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RESEARCH ARTICLE

PHARMACEUTICS

DESIGN AND CHARACTERIZATION OF GAS POWERED SYSTEM OF ZIDOVUDINE USING SYNTHETIC POLYMERS

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ABSTRCTS

Zidovudine is the first approved compound for the treatment of AIDS, and having short biological half-life and poor bioavailability. The present research work an attempt has been made to design the Zidovudine gas powered drug delivery system for controlled release. The gas powered tablets were prepared by direct compression. The sodium bicarbonates and citric acid were also used as a gas generating agent. Drug compatibility with excipients was checked by FTIR and DSC studies. No chemical interaction between drug and excipients was confirmed. The prepared gas powered tablets are evaluated to post-compressional parameters. In all the formulations, the post-compressional parameters evaluated were within prescribed IP limits. The floating lag time of the prepared formulations is good except for two formulation F1 and F2 and the floating time for all the formulations was >16 hrs except F1 and F2 which does not float at all. The results of lag time study and floating time, the values of floating lag time ranges from 5 to 20 min, and floating time ranges from 180-1440 min. The formulation F8 shows the lag time 5 min and buoyancy time >1440 min. Drug release kinetics was studied for prepared formulations, results were found to follow zero order kinetics. The stability study conducted as per the ICH guidelines and the formulations were found to be stable. From this study, it is concluded that, the formulations retained for longer period of time in the stomach and provides controlled release of the drug. Hence it may increasing the bioavailability of the drug and patient compliance.

KEY WARDS

Zidovudine, gas generated, controlled release, bioavailability.

INTRODUCTION

Oral drug delivery system represents one of the frontier areas of controlled drug delivery system; such dosage forms are having a major advantage is patient compliance. Floating drug delivery system belongs to oral controlled drug delivery system group that are capable of floating in the stomach by bypassing the gastric transit. These dosage forms are also defined as gas powered system (GPS), which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time. The release rate will be controlled depending upon the type and concentration of the polymer that swells, leads to diffusion and erosion of the drug.[1-3]

The investigation was concerned with design and characterization of Zidovudine (AZT) gas powered system for controlled release in order to improve efficacy and better patient compliance. Zidovudine is a dideoxynucleoside compound in which 3-hydroxy group on the sugar moiety can be replaced by group and this modification prevents the formation of phosphodiester linkages which are needed for the completion of nucleic acid chain. Zidovudine appears most promising because it crosses the blood brain barrier and be taken orally. Zidovudine the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of Zidovudine is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life of 0.8-1.5 hrs, and poor bioavailability 65%.[2-6] Zidovudine/Azidothymidine (AZT) the first anti-HIV compound approved for the clinical use is widely used for treatment of AIDS either along or in combination with other antiretroviral agent. Zidovudine acts as a metabolic antagonist of thymidine is time dependent so controlled release delivery of AZT is desired to maintain anti-AIDS effect and avoiding the severe side effects. By considering the above facts, Zidovudine Gas powered system is designed and characterized for controlled release in order to improve the patient compliance in such a way that it reduces dosing frequency, reduces side effects and increases the bioavailability of the drug.[7,8] Hence, the Zidovudine Gas Powered Tablets were Prepared by direct Compression Method using the different concentration of hydrophilic and hydrophobic polymer. The composition of Zidovudine GPS tablets is given in **Table 1.**

Table 1
Composition of the Zidovudine gas powered tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Zidovudine	300	300	300	300	300	300	300	300
Sodium bicarbonate	50	60	70	80	50	60	70	80
Crossed linked CMC	10	20	10	10	10	20	10	10
Sodium Alginate	10	20	10	10	10	20	30	30
HPMC K4M	60	50	50	60	60	50	50	60
HEC	10	20	30	40	-	-	-	-
Carbopol-934.	-	-	-	-	10	20	30	40
NaCMC	50	60	70	50	50	60	70	50
Lactose	80	30	30	30	80	30	10	10
Citric Acid	10	20	20	10	10	20	20	10
Talc	10	10	10	10	10	10	10	10
Magnesium Stearate	10	10	-	-	10	10	-	-
Total	600	600	600	600	600	600	600	600

MATERIALS AND METHODS

Zidovudine is obtained as gift sample from Emcure Pvt Ltd. HPMC K4M. Gift sample is also obtained from AstraZeneca Bangalore. Hydroxyl Ethyl Cellulose (HEC), Carbopol 934, Magnesium state and citric acid are purchased from Hi Media Laboratories Pvt. Ltd, Mumbai. India. Sodium CMC were purchased from Rajesh Chemical Mumbai, cross-linked polyvinyl pyrrolidone (PVP) from signet Chemical Corporation, Worli, Mumbai, Sodium bicarbonate, sodium alginate, lactose, mannitol and talc were purchased from SD Fine Chemicals, Mumbai. All other materials used as analytical grade.

Preparation of Zidovudine Gas powered Tablets: Gas powered Tablets were prepared by mixing the Zidovudine 300 mg with the gas generating component and the selling agent, the gas entrapping viscolyzing agent and including gel forming polymer, citric acid as acid source and lactose by geometric mixing in mortar and pestle for 10 min. The above powder was lubricated with magnesium stearate in mortar and pestle for 2 min. The lubricated blend was compressed into tablets using 11.9 mm flat-force round tooling on Remik Press rotary tablet machine.

Evaluation of Gas Powered Tablets:
Pre-compression Evaluation[9]:

a) Bulk Density: Both loose bulk density (LBD) and tapped bulk density (TBD) of the powder blend were determined using the following formula.
LBD= weight of the powder/ volume of the packing
TBD= weight of the powder/ tapped volume of the Packing
b) Carr's Consolidation Index: Compressibility index of the powder blend was determined by Carr's compressibility index.
Carr's index (%) = [(TBD-LBD) X 100] / TBD
c) Angle of repose: Angle of repose for prepared granules was determined by fixed funnel method. A funnel was fixed with its tip at a given height h above a flat horizontal surface to which a graph paper was placed. The granules were carefully poured through a funnel till the apex of the conical pile just touches the tip of the

funnel. The angle of repose was then calculated using the formula,

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

Where, 'θ' is the angle of repose 'h' is height of pile, 'r' is radius of base of the pile

Post-Compressional Evaluation:

a) Thickness: The thickness of the tablets was determined by using screw gauze. Thickness of ten tablets was determined randomly. It was expressed in mm.

b) Hardness: The Pfizer hardness tester was used to determine the tablet crushing strength. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gave a measure of the hardness of tablet. Hardness was expressed in Kg/ cm^2.

C) Friability: Friability was determined using Roche Friabilator. Twenty tablets were weighed and placed in the friabilator and then operated at 100 rpm for four minutes. The tablets were then dedusted and weighed. It was expressed in percentage. The difference in the two weights is used to calculate friability.

$$Friability = 100X(1 - W/W0).$$

Where W0 = Initial weight, W = Final weight

d) Weight Variation Test: For weight variation ten tablets were selected randomly from each formulation and weighed individually using a Shimadzu balance (BL-220H).

e) Drug Content: Drug content was performed to check dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. A quantity equivalent to 300 mg of Zidovudine was added in to a 100 ml volumetric flask and dissolved in 0.1N HCL, shaken for 10 minutes and made up the volume up to the mark and filtered. After suitable dilutions the drug content was determined by UV spectrophotometer at 266 nm against blank. (Using UV-VIS Spectrophotometer, Shimadzu 1700).

f) Floating or Buoyancy Test[10]: The time taken for tablet to emerge on the surface of the medium is called the floating lag time (FLT) or buoyancy lag time (BLT) and duration of time the dosage form constantly remains on the surface of the medium is called the total floating time (TFT).The buoyancy of the tablets was studied in USP type II dissolution apparatus at 37±0.5oC in 900ml of simulated gastric fluid at 0.1N HCl. The time of duration of floatation was observed visually.

g) Swelling index[7]: The swelling index of tablets was determined n 0.1 N HCl at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

Swelling index WU = (Wt - W0) X100/ W0

Where, Wt = Weight of tablet at time t.

W0 = Initial weight of tablet

h) In-vitro Release studies for floating tablets[11]: The *in-vitro* dissolution studied was carried out using USP XXIV Dissolution Apparatus No.2 (type) at 50 rpm. The dissolution medium consisted of 0.1N HCL for 2hrs.and for subsequent 22 hrs in Phosphate buffer pH 7.4 (900ml) maintained at 37 ± 0.5^0. The release studies were conducted triplet. Adequate of sample 5ml were withdrawn at specific time interval and drug content was determined spectrophotometrically at 266 nm.

RESULT AND DISCUSSION

The values of pre-compression parameters evaluated were within prescribed limits and indicated good free flowing property. The results of pre-compression parameters were given in **Table 2.**

Table 2
Evaluation of Pre-Compressional parameters.

FC	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.634 ± 0.02	0.747 ± 0.04	15.12 ± 0.10	1.17 ± 0.03	30.43 ± 0.14
F2	0.576 ± 0.04	0.734 ± 0.05	21.52 ± 0.04	1.27 ± 0.04	28.49 ± 0.16
F3	0.547 ± 0.05	0.675 ± 0.06	18.96 ± 0.12	1.23 ± 0.03	30.58 ± 0.18
F4	0.614 ± 0.03	0.766 ± 0.04	19.84 ± 0.08	1.24 ± 0.06	29.48 ± 0.13
F5	0.658 ± 0.04	0.873 ± 0.05	24.62 ± 0.12	1.32 ± 0.04	29.09 ± 0.11
F6	0.738 ± 0.02	0.823 ± 0.04	29.69 ± 0.11	1.11 ± 0.02	30.66 ± 0.12
F7	0.536 ± 0.03	0.688 ± 0.03	22.09 ± 0.09	1.28 ± 0.05	28.12 ± 0.12
F8	0.683 ± 0.06	0.759 ± 0.02	26.70 ± 0.13	1.11 ± 0.06	26.97 ± 0.14

The values represent mean ± S.D; n=3. FC= Formulation Code

In all the formulations, Thickness of the tablets ranges between 4.8 and 4.15 mm. Hardness test indicated good mechanical strength. The hardness and percentage friability of the tablets of all the batches remained in the range between 6.5 to 9.6 kg/cm^2, and from 0.39 % to 0.74 % respectively. Friability is less than 1%, indicated that tablets had a good mechanical resistance. The weight variation of tablets was ranges between 597 and 609. Weight variation test revealed that the tablets were within the range of pharmacopoeial limit. The evaluation parameters were within acceptable range for all the formulations. The results of thickness, hardness, friability and weight variation were shown in **Table 3.**

Table 3
Evaluation of Post-Compressional parameters

FC	Thickness mm	Hardness Kg/cm^2	Friability (%)	Average weight mg	Drug Content (%)	Swelling Index (%)
F 1	4.14 ± 0.02	9.6 ± 0.07	0.57	598	96.70	52.75
F2	4.12 ± 0.07	8.4 ± 0.05	0.49	603	99.88	74.5
F3	4.10 ± 0.04	6.5 ± 0.02	0.52	609	97.38	48.80
F4	4.08 ± 0.02	8.2 ± 0.03	0.39	602	98.62	69.40
F5	4.12 ± 0.04	6.5 ± 0.03	0.46	600	98.68	68.50
F6	4.14 ± 0.05	7.3 ± 0.02	0.60	608	99.26	78.42
F7	4.15 ± 0.07	7.4 ± 0.06	0.74	597	96.78	74.40
F8	4.10 ± 0.08	6.8 ± 0.04	0.62	602	99.87	65.38

**** The values represent mean ± S.D; n=3. FC= Formulation Code***

The drug content of the tablets ranges between 96.70% and 99.87% which is within acceptable limits. The swelling index of the tablets was in the range between 48.80 and 78.42.

The floating lag time **(Fig 1)** for all the formulations was found to be less than 12 minutes, except in F1, F2, and F5. F1 and F2 failed to float while F5 had taken 20 minutes to float. The floating duration **(Fig 2)** was found to be up to 24 hours in all formulations except F1, F2 and F10.

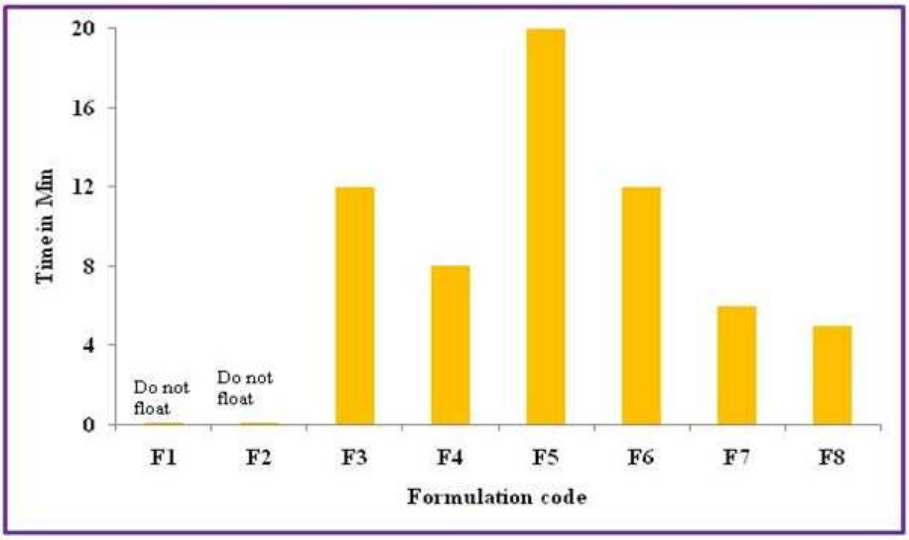

Fig 1. Floating Lag Times of the Formulations.

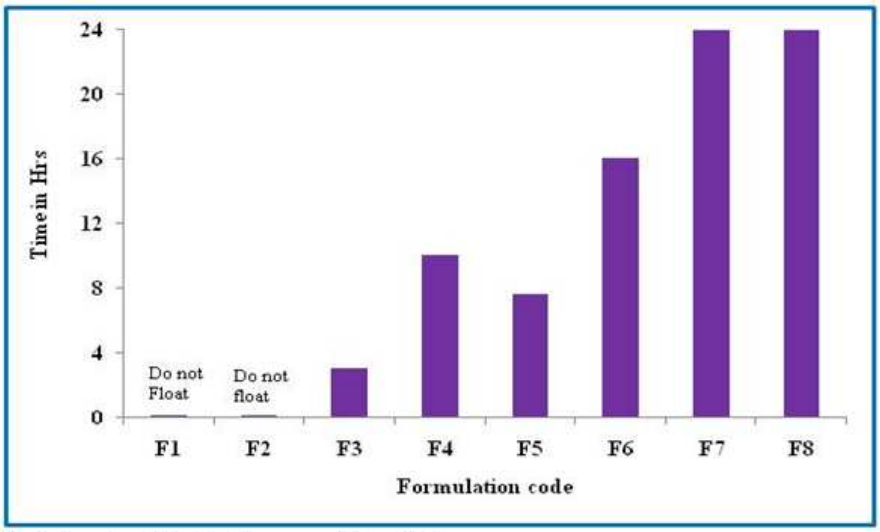

Fig 2. Duration of floating for prepared formulations.

Incorporation of HPMC K4M and carbopol along with sodium bicarbonate and citric acid was found to improve the floating lag time and the drug release was satisfactory. F1 and F2 might have failed to float due to extreme hardness of the tablet. The formulation F8 shows the lag time 5 min and buoyancy time >1440 min. The results were shown in **Table 4**. Sodium bicarbonate was added as a gas-generating agent. Sodium bicarbonate induced carbon dioxide generation in presence of dissolution medium (0.1 N hydrochloric acid). The combination of sodium bicarbonate and citric acid provided

desired floating ability and therefore this combination was selected for the formulation of the gas powered tablets. The results of in-vitro buoyancy time and lag time study revealed that as the concentration of sodium bicarbonate increases; there was increase in total buoyancy time and decrease in lag time. It is evident from the in-vitro dissolution data that increase in citric acid concentration increased the release rate but reduced the floating time, probably due to excess of carbon dioxide, disturbing the monolithic tablet. The citric acid level in the formulations greatly influenced the drug release.

Table no - 4
Floating ability of Zidovudine floating tablet

FC	Floating lag time (min)	Floating duration(min)
F 1	Not float	Not float
F2	Not float	Not float
F3	12	180
F4	8	600
F5	20	460
F6	12	960
F7	6	>1440
F8	5	>1440

***The values represent mean ± S.D; n=3. FC= Formulation Code**

The release of Zidovudine from all the formulations **(Shown in Figs 3-4)** ranges from 43.21 to 61.81% after 12 hrs, and from 83.03 to 99.79% at the end of 24 hrs. The results were given in **Table 5.** The preliminary studies revealed that the HPMC K4M matrix could not sustain the drug release for a period of 12 hrs, and this may be due to HPMC forms a hydrogel layer when comes in contact with water; which acts as a gel boundary for the delivery system. But it failed to retard the release of drug through the matrix because of the high solubility of drug in the stomach pH. The incorporation of Carbopol 934 not only retarded the release but also prolonged the release for a period of 12hrs. Carbopol 934 is a cross-linked polymer with high molecular weight (~2 × 106 Da) and viscosity; when contacted with water, it swells and holds water inside its microgel network. This particular property may be accounted for its release retardant effect.

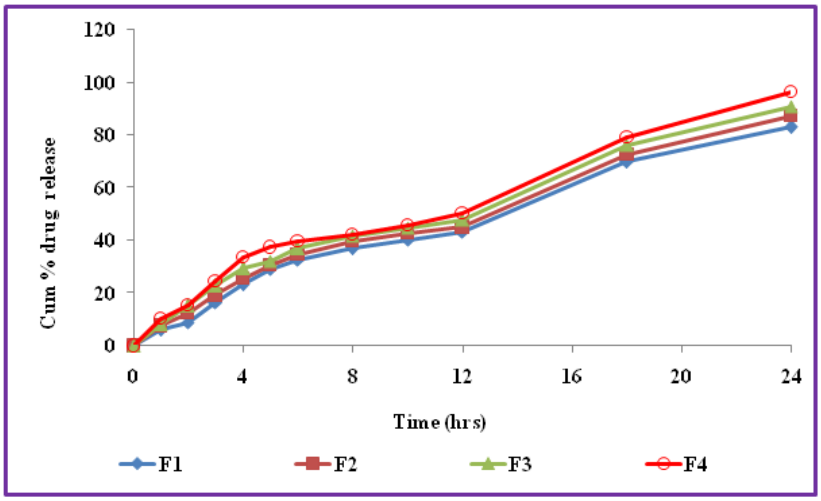

Fig 3: *In-vitro* release studies of formulation F1 to F4.

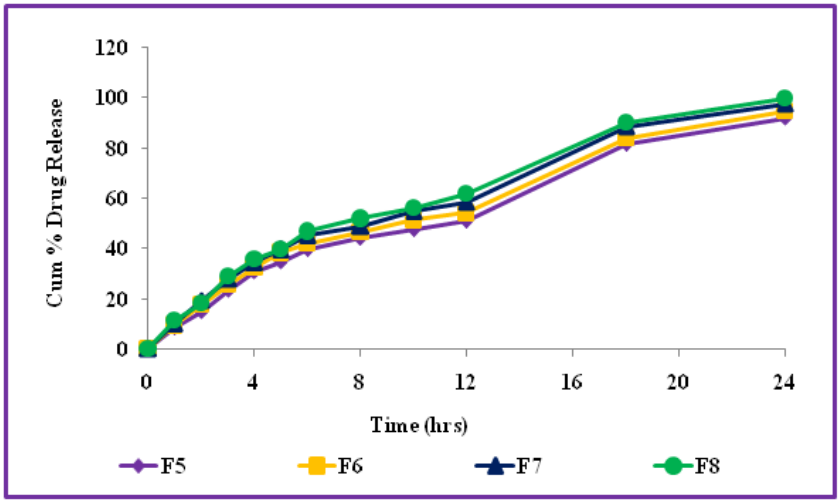

Fig 4: *In-vitro* release studies of formulation F5 to F8.

Table 5
In-vitro Release Profile of Zidovudine tablet

FC	% Drug release after 12 hrs ± SD	% Drug release at end 24 hrs ± SD
F1	43.21 ± 0.98	83.03 ± 1.71
F2	45.05 ± 1.25	87.48 ± 1.52
F3	47.67 ± 0.52	90.89 ± 0.80
F4	50.29 ±1.69	96.39 ± 0.21
F5	50.81 ± 0.91	91.93 ± 0.60
F6	54.22 ± 0.12	94.81 ± 0.18
F7	58.41 ±1.43	97.43 ± 0.98
F8	61.81 ±1.34	99.79 ± 1.09

**** The values represent mean ± S.D; n=3. FC= Formulation Code***

The IR Spectra of pure drug Zidovudine and formulation F1, F4, and F8 were shown in **Fig 5**. The IR Spectra of Zidovudine was recorded and it has showed short absorption peak due to -OH group present in the drug molecules. In this case -NH absorption peak present in the form of amine because of its weak characters exhibits a weak absorption at 3313 cm^{-1}. The aliphatic -CH absorption peak are seen from 3212-2800 cm^{-1}. The amide C=O present in the molecules gave a short absorption peak at 1683 cm^{-1}.

In this experiment of F1, F4 along with drug and polymer hydroxy ethyl cellulose (HEC) is taken for the studies. The IR spectrum of HEC showed the presence broad hump 3400 cm^{-1} for no. of -OH peaks and carbonyl absorption at 1680 cm^{-1}which in concurrence with structure of the HEC molecules. Corresponding to the NH_2, NH, OH functionalities and COOH, CO functional groups present in the drug suggesting that, this formulation is not a reaction product but it is a mixture of the drug and the polymer.

The formulation F8, gave a broad hump on at 3200 cm^{-1} and 1710 cm^{-1}. Supporting structure of carbopol is used as excipients. The formulation F8 containing drug Zidovudine, HPMC, and carbopol. It is observed that in the IR spectrum all the characteristics absorption peaks of functionality of drug as well as excipients have remained unaffected. It suggests that formulation obtained is a mixture of all these three constituents, but not the reaction mixture. Finally It was concluded that the drug as well as excipients are in the unreacted from.

The Formulation F1, F4 and F8 containing drug Zidovudine, HPMC and HEC were taken for the DSC measurements. The formulation product starts its melting process at 186.7°C and completes at 270°C. This large range of melting process indicated in the DSC Measurements indicates that formulated product starts it's melting process at 186°C and completes 266°C which is similarly observed during next formulation where HEC was replaced by Carbopol. The formulated product supported the idea that this formulation is also a mixture all the three constituents i.e. drug, HEC and Carbopol **(Fig 6)**.

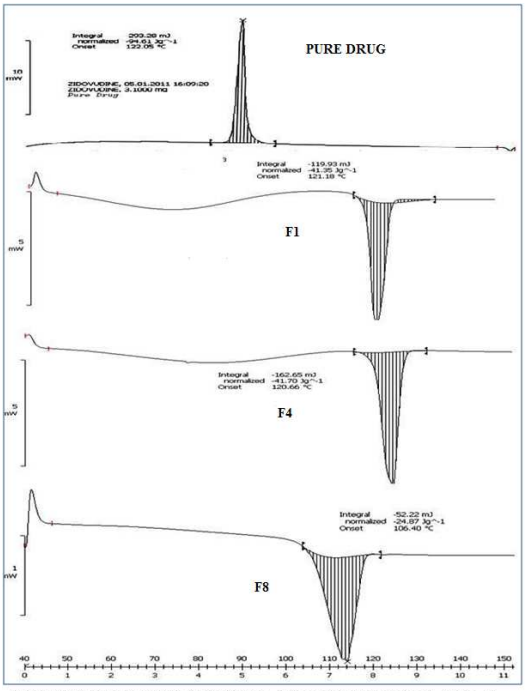

Fig 6: DSC Thermograms of pure drug Zidovudine, thermograms of formulation F1, F4 and F8.

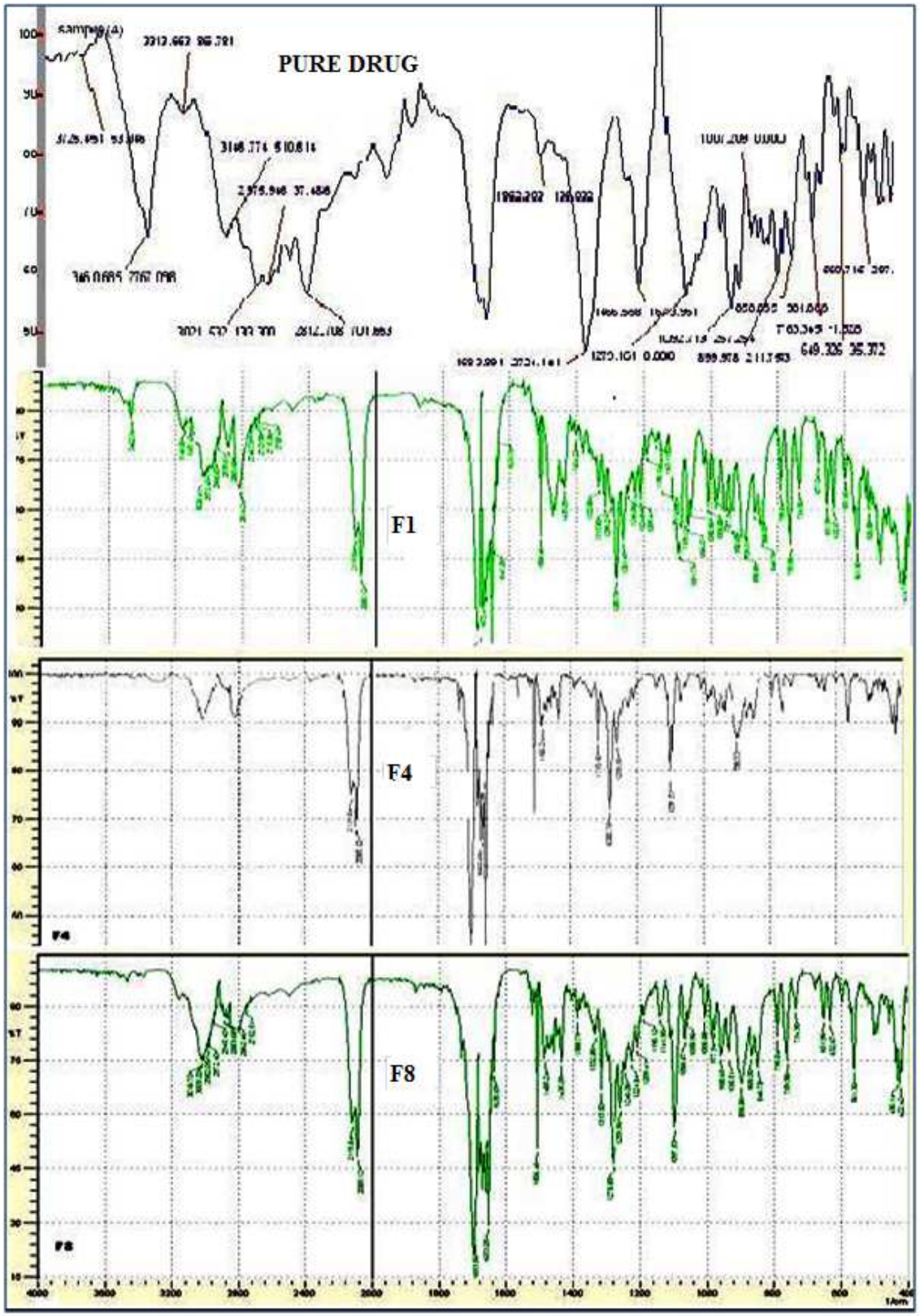

Fig 5: FT IR spectrum of pure drug Zidovudine, spectrum of formulation F1, F4 and F8.

The stability studies were carried out with the optimized formulation (F8) for 3 months in two conditions i.e. 25°C/60% RH and 40°C/75% RH. As per ICH guidelines, the formulations were subjected to drug assay, floating behavior and *in-vitro* dissolution studies. The statistical analysis of the parameters of dissolution data (**Table 4**) showed no significant changes in dissolution profiles, even after storage of 3 months. Thus, indicating that the drug were found stable in the formulation.

Table 6
Kinetics Release Parameters;

Formulation code	Zero Order (r^2)	First Order (r^2)	Higuchi Plots (r^2)	Peppa's plots	
				(r^2)	N
F1	0.9699	0.9640	0.9526	0.9737	0.83
F2	0.9692	0.9669	0.9570	0.9842	0.75
F3	0.9644	0.9321	0.9616	0.9794	0.71
F4	0.9550	0.8685	0.9557	0.9697	0.61
F5	0.9480	0.9552	0.9654	0.9775	0.72
F6	0.9450	0.9487	0.9739	0.9785	0.69
F7	0.9500	0.9228	0.9782	0.9777	0.68
F8	0.9380	0.9415	0.9812	0.9820	0.67

CONCLUSION

The gas powered drug delivery was a promising approach to achieve in-vitro buoyancy. The addition of gel-forming polymer methocel (K4M) and gas-generating agent sodium bicarbonate along with citric acid was essential to achieve in-vitro buoyancy. The drug release from the tablets was sufficiently controlled and non-Fickian transport of the drug from tablets was confirmed. The formulation retained for longer periods of time in the stomach and provides controlled release of the drug. Hence it may increase the therapeutic efficacy of the drug by increasing the bioavailability and patient compliance.

REFERENCES

1. Arora S, Javed A, Khar RK, et al. Floating Drug Delivery Systems: A Review. AAPS Pharm Sci Tech: 6 (3) Article 47.E372-390, (2005).
2. www.drug.com/Zidovudin.
3. S. C. Sweetman (Eds.), Martindale, The complete drug reference, 33rd Edition Pharmaceutical press: Great Britain; p.645-48, (2002).
4. Clark Analysis of Drug and Poisons.3rd edition, edited by C. Anthony, M. Mofft, David Osselton, Brain Widdep. Vol. 2, published by Pharmaceutical press of Great Britain; 1711-12, (2004).
5. Gurg S, and Sharma. "Gastro Retentive Drug Delivery System". Pharma Tech, 160-166, (2003).
6. Kusum VD, Roopa SP. Antiretroviral: Need for Effective Drug Delivery. Indian J. Pharma. Sci 68 (1), 1-6, (2006).
7. Sharma MC, Sharma S, Kohli DV, Chaturvedi SC., Formulation *In-vitro* Evaluation ,study of effect of Hardness on Buoyancy the time of Gastroretentive Film and Floating Tablet .J optoelectronic and Biomedical Materials: Dec. Vol 1, pp 353-358, (2009).
8. Chandira M, Muruganatham SV, Debjit, Jayakar KB. Formulation and Evaluation

of Sustained release Matrix Tablets of Zidovudine. Int J Current Pharma Research, Vol 1 (1) (2009).
9. Dalvi VV, Patil JS. Statistical Optimization and Development of Gastroretentive System of An Antiretroviral Drug using 3 2 Factorial Design. Ind J Pharma Edu Research.44 (3), Jul-Sep, (2010).
10. Vinay Pandit. et al. Gastroretentive Drug delivery System of Amoxicillin: Formulation And Evaluation. Int J Pharma and Bio Sci. Vol. (2), (2010).
11. Gupta SK. et al. Preparation and characterization of floating Drug Delivery System of Acyclovir. Int J Applied Pharma. Vol. 2 Issue 3, (2010).
12. Ganesh S. et al. *In-vitro* Evaluation of the effect of combination Hydrophilic and hydrophobic polymers on Controlled Release Zidovudine Matrix Tablets. Ind J Pharma Sci; Nov, (2003).
13. G. S. Banker, N. R. Anderson. The theory and practice of industrial pharmacy; L. Lachman, H. A. Lieberman, J. L. Kanig. Eds. 3rd: Varghese Pub. House: Bombay, P 297-300, (2003).