it is the first anti HIV compound approved for clinical use and widely used in the treatment of AIDS either alone (or) in combination with other antiviral agents. It is also sold under the names Retrovir, Retrovis, and as an ingredient in Combivir and Trizivir.

Figure 1. Structure of zidovudine



IUPAC Name:
1-[(2R,4S,5S)-4-azido-5-(hydroxymethyl)oxolan-2-yl]-5-methyl-1,2,3,4-tetrahydropyrimidine-2,4-dione.

The Food and Drug Administration (FDA) approved the drug (via the then-new-FDA accelerated approval system) for use against HIV, AIDS, and AIDS releated complex (ARC, a now-defunct medicalterm for pre-AIDS illness) on March 20, 1987, and then as a preventive treatment in 1990. It was initially administered in much higher dosage than today, typically 400mg every four hours (even at night) One of AZT'S side effects includes anemia, a common complaint in early trails.

Zidovudine, a structural analog of thymidine, inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA [1-30].

MATERIALS AND METHODS

ANALYTICAL METHODS

Standard graph of Zidovudine

An accurately weighed amount of 100mg Zidovudine was transferred into a 100 ml volumetric flask containing 0.1N HCl to dissolve and then the volume was made up to the mark with 0.1N HCl. From this necessary

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dilutions were made to give concentration ranging from 1-12 µg/ml solutions. The absorbance of the volumetric solutions was recorded at λ_{max} (264nm) of the drug and plotted graphically to give the standard graph of Zidovudine.This type of analysis of release behavior is valuable is to the formulator for comparative purposes (Hariharan et al., 1997b). The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

RESULTS AND DISCUSSION

The study started with the construction of standard calibration curves of Zidovudine. The $\lambda_{max}$of Zidovudine in 0.1N HCl was scanned and found to have the maximum absorbance at 264 nm. The standard graph of Zidovudine in 0.1N HCl was plotted by taking concentration ranging from 2 to 14 µg/mL and a good correlation was obtained with R^2 values of 0.999 respectively.

Floating Properties of Floating Tablets of Zidovudine

All the formulations were tested for floating properties like floating lag time and total floating time. The results of the tests were tabulated *in vitro* buoyancy. The results of the *in vitro* buoyancy study of Zidovudine tablets are shown in Figure. The figure clearly indicates the floating lag time (2 min) of the Zidovudine tablet and swelling tendency of the formulation. Hydroxy propyl methyl cellulose (HPMC) K4M, K15M, K100M was evaluated varying the sodium bicarbonate portion from 8% to 10%. Finally, lag time was observed less than 2 min for all the formulations and then optimizing the sodium bicarbonate portion at 8.5% w/w to the total tablet weight. Also the tablet integrity, swelling characteristics were found satisfactory. Floating characteristics like lag time, total floating time for all the formulations were studied and reported (Table).

IN–VITRO DRUG RELEASE DATA AND PROFILES

ii. Release profiles of formulations containing HPMC $K_{15}M$

iii. *In-vitro* drug release of ZD from HPMC K100M containing formulations

Selection of optimized formulation

The release from all the formulation was followed diffusion controlled release followed by zero order which was confirmed by higher correlation coefficient values for Higuchi and release exponent values of KorsemeyerPeppas equations.

All the formulations followed Higuchi profiles with R^2values more than 0.9, followed by Zero order which account for the diffusion controlled release from the formulations.

The formulation F8 showed high regression value of 0.887 for zero order and 0.985 for Higuchi order with complete drug release in 12 hrs made it to select as an optimized formulation compared with other formulations. Thus it was selected for *in vivo* investigation.

Higuchi model as it was evidenced by correlation coefficients ($r^2 = 0.97$).

Zero-order as it was evidenced by correlation coefficients ($r^2 = 0.887$).

First-order as it was evidenced by correlation coefficients ($r^2 = 0.935$).

The data was further treated as per the following equation:

$Mt/M\infty = K.\ tn$

Where, $Mt/M\infty$ is the fractional release of the drug, Mt is the amount released at time t,

$M\infty$ is the total amount of drug contained in the formulation,

t is the release time, K is a kinetic constant, and

n is the diffusional release exponent indicative of the operating release mechanism.

The n values obtained (n=0.5) by this equation indicated that the drug release was by non-Fickian model. The results are shown in Table 13.

Table 1. Materials Used

Name of Chemical	Source
Zidovudine	A generous gift from Euro Labs, Hyd
HPMC K4M	Signet Chemical Corporation, Mumbai
HPMC K15M	Signet Chemical Corporation, Mumbai
HPMC K100M	Signet Chemical Corporation, Mumbai
Magnesium stearate	S.D. Fine Chemicals, Mumbai
Talc	S.D. Fine Chemicals, Mumbai
Sodium bicarbonate	Merck, Specialities Pvt Ltd, Mumbai

Table 2. Equipment Used

Name of Equipment	Manufacturer
Rotary tabletting Machine	Riddhi, Ahmedabad
Digital weigh balance	Shimadzu, Japan
Monsanto Hardness tester	Pharma lab, Ahmedabad

Name of Equipment	Manufacturer
Vernier caliperse	Mitutoyo, Japan.
Roche Friablator	Tab-Machines, Mumbai
Dissolution apparatus	Tab- Machines, Mumbai
UV-VIS Spectrophotometer	Elico Pvt Ltd, Hyderabad
Hot air Oven	Tempo Instruments, Mumbai
Glass ware	Borosil & Anumbra
Stability Chambers	Labtop, Skylab Instruments Pvt Ltd, Thane.

Table 3. Formulae used to prepare Zidovudine floating tablets with HPMC K4M

Ingredients	F1	F2	F3	F4	F5
Drug	200	200	200	200	200
HPMC K4M	80	100	120	140	160
NaHCO3	50	50	50	50	50
MCC	150	130	110	90	70
Talc	10	10	10	10	10
Mg. stearate	10	10	10	10	10
Total	500	500	500	500	500

Table 4. Formulae used to prepare Zudovudine floating tablets with HPMC K15M

Ingredients	F6	F7	F8	F9	F10
DRUG	200	200	200	200	200
HPMC K15M	60	80	100	120	140
NaHCO3	50	50	50	50	50
MCC	170	150	130	110	90
Talc	10	10	10	10	10
Mg. stearate	10	10	10	10	10
Total	500	500	500	500	500

Table 5. Formulae used to prepare Zudovudine floating tablets with HPMC K100M

Ingredients	F11	F12	F13	F14	F15
DRUG	200	200	200	200	200
HPMC K100M	40	60	80	100	120
NaHCO3	50	50	50	50	50
MCC	190	170	150	130	110
Talc	10	10	10	10	10
Mg. stearate	10	10	10	10	10
Total	500	500	500	500	500

Table 6. Weight variation tolerances for uncoated tablets

Maximum % of weight difference allowed	Average weight of tablets(mg)	
	USP	**IP**
10	<130	<80
7.5	130 – 324	80-250
5	>324	>250

Table 7. Drug transport mechanism

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than	Supercase-ll	t^{n-1}

Table 8. Standard graph of Zidovudine in 0.1N HCl at 264 nm

Concentration (µg/ml)	Absorbance
0	0
2	0.127
4	0.243
6	0.375
8	0.517
10	0.649
12	0.764
14	0.914

Table 9. Floating properties of single unit matrix tablets

Formulation	Floating lag time (sec)	Floating time (h)
F1	55 ± 2.1	>12
F2	58 ± 2.6	>12
F3	61± 2.1	>12
F4	60 ± 2.5	>12
F5	68 ± 2.3	>12
F6	66 ± 3.2	>12
F7	65 ± 2.7	>12
F8	66 ± 0.9	>12
F9	58± 2.4	>12
F10	55 ± 1.4	>12
F11	247 ± 2.9	>12
F12	234 ± 3.1	>12
F13	228 ± 3.4	>12
F14	238 ± 4.1	>12
F15	244± 2.9	>12

Table 10. *In vitro* release of ZD floating tablets from HPMC K4M formulations

Time (hrs)	% drug release				
	F1	**F2**	**F3**	**F4**	**F5**
0	0	0	0	0	0
0.5	22.32± 2.1	16.94± 1.8	14.03± 2.3	13.27± 2.6	9.57± 2.7
1	39.85± 2.4	28.51± 2.8	25.32± 1.7	24.73± 1.9	18.82± 2.5
2	51.64± 1.9	40.14± 2.5	37.84±3.2	36.26± 2.3	28.78± 1.6
3	65.38± 2.7	58.24± 2.3	49.26±1.8	45.35± 2.4	39.59± 3.2
4	82.71± 1.9	72.47± 1.9	62.94± 2.6	59.49± 3	47.84± 2.5
6	97.47± 2	88.82± 2.6	78.84± 2.1	74.49± 2.9	59.85± 2.7
8		95.49± 2.4	89.37± 3.1	83.68± 1.6	67.45± 2.1
10			98.73± 2.7	91.28± 1.7	78.79± 1.9
12				96.26± 2.6	86.91± 1.6

Table 11. *In vitro* release of ZD from HPMC K15 containing formulations

Time (hrs)	% drug release				
	F6	**F7**	**F8**	**F9**	**F10**
0	0	0	0	0	0
0.5	31.29± 1.8	27.38± 2.4	14.69± 1.8	12.1± 1.9	10.32± 2.6
1	40.42±2.9	38.79± 1.9	25.49±1.6	18.46± 1.7	16.22±2.8
2	52.75± 3.2	49.08± 2.9	38.32± 1.9	27.92± 1.6	25.45± 2.6
3	76.64±2.7	59.89± 3.2	49.08± 2.8	38.41± 2.2	33.95± 2.2
4	93.83±2.6	69.46± 2.5	61.98±2.4	46.78± 2.6	44.73± 3.2

Time (hrs)	% drug release				
	F6	F7	F8	F9	F10
6	100± 2.5	82.17± 2.2	69.17± 2.8	59.49± 2.9	53.56± 2.9
8		95.74± 2.1	79.37± 3.2	68.17± 2.5	64.54± 2.6
10			88.47± 2.9	72.77± 3.2	70.57± 2.8
12			96.89± 2.6	80.96± 2.8	76.43± 3.2

Table 12. *In vitro* drug release of ZD from HPMC K100M containing formulations

Time (hrs)	% drug release				
	F11	F12	F13	F14	F15
0	0	0	0	0	0
0.5	16.16±2.8	15.56±3.2	12.43± 1.8	10.32± 1.9	8.63± 2.6
1	27.25± 1.9	24.92±1.8	13.29± 2.5	12.03±2.4	10.08± 2.8
2	38.98± 1.8	32.41± 1.6	21.29± 2.8	19.18± 2.6	16.64± 2.9
3	51.65± 3.2	44.75± 1.9	31.38± 2.9	28.38± 2.9	21.45± 3.2
4	63.87± 2.6	57.65± 2.5	42.37± 1.9	32.84± 2.7	29.56± 2.7
6	78.13± 2.9	69.18± 2.6	51.72± 1.5	49.35± 3.2	36.74± 2.8
8	91.15± 2.7	81.38± 2.8	66.4± 3.2	58.04± 2.8	51.27± 2.9
10		97.04± 3.2	78.85± 2.7	65.42± 2.9	62.52± 1.6
12			89.12± 3.2	78.53± 2.8	76.19± 2.9

Table 13. Regression values of floating matrix tablets of ZD

Formulation	r^2 value				
	zero-order	First-order	Higuchi	Peppas	
				r^2	n value
F1	0.925	0.931	0.997	0.985	0.578
F2	0.883	0.99	0.982	0.973	0.549
F3	**0.912**	**0.905**	**0.992**	**0.981**	**0.558**
F4	0.9	0.983	0.991	0.982	0.537
F5	0.928	0.971	0.99	0.976	0.581
F6	0.818	0.983	0.959	0.935	0.428
F7	0.836	0.94	0.975	0.983	0.379
F8	**0.887**	**0.935**	**0.985**	**0.97**	**0.5**
F9	0.912	0.985	0.99	0.977	0.526
F10	0.926	0.989	0.993	0.98	0.557
F11	0.901	0.976	0.989	0.979	0.53
F12	0.936	0.881	0.993	0.989	0.521
F13	**0.974**	**0.957**	**0.977**	**0.946**	**0.581**
F14	0.969	0.974	0.975	0.953	0.583
F15	0.985	0.953	0.949	0.951	0.613

Figure 2. Calibration curve of ZD in 0.1N HCl in at 264nm

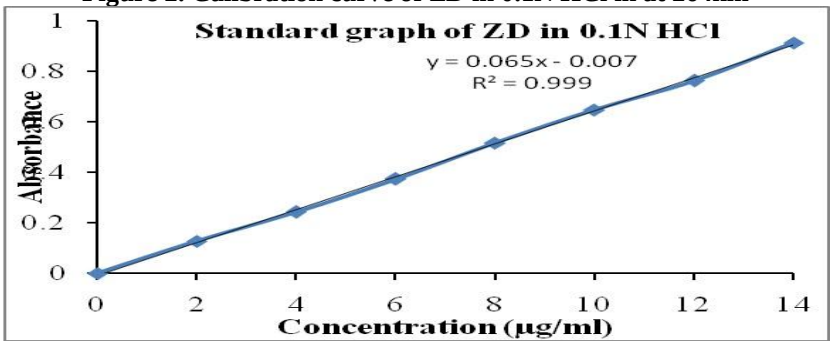


Figure 3. ***In-vitro*** **buoyancy of floating tablets in 0.1 NHCl**

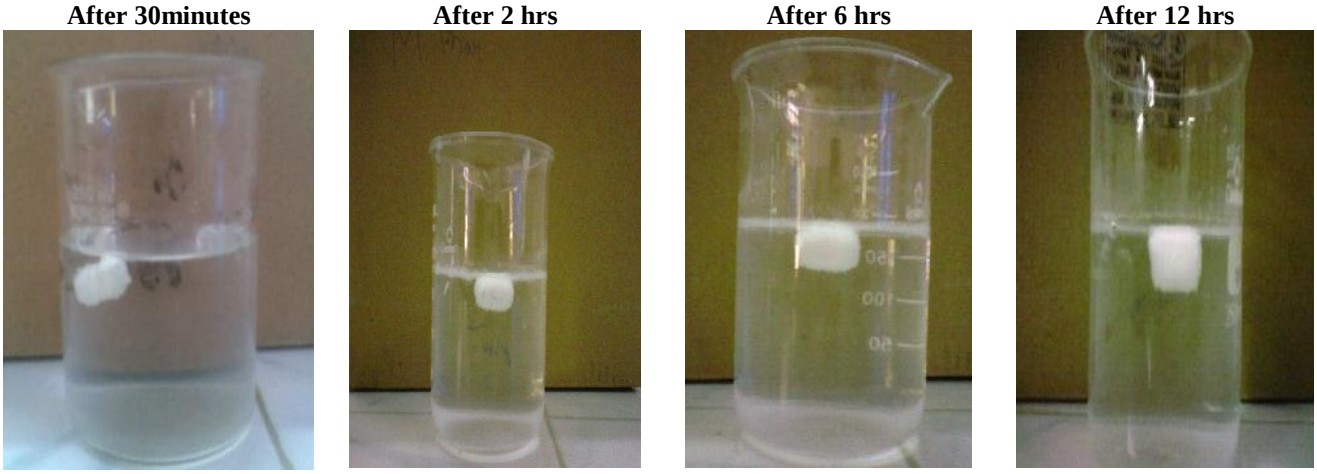


Figure 4. ***In vitro*** **drug release of ZD from HPMC K4M containing formulations**

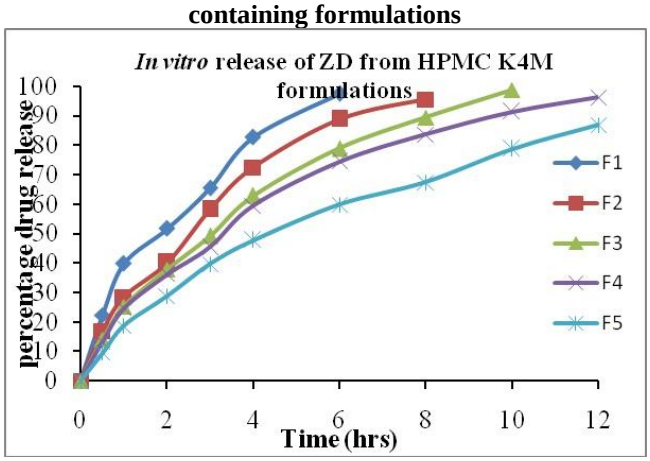


Figure 5. ***In vitro*** **drug release of ZD from HPMC K15M containing formulations**

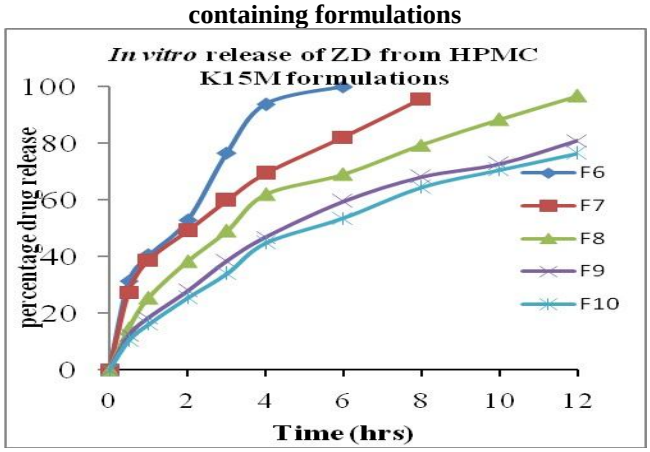
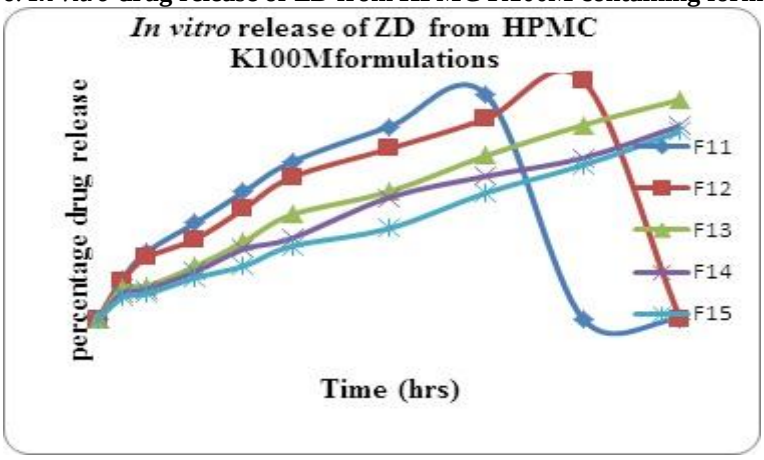


Figure 6. ***In vitro*** **drug release of ZD from HPMC K100M containing formulation**



CONCLUSION

In the present work, formulation and evaluation of floating drug delivery system were prepared. All the tablets were subjected to weight variation, floating time, drug content uniformity, and hardness, and friability, wetting time, dissolution, drug excipients interactions.

Based on the above study following conclusions can be drawn:

- Tablets prepared were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets was found to be

in the range The friability values were found to be in the range

- Disintegration time was found to be in the range.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- Formulations has shown faster drug release.
- Floating means were accurate.

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