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Formulation and Evaluation of Colon Specific Pulsatile Drug Delivery System of Zidovudine

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Abstract: Traditional dosage forms are vastly outclassed by PDDS (pulsatile drug delivery systems). It is more effective than regular doses since it is delivered at the proper time, location, and dose. After a lag period, the medication is delivered as a whole pulse. The release profile of these products is sigmoid. Chronopharmacological drugs and pharmaceuticals with a first-pass effect benefit from these systems. The early research of zidovudine as an anticancer therapy had mediocre results, thus it is presently utilised to treat HIV-infected individuals as a thymidine analogue. For the medicine Zidovudine, a colon-specific pulsatile drug delivery system was developed and assessed across a range of parameters. Proved Zidovudine's colon-specific administration, the pill demonstrates a five-hour lag time with 5 per cent drug release and 99 per cent in 24 h.

Keywords: Zidovudine, Pulsatile medication delivery, Colon specific, Release pattern

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Introduction

Research on medication delivery is gradually shifting away from conventional concepts of drug controlled release after half a century of pharmaceutical development. The chemical and physical characteristics of pharmaceutical excipients are typically the sole factors considered when developing drug release patterns in these models (Siepmann and Peppas, 2001; Fu *et al*., 2016; Reda *et al*., 2017). For improved therapeutic effects, complex drug controlled-release profiles (such as multiple active ingredients in one dosage form, multiple phases in one dosage form, simultaneous control of time and initial place, or specific control of place and release rate) are provided in new combined models that are constantly being developed. The development of new combination models is common (Brayden, 2003; Hsu *et al*., 2016; Tseng *et al*., 2017). Pulsatile drug delivery to the colon is one of a number of innovative medication-controlling models that are

now accessible. After a predefined lag period, this model releases medicines into the colon in a time- and site-specific manner. It is one method of administering medications. Common ailments like angina pectoris and asthma may all be helped by it, as well as hypertension, rheumatoid arthritis, and even colorectal cancer (Vemula *et al*., 2015).

In the early stages of its development, the thymidine analogue zidovudine was tested as an anti-cancer agent, but the findings were inconclusive. Fluorouracil and methotrexate were shown to increase zidovudine's antiproliferative efficacy in cancer cells in a thorough preclinical research (Danesi *et al*., 1998). Tumor development was significantly reduced in mice with human colon cancer xenografts when zidovudine 300 to 600 mg/kg was administered intraperitoneally.

In the HT-29 colon cancer cell line, Brown *et al*. (2003) established Zidovudine's telomerase suppression efficacy Fang *et al*. (2017) have shown that zidovudine's anticancer effect in colon cancer cells is mediated by enhanced expression of the p53-Puma/Bx2/Noxa pathways favouring apoptosis and activation of the p53-p21 pathways encouraging cell cycle arrest.

Materials and Methods

Materials:

Emcure Pharmaceuticals, Pune, provided a free sample of zidovudine. Thomas Baker (Chemicals) Pvt. Ltd. (Mumbai) supplied PVP and sodium hydroxide. Acrylonitrile (purity not less than 99.80%), methanol, triple distilled water, and o-phosphoric acid (KH_2PO4) were obtained from Merck India Ltd. (Mumbai, India). HPMC E5 was obtained from Loba Chemie Pvt. Ltd. (Mumbai). PVP, Methanol, Chloroform, Dibutyl phthalate, and DMSO was purchased from Research-Lab Fine Chem Industries (Mumbai). Rohm Pharma in Germany provided Eudragit L100 for this project. Reagents other than those from Shaimil Laboratories Ltd. in Baroda were all analytical grades. (Quality 99.69–99.99%)

Making Zidovudine cores into pills:

Direct compression was used to make core pills containing 100 mg of Zidovudine as the active component in this research investigation. After passing through a 60# sieve, the medication and additional excipients other than glidant and lubricant were combined for 5 to 10 min in a plastic bag (Table 1). It was then compacted into tablets (120 mg) using flat 6 mm round punches and greased with lubricant and glidant.

Preparation of zidovudine double-compression coated pills:

Various polymers were applied to the coated core tablets by the double-compression coating process after they were manufactured (compositions shown in Table 2). A first layer of sodium starch glycolate was applied to the core tablets, followed by an outer coating of HPMC K15M/sodium alginate as a release-controlling compression coat. By pouring half of the coating material into the die cavity, carefully placing cores in the centre, and then lastly depositing the other half of coating material, the inner and outer layers were squeezed using 8 mm and 10 mm circular flat punches, respectively, to a weight of 120 mg.

In order to make up the compression coat weight, each formulation comprises 1% Magnesium Stearate, 2% Talc and Avicel PH 102.

Compression-coated tablet evaluation:

Various physical criteria such as weight fluctuation, hardness, friability and drug content homogeneity were tested after the successful compression coating. A Shimadzu Electronic Weighing Scale (AW 120, Japan) was used to weigh twenty tablets of each formulation and determine the average weights of the tablets to check for weight variation. As a last step, we tested the hardness and friability of the created tablets. utilising a Monsanto Hardness Tester, we were able to assess the tablet's hardness and its friability (Electro Lab, Mumbai, India). This was done to ensure that the amount of medication in each formulation was consistent by crushing ten tablets and dissolving 50 mg of the powder in phosphate buffer solution (pH 6.8). Zidovudine

Table 1: Composition and characterization of Zidovudine core tablets

Ingredients	Quantity (mg)
Zidovudine	100
Avicel	12.4
Crosspovidone	4
Talc	2.4
Magnesium stearate	1.2

Table 2: Composition of Zidovudine double-compression coated tablets

Formulation code	Core tablet (mg)	Inner compression coat (90 mg)* Sodium starch glycolate	Outer compression coat (90 mg)*			Total Tablet weight (mg)
			Sodium Alginate (mg	HPMC K15M (mg)	Eudragit L100	
ZF1	120	30	15	-	-	300
ZF2	120	30	30	-	-	300
ZF3	120	30	45	-	-	300
ZF4	120	30	-	15	-	300
ZF5	120	30	-	30	-	300
ZF6	120	30	-	45	-	300
ZF7	120	30	-	-	15	300
ZF8	120	30	-	-	30	300
ZF9	120	30	-	-	45	300

*Each compression coat formulation contains 1% Magnesium stearate, 2% Talc and Avicel PH 102 to make up the compression coat weight.

was measured using a UV spectrophotometric technique at 267 nm after the solution had been filtered and diluted.

A study of drug release in vitro:

Study n 14 3 was designed to use USP type II dissolve equipment at 50 rpm at a temperature of 37°C- 50°C for the *in vitro* drug release tests (0.1 N HCl for first 2 h; 3-4 h in 5.5 pH buffer and then in phosphate buffer pH 6.8 for 5 to 24 h). It was necessary to remove and replace an aliquot (5 ml) with pre-warmed fresh dissolving media at predetermined intervals. Samples were filtered and tested for Zidovudine using Spectrophotometric analysis at 267 nm. As a result of the dissolution data, the mean dissolution time (MDT- the sum of different release fraction periods during dissolution studies divided by the initial loading dose) (Talukder and Fassihi, 2008), T 10% and T 80% (time in hours to take 10 per cent and

Table 3: Physicochemical Parameters of formulated tablets

Formulation code	Average weight (mg)[n=20]	Thickness(mm) [n=3]	Hardness Kg/cm² [n=3]	Friability (%)	Content (%)
ZF1	298±4.38	3.90±0.01	6.5±0.3	0.18	98.61±0.34
ZF2	299.5±4.755	3.90±0.02	6.0±0.6	0.23	99.1±0.92
ZF3	305.5±3.56	3.94±0.02	6.5±0.2	0.23	99.22±0.78
ZF4	304±4.4	3.94±0.01	6.0±0.2	0.22	100.05±0.97
ZF5	303.5±3.55	3.96±0.02	6.5±0.4	0.19	98.93±0.54
ZF6	305±3.85	4.00±0.01	6.0±0.3	0.29	99.87±0.76
ZF7	305.5±4.10	3.94±0.01	6.0±0.2	0.28	99.45±0.45
ZF8	306.12±4.26	3.94±0.02	6.5±0.2	0.34	101.12±0.10
ZF9	295.5±3.42	3.98±0.01	6.0±0.4	0.27	100.12±0.98

80 per cent drug release, respectively) were calculated to explain the drug release from compression-coated tablets (Vemula and Veerareddy, 2013).

Kinetics of drug release:

In vitro release of drug data was shown in different kinetic models, including Higuchi's model (cumulative percentage of drug released vs square root of time), zero-order (cumulative quantity of drug released vs time), and first-order (log cumulative percentage of drug remaining vs time) (Higuchi *et al*., 1963; Hadjiioannou *et al*., 1993; Banker and Rhodes, 2002).

Pharmacological mechanism of action:

The Korsmeyer equation (log cumulative percentage of drug released versus log time) was used to determine the mechanism of drug release for the constructed TDDS, and the slope of the straight line was used to determine the exponent n (Korsmeyer *et al*., 1983).

Results and Discussion

Core and double-coated Zidovudine pills evaluation:

The physical characteristics measured in the core tablets were all confirmed to be within the pharmacopeial limitations. In only 15 min, the cumulative percentage of drug release was determined to be 99.98%. For double-compression coated tablets, all of the physical characteristics are listed in Table 3. The pharmacopeial limits for tablet weight variation were determined between 295.53.42 to 306.124.26 mg in the weight variation test. Approximately 6 kg/cm² of tablet hardness and less than 0.5 per cent of tablet friability were measured, showing that tablets are solid and unbreakable. The 98.61 0.34 to 101.12 0.98 range was detected in the assay of the produced tablets.

In vitro investigations of drug release:

For sodium alginate and HPMC K15M and Eudragit S100 formulations, the ZF5

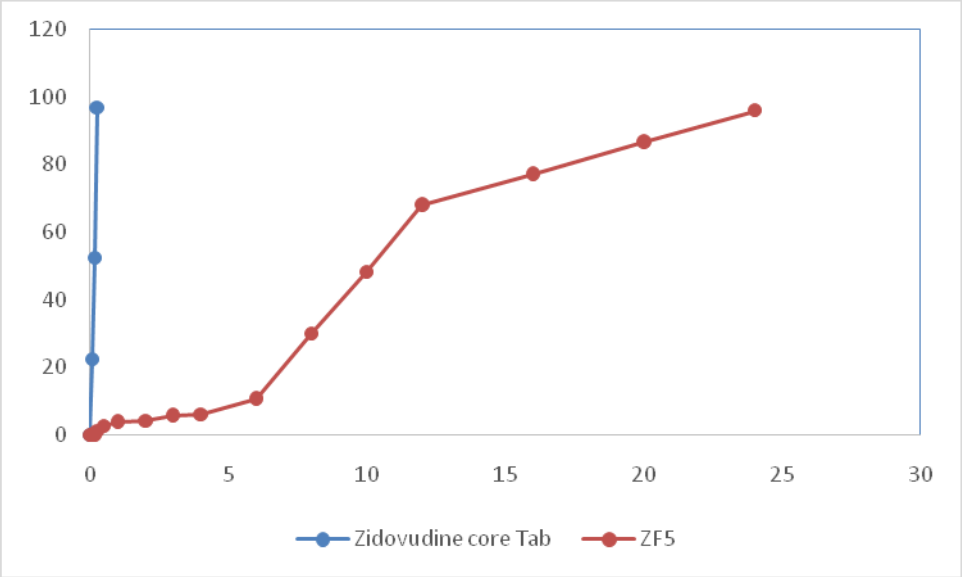

Fig. 1: Release Profile of Core tablet and double compressed tablets of Zidovudine

demonstrated 5% drug release in 5 h and 99% drug release in 24 h from the dissolving investigations of sodium alginate and HPMC K15M and Eudragit S100. In comparison to HPMC K15M and Eudragit S100 formulations, which demonstrated superior drug release control and acceptable compressibility, sodium alginate formulations exhibited some compressibility problems and were less successful as sustained release polymers. Core pills and ZF5 formulations are shown in Figure 1. The MDT ranged from 3.16 to 12.94 for all formulations. ZF5's T10 and T80 per cent values were determined to be 5.5 and 19.8 h, respectively, for the optimum formulation (Fig. 1). The regulated release of Zidovudine was shown by using the Higuchi model and the zero-order release mechanism.

Conclusion

Zidovudine, a medication used in this trial, was administered using a colon-specific pulsatile drug delivery system. Polymers of varied concentrations were used in the formulation of the core tablet and the doubly compressed tablets. It took 15 min for the core tablet to be released, and 24 h for the doble compressed tablet to be released. They were tested on a variety of factors and passed all of them with flying colours. With an initial lag time of 5 h, the best formulation out of the nine was ZF5, which demonstrated well-regulated release throughout a 24 h period. As a result, it was found that the formulation for Zidovudine might be utilised to improve its release profile in a beneficial way using a colon specific pulsatile drug delivery system.

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