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Research Article

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Formulation of Colon Specific Didanosine Enteric Coated Matrix Tablets Using pH Sensitive Polymer

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Abstract The objective of present study is to develop the colon specific Didanosine enteric coated matrix tablets using release retardant polymer and pH sensitive polymer Eudragit L100 that retard the liberation of drug in upper gastro intestinal system and also show progressive release in colon. The influence of core tablet compositions, polymer combination ratios and coating levels on the in vitro release rate of Didanosine from coated tablets was investigated. The results showed that less than 10% drug was released in 0.1 N HCl within 2 hr, and about 90% of the drug was released in the pH 7.4 phosphate buffer for 24 hr. The in vitro drug release studies indicated that formulation F17 was a promising system to provide targeting of DDI to the colon. The release pattern of the above formulation was best fitted to zero-order model. Mechanism of drug release followed was non fickian (super case-II) transport mechanism. FTIR spectral studies showed that there is no interaction between the drug and excipients. The results of the present study have demonstrated that the pH-dependent tablet system is a promising vehicle for preventing rapid hydrolysis in gastric environment and improving oral bioavailability of Didanosine for the treatment of HIV infections.

Keywords Didanosine, colon targeted drug delivery, enteric coating, In vitro dissolution, pH Dependent delivery system.

Introduction

Didanosine is a nucleoside analogue and a highly potent nucleoside reverse transcriptase inhibitor, which has been used in the treatment of human immunodeficiency virus (HIV) infections. It acts by inhibiting reverse transcriptase, an enzyme required for replication of the Human Immunodeficiency Virus (HIV), and by blocking viral DNA synthesis, thus causing termination of DNA molecular chain [1].

Didanosine has been approved for the treatment of HIV infection in patients who are unable to tolerate ZDV because of adverse effects (e.g., anemia and neutropenia) or who experience clinical or immunologic deterioration while receiving ZDV. Compared with ZDV, DDI has a long intracellular half-life and negligible bone-marrow toxicity. It also has in vitro activity against ZDV-resistant strains of HIV. Phase I studies indicate that ddI has a beneficial effect on the $CD4^+$ cell counts and HIV p24 antigen concentrations. As a result of the acid-labile nature of ddI, oral formulations are buffered or must be mixed with antacid to neutralize gastric pH. Bioavailability then averages 20-40 percent, depending on the dose and formulation given. The plasma half-life, total body clearance, and volume of distribution of ddI are one to two hours, 0.7-1 L/kg/h, and 0.8-1 L/kg, respectively. Painful peripheral neuropathy and pancreatitis (dose-limiting toxicities of DDI) occurred in 34 and 9 percent of patients in Phase I studies, respectively [2-3].

It is among the most durable agents in this class i.e. viral resistance develops most slowly. The main drawback of the agent is that its acid lability requires administration on empty stomach with a substantial quantity of antacid, which can lead to gastrointestinal intolerance. And its *in vivo* bioavailability is incomplete and erratic (*i.e.* irregular or no regular pattern) even when co-administered with antacids. The low and variable absorption of Didanosine can be partially attributed to first pass elimination by liver. Further once daily Didanosine doses lead to significant

reduction in Bioavailability in comparison to the same amount given twice daily, suggesting the involvement of saturable process [4-5].

Didanosine treatment was found to be a useful and effective alternative in patients who did not tolerate or not respond to zidovudine, the mainstay of anti HIV-1 drugs. It has lower and more highly variable bioavailability in comparison to with other nucleoside reverse transcriptase inhibitors. In the gastric medium it is rapidly degraded due to acid hydrolysis. Such a problem, together with need for repetitive dosing, low plasma protein binding (5%), brief plasma elimination half life (30 min-4 hr),dose related toxicity, in addition to a relatively low daily dosage (250-400mg), make this drug a suitable candidate for incorporating into oral delayed release dosage forms [6-7].

Experimental Methodology

Analytical Method Development for Didanosine

λ Max Determination

Didanosine λ_{max} was determined by using 0.1 N HCl, 6.8 pH phosphate buffer medium, 7.4 pH phosphate buffer medium. First dissolve 100mg of pure drug in 100ml buffer, this is primary stock solution. From this 10µg/ml solution was prepared by using buffer. 10µg/ml solution absorbance was measured at 200-400 nm range by spectrophotometrically using buffer as reference solution.

Preparation of Standard Graph of Didanosine

Accurately weighed amount of 100 mg of DIDANOSINE was transferred into a 100 mL volumetric flask. Primary stock solution was made by adding 100 mL of 0.1N HCl/5.8 pH phosphate buffer/pH 7.4 phosphate buffers. This gives a solution having concentration of 1 mg/mL of DDI stock solution. From this primary stock 10 mL was transferred in to another volumetric flask and made up to 100 mL with 0.1N HCl/6.8 pH phosphate buffer/7.4 pH phosphate buffer, this gives a solution having concentration of 100 µg/mL of DDI stock solution from this secondary stock 10 mL was taken separately and made up to 100 ml with 0.1N HCl/6.8 pH phosphate buffer/7.4 pH phosphate buffer, to produce 10 µg/mL. The absorbance was measured at 248 nm using a UV spectrophotometer (Systronic, Ahmedabad, India) for 0.1N HCl, in case of pH 6.8 phosphate buffer & pH 7.4 phosphate buffer, the absorbance was measured at 254 nm using a UV spectrophotometer. From the secondary stock 0.3, 0.6, 0.9, 1.2,1.5, and 1.8ml, was taken separately and made up to 10 ml with 0.1N HCl/6.8 pH phosphate buffer/7.4 pH phosphate buffer, ,to produce 3,6,9,12,15 and 18µg/ml respectively. The absorbance was measured at 248nm (0.1N HCl) and 254 nm(6.8pH and 7.4pH) using a UV spectrophotometer. The standard calibration curve of DIDANOSINE (0.1N HCl) was shown in Figure 1, pH 6.8 phosphate buffer standard calibration curve in Figure 2, pH 7.4 phosphate buffer standard calibration curve in Figure 3.

Preparation of Enteric Coated Didanosine Tablets

Preparation of Didanosine Core Tablets

Each core tablet (average weight 500 mg) for *in vitro* drug release studies consisted of DIDANOSINE, Microcrystalline cellulose, polymer (HPMC K4M, Combination of HPMC k4M and Ethyl Cellulose, HPMC K100M, Guar gum, POLYOX WSR 303), Talc and Magnesium Stearate were added to get sustained release of Didanosine. The materials were weighed, mixed and passed through a mesh No 60 to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 9 mm round, flat and plain punches on a single station tablet machine (Cadmach, Ahmedabad). Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the core tablets. Composition of different formulations were given in the following Tables 1, 2 and 3.

Table 1: Composition of Core Tablets Containing HPMCK4M AND ETHYL CELLULOSE

Ingredients	F1	F2	F3	F4	F5	F6
DDI	200mg	200mg	200mg	200mg	200mg	200mg
HPMC K4M	100mg	150mg	200mg	100mg	150mg	200mg
ETHYLCELLULOSE	-	-	-	50mg	50mg	50mg
Microcrystalline Cellulose	185mg	135mg	85mg	135mg	85mg	35mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg
Talc	10mg	10mg	10mg	10mg	10mg	10mg
Total tablet weight	50 0mg	500mg	500mg	500mg	500mg	500mg

Table 2: Composition Of Core Tablets Containing HPMCK100M, GUAR GUM.

Ingredients	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
DDI	200mg	200mg	200mg	200mg	200mg	200mg
HPMC K100M	100mg	150mg	200mg	-	-	-
GUAR GUM	-	-	-	100mg	150mg	200mg
Microcrystalline Cellulose	185mg	135mg	85mg	185mg	135mg	85mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg
Talc	10mg	10mg	10mg	10mg	10mg	10mg
Total tablet weight	500mg	500mg	500mg	500mg	500mg	500mg
Ingredients	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
DDI	200mg	200mg	200mg	200mg	200mg	200mg
HPMC K100M	100mg	150mg	200mg	-	-	-
GUAR GUM	-	-	-	100mg	150mg	200mg
Microcrystalline Cellulose	185mg	135mg	85mg	185mg	135mg	85mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg
Talc	10mg	10mg	10mg	10mg	10mg	10mg
Total tablet weight	500mg	500mg	500mg	500mg	500mg	500mg

Table 3: Composition Of Core Tablets Containing POLYOX WSR 303

Ingredients	**F13**	**F14**	**F15**
DDI	200mg	200mg	200mg
POLYOX WSR 303	100mg	150mg	200mg
Microcrystalline Cellulose	185mg	135mg	85mg
Magnesium stearate	5mg	5mg	5mg
Talc	10mg	10mg	10mg
Total tablet weight	500mg	500mg	500mg

Enteric Coating of Core Tablets

The core tablets were enteric coated with coating material Eudragit-L-100 and containing the plasticizer 0.5% in the polymeric solution. Polymeric solution of 5% has prepared in acetone solvent. The coat weights of 5%, 7% and 10% (525mg, 535mg, 550mg) were prepared.

Table 4: Composition of enteric coated tablets containing different coat weights.

Ingredients	**F16**	**F17**	**F18**
DDI	200mg	200mg	200mg
POLYOX WSR 303	200mg	200mg	200mg
% Coat Weight	5	7	10
Microcrystalline Cellulose	85mg	85mg	85mg
Magnesium stearate	5mg	5mg	5mg
Talc	10mg	10mg	10mg
Total tablet weight	525mg	535mg	550mg

Characterization of Powder Mixture [7-9]

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced.

The various characteristics of blends tested are as given below:

Angle of Repose

The frictional force in a loose powder can be measured by the angle of repose (θ). It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force.

The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose (θ) was calculated using the following formula:

Tan θ = h/r

Where; θ = Angle of repose

h = Height of the cone

r = Radius of the cone base

Angle of repose less than 30^0 shows the free flowing of the material.

Bulk Density

Density is defined as weight per unit volume. Bulk density, ρ_b, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together.

Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment.

30 g powder blend introduced into a dry 100 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo. was read. The bulk density was calculated using the formula:

$$\rho_b = M / Vo$$

Where ρb = Apparent Bulk Density

M = weight of sample

V = apparent volume of powder

Tapped density

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped 500 times initially followed by an additional tap of 750 times until difference between succeeding measurement is less than 2 % and then tapped volume, V_f was measured, to the nearest graduated unit. The tapped density was calculated, in gm per ml, using the formula:

$$\rho_{tap} = M / V_f$$

Where ρ_{tap} = Tapped Density

M = Weight of sample

V_f = Tapped volume of powder

Measures of Powder Compressibility [10-14]

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of inter particulate interactions. In a free-flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$$

Where ρ_b = Bulk Density

ρ_{tap} = Tapped Density

Evaluation of Tablets [15-18]

Physicochemical Characterization of Tablets

The designed formulations core and Enteric coated Didanosine tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation Test

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. The percent deviation was calculated using the following formula.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Tablet Hardness

Hardness of tablet is defined as the force applied across the diameter of the tablet in the order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using Monsanto hardness tester and the average is calculated and presented with standard deviation.

Tablet Thickness

Tablet thickness is an important characteristic in reproducing appearance. Twenty tablets were taken and their thickness was recorded using Digital Micrometer. The average thickness for core and coated tablets is calculated and presented with standard deviation.

Friability

It is measured of mechanical strength of tablets. Roche friabilator, was used to determine the friability by following procedure. Pre weighed tablets (20 tablets) were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = $[(W_1 – W_2) / W_1] \times 100$

Where, W_1 = Initial weight of 20 tablets

W_2 = Weight of the 20 tablets after testing

Determination of Drug Content

Both the core tablets and Enteric coated tablets of Didanosine were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 200mg of Didanosine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml of methanol and allowed to stand for 5 h with intermittent sonication to ensure complete solubility of the drug. The mixture was made up to volume with methanol. The solution was suitably diluted and the absorption was determined by UV-Visible spectrophotometer at 254nm. The drug concentration was calculated from the calibration curve.

***In Vitro* Drug Release Studies**

Drug Release Studies of Didanosine Core Tablets

The core tablets containing 200mg of Didanosine were tested in SGF (0.1N HCl), SIF (pH 6.8), and SIF (pH 7.4) solutions for their dissolution rates. Dissolution studies were performed using USP dissolution test apparatus (Apparatus 2, 50 rpm, 37±0.5 °C). At various time intervals, a sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at 254 nm.

Drug Release Studies of Enteric Coated Didanosine Tablets

The release of Didanosine from Enteric coated tablets was carried out using USP basket-type dissolution apparatus at a rotation speed of 100 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, 0.1N HCl) for the first 2 h as the average gastric emptying time is about 2 h. Then, the dissolution medium was replaced with simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3 h, as the average small intestinal transit time is about 3 h, and finally simulated intestinal fluid (SIF, pH 6.8) was used for 19 h to mimic colonic pH conditions. Drug release was measured from Enteric coated Didanosine tablets, added to 900 ml of dissolution medium. Samples withdrawn at various time intervals were analyzed spectrophotometrically at 254 nm. All dissolution runs were performed in triplicate.

Evaluation of Release Rate Kinetics [19-20]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data are fitted to the following equation.

$$F = K_o t$$

Where; ‘F’ is the drug release at time‘t’, and ‘K’ is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics

The release rate data are fitted to the following equation.

$$\text{Log } (100 – F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\,t^{1/2}$$

Where; 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to korsmeyer-peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight line.

$$M_t/M_\infty = Kt^n$$

where, M_t/M_∞ is fraction of drug released at time '*t*', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case II transport), n = 1; and for supercase II transport, n > 1 (Peppas, 1985). In this model, a plot of log (M_t/M_∞) versus log (time) is linear.

Results and Discussion

The present study was aimed to developing enteric coated Didanosine formulations for colon targeting using Eudragit L100 as an enteric coat polymer. It was reported earlier that Eudragit S100, Eudragit RS100, HPMC could be used as a carrier for colon-specific drug delivery in the form of either a matrix tablet or as a enteric coat over a core tablet.

The present study discloses an active pharmaceutical agent formulated as a tablet, which is enteric coated by Eudragit L100 polymer. If a tablet is described as having an 'enteric coating' (e/c) or 'gastro-resistant' it means that there is a coating which is designed to hold the tablet together when in the stomach. This is quite clever science which relies on the fact that the stomach is acid and the intestines, where food goes after the stomach, are not. The coating is designed to hold together in acid conditions and break down in non-acid conditions and therefore release the drug in the intestines.

Attempts were made to minimize the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of colon by applying Eudragit as an enteric coat over the DDI core tablets. DDI core tablets are formulated with HPMC K4M, ETHYL CELLULOSE, HPMC K100M, GUAR GUM, POLYOX WSR 303. So, enteric-coated tablets were developed for colon specific delivery of DDI.

Analytical method development for Didanosine

Determination of λ_{max} of Didanosine by UV

Didanosine λ_{max} was determined by usin 0.1 N HCl, 6.8 pH phosphate buffer medium, 7.4 pH phosphate buffer medium. First dissolve 100mg of pure drug in 100ml buffer, this is primary stock solution. From this 10µg/ml solution was prepared by using buffer. 10µg/ml solution absorbance was measured at 200-400 nm range by spectrophotometrically using buffer as reference solution

Construction of standard graph of Didanosine

The standard graph of Didanosine in SGF (0.1N HCl) showed good linearity with r^2 value of 0.999, which suggest that it obeys the "Beer – lambert" law. The standard graphs in SIF (pH 7.4) and SIF (pH 6.8) had r^2 values of 0.999 and 0.997 respectively. Calibration curves were shown in Figure 1, 2, and 3.

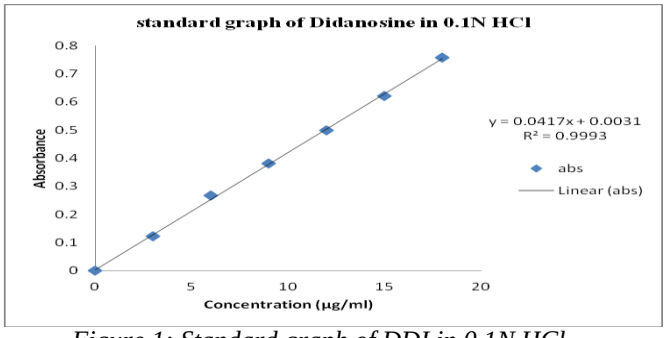

Figure 1: Standard graph of DDI in 0.1N HCl

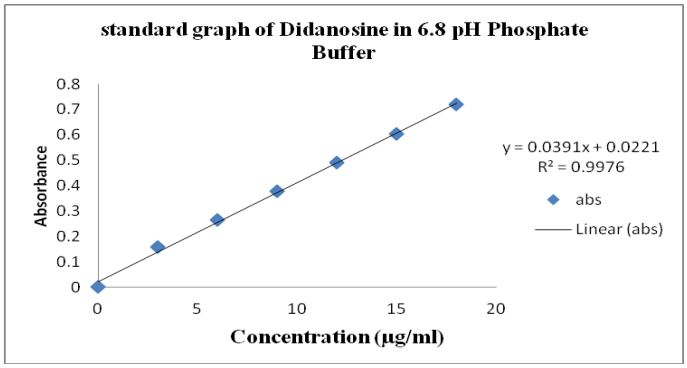

Figure 2: Standard graph of DDI in 6.8pH Phosphate Buffer

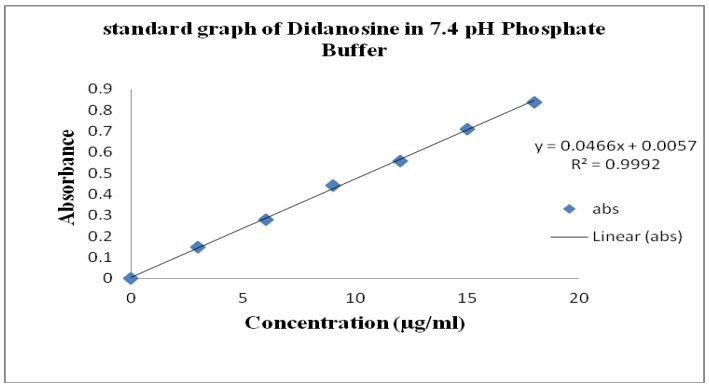

Figure 3: Standard graph of DDI in7.4 pH Buffer

FTIR Studies

The pure drug, the optimized Didanosine enteric coated tablet formulation and placebo formulation were subjected to FTIR studies.

The IR absorption spectra of the pure drug was taken in the range of 4000-400 cm-1 using KBr disc method .The major peaks were reported for evaluation of purity. The results were showed that there is no interaction between the drug and excipients.

The IR spectra of pure DDI drug showed the characteristic absorption bands and drug-polymer interaction was not observed in the FTIR spectra of the powder mixture of optimized formulation since the absorption peaks of the drug still could be detected in the mixture.

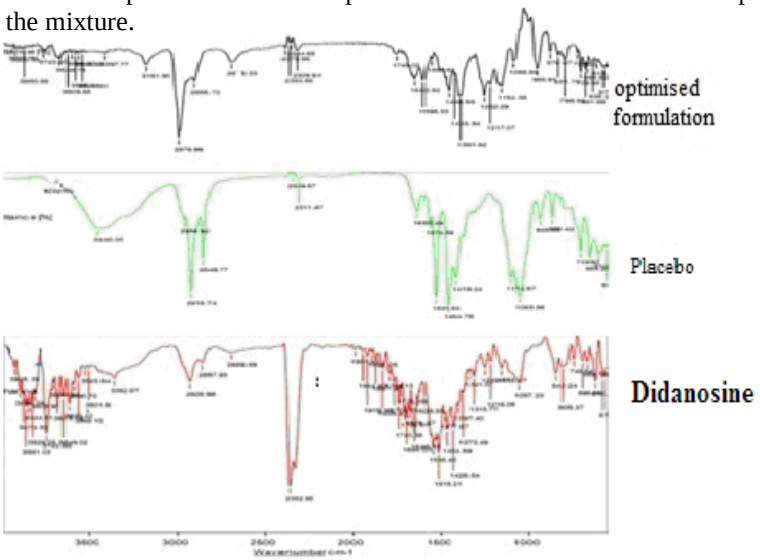

Figure 4: Ftir Studies For The Pure Drug, The Optimized Didanosine Enteric Coated Tablet Formulation And Placebo

Powder characterization (Pre Compression analysis)

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), and compressibility index and their values were shown in Table 5.

The apparent bulk density and tapped bulk density values ranged from 0.286 to 0.365 and 0.341 to 0.469 respectively. The results of angle of repose and compressibility index (%) ranged from 25.12±1.13 to 32.95±1.35 and 15.769 to 22.17 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture.

Table 5: Characterization of powder mixture

Formulation code	Angle of Repose (°)	Bulk density (gm/cc^3)	Tapped Bulk density (gm/cc^3)	% Carr's Index (%)
F1	29.12±1.24	0.321±0.032	0.402±0.078	20.149±0.59
F2	31.23±1.32	0.332±0.056	0.412±0.058	19.417±0.34
F3	30.35±1.35	0.312±0.021	0.386±0.065	19.170±0.58
F4	29.56±1.46	0.323±0.025	0.398±0.038	18.844±0.67
F5	27.12±1.13	0.325±0.085	0.405±0.095	19.753±0.67
F6	30.35±1.35	0.365±0.023	0.469±0.037	22.174±0.38
F7	32.12±1.84	0.344±0.065	0.436±0.064	21.100±0.82
F8	30.65±1.35	0.332±0.059	0.412±0.018	19.417±0.72
F9	29.56±1.86	0.315±0.056	0.402±0.085	21.641±0.37
F10	32.12±1.23	0.312±0.085	0.384±0.056	18.750±0.64
F11	30.35±1.55	0.316±0.045	0.391±0.075	19.181±0.28
F12	29.56±1.46	0.323±0.025	0.398±0.038	18.844±0.67
F13	27.12±1.13	0.325±0.085	0.405±0.095	19.753±0.67
F14	30.35±1.35	0.365±0.023	0.469±0.037	22.174±0.38
F15	29.13±1.26	0.302±0.072	0.378±0.086	20.105±0.12
F16	25.12±1.13	0.291±0.646	0.354±0.061	17.796±0.31
F17	32.95±1.35	0.294±0.034	0.349±0.088	15.759±0.62
F18	30.56±1.16	0.286±0.094	0.341±0.065	16.129±0.68

Data represents mean ± S. D (n=3)

Evaluation of Tablets

DDI Tablet Characteristics

DDI powder was compressed directly into a core tablet by using direct compression vehicle such as Microcrystalline Cellulose. The mean percent drug content of the DDI core tablets was found to be 99.2±1.76% of the labeled amount indicating uniformity of drug content in the formulation (Table 16). The hardness of the core tablets of DDI was found to be 4.4±0.59 to 6.0±0.64 kg/cm^2. The hardness of the enteric coated core tablets of DDI was found to be 5.0±0.64 to 6.0±0.64 kg/cm^2. The tablets of DDI were also found to comply with the friability test since the weight loss was found to be 0.4%. The core tablets thickness was found to be 5.74±0.023 mm. The enteric coated tablets thickness was found to be 6.38±0.74 to 7.57±0.039 mm (Table 7). From that coat thickness should be 0.64±0.74 to 1.83±0.039. In weight variation test, the pharmacopoeial limit for the tablets of more than 300 mg ± 2.5%. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations passed the uniformity of weight as per official requirements (India Pharmacopoeia, 1996). Thus the tablets of DDI formulated in the study were found to have the required characteristics.

Eudragit L 100 was used as a coating material to prepare enteric coated tablets. The enteric-coated tablets were prepared by dip coating method. Enteric coating is done to the F8 formulation which showed good controlled and sustained release. The disintegration time of the tablets in 0.1 N HCl, 6.8 pH phosphate buffer and 7.4 pH phosphate buffer was conducted the results were shown in the Table 8. From the study of disintegration time of enteric coated tablets containing Eudragit L100 as a coating material indicates that Eudragit S100 disintegrates within the time of 120 minutes when the tablet coat was 5% - 7% when it is 10% disintegrating after 120 min, So, the tablets used for the colon targeting disintegrating within the time of 120 minutes may not give the colon targeting, Eudragit L100 used as coating material for successful colon targeting.

Table 6: Physical properties of DDI core and compression coated tablets

Formulation Code	Hardness (Kg/cm^2)	Weight variation (mg)	Friability (%)	Drug Content (%)
F1	5.0±0.61	502±1.56	0.05	95.9±0.61
F2	5.2±0.35	498.4±1.12	0.33	95.8±1.74
F3	5.1±0.42	489.6±2.54	0.17	103.2±0.35
F4	5.0±0.25	498.0±2.68	0.34	96.6±0.28
F5	5.4±0.64	494.3±1.86	0.26	103.0±0.76
F6	4.6±0.70	501.2±2.45	0.64	95.6±0.61
F7	4.4±0.58	500.5±1.63	0.54	97.2±0.28
F8	4.8±0.46	499.7±2.02	0.58	99.9±0.70
F9	5.2±0.35	498.4±1.12	0.33	95.8±1.74
F10	5.0±0.61	502.2±1.56	0.05	95.9±0.61
F11	5.0±0.25	498.0±2.68	0.34	96.6±0.28
F12	5.0±0.86	498.1±2.36	0.45	100.6±1.74
F13	5.2±0.46	499.6±1.74	0.38	95.0±0.35
F14	6.0±0.38	500.3±2.68	0.62	98.2±0.70
F15	5.6±0.52	502.0±2.86	0.52	98.0±0.76
F16	6.0±0.76	520.0±3.02	0.68	95.6±0.61
F17	5.5±0.62	532.5±2.56	0.46	96.0±0.28
F18	5.3±0.28	546.3±1.28	0.34	97.1±0.70

Data represents mean ± S. D (n=3)

Table 7: Thickness of core and enteric coated tablets

Formulation Code	Total Thickness of Tablets (mm)	Coat Thickness (mm)
Core	5.74±0.023	-
F16-F19	6.38±0.74 to 7.57±0.039	0.64±0.74 to 1.83±0.039

Table 8: Evaluation Data for Enteric coated Tablets

Batch details	Disintegration time(0.1N HCl)	Disintegration time(6.8 pH phosphate buffer)	Disintegration time (7.4 pH phosphate buffer)
5%	58	36	18
15%	112	90	32
20%	189	132	43

In vitro dissolution data

The *in vitro* dissolution profile of each of prepared formulation was determined by USP paddle method by half dilution method. The *in vitro* dissolution profile of each of prepared formulation were carried out at different pH conditions with varying time in order to test the suitability of the developed formulations for colon specificity. These results were given in Table 9 to 12 and graphical representation was showed in figures 5 to 7. From the graphical representation; it was revealed that the drug release from the developed dosage from was minimal in 0.1 N HCl (which found to be less than 20%). The drug release in pH 7.4 was found to range from 80% to 105%. The dissolution was carried out for a maximum of 24 h.

Table 9: Evaluation Data for % cumulative Drug release of DDI core tablets containing different ratios of Drug:polymer

Time	FT-1	FT-2	FT-3	FT-4	FT-5	FT-6
0	0	0	0	0	0	0
1	49.32±0.24	47.32±0.27	41.93±0.14.	33.48±0.24	25.65±0.24	16.82±0.24
2	68.48±0.34	57.78±0.14	47.02±0.24	37.59±0.14	33.05±0.12	20.58±0.12
3	73.96 ±0.24	62.56±0.28	54.55±0.16	41.16±0.13	41.73±0.15	25.41±0.13
4	84.5±0.15	71.27 ±0.26	59.79±0.19	50.85±0.24	51.71±0.13	31.54±0.14
5	99.2±0.1	79.59 ±0.24	63.55±0.21	59.83±0.15	60.69±0.12	40.98±0.24
6		84.42 ±0.2	74.63±0.24	70.05±0.24	69.85±0.12	49.32±0.14
8		96.56±0.25	80.98±0.16	79.21±0.24	80.07±0.14	56.81±0.12

10	95.45±0.12	87.89±0.14	89.81±0.16	73.05±0.14
12		96.57±0.12	95.32±0.12	81.15±0.24
14				89.1±0.25
16				97.52±0.24

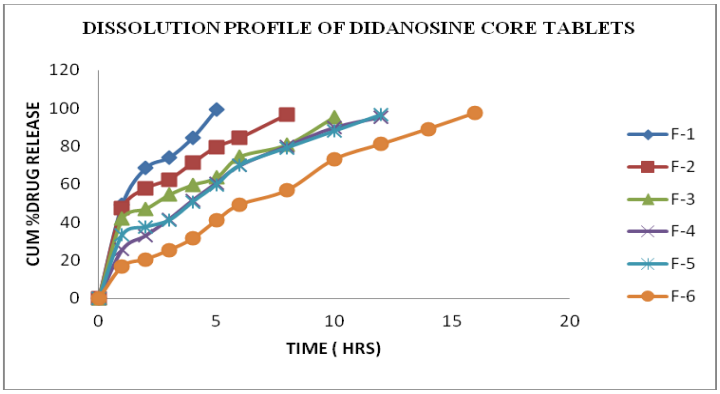

Figure 5: % cumulative Drug release of DDI core tablets containing different ratios of Drug:polymer

Table 10: Evaluation Data for % cumulative Drug release of DDI core tablets containing different ratios of Drug: polymer

Time	FT-7	FT-8	FT-9	FT-10	FT-11	FT-12
0	0	0	0	0	0	0
1	24.65±0.12	15.32±0.1	9.65±0.12	24.31±0.1	16.42±0.12	12.04±0.12
2	31.07±011	19.45±0.16	14.25±0.1	29.21±0.12	23.45±0.1	20.55±0.1
3	39.52±0.15	24.32±0.12	19.35±0.15	32.46±0.18	28.64±0.12	27.64±0.14
4	47.02±0.12	30.57±0.1	24.65±0.19	41.25±0.12	34.64±0.17	32.52±0.19
5	52.55±0.17	36.95±0.12	29.71±0.12	47.24±0.15	41.91±0.19	37.23±0.18
6	62.79±0.12	44.65±0.15	33.24±0.14	52.61±0.19	47.52±0.15	43.24±0.13
8	74.65±0.15	53.28±0.10	41.91±0.16	67.42±0.18	51.62±0.18	49.91±0.12
10	82.45±0.19	65.85±0.12	48.34±0.12	79.21±0.11`	59.64±0.12	51.34±0.1
12	95.04±0.17	75.23±0.18	56.01±0.1	96.24±0.12	67.17±0.1	56.01±0.12
14		84.65±0.19	63.21±0.12		75.28±0.12	64.21±0.12
16		90.89±0.13	69.41±0.19		84.9±0.14	79.41±0.1
18		96.36±0.15	78.21±0.15		94.25±0.12	85.21±0.12
20			86.34±0.12			96.34±0.15
22			95.84±0.1			

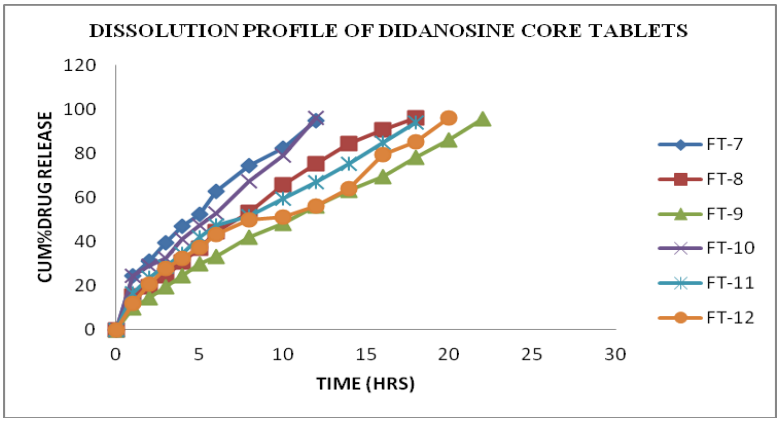

Figure 6: % cumulative Drug release of DDI core tablets containing different ratios of Drug:polymer

Table 11: Evaluation Data for % cumulative Drug release of DDI core tablets and enteric coated tablets containing different coat weights

Time	FT-13	FT-14	FT-15	FT-16	FT-17	FT-18
0	0	0	0	0	0	0
1	18.09±0.12	12.32±0.1	8.42±0.11	0	0	0
2	24.23±0.1	17.44±0.12	12.21±0.14	5.7±0.12	1.2±0.17	0.21±0.12
3	32.21±0.15	21.23±0.15	18.65±0.12	11.24±0.18	4.35±0.12	2.46±0.18
4	39.34±0.11	26.21±0.1	24.36±0.17	17.65±0.16	12.65±0.13	11.78±0.16
5	46.78±0.12	30.43±0.12	29.85±0.18	20.37±0.12	19.58±0.12	18.89±0.14
6	52.32±0.13	35.21±0.15	32.85±0.13	24.98±0.19	24.58±0.18	22.63±0.12
8	66.32±0.12	43.21±0.13	40.69±0.14	32.62±0.11	31.87±0.12	30.85±0.1
10	74.76±0.15	52.65±0.1	50.25±0.18	40.58±0.14	40.59±0.11	38.69±0.12
12	83.65±0.16	60.43±0.12	58.65±0.12	49.63±0.12	48.64±0.12	47.36±0.12
14	94.54±0.18	69.35±0.2	65.27±0.1	56.35±0.16	55.68±0.1	54.65±0.13
16		78.32±0.22	75.36±0.19	64.25±0.18	64.85±0.12	63.52±0.16
18		85.76±0.12	83.24±0.12	73.59±0.12	71.97±0.14	70.85±0.14
20		96.32±0.15	93.62±0.11	80.36±0.11	80.85±0.11	78.69±0.18
22			96.58±0.16	90.65±0.12	91.25±0.13	85.58±0.12
24				95.25±0.1	95.28±0.12	90.54±0.1

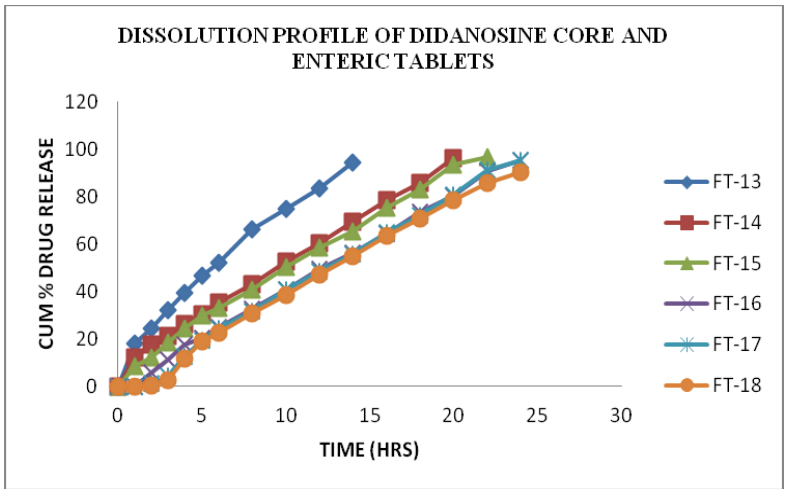

Figure 7: % cumulative Drug release of DDI core tablets and enteric coated tablets containing different coat weights

For targeting the drug in colonic region, the matrix tablets with different ratios of polymers were prepared by direct compression method. F15 formulation prepared using polymer (polyox wsr 303) showed better drug release when compared to other batches. So, F15 is best suited for DDI core tablet formulation, among the core tablet formulations containing different polymers and different viscosity grades of HPMC polymers. These tablets were coated with Eudragit L100 for different enteric coated weights of 5%, 7%, and 10%. These tablets showed good physicochemical properties such as hardness, friability, weight variation and drug content. The *in vitro* drug release profile of these tablets showed delayed release characteristics.

Drug release kinetics data of Didanosine enteric coated tablets:

The results obtained in vitro release studies were plotted in different models of treatment as follows

- Cumulative percent drug released v_s time (Zero order rate kinetics)
- Log cumulative percent drug retained v_s time(First order rate kinetics)
- Log cumulative percent drug released v_s square root of time(Higuchi's Classical diffusion Equation)
- Log of cumulative % drug release v_s log time(Peppas exponential equation)

The kinetics values obtained for formulations FT-1 to FT-18 were shown in table 12.The values of invitro release were attempted to fit into various mechanical methods. Plots of zero order, first order, higuchis matrix, peppas model were depicted in Fig 8 to 11.

Most of the tablet formulation follows the zero order. The mechanisms of drug release are non-fickian diffusion

(super case-II), since they fitted well with Korsmeyer & Peppas models as with n value above 1. This indicates that drug release depends on swelling, relaxation and erosion of polymer with zero order release kinetics.
All the parameters were three times (n=3).The difference in mean of zero order, First order, Higuchis kinetics, Peppas equation between batch series FT-1 and batch FT-18 was indicating significant ($p \leq 0.5$)

Table 12: Release kinetics of all formulations

Formulation code	Zero order	First order	Higuchi	Korsmeyer & Peppas	
	R^2	R^2	R^2	R^2	N
F-1	0.8661	0.7851	0.9499	0.9767	0.4066
F-2	0.8188	0.9269	0.9384	0.9798	0.3405
F-3	0.5957	0.6370	0.9397	0.8021	0.2603
F-4	0.9189	0.9314	0.8997	0.9452	0.4689
F-5	0.9315	0.9730	0.9042	0.9882	0.5676
F-6	0.9828	0.8826	0.9079	0.9737	0.6963
F-7	0.9550	0.9188	0.8975	0.9856	0.5635
F-8	0.9834	0.9267	0.9122	0.9832	0.6969
F-9	0.9934	0.8540	0.9181	0.9971	0.7502
F-10	0.9739	0.8252	0.8866	0.9445	0.5670
F-11	0.9694	0.8971	0.9019	0.9941	0.5999
F-12	0.9662	0.8177	0.9039	0.9864	0.6433
F-13	0.9741	0.9245	0.9016	0.9930	0.6512
F-14	0.9946	0.8470	0.9118	0.9877	0.7067
F-15	0.9949	0.8752	0.9234	0.9966	0.8182
F-16	0.9983	0.8782	0.9283	0.9326	1.3233
F-17	0.9952	0.8777	0.9347	0.9448	1.5824
F-18	0.9931	0.9379	0.9338	0.8591	1.8045

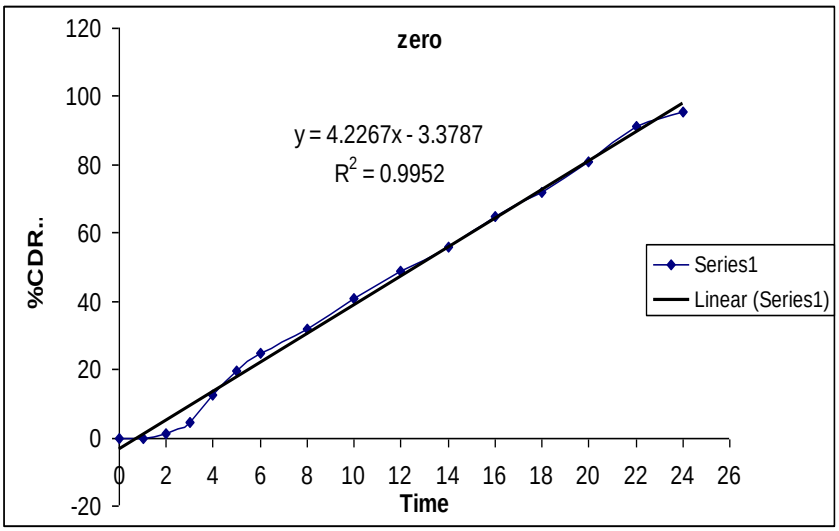

Figure 8: Zero Order Kinetics

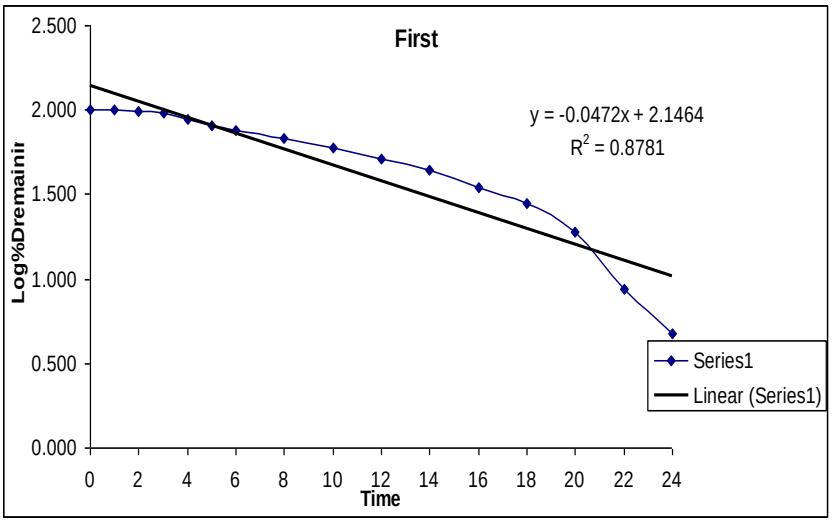

Figure 9: First Order Kinetics

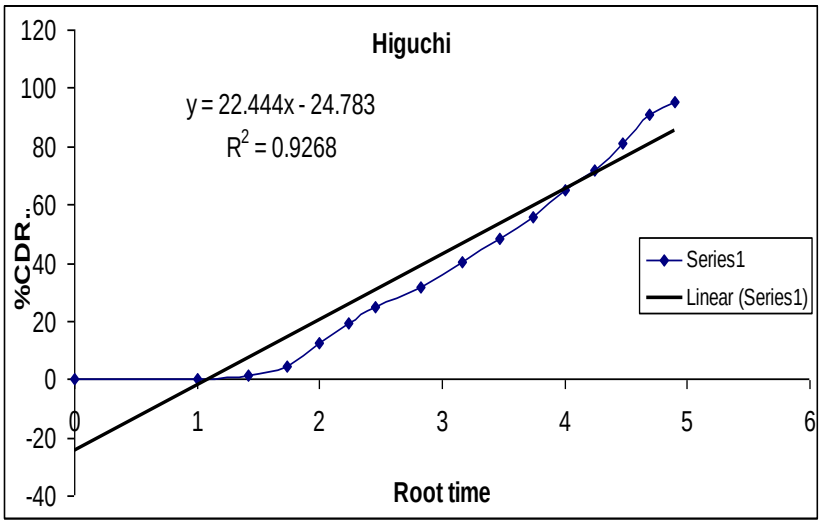

Figure 10: Higuchi Kinetics

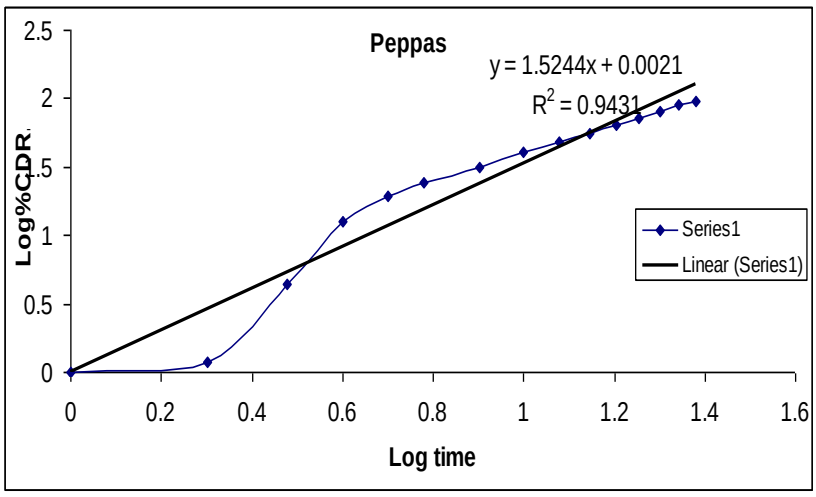

Figure 11: Peppas Kinetics

Conclusion

The polymer composition consisting of Polyox wsr 303 as a drug release retarding agent in combination with acid resistant enteric coated polymers such as Eudragit L100 which can be successfully used to protect the drug from being released under conditions mimicking mouth-to-colon transit. DDI colon specific enteric coated matrix tablets were prepared using POLYOX WSR 303 as time-dependent polymer and Eudragit L100 as pH sensitive polymer for colon targeting and they were characterized. If properly projected this kind of dosage forms can lead to a major key role for overcoming the different problems associated with the drug. The combination of above polymers, in the form of enteric coated tablets is capable of protecting DDI from being released in the upper region of GI system, i.e. stomach and small intestine. The *in vitro* drug release studies indicated that formulation F17 was a promising system to provide targeting of DDI to the colon. The release pattern of the above formulation was best fitted to zero-order model. Mechanism of drug release followed was non fickian (super case-II) transport mechanism. FTIR spectral studies showed that there is no interaction between the drug and excipients. The comparision of dissolution profile before and after stability studies of the best batch, the data was found that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed after stability studies. Hence the results of stability studies reveal that the developed formulation has good stability.

From the above results the F17 formulation was considered better among other formations.

Further investigations will be carried out like *in vivo* studies, x-ray studies, □-scintigraphy to evaluate the efficiency of Didanosine enteric coated tablets.

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