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Formulation Development and Evaluation of Sustained Release Matrix Tablet of Zidovudine

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ABSTRACT

The objective of the research was firstly to investigate the behavior of Surelease (release retardant binder) alone and in combination with other hydrophilic polymers on the release of zidovudine from sustained release matrix tablet. Secondly, to compare between the release pattern of polyethylene oxide and Methocel K100M alone and in combination. A randomized surface methodology (RSM) was applied to study the effect of polymers on drug release. The independent variables of the formulation were: the type of polymers (X1), concentration of polymers (X2) in the tablet and dependent variables are the percentage drug release at 2 hours (Y1) and the percentage drug release at 12 hours (Y_2). Release kinetics were analyzed using zero-order, first order, higuchi's square root and korsmeyer-peppas empirical equations in terms of r^2. Results of *in-vitro* drug release kinetics study suggests that, all formulations follows zero order kinetics with r^2 value in range of 0.99 and fitting the release data to korsmeyers equation release exponent n ranged from 0.83 to 1.22 and followed non-Fickian diffusion mechanism (anomalous transport) and super case II transport for Surelease formulations. Among all the formulations, F14 matrix tablet containing combination of Surelease and polyoxWSR301 shows 102.37% of drug release at the end of 12 hours.

Keywords: Zidovudine, sustained release, hydrophilic and hydrophobic polymers, release kinetics, matrix tablet.

INTRODUCTION

Zidovudine (AZT) (3'-azido-3'-deoxythymidine) an anti HIV (Human Immunodeficiency Virus) compound widely used alone or in combination with other antiviral agents for treatment of AIDS(Acquired Immunodeficiency Syndrome)[1] . AZT is analogue of thymidine in which the 3-hydroxyl group (-OH) is replaced by an azido group ($-N_3$). By the sequential action of the cellular enzymes, AZT is converted to the active metabolite, AZT 5′- triphosphate (AztTP) and prevents the HIV virus replication. As the peak plasma concentration of 1.2 µg/mL at 0.8 hours and has a biological half-life 3-4 hours, the drug needs to administered 3 -4 times a day to maintain constant therapeutic drug levels[2-3.] Since its antiviral effect is time dependent, and also to avoid strong side effects associated with high plasma concentration of AZT, an adequate zero order release, is desired. Being class I drug it is completely and rapidly absorbed throughout GIT and is freely soluble at all pH. The drug release can be modulated by incorporating it in a matrix system. Therefore formulation of sustained release tablets of AZT was much desirable and preferred to offer better patient compliance, maintain uniform drug levels, reduce dose and side effects, and increase safety margin for high-potency drugs [4]. Several polymers have been used in the formulation of matrix based sustained release drug delivery systems. Reports were found on usage of polymers like hydroxypropyl methylcellulose (HPMC K4M),ethyl cellulose (EC), carbopols (CP 971P)[5], guar gum, polyvinyl pyrolidone (PVP-K-30)[6], eudragit RLPO, eudragit RSPO[7], xanthan gum, Sodium carboxy methyl cellulose[8] in different combination for the purpose of Sustained release formulations. However, no literature has been found on comparison between oral sustained release tablets of AZT prepared using Methocel K100M, Polyethylene oxide (polyoxWSR301) and Surelease separately and in combination with each other, as release retardant materials. Hence, in the present work, an attempt has been made to investigate the behavior of Surelease (release redardant binder) alone and in combination with other hydrophilic polymers on the release of AZT from sustained release matrix tablet. Secondly, to compare between the release pattern of PolyoxWSR301 and Methocel K100M alone and in combination.

MATERIALS AND METHODS

Materials

Drug AZT was obtained as a gift sample from Emcure Pharmaceuticals Limited, Emcure House, Bhosari, Pune. Hydroxypropyl methyl cellulose (Methocel K100M /HPMC K100M), Polyethylene oxide (PolyoxWSR 301) and Surelease was obtained from Colorcon Asia Pvt. Ltd., Goa, India, All other ingredients used were of analytical grade.

Drug–excipient interaction studies

To study the compatibility of various formulation excipients with AZT, solid admixtures were prepared by mixing the drug with each formulation excipient separately in the ratio of 1:1 and characterized using Fourier transform infrared spectroscopy (FTIR Shimadzu IR Affinity 1, Japan) and Differential scanning calorimetry (DSC).

Calculation of Loading and Maintenance dose[9]

Oral dose = X_0 **;** Elimination half life = $t_{1/2}$; Dosing interval = τ **;**Time of Peak Concentration = t_p

Elimination rate constant (K_e) = $0.693/t_{1/2}$; Initial dose (Di): Css.Vd / F ; But, Css = F.Xo/ Ke.Vd.τ ; Thus, Di = F.Xo /

Ke.Vd.τ * Vd / F; Di = Xo / Ke* τ ;Desired rate of drug release (Ks) = Di * Ke ; Maintenance dose (Dm) = Ks * τ ;Corrected initial dose (Di*) = Di – (Ks * tp)

Total dose (Dt) = Dm + Di*

Methods

Precompression Characteristics Evaluation

Prior to compression, lubricated granules and powder mixture were evaluated for their characteristic parameters. Angle of repose was determined by funnel method. Bulk density and tapped density were determined by cylinder method, and Carr's index (CI) was calculated using the following equation[10].

$$CI = (TD-BD) \times 100/TD$$

Where, TD is the tapped density and BD is the bulk density.

Formulation of a matrix tablet

Optimization design

Response surface methodology optimization technique using two factor, one factor at three levels and second at six levels design was employed for optimization study. This gives 23 runs with 5 replicate runs, and hence in this design 2 factors were evaluated at all 23 possible combinations. The independent variables were type of polymer(X_1) and concentration of Polymer(X_2) and dependent variables were % drug release at 2hrs(Y_1) and 12hrs(Y_2) respectively Table 1. The formulation layout for the optimization batches (F1-F23) is shown in Table 2. Depending upon these ranges all formulations were formulated as per response surface method with D optimal design type by direct compression, wet granulation technique. Tablets were compressed on a tablet compression machine (Labpress) using 12 mm punches.

Post Compression Characteristics evaluation

The prepared matrix tablets were evaluated for Weight variation, hardness, friability and content uniformity were determined using reported procedure. Weight variation was evaluated on 20 tablets using an electronic balance and test was performed according to official method. Friability was determined by taking 10 tablets in a Roche Friability apparatus for 4 min at 25 rpm. Tablet hardness was determined for 6 tablets using a Monsanto hardness tester[11]

Drug content

Powdered tablet equivalent to 100 mg of AZT was accurately weighed and transferred to a 100 ml volumetric flask. The volume was made up to 100 ml with phosphate buffer and then filtered by using of 0.45µm membrane filter paper. The filtrate was suitably diluted with pH 6.8 phosphate buffers and analyzed against blank (pH 6.8 phosphate buffers) solution for the drug content by spectrophotometerically at 266 nm.

In vitro Drug Release Studies

The release rate of AZT from matrix tablets was determined up to 12 hours using USP-type II dissolution testing apparatus (paddle type). The dissolution test was performed using the dissolution medium (900ml) consisted of 0.1N hydrochloric acid for first 2 hours and the phosphate buffer pH 6.8 from 3 to 12 hours, maintained and at 50 rpm. Cumulative percentage drug release was calculated using an equation obtained from a standard curve.

Kinetic data analysis

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics, the dissolution profiles

were analysed according to the zero-order, first-order[12], Higuchi's square root equations[13] and Korsmeyer Peppas Model[14].

Determination of swelling behaviour

The swelling behaviour of matrix tablets was determined by the method reported. Matrix tablet was introduced into the dissolution apparatus under the standard set of conditions as specified for determination of *in vitro* drug release. The tablets were removed using a small basket and swollen weight of each tablet was determined. Swelling was calculated according to the following formula, where S is the weight of the matrix after swelling; and T is the initial weight of the matrix[15].

% Swelling = (S-T)/T x 100

RESULT AND DISCUSSION

Calculation of Loading and Maintenance dose[12]

Total dose needed for AZT sustained release matrix tablets for twice daily administration as follows:- Oral dose = 100 mg ; Elimination half life ($t_{1/2}$) = 1.5 hour Dosing interval (τ) = 12 hours ; Time of Peak Concentration ($t_{p)}$ = 1 hour Elimination rate constant (K_e) = 0.462/hour ; Initial dose (Di) = 25 mg

Desired rate of drug release (Ks) =11.55 mg / hour ;Maintenance dose (Dm) =138.6 mg

Corrected initial dose (Di*) = 82.68 mg ; Total dose (Dt) = 221.28 mg ~ 225 mg

Drug–excipient interaction studies

The supplied drug passed the various tests of identification and analysis. The pure drug AZT and the solid admixture of drug and various excipients used in the preparation of sustained release tablet formulations were characterized by FTIR spectroscopy to know the compatibility. As shown in the Figure1, there was no significant difference in the FTIR spectra of pure AZT and drug along with polymers (PolyoxWSR301, Methocel K100M, Surelease). The characteristic peak of carbonyl group at 1,670 cm^{-1} and azide group at 2,044 cm^{-1} present in all the spectrum indicates the stable nature of AZT in the solid admixtures. This was further supported by DSC studies as shown in Figure 2. IR studies indicated good compatibility between drug, polymer and excipients.

Precompression Characteristics Evaluation[11]

The granules and powder blends indicated good flow ability with the angle of repose values ranging from 27° to 35° according to fixed funnel method. The results of bulk density, tapped density and compressibility index are shown in Table 3. The result of compressibility index indicates good to fair flow properties.

Post Compression Characteristics evaluation

The tablet hardness, friability, weight variation and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 3. The hardness of all the tablets was between 5.79±0.28 and 7.5±0.31 kg/cm. In the present study, the loss in total weight in friability test was in the range of 0.28% to 0.58% that indicates, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets weighing more than 250 mg is ±5%. The average percentage deviation of all tablet formulations was found to be within limit, and hence all formulations passed the test for uniformity of weight as per official requirement. Good uniformity in drug content was found among different batches of the tablets.

In-vitro drug Release

The *in-vitro* drug release profiles of AZT from tablets containing Methocel K100M, Polyox WSR 301 and Surelease in different ratios were studied as per response surface D-optimal factorial design. The *in-vitro* drug release was studied for two responses (Dependent variables) Y_1, drug release at the end of 2 hours and Y_2, drug release at the end of 12 hours.

Data fitting to the model

A two-factor, one at three levels and second at six levels optimal design as the response surface methodology (RSM) provides 23 runs with 5 replicates runs. All batches showed the drug release at 2hour (Y1) in the range between 7.52% - 28.77% and the formulations which extend the drug release upto 12^{th} hour (Y2) is in the range between 45.88%-102.37% Figure3. All the responses observed for 23 formulations were simultaneously fitted to linear, 2FI and quadratic model when using Design Expert (State ease – Ver. 8.0.7.1) and the comparative values of R^2 and standard deviation are given in Table 4.along with the regression equation generated for each response. Only statistically significant ($p < 0.05$) coefficients are included in the equations.

Behavior of Surelease: (release retardant binder) alone and in combination with other hydrophilic polymers

Hydrophobic polymer Surelease was formulated as 1ml/tablet, 2ml/tablet and 4ml/tablet as F3, F13, and F1 respectively. The results for response Y_1 and Y_2 was found to decrease in drug release with increase in concentration of the release retardant binder is due to the behavior of Surelease. During granulation it increases the particle size and reduce the surface area of drug particles. As it develops partial bonding between drug-drug and drug-excipient particles on drying and decreases the dissolution rate of drug in polymer matrix.

Combination of both granulation of the drug with Surelease and incorporation into Methocel K100M matrix were studied in formulations F4, F8, and F5.Granulation of drug with Surelease resulted in a slower release profiles, with a reduced initial burst effect. Similarly effect of granulation of the drug with Surelease and incorporation into Polyox WSR301 matrix were studied in formulations F14, F11, and F9.This resulted in a slower release profiles with drug release. This indicates that with increasing the amount of granulating fluid results in more retardation of drug release. Comparative dissolution profile of Surelease alone and in combination with PolyoxWSR 301 and Methocel K100M is depicted in Figure.4.

Release pattern of polyethylene oxide (Polyox WSR301) and Methocel K100M alone and in combination

Polyox WSR 301 was formulated as F7, F15, and F17 respectively. Y_1 was found to be 25.03%, 22.35% and 19.24% respectively and 100 % drug release at the end of 8 hour, 9 hour and 11 hour respectively. Extremely fast hydration and gel forming properties of polymer Polyox WSR301 results into decrease in drug release with increase in polymer concentration. Comparative dissolution profile of PolyoxWSR301 alone and in combination with Methocel K100M and Surelease was depicted in Figure.5

In Methocel K100M based formulations, F18, F6, and F10 shows Y_1 varied between18.54% to 28.84% .The F18 formulation showed complete 100% drug release at the end of 7 hour. Formulation F6 and F10 were able to extend the drug release upto 9 hour and 11 hour respectively. Initial burst release was observed in F18 formulation. This initial burst release may be due to low polymer concentration that leads

to formation of weak gel barrier which undergoes quick erosion upon hydration and at the same time higher solubility of drug led to rapid dissolution of drug from the matrix tablet. But the release was found to be more controlled in later stages in the tablets with higher proportion of the polymer. In presence of aqueous medium the swellable polymers starts absorption of water, causing the polymer to swell and changing its state. Increasing in polymer concentration the tablets formulations were found to swell to different extents forming a gel like structures which further increases diffusional path length and decreases the drug release.

Effect of combinations of Methocel K100M and Polyox on drug release (Ratio 1:1) were studied in the formulation F2, F12 and F16 in the ratio 1:1. It showed that when increasing the amount of excipients the release of drug was decreasing with the time. Comparative dissolution profile of Methocel K100M alone and in combination with Surelease and PolyoxWSR301 is depicted in Figure 6. The formulations F19–F23 are the replicate formulations of F12, F13, F6, F11 and F15 respectively.The release pattern of AZT from conventional marketed tablet and from optimised matrix tablet (F14) formulation was compared; the conventional tablet showed complete dissolution (99.44% ± 1.2% drug release) in 1 hour (0.1N HCl). Tablets containing release modifiers exhibited slow release of AZT as compared with conventional tablets.

Kinetic data analysis[13,14]

Results of *in-vitro* drug release kinetics study Table 5 suggests that, all formulations follows zero order kinetics with r^2 value in range of 0.99 and fitting the release data to korsmeyers equation release exponent (n) ranged from 0.83 to 1.22 this indicated that the nature of drug release from the matrix tablets followed non-Fickian diffusion mechanism (anomalous transport) and super case II transport for Surelease formulations.

Swelling behavior studies[7,15]

The swelling index was increased proportionally with respect to time and polymer concentration. As the concentration of polymer increases swelling index increases. The % swelling index of combination of PolyoxWSR301 and Methocel K 100M were found to be more as compared to Polyox WSR 301 and Methocel K 100M alone. Formulations containing Surelease alone show least swelling index. Results of swelling index were shown in Figure 7.

CONCLUSION

Results of present work demonstrated that combination of both hydrophilic and hydrophobic polymers could be successfully employed for formulating sustained release matrix tablets of AZT. The F14 formulation combination of Surelease and polyox WSR301 was capable of extending the drug release up to 12 hours and overcome the disadvantages associated with repeated administration of conventional AZT tablets.

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Table 1. Independent variables factors and levels for response surface method optimal design

Factor X1(A) (Type of Polymer)A	Factor X2(B)(Concentration/Levels of Polymer)		
Levels	-1	0	+1
S(Surelease)	1ml	2ml	4ml
P(Polyox WSR 301)	150mg	300mg	450mg
H(HPMCK100M)	150mg	300mg	450mg
S:H(Surelease:HPMCK100M)	1ml:150mg	2ml:300mg	3ml:450mg
S:P(Surelease :Polyox)	1ml:150mg	2ml:300mg	3ml:450mg
H:P(HPMCK100M:Polyox)(1:1)	150mg	300mg	450mg

Table 2. Response surface method optimal design layout for sustained release matrix tablet

Formulation No.	X1	X2	Formulation No.	X1	X2
F1	S	1	F12	P:H	0
F2	P:S	-1	F13	S	0
F3	S	-1	F14	P:S	-1
F4	S:H	-1	F15	P	0
F5	S:H	1	F16	P:H	1
F6	H	0	F17	P	1
F7	P	-1	F18	H	-1
F8	S:H	0	F19	P:H	0
F9	P:S	1	F20	S	0
F10	H	1	F21	H	0
F11	P:S	0	F22	P:S	0
			F23	P	0

Table 3. Pre and post compression characteristics evaluation

Formulation	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Compressibility Index	Hausners Ratio	Angle of Repose (°)	Weight Variation (n=20)	Hardness kg/cm2 (n=6)	%Drug content(n=3)	%Friability (n=10)
F1	0.4214±0.0068	0.5245±0.0013	19.64±0.5020	1.24±0.0070	34.75±0.003	679.47±0.04	7.01±0.28	97.06±0.39	0.41
F2	0.3683±0.0009	0.4473±0.0002	17.66±0.0212	1.21±0.0212	34.21±0.006	680.32±0.07	7.50±0.31	97.14±0.76	0.37
F3	0.4082±0.0071	0.4808±0.0020	15.09±1.4495	1.17±0.0141	31.60±0.017	375.67±0.14	7.24±0.22	96.54±0.46	0.39
F4	0.3925±0.0026	0.4614±0.0028	14.93±0.9545	1.16±0.0070	32.61±0.001	680.46±0.17	6.68±0.39	99.07±0.52	0.41
F5	0.3100±0.0035	0.3655±0.0031	15.19±0.2969	1.17±0.0070	35.23±0.001	680.32±0.11	7.10±0.27	98.17±0.64	0.38
F6	0.2896±0.0014	0.3449±0.0013	16.04±0.3676	1.18±0.0424	33.86±0.002	680.23±0.03	6.89±0.39	98.21±0.93	0.29
F7	0.3910±0.0014	0.4650±0.0036	15.90±0.3040	1.16±0.0070	34.99±0.003	679.28±0.07	6.90±0.39	99.27±0.78	0.36
F8	0.3823±0.0032	0.4852±0.0044	20.01±0.0848	1.26±0.0000	35.12±0.019	680.37±0.06	7.23±0.31	99.34±1.04	0.28
F9	0.4227±0.0038	0.5231±0.0253	19.19±0.0565	1.23±0.0071	27.47±0.027	680.18±0.07	7.50±0.11	98.85±0.25	0.31
F10	0.4127±0.0180	0.4821±0.0029	14.36±0.7566	1.16±0.0000	29.24±0.008	680.36±0.13	6.40±0.22	96.98±0.99	0.35
F11	0.4230±0.0020	0.4766±0.0033	11.23±0.1272	1.12±0.0035	35.15±0.041	680.48±0.21	7.40±0.40	95.67±0.66	0.39
F12	0.4236±0.0026	0.4854±0.0018	12.73±0.0494	1.14±0.0014	35.13±0.032	680.56±0.27	7.10±0.32	97.93±0.62	0.34
F13	0.4335±0.0016	0.4865±0.0004	10.88±0.0000	1.12±0.0084	32.39±0.091	525.48±0.08	7.50±0.09	95.43±0.82	0.37
F14	0.4244±0.0014	0.4757±0.0032	10.78±0.2050	1.11±0.0077	33.17±0.036	680.13±0.13	5.79±0.28	98.83±0.51	0.42
F15	0.4230±0.0034	0.5240±0.0070	19.26±0.1555	1.23±0.0063	33.94±0.028	679.34±0.35	7.08±0.31	97.65±0.44	0.47
F16	0.4373±0.0037	0.5050±0.0070	13.39±0.4666	1.15±0.0023	28.36±0.029	680.52±0.09	6.29±0.29	99.05±0.63	0.33
F17	0.4472±0.0039	0.5050±0.0035	11.88±0.1697	1.13±0.0036	31.79±0.017	680.34±0.08	7.24±0.35	99.37±0.97	0.58
F18	0.4325±0.0034	0.5025±0.0035	13.92±0.0848	1.16±0.014	30.11±0.004	680.41±0.73	6.84±0.33	97.29±0.48	0.43
F19	0.4236±0.0026	0.4854±0.0018	12.73±0.0494	1.14±0.0014	35.13±0.032	680.56±0.27	7.10±0.32	97.93±0.47	0.34
F20	0.4335±0.0016	0.4865±0.0004	10.88±0.0000	1.12±0.0084	32.39±0.091	525.48±0.08	7.50±0.09	95.43±0.73	0.37
F21	0.2896±0.0014	0.3449±0.0013	16.04±0.3676	1.18±0.0424	33.86±0.002	680.23±0.03	6.89±0.39	98.21±0.84	0.29
F22	0.4230±0.0020	0.4766±0.0033	11.23±0.1272	1.12±0.0035	34.15±0.041	680.48±0.21	7.40±0.40	95.67±0.67	0.39
F23	0.4230±0.0034	0.5240±0.0070	19.26±0.1555	1.23±0.0063	33.94±0.028	679.34±0.35	7.08±0.31	97.65±0.48	0.47

Table 4. Summary of results of regression analysis for response y_1 and y_2

Response	Models	R^2	Adjusted R^2	Predicted R^2	S.D	Remarks
Y_1	Linear	0.9735	0.9636	0.9368	1.25	Suggested
	2FI	0.9913	0.9826	0.8993	0.86	Suggested
	Quadratic	0.9914	0.9811	0.8689	0.90	-
Y_2	Linear	0.9739	0.9642	0.9379	7.42	Suggested
	2FI	0.9920	0.9839	0.9077	4.97	Suggested
	Quadratic	0.9920	0.9824	0.8783	5.20	_
Regression equation of linear fitted model **Y_1= -3.11A-4.05B1+4.22B2+5.55B3-4.53B4+7.60B5** **Y_2=-18.68A-24.19B1+25.34B2+33.29B3-27.25B4+45.43B5**						

Table 5. Release kinetic parameters of designed sustained release matrix tablets of zidovudine

Formulation No.	Zero order (r^2)	First order (r^2)	Higuchi (r^2)	Korsmeyer-Peppas(r^2)	Korsmeyer-Peppas (n)
F1	0.994	0.977	0.972	0.993	1.062
F2	0.998	0.867	0.964	0.997	0.858
F3	0.998	0.846	0.974	0.995	1.038
F4	0.993	0.967	0.955	0.967	0.885
F5	0.995	0.985	0.955	0.984	0.831
F6	0.981	0.851	0.95	0.966	0.823
F7	0.994	0.881	0.967	0.977	0.863
F8	0.983	0.881	0.956	0.979	0.884
F9	0.997	0.987	0.958	0.996	0.882
F10	0.998	0.808	0.972	0.992	0.835
F11	0.998	0.941	0.969	0.977	0.864
F12	0.993	0.884	0.967	0.986	0.874
F13	0.997	0.933	0.97	0.99	1.075
F14	0.998	0.766	0.969	0.995	0.873
F15	0.994	0.875	0.97	0.972	0.83
F16	0.999	0.806	0.964	0.987	0.857
F17	0.998	0.842	0.966	0.992	0.839
F18	0.995	0.865	0.958	0.981	0.86
F19	0.993	0.884	0.967	0.986	0.874
F20	0.997	0.933	0.97	0.99	1.075
F21	0.981	0.851	0.95	0.966	0.823
F22	0.998	0.941	0.969	0.977	0.864
F23	0.994	0.875	0.97	0.972	0.83
Marketed formulation	0.963	0.772	0.842	0.953	1.22

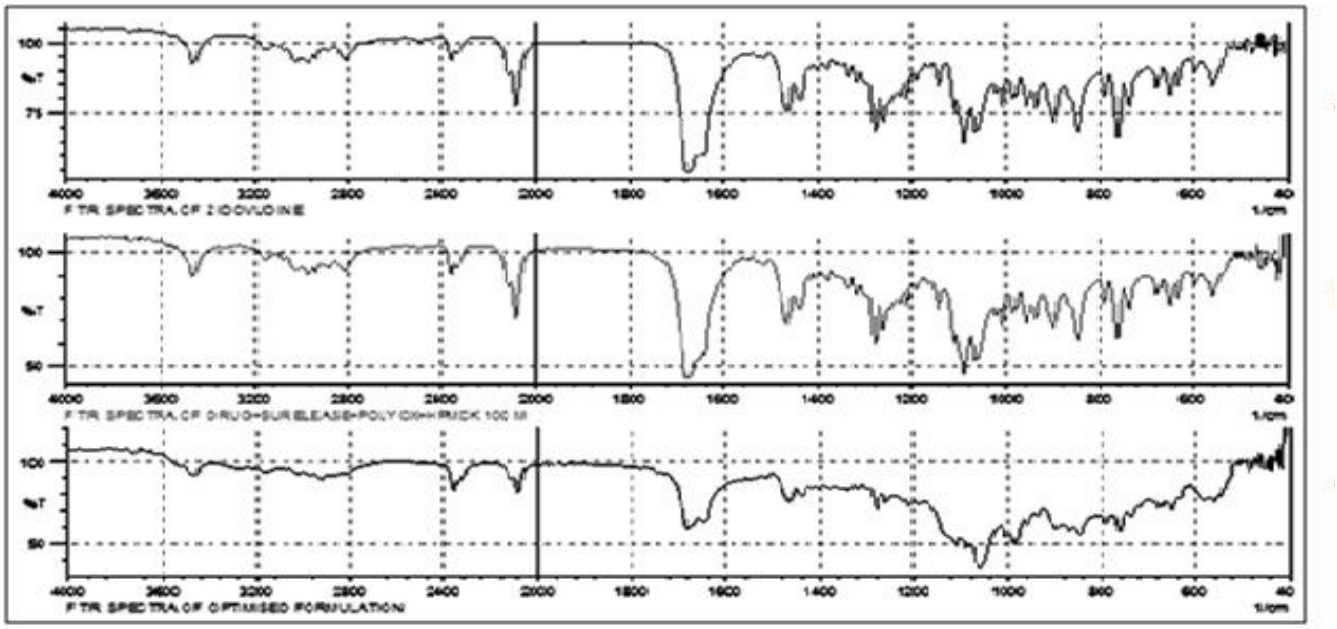

Figure 1. FTIR spectrum of pure AZT (A),solid mixtures of AZT with Methocel K100M,Polyox WSR301 and Surelease (B),Optimised formulation(C)

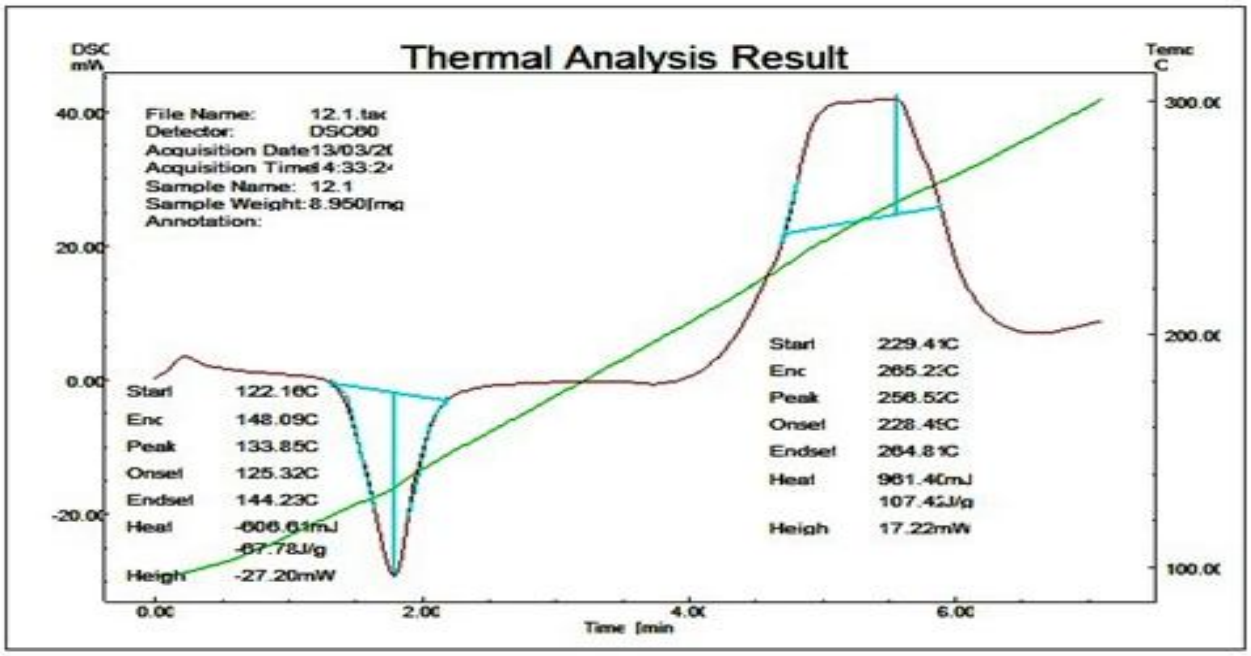

Figure 2(a) DSC Thermograms obtained for pure AZT

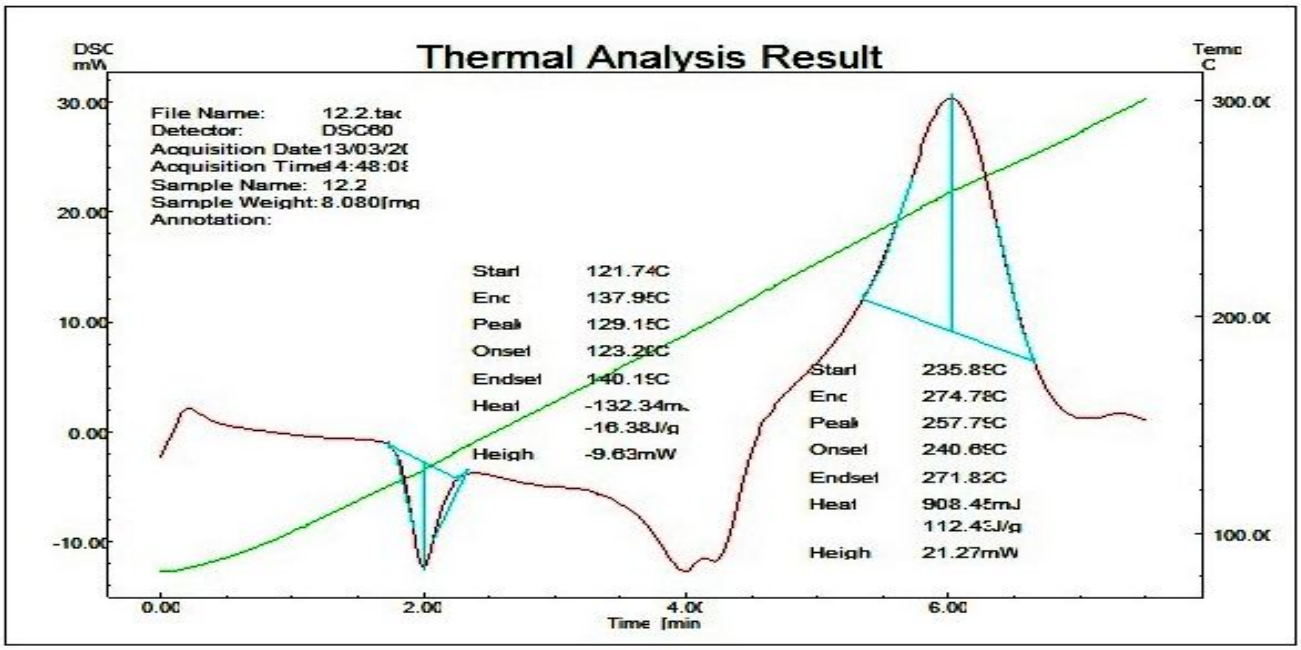

Figure 2(b) DSC Thermograms obtained for Optimised formulation F14 at a heating rate of 10° C/min using nitrogen environment

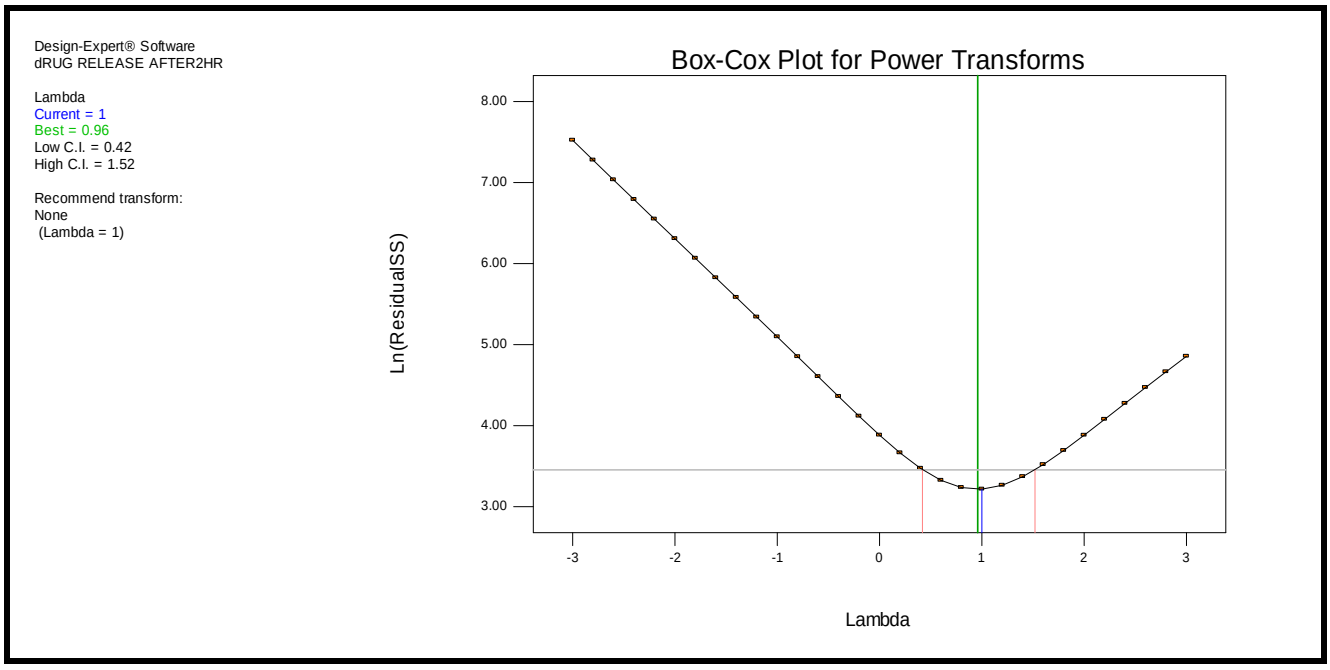

Figure 3(a) Box-Cox plot for response $Y_{1\,(a)}$

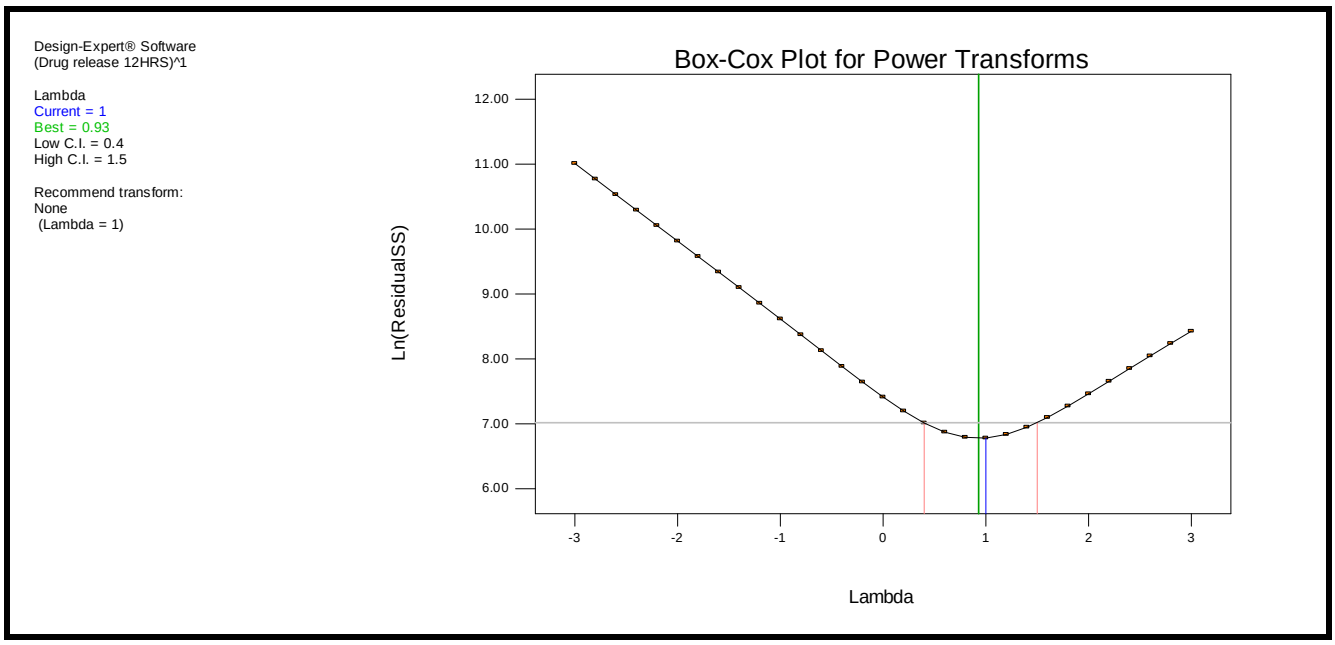

Figure 3(b) Box-Cox plot for response $Y_{2\,(b)}$

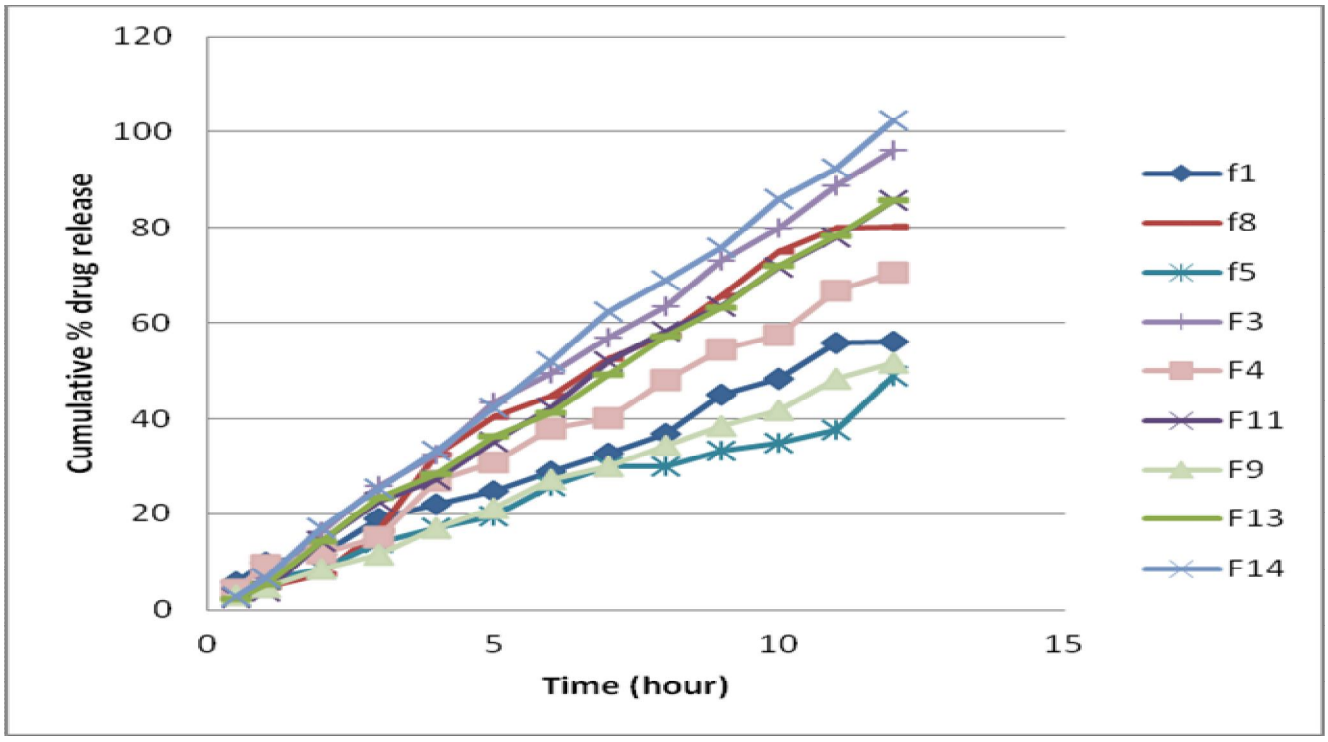

Figure 4 Comparative dissolution study of Surelease alone and in combination with Polyox WSR301 and Methocel K100M

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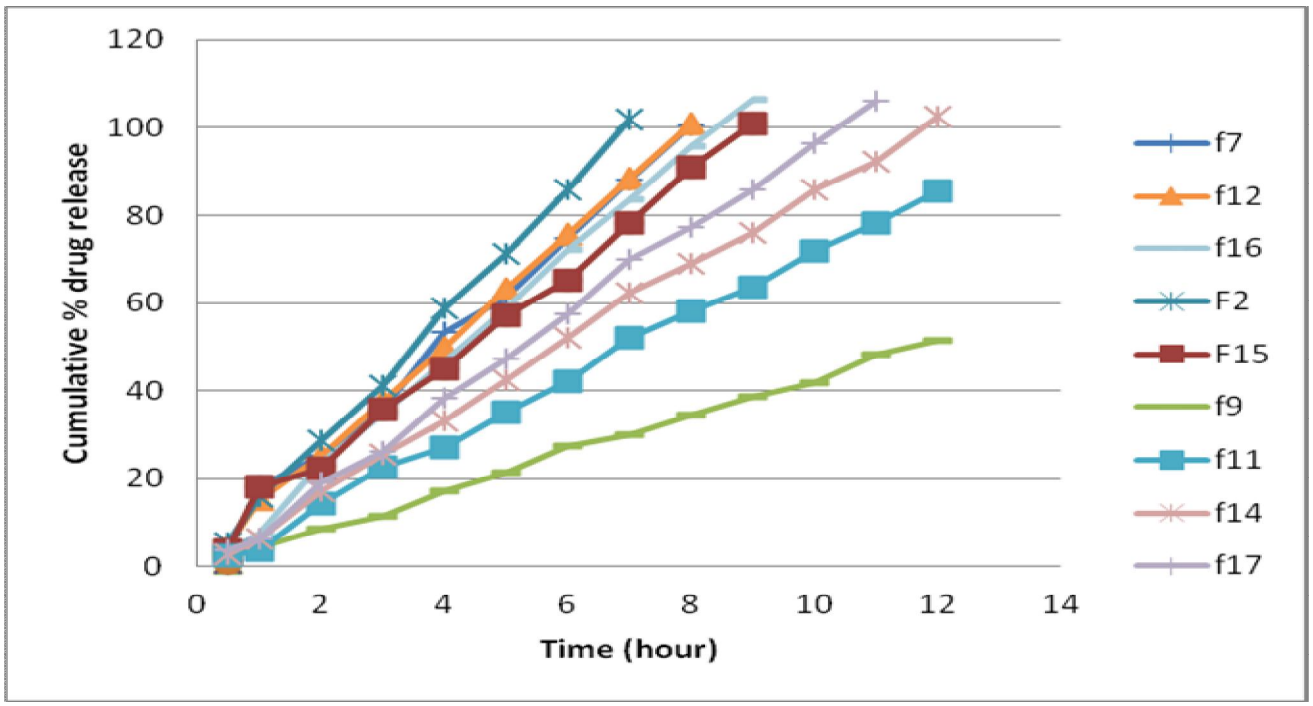

Figure 5 Comparative dissolution study of Polyox WSR 301 alone and in combination with Methocel K 100M and Surelease

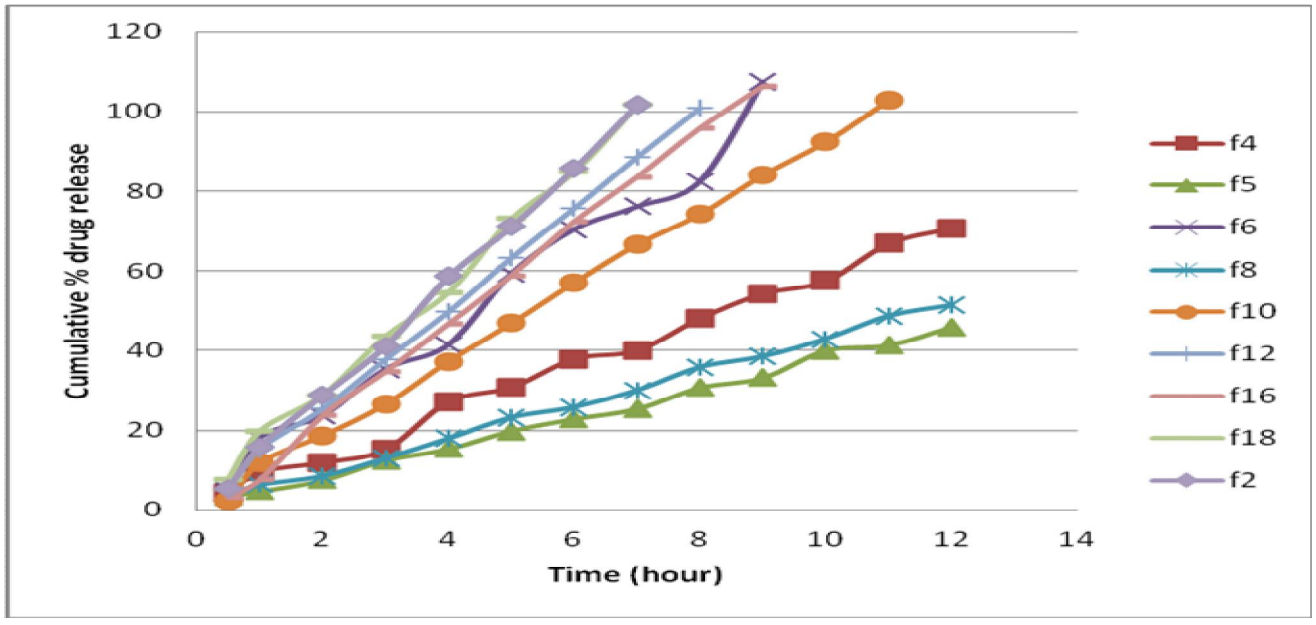

Figure 6 Comparative dissolution study of Methocel K 100M alone and in combination with Surelease and Polyox WSR301

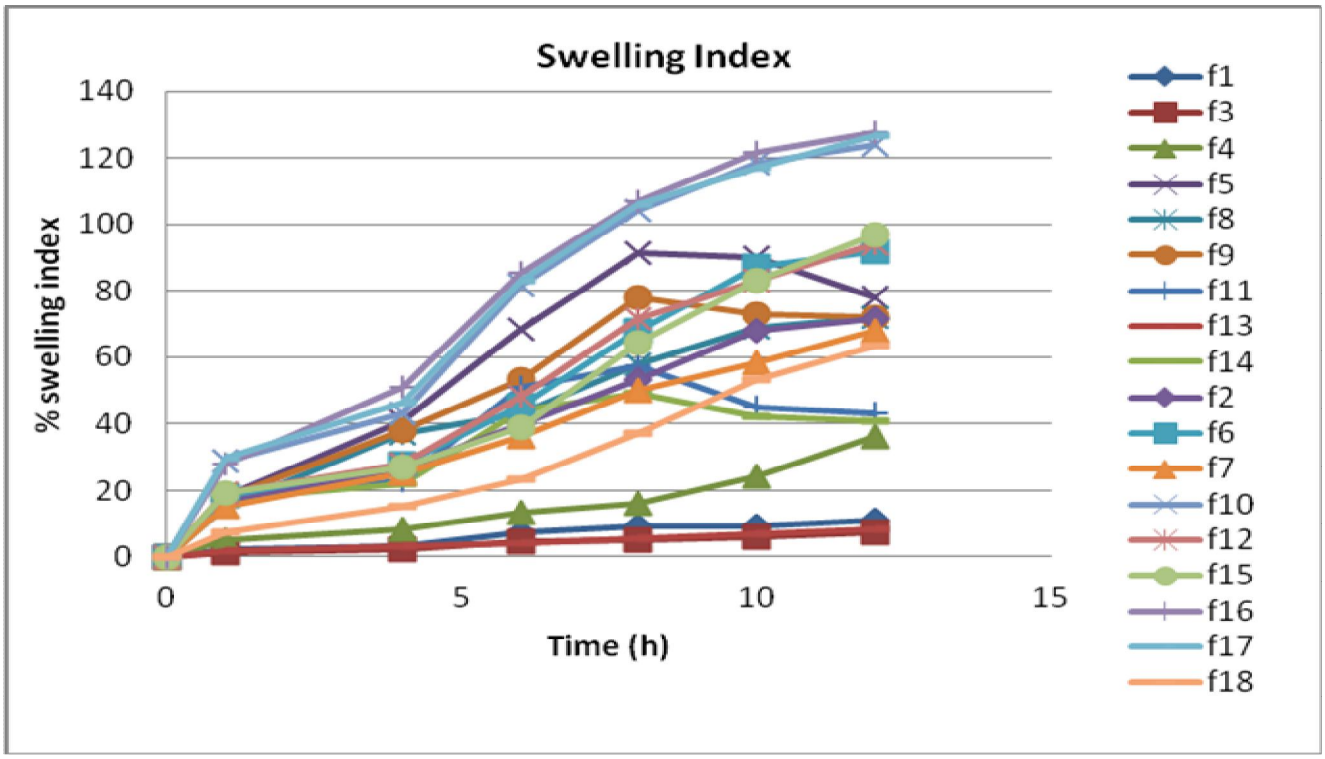

Figure 7 % swelling index of Sustained release matrix tablets