ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and evaluation of sustained release matrix tablet of zidovudine using different polymers

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ABSTRACT

In the present investigation, an attempt was made to formulate the oral sustained release matrix tablets of zidovudine in order to improve efficacy, reduce the frequency of administration, and better patient compliance. Differential scanning calorimetric analysis confirmed the absence of drug polymer interaction. The sustained release tablets were prepared by wet granulation method using different polymers viz, hydroxypropyl methylcellulose, xanthan gum, and ethyl cellulose as release retardant polymers, alcoholic solution of polyvinylpyrrolidone were used as granulating agent. *In- vitro* release studies were carried out at pH1.2 for first 2 hrs followed by phosphate buffer at pH7.4 over a period of 8hrs using USP dissolution apparatus. The formulated granules showed satisfactory flow properties. All the tablets formulation showed acceptable pharmaco technical properties and complied with pharmacopoeial standards. The *in-vitro* release profiles from tablets of drug and different polymer ratio were applied on various kinetic models. Based on $t_{90\%}$ values the formulation F9 was found to show good initial release (12% in 2 hrs) and may extend the release (90% in 10 hrs) and can overcome the disadvantages of conventional tablets of Zidovudine. The n value obtained from korsmeyer – peppas model confirmed that the drug release was non- fickian diffusion mechanism.

Keywords: Zidovudine, Matrix tablets, Hydroxypropylmethylcellulose, Xanthan gum, Ethyl cellulose.

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ISSN: 0975-8585

INTRODUCTION

Oral route is the most preferred route for administration of drugs, majority of current available medicines of anti HIV agents are formulated as solid dosage form. Tablets are the most popular oral formulation available in the market and preferred by the patients and physicians alike. In long term therapy for the treatment of chronic disease condition, conventional formulations are required to be administered in multiple doses, and there fore have several disadvantages [1].

Acquired immuno deficiency syndrome (AIDS), which threatens to cause a great plague in the present generation, was first identified in California in 1981. AIDS, caused by human immune deficiency virus (HIV), is an immune suppressive disease that results in life threatening opportunistic infection and malignancies [2]. AIDS is a condition in which a person experiences a telltale assortment of infection due to the progressive destruction of immune system cells by the HIV. AIDS represent the end stage of infection by HIV. Human immune deficiency virus infects human cells and mainly damage helper T cells initially helper T cells replaced as fast as they are destroyed. Over 10 billion viral copies may be produced each day. This can lead to an increase in non compliance of drug [3].

This problem is very series in case of drugs having shorter biological half life because they must be take more number of times a day. It is crucial for the success of AIDS therapy for the treatment of HIV virus. One approach to solve the problem by sustained drug delivery system is designed to achieve continuous delivery of drugs at predictable and reproducible manner over an extended period of time in the circulation. The potential advantages of this concept include minimization of drug related side effects due to controlled therapeutic blood levels, improved the patient compliance due to reduced frequency of dosing and the reduction of the total dose of drug administration [2].

Zidovudine is the FDA approved drug for clinical use for the treatment of adults and children with HIV infections monotherapy or including with other other anti viral agents. It is also is approved for preventing prenatal transmission for virus in pregnant women with HIV infection and is recommended for post exposure chemoprophylaxis in HIV exposed health care workers.

Zidovudine is a synthetic thymidine analog active against HIV -1, HIV -2, and human T cell lymphotrophic virus 1 and 2. After entering the host cell, zidovudine is phosphorylated by thymidine kinase to a monoposphate, then by thymidylate kinase to the diphosphate, and finaly by nucleoside diphosphate kinase to active zidovudine 5 tri phosphates. Zidovudine 5 tri phosphate terminates viral DNA chain elongation by competing with thymidine tri phosphate for incorporation in to DNA.

Zidovudine is typically administered orally as tablets, capsule and an oral solution. The drug has a short half life (3 h) this necessitating frequent administration to maintain the

constant therapeutic drug level. However patient receiving zidovudine develops neuropathy and lactic acidosis. The side effect of zidovudine is dose dependent and reduction of the total administered dose reduced the severity of the toxicity [4].

MATERIALS AND METHODS

Materials

Zidovudine was obtained from Aurobindo Pharmaceutical, (Hyderabad, India).HPMC K100M, polyvinyl pyrrolidone, microcrystalline cellulose (AVICEL PH 102), was received as gift samples from Nickon Laboratories Pvt.Ltd., (Pondicherry, India). Xanthan gum, ethyl cellulose, talc, magnesium stearate was purchased from Loba Chemie Pvt.Ltd., (Mumbai, India).

Methods

Differential Scanning Calorimetry (DSC)

The DSC analysis of pure drug, drug+ HPMC K100M, drug+ ethyl cellulose and drug+ xanthan gum were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible drug-polymer interaction. The 2 mg sample were heated in a hermetically sealed aluminum pans in the temperature range of 40-300ºC at heating rate of 10ºC /min under nitrogen flow of 20 ml/min [5].

Preparation of matrix tablets

The composition of different formulations of Zidovudine matrix tablets is shown in Table 1. Different tablet formulations were prepared by wet granulation technique. All the powders passed through sieve No.80.The required quantity of drug, various polymers and other ingredients were mixed thoroughly, and a sufficient volume of granulating agent (iso propyl alcoholic solution of polyvinylpyrrolidone) was added slowly. After enough cohesiveness was obtained, the wet mass was sieved through sieve No.8. The granules were dried at 60° C for 30 minutes and then the dried granules were passed through sieve No.16. Talc and magnesium stearate were finally added as a glidant and lubricant respectively. The granules was directly compressed (11mm diameter, biconcave punches) using a single punch tablet compression machine (Cad mach, Ahmedabad, India). Each tablet contained 300 mg of Zidovudine [6, 7].

Evaluation of granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were

allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation [8].

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the granules cone.

Loose Bulk Density (LBD)

An accurately weighed granules from each formulation was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the granules was measured which gave bulk volume. The loose bulk density (LBD) of granules was determined using the following formula [9].

Loose bulk density = Total weight of granules / Total volume of granules

Tapped bulk density (TBD)

An accurately weighed granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of granules was determined by the following formula [9].

Tapped bulk density= Total weight of granules / Tapped volume

Carr's Compressibility Index

It is a simple index that can be determined on small quantities of granules. In theory, the less compressible a material the more flowable it is. The compressibility index of the granules was determined using following formula [10].

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100
Where, TBD = Tapped Bulk Density
LBD = Loose Bulk Density

Hausner's ratio

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules [10].

Evaluation of matrix tablet

Appearance

The tablets were visually observed for capping, chipping, and lamination.

Dimension (Thickness and Diameter)

The thickness and diameter of tablets were important for uniformity of tablet size. The thickness and diameter of the tablets was determined using a Vernier caliper. Ten tablets from each type of formulation were used and average values were calculated [11].

Tablet Hardness

For each formulation, the hardness of 10 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2 [11].

Percent Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. A loss of less than 1 % in weight is generally considered acceptable. Percent friability (% F) was calculated as follows [11].

$$\%\mathbf{Friability} = \frac{\mathbf{Initial\ weight} - \mathbf{Final\ weight}}{\mathbf{Initial\ weight}} \times \mathbf{100}$$

Weight Variation

To find out weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight. The test was performed according to the official method [12].

Drug content

The drug content in each formulation was determined by triturating 20 tablets and powder equivalent to 25 mg was added in 25 ml of pH 6.8 phosphate buffer followed by stirring for 10 minutes. The solution was filtered through a 0.45µ membrane filter, diluted suitably and

the absorbance of resultant solution was measured by using Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer at 266 nm using pH 6.8 phosphate buffer as blank [13].

In- vitro release studies

The release rate of Zidovudine from matrix tablets was determined using United States Pharmacopeia (USP) Dissolution Testing Apparatus II (paddle method; Veego Scientific VDA-8DR, Mumbai, India). The dissolution test was performed using 900 ml of pH 1.2 for the first 2 hrs and phosphate buffer pH 7.4 from 2-8hrs at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted suitably; Absorbance of these solutions was measured at 267 nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were analyzed to study the release kinetics using zero order, first order, matrix, and korsmeyer-peppas equations by using PCP disso V3 software [14, 15].

RESULT AND DISCUSSION

Granulation is the key process in the production of many dosage forms. To ensure good content uniformity and avoid flow related inter tablet weight variation problems. Wet granulation is preferred in routine commercial production. Wet granulation was thus used in the present study.

The prepared granules of the different formulation were evaluated for angle of repose, loose bulk density, tapped bulk density, compressibility index, and Hausner's ratio. The prepared matrix tablets were evaluated for thickness, weight variation, hardness, friability, drug content, in vitro drug dissolution studies and stability studies. All the studies were performed in triplicate, and results are expressed as mean ± SD.

Characterization of granules

The granules prepared for compression of matrix tablets were evaluated for their flow properties, the results were shown in Table 2. Angle of repose was in the range of 19.38±0.17 to 21.18°±0.01 which indicates excellent flow of the granules for all formulations. The bulk density of the powder formulation was in the range of 0.454±0.00 to 0.500±0.00 g/ml; the tapped density was in the range of 0.526±0.00 to 0.555±0.00 g/ml, which indicates that the powder was not bulky. The Carr's index was found to be in the range of 9.505±0.00 to 14.234±0.00, which indicates excellent flow of the granules for all formulation. Hausner's ratio was found to be in the range of 1.10±0.00 to 1.16±0.00, these values indicate that the prepared granules exhibited good flow properties.

Differential Scanning Calorimetry (DSC)

Any possible drug polymer interaction can be studied by thermal analysis. Zidovudine exhibits a sharp endothermic peak at 126.08 °C shown in figure 1a, which corresponds to its melting point. The Zidovudine+ HPMC K100M exhibit a sharp endothermic peak at 125.06ºC, Zidovudine+ Ethyl cellulose exhibit a sharp endothermic peak at 124.89ºC and Zidovudine+ Xanthan gum exhibit a sharp endothermic peak at 125.25ºC shown in figure 1b, 1c and 1d respectively. Hence DSC study shows that there is no any drug polymer interaction.

Evaluation of matrix tablets

The matrix Zidovudine tablets were white, smooth, and round, biconcave shaped in appearance. The results of physicochemical characterizations are shown in Table 3. The thickness of matrix tablets was measured by vernier caliper and was ranged between 5.93±0.04 and 6.30±0.00 mm for all formulation. The weight variation for different formulations (F1 to F9) was found to be 0.299 ±0.22% to 0.657 ±0.43%, showing satisfactory results as per Indian Pharmacopoeia (IP) limit. The hardness of the matrix tablets was measured by Monsanto tester and was controlled between 7.9±0.21 and 10.15±0.24 kg/cm^2. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The percentage of drug content for F1 to F9 was found to be in between 98.89±0.22 to 100.70±0.30 of Zidovudine, it complies with official specifications.

In- vitro release study

In-vitro dissolution studies of all the formulations of matrix tablets of Zidovudine were carried out in pH 1.2, pH 7.4 buffer solution. The study was performed for 8 hours, and percentage drug release was calculated at 1 hours time intervals. The results of *in- vitro* dissolution studies of all formulations were shown in Figures 2 to 4. The lower initial drug dissolution was observed in tablets containing xanthan gum (F3) and ethyl cellulose (F9). This showed that in high concentration polymers in the presence of pH 1.2 and pH 7.4 buffer solution. The variation in drug release was due to different types of polymers and different concentrations of polymer in all the nine formulations. It is expected that the developed formulation should have the follow theoretical drug release profile. The drug released from formulation F1 to F3 containing xanthan gum at three concentration levels of 10%, 20%, 30% were found to be 91.280± 0.60, 88.836± 1.44, and 77.647± 0.19 for Zidovudine respectively. The drug released from formulation F4 to F6 containing HPMC K100M at three concentration levels of 10%, 20%, 30% were found to be 99.231± 0.51, 89.787± 0.46 and 79.709± 0.38% for Zidovudine respectively. The drug released from formulation F7 to F9 containing ethyl cellulose at three concentration levels of 10%, 20%, 30% were found to be 86.352± 0.60, 82.708± 0.50 and 71.758± 0.45% for Zidovudine respectively at the end of 8 hours (2hrs in 0.1N HCl and 6hrs in pH 7.4).

The release rate from the ethyl cellulose polymer was found to be less as compared to HPMC K100M, xanthan gum. This might be due to slow erosion of matrix and its property which retard the drug release from the tablet for long duration.

The regression coefficient obtained for formulation F1 to F9 korsmeyer peppas kinetics were found to be higher (R^2: 0.9920 to 0.9970) when compared with others kinetic model (first order, zero order, higuchi). The results were shown in Table 4. Drug release data was also fitted to peppas model, which showed the slope (n) value (0.5480 to 0.7376), indicating a anomalous diffusion release mechanism Zidovudine exhibited anomalous diffusion as dominated mechanism for optimized formulation (F9).

Based on the *In- vitro* drug release data the $t_{50\%}$, $t_{90\%}$ parameters were calculated and the results given in the Table 5. From this data, the formulation F9 showed the maximum retardation of drug release (10 hours to release the 90% of drug) and it shows anomalous diffusion mechanism, for these reasons, it was considered that the formulation F9 was best formulation among all the nine formulations.

CONCLUSION

This study deals with the investigation carried out with the objective of developing oral sustained release formulation of Zidovudine using xanthan gum, HPMC K100M, ethyl cellulose. Preparation of matrix tablet by wet granulation technique was found to be more effective in sustaining the release of drug. Drug content all formulation was found to be complies with pharmacopoeial standard. Formulation F9 containing Ethyl Cellulose with hardness 10 kg/cm^2. Formulation F9 showed sustained drug release $t_{90\%}$ value as 10 hours. The kinetics of drug release was optimized formulation explained by peppas equation. The drug release from the tablets was sufficiently sustained and anomalous diffusion mechanism of the drug from tablets was confirmed. Based on the *in- vitro* drug release data the formulation F9 it was concluded as best formulation. In conclusion the present study demonstrated the successful preparation of sustained release matrix tablet of Zidovudine.

ACKNOWLEDGEMENTS

The authors are sincerely thankful to Adhiparasakthi College of Pharmacy, Melmaruvathur for provided us infrastructure facilities and moral support to carry out this research work. I sincerely express my gratitude to Aurobindo Pharmaceutical, (Hyderabad, India) for providing zidovudine as a gift sample and Nickon Laboratories Pvt. Ltd., (Pondicherry, India) for providing HPMC K100M, polyvinyl pyrrolidone, micro crystalline cellulose.

ISSN: 0975-8585

Table 1: Composition of Zidovudine matrix tablet

Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zidovudine	300	300	300	300	300	300	300	300	300
Xanthan gum	60	120	180	-	-	-	-	-	-
HPMC K100M	-	-	-	60	120	180	-	-	-
Ethyl cellulose	-	-	-	-	-	-	60	120	180
Microcrystalline cellulose pH 102	192	132	72	192	132	72	192	132	72
Polyvinyl pyrrolidone	30	30	30	30	30	30	30	30	30
Isopropyl alcohol(ml)	qs	qs	qs	qs	qs	qs	qs	qs	qs
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	12	12	12	12	12	12	12	12	12

Table 2: Flow properties of granules

Formulation code	Angle of repose (^{0})*	Loose bulk density (g/ml)*	Tapped bulk density (g/ml)*	Hausner ratio (HR)*	Carr's index (IC)*
F1	21.02±0.42	0.500±0.00	0.555±0.00	1.11±0.00	9.909±0.00
F2	19.47±0.09	0.500±0.00	0.555±0.00	1.11±0.00	9.909±0.00
F3	21.18±0.01	0.476±0.00	0.526±0.00	1.10±0.00	9.505±0.00
F4	19.38±0.17	0.476±0.00	0.555±0.00	1.16±0.00	14.234±0.00
F5	20.10±0.44	0.454±0.00	0.526±0.00	1.15±0.00	13.688±0.00
F6	21.11±0.48	0.476±0.00	0.555±0.00	1.16±0.00	14.234±0.00
F7	20.52±0.55	0.476±0.00	0.555±0.00	1.16±0.00	14.234±0.00
F8	20.33±0.34	0.454±0.00	0.526±0.00	1.15±0.00	13.688±0.00
F9	21.09±0.47	0.476±0.00	0.555±0.00	1.16±0.00	14.234±0.00

*All the values are expressed as mean± SE, n=3.

Table 3: Physico-chemical characterization of Zidovudine matrix tablets

Formulation Code	Thickness (mm)*	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)	Drug content (%)**
F1	5.96±0.05	0.657±0.43	10.1±0.21	0.098	99.58±0.57
F2	6.16±0.06	0.433±0.28	7.9±0.21	0.113	99.14±0.07
F3	5.96±0.05	0.448±0.28	8.1±0.21	0.099	99.01±0.12
F4	6.27±0.04	0.416±0.27	9.0±0.23	0.083	98.89±0.22
F5	6.30±0.00	0.299±0.22	8.05±0.15	0.067	99.96±0.44
F6	6.30±0.00	0.516±0.30	10.15±0.24	0.033	100.70±0.30
F7	5.93±0.04	0.595±0.40	8.05±0.15	0.099	100.05±0.56
F8	6.18±0.04	0.655±0.37	8.0±0.23	0.099	99.84±0.15
F9	6.17±0.04	0.466±0.33	9.95±0.15	0.099	100.03±0.91

*All the values are expressed as mean± SE, n=10; **All the values are expressed as mean± SE, n=3.

ISSN: 0975-8585

Table 4: Different Kinetic models for Zidovudine matrix tablets (F1 to F9)

Code	Zero order		First order		Higuchi		Korsemeyer- Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mg\ h^{-1/2}$)	R^2	n	
F1	0.991	11.999	0.951	0.246	0.922	27.968	0.992	0.548	Peppas
F2	0.993	11.217	0.943	0.213	0.918	26.084	0.994	0.582	Peppas
F3	0.992	10.220	0.975	0.170	0.919	23.794	0.993	0.573	Peppas
F4	0.993	12.396	0.813	0.362	0.900	28.628	0.995	0.614	Peppas
F5	0.994	11.254	0.930	0.222	0.906	26.036	0.996	0.612	Peppas
F6	0.991	11.421	0.970	0.213	0.935	26.748	0.992	0.582	Peppas
F7	0.995	10.290	0.956	0.176	0.917	23.911	0.995	0.651	Peppas
F8	0.993	09.994	0.961	0.167	0.908	23.151	0.996	0.693	Peppas
F9	0.992	9.085	0.977	0.138	0.919	21.152	0.997	0.671	peppas

Table 5: t50%, t90% drug release of formulation F1 to F9

parameter	Formulation code								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
$t_{50\%}$ (hrs)	4.2	4.5	4.9	4.0	4.4	5.0	4.4	4.9	5.5
$t_{90\%}$(hrs)	7.5	8.0	8.8	7.3	8.0	9.0	7.9	8.7	10.0

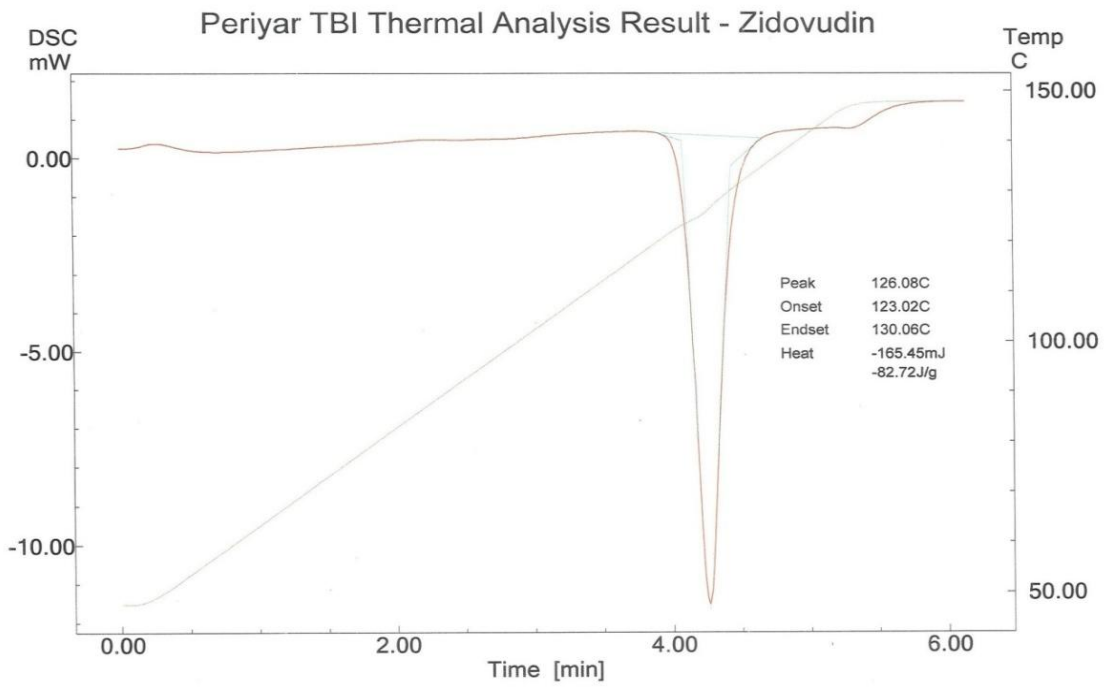

Figure 1a: DSC thermal analysis of Zidovudine

ISSN: 0975-8585

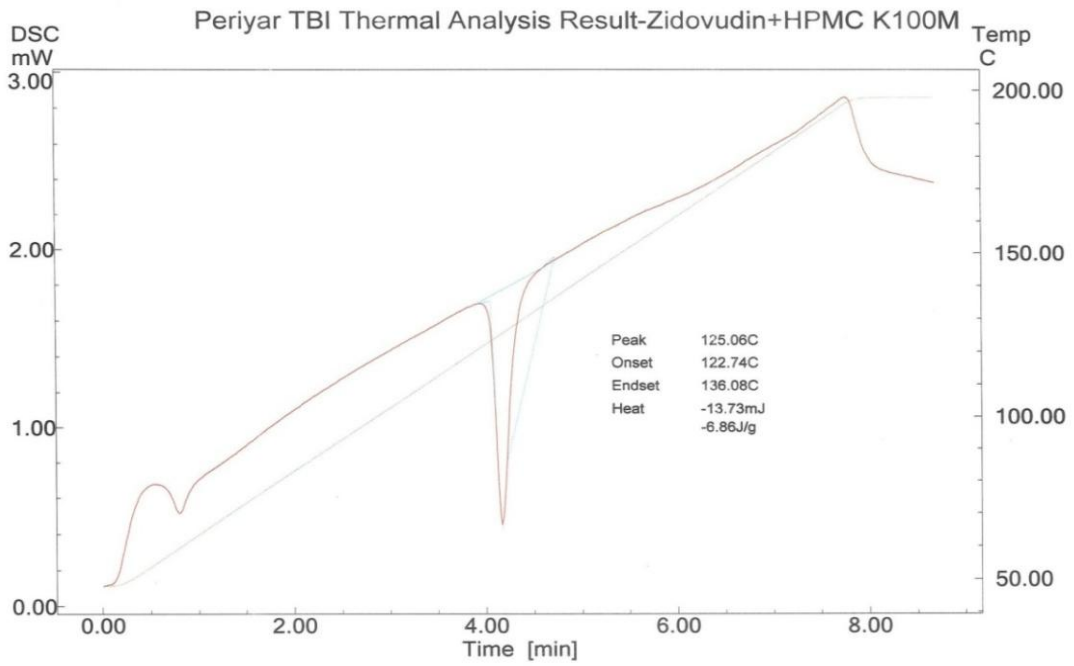

Figure 1b:

DSC thermal analysis of Zidovudine+ HPMC K100M

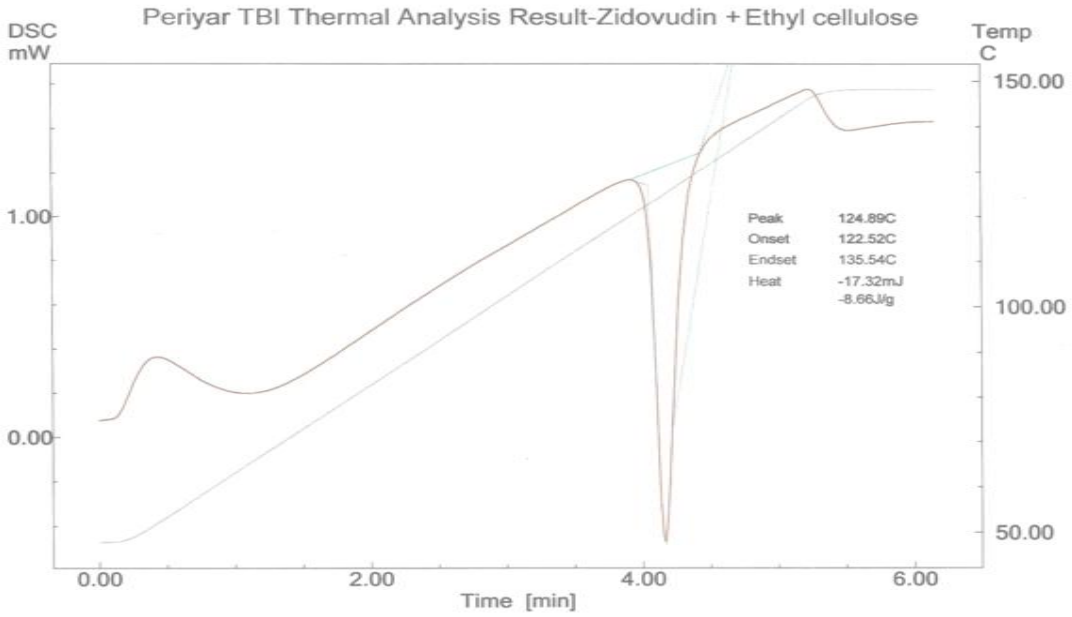

Figure1c: DSC thermal analysis of Zidovudine+ Ethyl cellulose

ISSN: 0975-8585

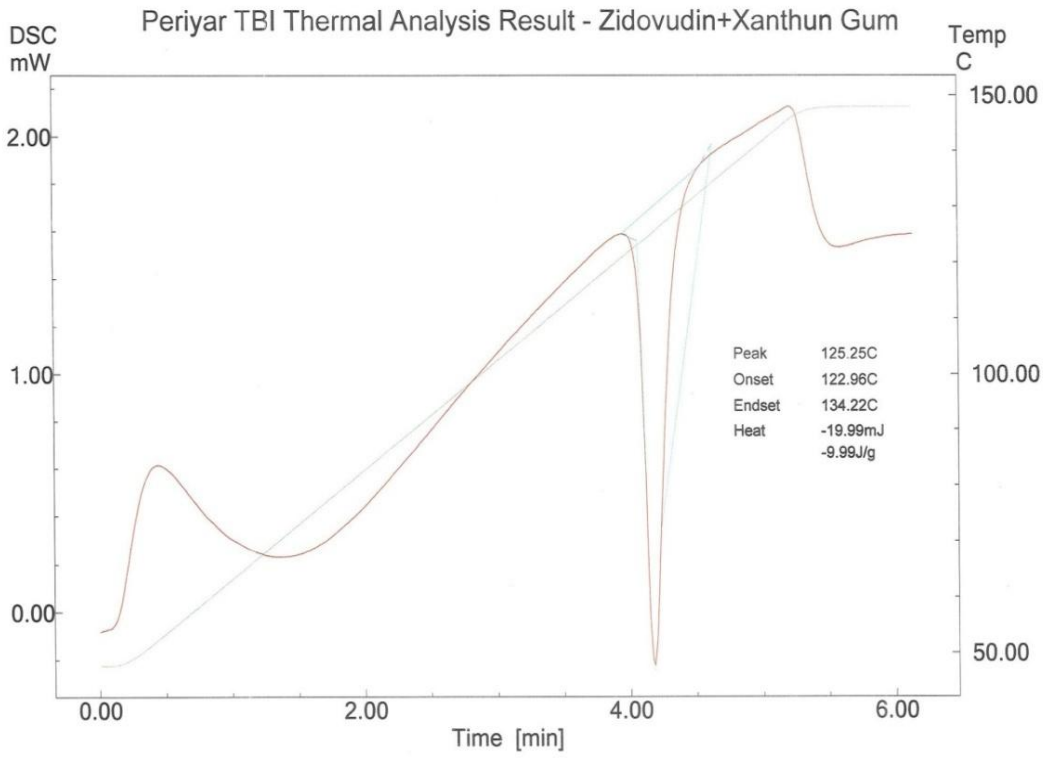

Figure1d: DSC thermal analysis of Zidovudine+ Xanthan gum

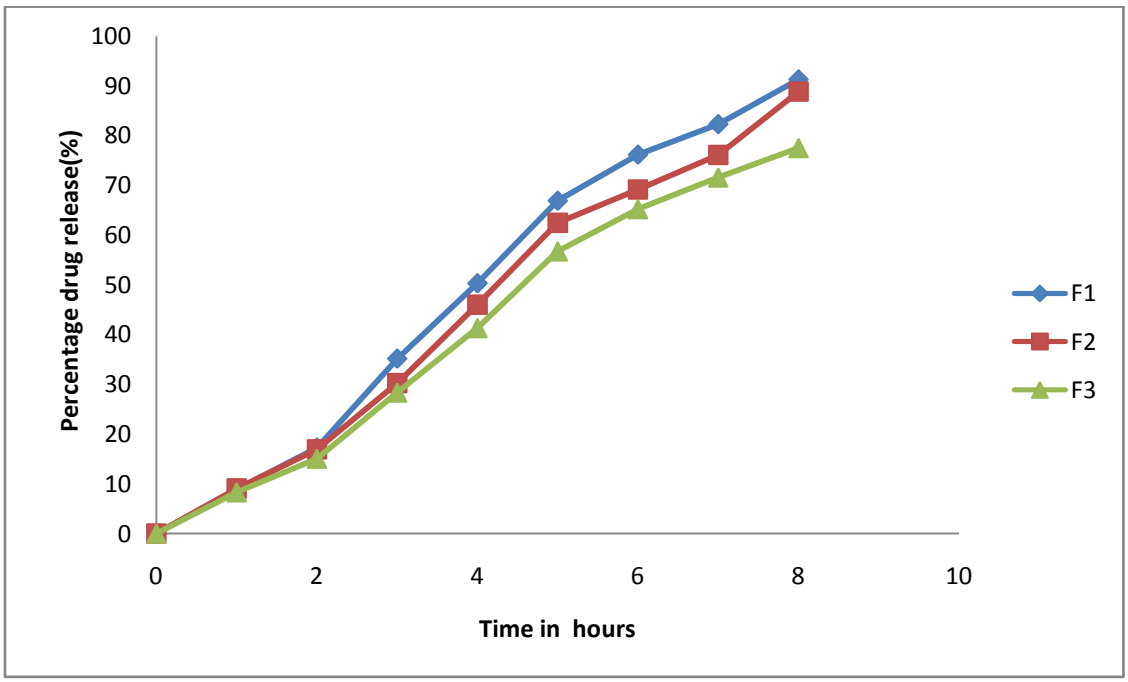

Figure 2: *In- Vitro* drug release of formulation F1 to F3

ISSN: 0975-8585

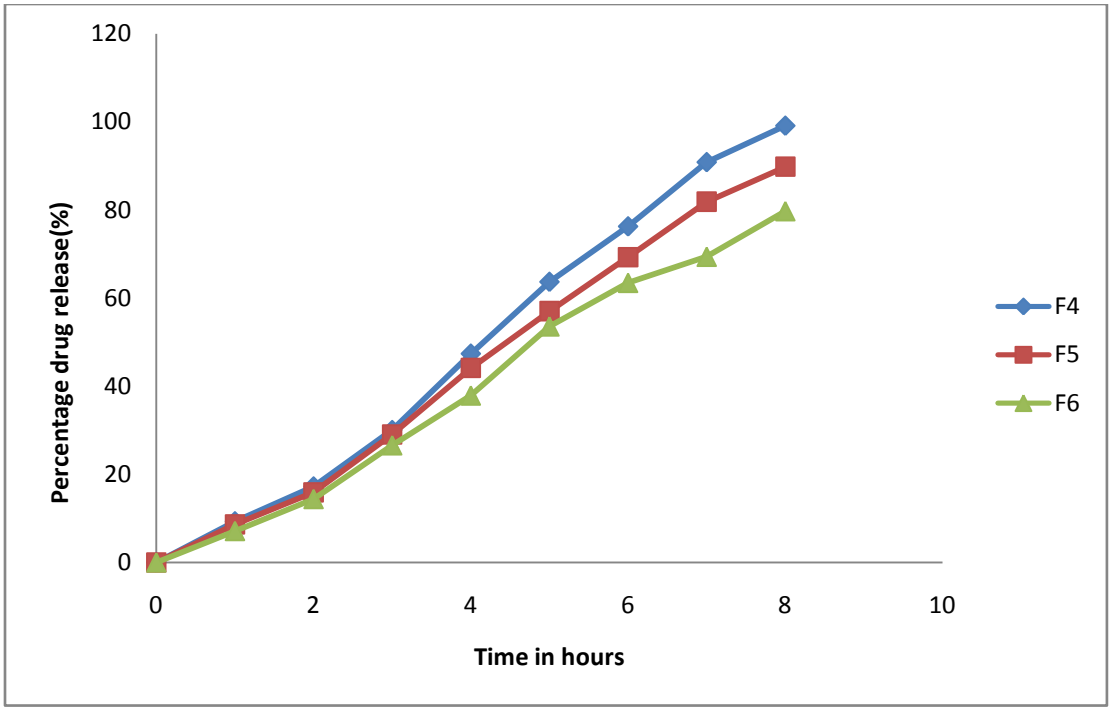

Figure 3: *In- Vitro* drug release of formulation F4 to F6

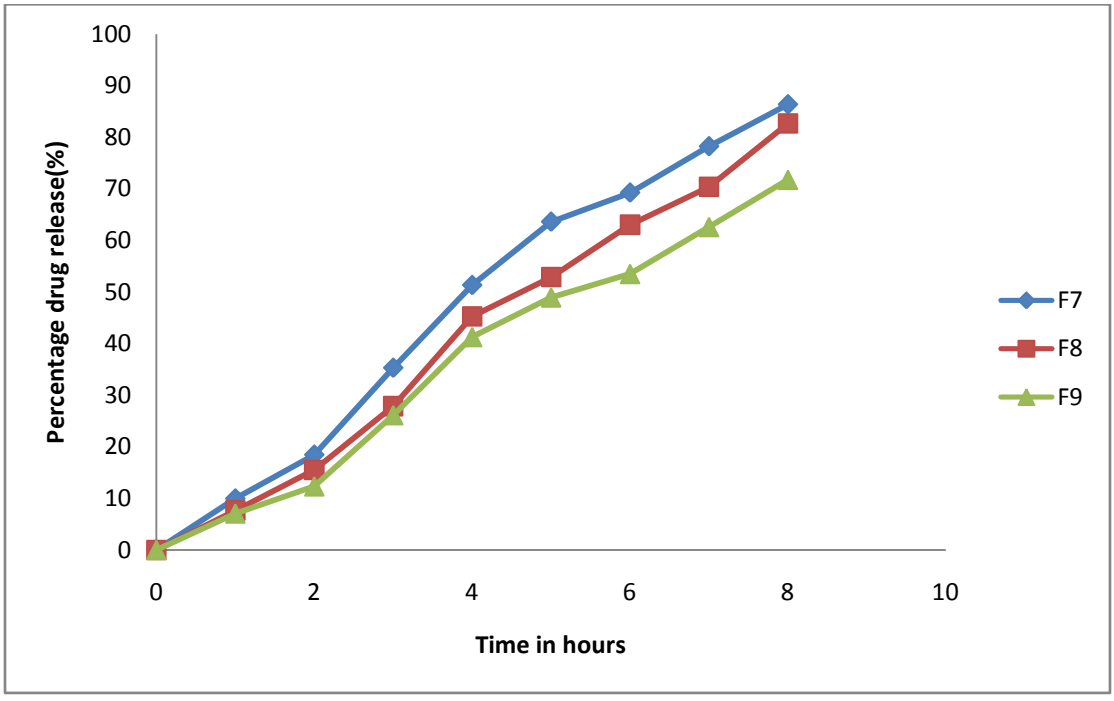

Figure 4: *In- Vitro* drug release of formulation F7 to F9

ISSN: 0975-8585

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