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Research Article

Evaluation of Push-Pull Osmotic Tablets of Anti-Retroviral Drug-Zidovudine

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ABSTRACT

Push-pull osmotic tablets can be used for the delivery of drugs which are poorly water-soluble and water soluble at a sonstant rate. Zidovudine is pyrimidine nucleoside analogue, first US FDA approved drug used for selective action against Human Immuno deficiency Virus. It is commercially available in the form of capsules, tablets, and syrup for oral administration of dose of three to four times a day. The objective of this study is to develop Push-pull osmotic tablets of antiretroviral drug, Zidovudine and evaluate its compatibility and suitability in the applications meant for sustained release oral drug delivery system providing, enhanced efficacy, reduced side effects and improves patience compliance. Preparation of PPOP involved the fabrication of bilayered tablets with the dug layer, containing zidovudine, HPMC 3000 cps and polymeric expansion push layer containing HPMC K4M. The effect of polymer ratios on release characteristics and optimization of suitable concentration of cellulose acetate coat formulations for forming rigid, stable, sustained release film were investigated. The coated tablets are manually drilled at the face of drug layer using a 0.5 mm gauge size needle. The pre-coated and coated tablets were subjected to various post–compression evaluation studies and appearance, *in-vitro* drug release and welling index of PPOTS were studied. The drug release from the formulations were found to follow of

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Korsmeyer-Peppas kinetics and FTIR and DSC studies revealed that the dug is stable and there is no interaction with the excipients.

Key words: Drug layer, Push layer, Osmotic agent, HPMC, Wet granulation, Coating.

INTRODUCTION

Zidovudine are classified as a Class-III drug[1] characterized as a high soluble and a low permeable active compound according to Biopharmaceutics Classification System (BCS). It is a synthetic nucleoside, thymidine analog reverse-transcriptase inhibitor, active against HIV-1 and 2 and act as chain terminators[1] of viral reverse transcription by selectively inhibiting viral reverse transcriptase, the enzyme that helps HIV to make DNA copy of its RNA and the production of viral double stranded DNA is stopped. It is commercially available in the form of capsules, tablets, and syrup for oral administration and are usually taken three to four times a day. However, the elimination half life of parent compound is considerably shorter than that of active metabolite, zidovudine 5'-triphosphate which is 3-4 hours. The therapeutic effectiveness of zidovudine is limited by haematological toxicity depended on its dose, poor therapeutic index, short therapeutic index and low biological half-life and less bioavailability. It has a short half life of 1-1.5 hours after administration through oral route and undergo quick absorbtion from the gastro intestinal (GI) tract, showing a concentration of 1.2 µg/ml peak plasma concentration in 0.8 hours and consequently high toxicity. Due to its considerable first pass metabolism, frequent administration of large doses (200 mg for every 4 hours) is required to maintain therapeutic drug level[2].

Push-pull osmotic tablet (PPOT) or Push-Pull Osmotic Pump (PPOP) is a customized multi chambered Elementory Osmotic Pump (EOP)[3], characterized by the delivery of drugs which are soluble in water. They have been successfully manufactured and marketed to deliver drugs for various indications and drugs. PPOPS were reputed as a drug delivery system with less interaction with food, which is usually found in the case of poorly soluble drug substances, enables a once-a-day administration and hence improves treatment tolerability as well as patient compliance[4].

MATERIALS AND METHODS

Zidovudine was received from Matrix Laboratories (Hyderabad, India) as a gift. HPMC 3000 cps and HPMC K4M were used as sustained release swellable polymers and were obtained

from SD Fine-Chem Ltd (Mumbai, India). Sodium chloride was used as osmogen was purchased from SD Fine-Chem Ltd (Mumbai, India). Ethyl cellulose was obtained from Chemspure Pvt Ltd (Chennai, India). PVP K30, sodium bicarbonate, microcrystalline cellulose, amaranth and isopropyl alcohol were purchased from SD Fine-Chem Ltd (Mumbai, India). Lactose monohydrate was obtained from Himedia laboratories Pvt. Ltd (Mumbai). Magnesium stearate was purchased from Paxmy speciality chemicals, Chennai (India).

METHODOLOGY

Drug excipient compatability studies

Fourier transform infrared (FT-IR) spectroscopy: The IR spectra of pure Zidovudine and F3 formulations were analyzed by KBR pellet method. The KBr pellet was mounted over suitable holder in FT-IR spectrophotometer and the FT-IR spectrum and were analyzed by an IR spectrophotometer (Perkin Elmer Spectrum RSI, Germany) recorded from 4000 cm^{-1} to 400 cm^{-1}. The obtained peaks of pure drug and the F3 formulation were correlated[5,6].

Differential scanning calorimetry (DSC)/ Thermal gravimetric analysis (TGA): The thermal behaviour of pure drugs and physical mixture were studied using DSC (TA instrument, Q100, USA) to confirm the solid complex formation. Around 5 mg of the samples were kept in alumina pan and heated at 10°C per minute upto 500ºC and the results were represented as weight loss and heat flow against temperature. The obtained patterns of the pure drug and F3 formulation is correlated[7,8].

Formulation development

Preparation of core tablets:

Table 1: Formulation composition of tablet cores

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
Drug layer (188 mg)			
Zidovudine	20	20	20
Sodium chloride	9	9	9
HPMC 3000 cps	18.8	56.40	37.60
Ethyl cellulose	18.8	18.8	18.8
PVP K 30	13	13	13
Magnesium stearate	2	2	2
Amaranth	1	1	1

Table 1: Formulation composition of tablet cores

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)
Microcrystalline cellulose	73.78	47.46	60.62
Lactose	31.62	20.34	25.98
Push layer (62 mg)			
HPMC K 4 M	25	25	25
Sodium bicarbonate	16	16	16
PVP K 30	6	6	6
MCC	8.8	8.8	8.8
Lactose	6.2	6.2	6.2

The bilayered core tablets of Zidovudine was prepared by conventional wet granulation technique. Drug and excipients for drug layer were weighed for 188mg tablets each, sieved and blended together except the lubricant, magnesium stearate. Alcoholic solution (isopropyl alcohol) of PVP K30M was added to get a damp mass, and it is passed through # 16 sieve and dried at 45 °C upto 30 mins. The granules after drying are sieved in a # 22 mesh and are mixed with lubricant. The push layer excipients were weighed for 62 mg tablets each and were granulated in a similar way. Colouring agent, amaranth, was added to differentiate push layer from drug layer. The drug layer tablets were pre-compressed with minimum hardness at an average weight of 188 mg and push layer granules corresponding to an average tablet weight of 62 mg was added and is compressed together with drug layer at an optimum hardness using single punch tablet press[9,10] . The drug layer and push layer (Figure 1a& b) compositions were shown in Table 1.

Coating of bilayer tablet formulations:

Table 2: Formulation composition of coating solution

Formulations	Ingredients						
	Cellulose acetate (g)	Acetone (ml)	DCM (ml)	PEG (ml)	Ethanol (ml)	Water (ml)	Total quantity (ml)
F1	0.100	100	-	0.400	-	-	100
F2	1	-	10	0.400	4	-	14
F3	1	-	90	0.400	50	-	140

Table 2: Formulation composition of coating solution

Formulations	Ingredients						
	Cellulose acetate (g)	Acetone (ml)	DCM (ml)	PEG (ml)	Ethanol (ml)	Water (ml)	Total quantity (ml)
F4	5	-	100	1	40	-	140
F5	0.900	90	-	0.100	-	10	100
F6	9	90	-	1	-	10	10
F7	9	225	-	1	-	25	250
F8	1.8	90	-	0.2	-	10	100
F9	0.8	90	-	0.2	-	10	100
F10	3	150	-	0.15	-	30	180
F11	7.5	95	-	5 *	-	5	100
F12	7.5	95	-	25*	-	5	125
F13	7.5	190	-	25 *	-	5	220
F14	9	90	-	20 *	-	10	120

**PEG concentration in mg*

The tablets were coated in pan coater with different quantities of coating formulations containing a cellulose acetate polymer and PEG plasticizer dissolved in various sovents (Table.2). The optimized coated formulation was selected for PPOT formulations. The coating parameters were optimized as follow: pan diameter- 6inch; spray gun (type 68-pilot spray gun); baffles-4; speed of pan-25 rpm; spray pressure-15 lbs/inch^2 drying temperature-45°C. The coated tablets are dried overnight at 45 °C to remove any residual solvent [9,10] (Figure 1c).

Drilling of orifice: The bilayered coated tablets were drilled manually at the face of drug layer using a 0.5 mm gauge size needle[9,10] (Figure 1d).

Evaluation tests

Pre-compression Parameters

Angle of repose (θ): Funnl method was used to measre angle of repose. Granules are flowed through a funnel which has its tip kept at 6 cm height above the basis. The granule samples were passed through the funnel until it forms a heap. The height of the heap and diameter of the circle drawn across the heap were noted. Radius of the circle is determined. The

procedure was repeated for 3 times and average θ value was taken[11]. The angle of repose is measured by using the equation:

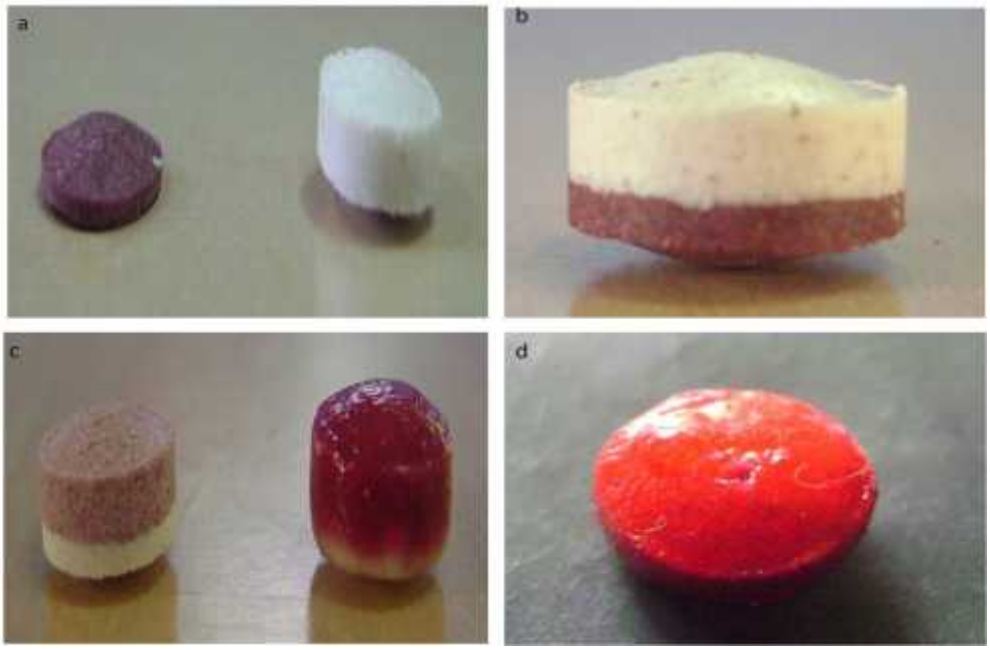

Fig 1: Photographic images of a) Push layer and drug layer separated, b) Bilayer tablet core c) Bilayer tablet core & PPOT, d) Drug delivery orifice

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

Where, h= pile height (cm)

R= radius occupied by pile (cm)

Bulk density (D_b): 4 g of granules were transferred in a measuring cylinder of 50 ml and the volume (vol) occupied by the granules without tapping was measured. Bulk density is calculated by the equation[11]:

D_b = Mass of granules/ Bulk vol

Tapped density (D_t): 4g of granules were transferred in a measuring cylinder of 50 ml and occupied volume of was measured. The cylinder was tapped gently on a wooden surface from 1 inch height in 2 seconds internvals (500 taps) and tapped volume was measured. Tapped density is determined by using the equation[11]:

D_t = Mass of the granules/ Tapped vol

Carr's index: Carr's index is calculated using the equation[12]:

Carr's index = $(D_t - D_b) / D_t \times 100$

Determination of Hausner ratio: Ratio of tapped density and bul density is the measurement of resistance developed due to frictional force between the granules. Frictional resistance of the drug is determined by Hausner ratio[12].

Hausner ratio = Tapped density/ Bulk density = D_t/ D_b

Post-compression parameters

Weight variation: Twenty tablets from each formulations were individually weighed and their average weight along with percentage deviation was calculated. The test was performed according to pharmacopoeia[11,13].

% weight variation = $(W_A - W_I) \times 100 / W_A$

Where, W_A = average tablet weight

W_I = individual tablet weight

Hardness: Monsanto type hardness tester (Dolphin tablet harness tester) was used to measure tablet hardness[14]. Hardness of tablet is the measure of strength required to break it crosswise the diameter. It is determined to find the withstanding capacity of tablet against the pressure and stress applied on it during handling and transportation. The force is measured in kilograms and the hardness of about 4 – 5 kg is optimum to pass IP limits for uncoated tablet. The compression force applied to break tablets were measured in kg/ cm^2.

Friability**:** Friability (F) is the measure of weight loss from the tablets in the container/package, due to discharge of fine tablet fragments from the edges and surface. This in-process quality control evaluation studies were done to assure the capacity of tablets to bear the shocks during processing, handling, transportation and shipment. The friability of tablets is indicated by chipping, capping or breaking. The extent of friability is estimated using Roche friabilitor. It is expressed as percentage w/w. The allowable friability is less than 0.8 – 1.0 %. The tablet friability were measured with Lab India friability tester (FT 1020)[14]. F is calculated by the equation:

$F = (1-W_i / W) \times 100$

Where W_i = initial weightof the tablets

W = final weight of tablet after the run

Tablet thickness and Tablet diameter: The thickness and the diameter were determined using vernier (Mitutoyo,Japan). Three tables from each formulations were used, average thickness and diameter wirh standard deviation were calculated[14].

Drug contend: Three tablets from each formulations were powdered. 20 mg equivalent weight of the Zidovudine was dissolved in 5 ml methanol and made to volume of 100 ml with distilled water. It is sonicated for 30 minutes and 1 ml of this dilution was further made upto 100 ml with distilled water to get 20 µg per ml drug solution and is filtered. All the dilutions were done using standard volumetric flasks. The solution is analyzed against distilled water as blank in UV-Vis spectrophotometer at 266 nm[14].

Disintegration test: Disintegration test was conducted as per pharmacopoeia using Lab India Disintegration Tester (DT 100) with three tablets from each formulations in 900ml distilled water at 37± 2 ºC. The tablets were observed for the evidence of disintegration, cracking or softening and time taken by the tablet for disintegration is determined[15]. The tame taken for the complete disintegration of tablet without any noticeable mass is noted.

In-vitro release study: *In-vitro* release of drug for PPOP formulations and uncoated formulations were studied using the USP II dissolution test apparatus (Lab India DS 8000). The test was done in 500 ml distilled water kept at 37±5°C and the paddle speed rotated at 100 rpm. 5 ml of samples were taken out and made to the initial volume with 5 ml new media at specified time intervals. The samples were analyzed by UV-Vis at 266 nm. The experiments were performed in triplicate [9].

Elucidation of release mechanism: The release parameters and mechanism of release of Zidovudine tablets was investigated by fitting the data to Zero-order, First order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models.

Swelling index: The swelling response of PPOTs containing drug were studied by hydration study. The F4, F5 and F6 formulation tablets were weighed individually to determine initial weight of each tablets using electronic balance. They are placed in separate petridishes containing 10 ml water and are kept at room temperature. The tablets were removed from the petridishes at regular interval and water in excess was carefully blotted and the swoollen tablets were weighed and replaced to the petridishes[11,16,17]. This process is continued for 6 hours and the percentage of water uptake (WU%) were calculated using the equation:

WU%=(weight of tablet after swelling-initial weight)/initial weight ×100

RESULTS AND DISCUSSION

Fourier Transform Infra Red (FTIR) spectroscopy: The FTIR spectrum of F3 formulation was compared with spectrum of pure Zidovudine (Figure 2). The IR peaks of pure Zidovudine were formed at 3463.79cm^{-1} corresponding to amine group (N-H stretch), 2817.81cm^{-1} corresonding to acid group (O-H stretch), 1692.18cm^{-1} corresponding to carbonyl group (C=O stretch), 1093.77 cm^{-1} corresponding to alcohol group (C-O stretch) and 20865 cm^{-1} showing azido group. The IR peaks of optimized formulation were formed at wave number 3384.52cm^{-1} corresponding to amine group (N-H stretch), 2921.58cm^{-1} corresonding to acid group (O-H stretch), 1677.01cm^{-1} corresponding to carbonyl group (C=O stretch), 1064.92cm^{-1} corresponding to alcohol group (C-O stretch) and 2108.31 cm^{-1}

showing azido group. The drug-polymer interaction study by FTIR analysis showed that IR peaks of F3 formulation showed a slight shift in the absorption peaks compared to peaks of pure drug which may due to a slight interaction of HPMC 3000 cPs, HPMC K4M or ethylcellulose with Zidovudine [18].

Differential Scanning Calorimetry (DSC)/ Thermal Gravimetric Analysis: The DSC/TGA patterns of pure drug (Figure 3a) and the F3 formulation (Figure 3b) containing 30% HPMC 3000 cPs along with suitable excipients showed a sharp endothermic peak at 124.98 °C and 122.43 °C respectively, corresponding to their melting point. From the DSC pattern of pure drug it is clear that, the decomposition of the pure sample starts at 236.60°C and is completely decomposed at 285.70 °C, where in TGA curve, a sharp decline

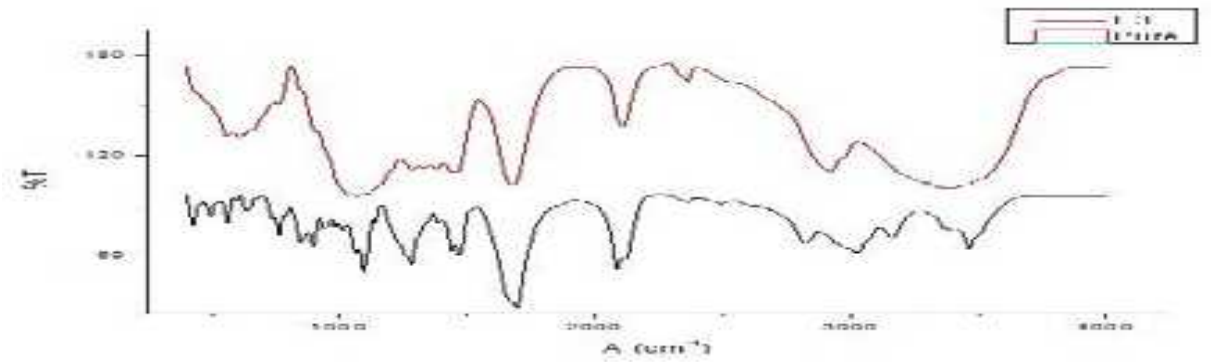

Fig 2: FT-IR spectra of pure drug Zidovudine and F3 formulation

in the curve is appeared corresponding to a sharp decrease in the weight loss of pure Zidovudine. The DSC pattern of F3 formulation showed that the decomposition of the drug in physical mixture starts at 220.00 °C whereas, the decomposition temperature was not detected in the TGA pattern, which may be due to the formation of hydrogen bonding between the drug and the polymer. The DSC/TGA analysis of F3 formulation compared with pure Zidovudine showed a slight shift in the melting point which corresponds to the melting point of drug in pure drug sample (124.98 ° C to 122.43 °C) . The results concluded that the drug is thermally stable and showed no interaction with the polymers.

Pre-compression parameters

Angle of repose**:** The values for angle of repose of drug layer granules were found in the range of 20.02 ± 1.0 to 23.45 ± 2.5and the values of angle of repose for of push layer granules is 20.02 ± 1.0. The results showed that the formulations F1, F2 and F3 formulation with10%, 20% and 30% HPMC 3000 cPs polymer respectively, showed good flow properties respectively and the study concluded that the excellent flow property could be achieved with increase in polymer concentration.

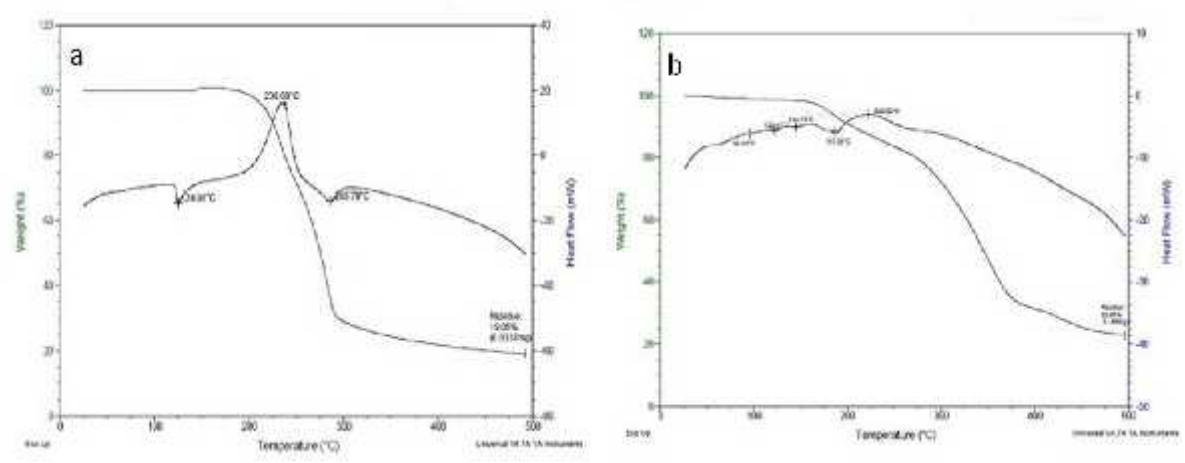

Fig 3: DSC/TGA pattern of a) pure drug Zidovudine, b) DSC/TGA pattern of F3 formulation

Table 3: Pre-compression parameters of granules for PPOT formulations

Formulations		Angle of repose (°)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner ratio
Drug layer	F1	23.45 ± 2.5	0.326	0.380	14.21	1.16
	F2	21.96 ± 0.4	0.280	0.323	13.31	1.15
	F3	20.14 ± 1.9	0.285	0.324	12.16	1.13
Push layer	F1, F2, F3	20.02 ± 1.0	0.290	0.330	12.12	1.13

Bulk density: The values for bulk density of drug layer granules calculated were between 0.285 gm/ml to 0.326 gm/ml and the values for bulk density of push layer granules is 0.29 gm/ml. The result clearly showed that the bulk density decreases varies with polymer concentrations.

Tapped density: The values for tapped density of drug layer granules calculated were between 0.324 gm/ml to 0.380 gm/ml and the values for tapped density of push layer granules is 0.330 gm/ml. The result clearly showed that the tapped density varies with polymer concentrations.

Carr's index: Carr's index values of drug layer formulations F1, F2 and F3 are 14.21 %, 13.31 % and 12.16 % respectively and Carr's index values of push layer formulation is 12.12 %. The result showed that the F3 formulation containing 30% HPMC 3000 cPs polymer and

the push layer granules with Carr's index of 12.12% showed good flow properties. The study concluded that good flow properties can be achieved with increase in polymer concentration.

Hausner ratio: Hausner ratios of drug layer formulations F1, F2 and F3 are 1.16, 1.15 and 1.13 respectively and Hausner ratio of push layer formulation is 1.13. The F1, F2 and F3 formulations with Hausner ratio lesser than 1.25 indicates better flow properties and study concluded that Hausner ratio decreases with increase in polymer concentration.

Evaluation studies for tablets

Table 4: Post-compression parameters push pull osmotic tablets

Formulations	F1	F2	F3	F4	F5	F6
Weight variation (mg)	280.2 ± 5	269.8 ± 3	251.8 ± 4	339.5±7	324.52±4	301.38±5
Thickness (mm)	5.21 ± 0.04	5.20 ± 0.03	5.15 ± 0.04	6.98±0.12	6.14±0.33	6.32±0.27
Diameter (mm)	8.74 ± 0	8.74 ± 0	8.74 ± 0	9.16±0.2	9.48±0.4	9.3±0.3
Hardness (kg/cm^2)	2.66 ± 0.3	2.6 ± 0.25	2.5 ± 0.4	3.33±0.29	3.0±0.5	2.83±0.58
Friability (%)	0.94	0.89	0.84	-	-	-
Disintegration time (hr)	2.15 ± 0.63	4.95 ± 0.35	> 6	> 6	> 6	> 6
Assay (%)	101.8	99.5	99.7	-	-	-
Percentage weight gain after coating (%)	-	-	-	21.16	20.28	19.69

Weight variation test: The average weight of F1, F2, F3, F4, F5 and F6 formulations were 280.2 ± 5, 269.8 ± 3, 251.8 ± 4, 339.5±7, 324.52±4 and 301.38±5 respectively. The results showed that the weight of all the formulations were under pharmacopoeia limit.

Hardness: The results showed that F1, F2, F3, F4, F5and F6 were 2.66 ± 0.3, 2.6 ± 0.25, 2.5 ± 0.4, 3.33±0.29, 3.0±0.5 and 2.83±0.58 respectively .The results showed that hardness of all the formulations were under pharmacopoeia limits.

Friability: The percentage friability of all the formulations lies in the range between 0.84 % to 0.94 %. The results showed that the percentage friability of all the formulations were under pharmacopoeia limits.

Thickness: The average thickness of uncoated bilayer core tablets, F1, F2, F3 and coated PPOTs, F4, F5, F6 formulations were 5.21 ± 0.04, 5.20 ± 0.03, 5.15 ± 0.04, 6.98±0.12, 6.14±0.33 and 6.32±0.27 respectively. The results showed that average thickness of all the core tablet formulations and PPOTs were similar.

Tablet diameter: The diameter of all the uncoated formulations F1, F2 and F3 were 8.74 ± 0 respectively and diameter of coated formulations F4, F5 and F6 were 9.16±0.2, 9.48±0.4 and 9.3±0.3. The results showed that the average diameter of all the core tablet formulations and PPOTs were similar.

Contend uniformity: The percentage dug contend of the formulations F1, F2 and F3 formulations were 101.8±0.63, 99.5±0.75 and 99.7±0.28 % respectively. This result showed that there was uniform distribution of the drug throughout all the formulations.

Disintegration test: Disintegration time of F1, F2 and F3 are 2.15 ± 0.63, 4.95 ± 0.35 and > 6 hours respectively and for the PPOTs were greater than 6 hours. The result showed that F3 formulation with 30 % HPMC 3000 cps and all the coated formulations F4, F5 and F5, did not disintegrated even in 6 hours. The result concluded that disintegration time can be increased with increase in polymer concentration and the optimized cellulose acetate coating film of PPOT formulations were stable and rigid for more than 6 hours even after disintegration test.

In-vitro dissolution study: The drug profile data of uncoated bilayer showed that the drug release from uncoated core tablets and PPOTs depends on the polymer concentration. Formulation F1 containing polymer 10% HPMC 3000 cPs released 110% of the drug in 6 hours whereas formulation F2 containing 20% HPMC 3000 cPs and F3 containing 30 % HPMC 3000 cPs released 87% and 81% of drug in 6 hours respectively (Figure 4a). The data reveals that the increase in polymer concentration delayed the drug and makes release slow. The coated PPOT formulations of Zidovudine showed the drug release in sustained manner. The PPOT formulation F4 containing 10% HPMC 3000 cPs released 88% of the drug in 6 hours whereas formulation F2 containing 20% HPMC 3000 cPs and F3 containing 30 % HPMC 3000 cPs released 83% and 78% of drug in 6 hours respectively (Figure 4b). When compared to drug release of uncoated tablets the coated tablets shows slow release, this may be due to the presence of semi-permeable membrane which helps in retarding the drug from the formulation. This reveals that cellulose acetate coat has occurred and has the influenced

in drug release. From the *in-vitro* drug release data we could infer that sustained drug release could be achieved by increase in the concentration of polymers in the drug layer for all the formulations and the study concluded that the PPOT formulations showed more controlled release compared to the uncoated bilayer core formulations.

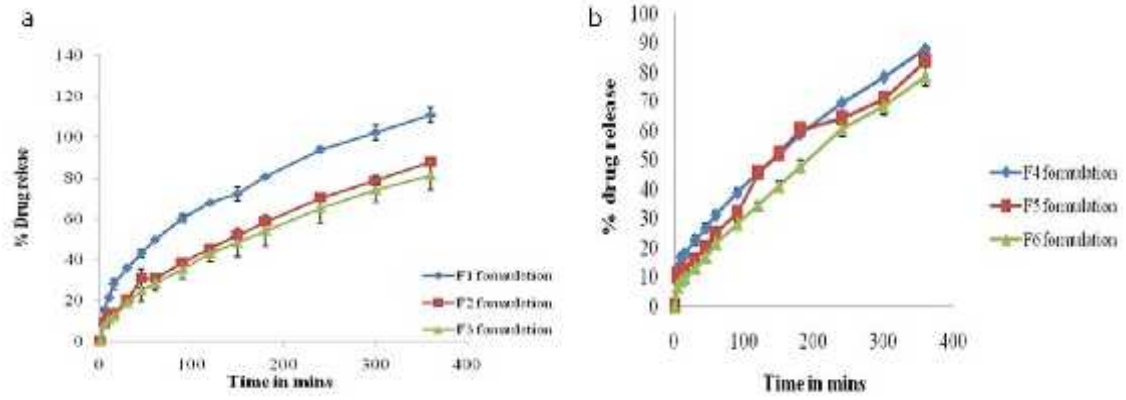

Fig 4: in-vitro drug release profile of a) core tablet formulations b) profile of PPOT formulations

Kinetic analysis of dissolution data

Table 5: Kinetic modelling of bilayer core tablet formulations

Formulations	Zero order model	First order model	Higuchi model	Hixson-Crowell model	Korsmeyer-Peppas model	
	r^2					N
F1	0.6382	0.9445	0.9936	0.9236	0.9992	0.449
F2	0.8355	0.9688	0.9910	0.9521	0.9971	0.564
F3	0.8590	0.9765	0.9889	0.9596	0.9992	0.585
F4	0.8015	0.9465	0.9906	0.9273	0.9928	0.537
F5	0.8268	0.9400	0.9444	0.9233	0.9559	0.593
F6	0.9443	0.9859	0.9516	0.9848	0.9961	0.709

The release pattern of the uncoated bilayered core tablet formulations were analyzed by means of kinetic modelling. The data obtained for *in-vitro* release was fitted into various kinetics equations and the r^2 value and release exponent (n) obtained for Korsmeyer Peppas model was estimated. The r^2 values of formulations, F1, F2 and F3 were 0.999, 0.997 and 0.999 respectively. Kinetic analysis of dissolution data showed that release of drug from all the three formulations follow Korsmeyer- Peppas model and except formulation F1 the remaining formulations followed anomalous non-fickian movement.

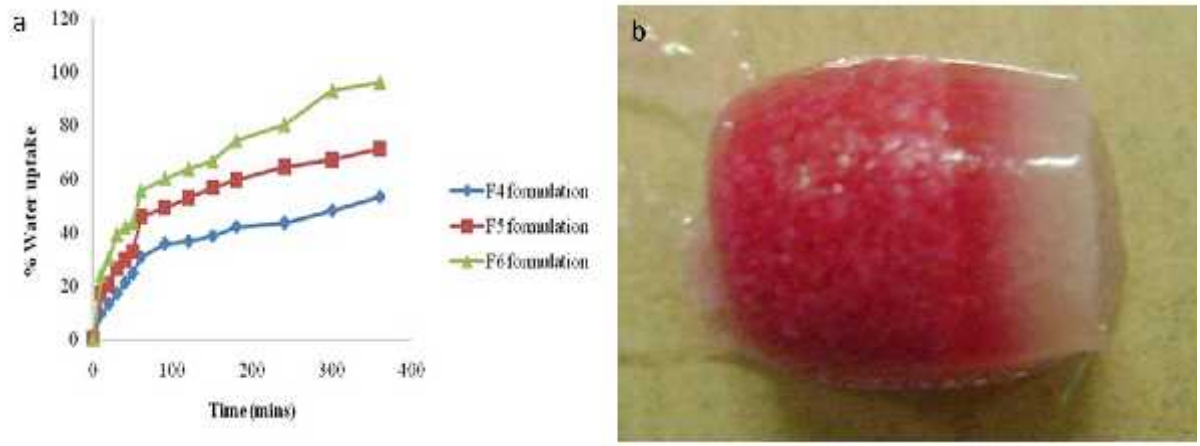

Fig 5: Effect of polymer concentration on a) swelling index b) PPOT after 6 hour in-vitro release study.

Table 6: Visual characteristics of coat formulations used for push pull osmotic tablets of zedovudin

Formulations	Clarity	Turbidity	Inference
CF1	Transparent	Low	No film formed on tablets
CF2	Transluscent	Low	No film formed on tablets
CF3	Transparent	Low	Easily degrading films
CF4	Transparent	Medium	Transparent,shiny film and tablets are stable in water under stirring for 20 mins
CF5	Transluscent	Low	Easily degrading films
CF6	Opaque	High	Difficulty in spraying

Table 6: Visual characteristics of coat formulations used for push pull osmotic tablets of zedovudin

Formulations	Clarity	Turbidity	Inference
CF7	Transluscent	Low	Non-shiny, porous, and easily degrading coats (degrades in water even without stiring in few minutes)
CF8	Transluscent	Low	Orange peeling/Rough coat
CF9	Transparent	Low	Orange peeling/Rough coat
CF10	Transparent	Medium	Orange peeling/Rough coat
CF11	Transluscent	High	Easily degrading films
CF12	Transluscent	Medium	Peeling at edges
CF13	Transluscent	Low	Stable coat
CF14	Transluscent	Low	Stable coat

The release pattern of the uncoated bilayered core tablet formulations were analyzed by means of kinetic modelling shown in Table.5. The data obtained for *in-vitro* release was fitted into various kinetics equations and the r^2 value and release exponent (n) obtained for Korsmeyer Peppas model was estimated. The r^2 values of formulations, F4, F5 and F6 were 0.992, 0.955 and 0.996 respectively and with n values between 0.5 to 1.0. Kinetic analysis of dissolution data showed that release of drug from all the three formulations follow Korsmeyer- Peppas model with anamolous non-fickian movement.

Hydration study: The percentage water uptake by F4, F5 and F6 formulation were found to be 53.44%, 71.34% and 99.17% respectively (Figure 5a). From the results it is clear that F6 formulation containing 30% HPMC 3000 cps showed maximum uptake of water and maximum swelling (Figur 5b) and from the results it can be concluded that water uptake and swelling increase with increase in polymer concentration.

Visual properties of coating solutions and appearance of coated tablets: Majority of coat formulations from CF1 to CF12 formed were unstable, viscous and transluscent in nature. The tablets spray coated with these formulations were unstable, easily degrading and were peeling out while drying. The tablets dip coated with formulation CF13 and CF14 showed stable and rigid coats. Rigidity and stability of coats were increasing with increased cellulose acetate concentration with an increase in viscosity.

CONCLUSION

Push-pull osmotic tablets were developed for the delivery of anti retroviral drug, Zidovudine by varying the concentration of HPMC 3000 cPs in the drug layer. Kinetic analysis of dissolution data showed that the release of drug from all the formulation followed Korsmeyer-Peppas model with anamolous non-fickian movement. Wet granulation process was employed for granulation and the granules were tested for pre-compression parameters. Bilayer tablet core were made using single punch, coated with optimized cellulose acetate coat formulation and finally drug release orifice is drilled at the face of drug layer. The core tablets and PPOT formulations were subjected to various post compression evaluation tests. FT-IR and DSC/TGA analysis of the pure Zidovudine compared to the F3 formulation showed that the drug is compatible with the polymer and is thermally stable. The *in-vitro* drug release profiles of core tablet formulation and PPOT formulation showed that the drug release from PPOTs showed more sustained release comparing to uncoated tablet cores and in-vitro study concluded that the release rate can be controlled with the increase in the concentration of the polymer. Hydration study of PPOT formulations concluded that the water uptake and swelling rate could be increased with increase in polymer concentration. Futures studies are required to optimize the polymer concentration, osmotic agent proportion in core tablets and suitable coat formulation for once-a-day PPOTs of Zidovudine in anti retroviral therapy.

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