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Original Article

Development and Optimization of Phenytoin Sodium Controlled Release Tablet Using Wax Matrix Using Design of Experiment

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ABSTRACT

An attempt was made to optimize an erosion matrix based drug delivery system for Phenytion sodium (PhNa) using a combination of Cetostearyl alcohol (CSA) and Stearic Acid (SA). The ratio of drug to level of CSA and SA and the effect of Plasdone (PVP K30) as pore former on the in vitro dissolution profile were evaluated using a 2^3 Design of experiments. The USP dissolution Test 1 specification for Phenytion Sodium Controlled Release tablet was considered for the optimization study.

Keywords: Phenytion sodium (PhNa), Cetostearyl alcohol (CSA), Stearic acid (SA), pore former (PVP K30), Microcrystalline Cellulose (MCC), Design of experiments.

INTRODUCTION

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations[1]. Melt granulation process is currently applied in the pharmaceutical for the manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets.[2,3]

It is a commonly used antiepileptic. Phenytion acts to suppress the abnormal brain activity seen in seizure by reducing electrical conductance among brain cells by stabilizing the inactive state of voltage-gated sodium channels. Aside from seizures, it is an option in the treatment of trigeminal neuralgia in the event that carbamazepine or other first line treatment seems inappropriate.[5,6]

MATERIALS AND METHODS

Chemicals and Reagents

Phenytion Sodium USP (EMCO Industries Hyderabad), Cetosteryl Alcohol (Abitec k US), Stearic Acid-(Nitika Industries Hyderabad), (PVP K30) -Ashland speacality chemicals, Microcrystalline cellulose (MCC) –FMC Biopolymer·

In order to get a statistically relevant data and to remove experimental bias Optimization of Phenytion sodium formulation was done using 2^3 full factorial designs. The effect of concentrations of the 3 polymers was studied in DOE enviroment by using a 2^3 expermimental design.[7] The design was developed using the DOE PRO XL software.[9]

The mean dissolution value at each time point was considerd as the measurable parameter and the DOE was run for each time point. This gives the idea of the effect of combination of polymers on both the rate as well as the extent of dissolution.[11]

The controlled release product of Phenytion sodium is official in the US pharmacopoeia[12] and has the dissolution a requirement as given in Table 1

The aim of the present work was to evaluate the effect of two waxes, Cetostearyl alcohol and Stearic acid and one pore former, PVP K30 on modulating drug release to achieve the USP defined dissolution specification.

The two waxes were selected on the basis of their differing melting points. The study was conducted using 2^3 full factorial design of experiments

Target Dissolution Profile for Phenytion sodium as per the USP Pharmacopeia[11] as shown in table 1

EXPERIMENTAL

Wax matrixes Tablet of 500 mg weight were prepared by the Melt Extrusion method. The composition is given in Table 2.

The process of fabricating the tablets is shown process flow chart (Fig 1). The physical properties[4] of the tablets were measured and are given in Table 3. The in vitro dissolution profile studies were carried out using USP Type I apparatus, 900 ml water as the dissolution medium. The samples were withdrawn at 30 minutes, 60 minutes and 120 minutes time points and were analyzed spectrophotometrically at 240 nm wavelength

RESULTS AND DISCUSSION[9, 10]

The amount of drug dissolved was calculated and the dissolution data were shown in table 4 and the dissolution profile graphs are shown in Fig 2.

The values of dissolution at all three time points were fed into DOE ProXL[11] software and the surface response plots are shown in Fig 3, 4 and 5. The design space identified by the software is given in Table 5.

Based on this, three formulations were fabricated within the design space Table 6, the in vitro dissolution data is shown in table 7and the dissolution profile is shown in Figure 6

This indicates that it is possible to fabricated a wax matrix formulation of Phenytion sodium controlled release product and a soluble polymer like PVP plays an important role in modulating the drug release as per the critically defined target product profile.

CONCLUSION

The aim of this project was to achieve a control release formulation of Phenytion sodium using a combination of wax matrix along with pore former PVP k30. The experiments were designed using DOE Pro Xl software at 2 use levels Low and High. The focus of this work was to optimize the Phenytion sodium tablets using Design of Experiment. On finding the three Critical Formulation Ingredients or parameters, a 2^3 experimental design using DOE was run to identify the interaction between these parameters.

A strong correlation was found between these parameters and a design space within which the formulation passes the acceptance criteria of percentage drug release in water was determined.

Design Space for the three CFI in which the tablets pass acceptance criteria in water were shown in table 5

This work demonstrates a simple method of preparing once a day Phenytion sodium tablets using a simple process and commonly used excipients.

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Table 1. Target dissolution profile :(based on usp pharmacopiea)[12]

TIME(Min)	MEAN % DRUG DISSOLVED
0	0
30	Not More than 45% Q
60	Not More than 60% Q
120	Not Less Than 70% Q

Table 2. Phenytoin sodium tablet preparation (design of experiment)[9,10]

S.NO	INGREDIENTS	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
		LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
1	Phenytion Sodium	100	100	100	100	100	100	100	100
2	Stearic acid	74	74	80	80	74	74	80	80
3	Cetostearyl alcohol	74	74	74	74	80	80	80	80
4	PVP K30	2	5	2	5	2	5	2	5
5	MCC	210	213	216	219	216	219	222	225
6	Magnesium Stearate	5	5	5	5	5	5	5	5
7	Aerosil	5	5	5	5	5	5	5	5
8	Total	500	500	500	500	500	500	500	500

Table 3. Physicochemical properties of phenytion sodium tablet

Formulations	Weight variation	Hardness	Thickness	Friability
F1	492±2.13	6.4± 0.123	5.01 ± 0.016	0.43
F2	488±2.8	7.1 ± 0.145	5.03 ± 0.012	0.39
F3	485±3.1	7.3 ± 0.121	4.8 ± 0.015	0.41
F4	501±2.5	6.9±0.126	4.01±0.012	0.41
F5	499±2.3	7.1±0.132	5.1±0.032	0.38
F6	500±2.6	7.0±0.123	4.2±0.013	0.42
F7	499±3.3	6.8±0.127	5.0±0.013	0.43
F8	501±2.1	7.1±0.142	4.8±0.032	0.39

Table 4. Dissolution profile for phenytion sodium tablet in water design of experiment

S. NO	TIME (min)	TPP LOW	TPP HIGH	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
1				LLL	LLH	LHL	LHH	HLL	HLH	HHL	HHH
2	0	0	0	0	0	0	0	0	0	0	0
3	30	10	45	50.27	50.16	54.07	48.48	46.12	56.75	45.12	73.21
4	60	40	65	60.61	60.59	69.49	64.85	54.28	68.35	55.22	82.88
5	120	70	100	71.21	70.69	79.86	77.67	64.45	75.36	62.71	90.33

Table 5. Design space for phenytoin sodium

S.No	FORMULATION COMPONENT	LOWER LIMIT (mg)	UPPER LIMIT (mg)
1	Cetostearyl Alcohol	74	78
2	Stearic Acid	74	74.5
3	PVPk30	1.3	1.7

Table 6. Optimum formulations of phenytoin sodium

Name of the Ingredient	F_9 (in mg)	F_{10} (in mg)	F_{13} (in mg)
Phenytion sodium	100	100	100
Micro crystalline cellulose	240.7	238.3	235.8
Stearic acid	74	74.2	74.5
Cetostearyl alcohol	74	76	78
PVP K30	1.3	1.5	1.7
Magnesium stearate	5	5	5
Aerosol	5	5	5
Total	500	500	500

Table 7. F Optimum formulation dissolution data for phenytoin Sodium

Time(min)	TDP LOW	TDP HIGH	F_9	F_{10}	F_{11}
0	0	0	0	0	0
30	10	45	37.21	40.1	44.61
60	40	65	49.87	56.31	61.12
120	70	100	81.32	75.54	79.82

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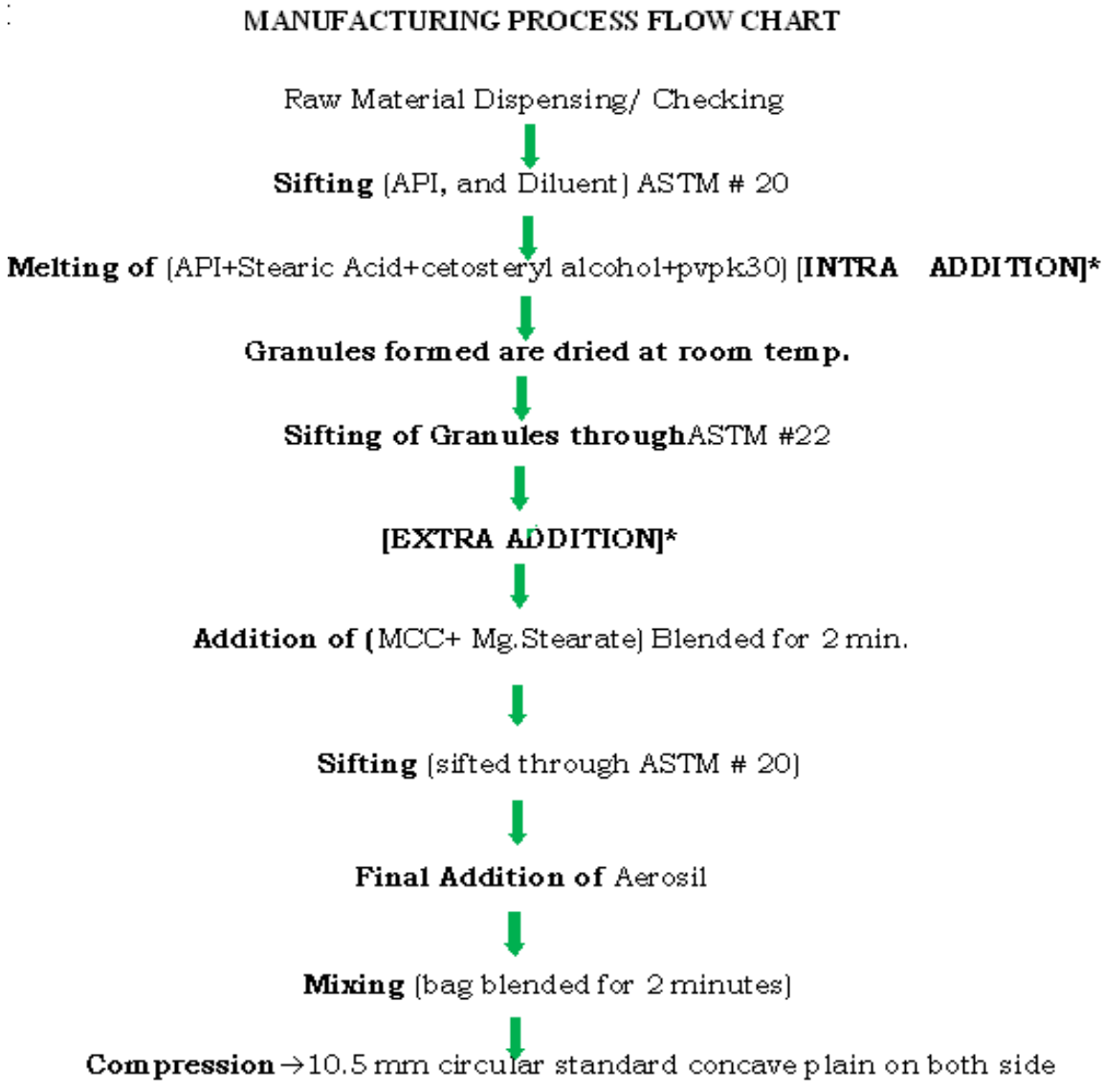

Figure 1. Manufacturing process flow chart

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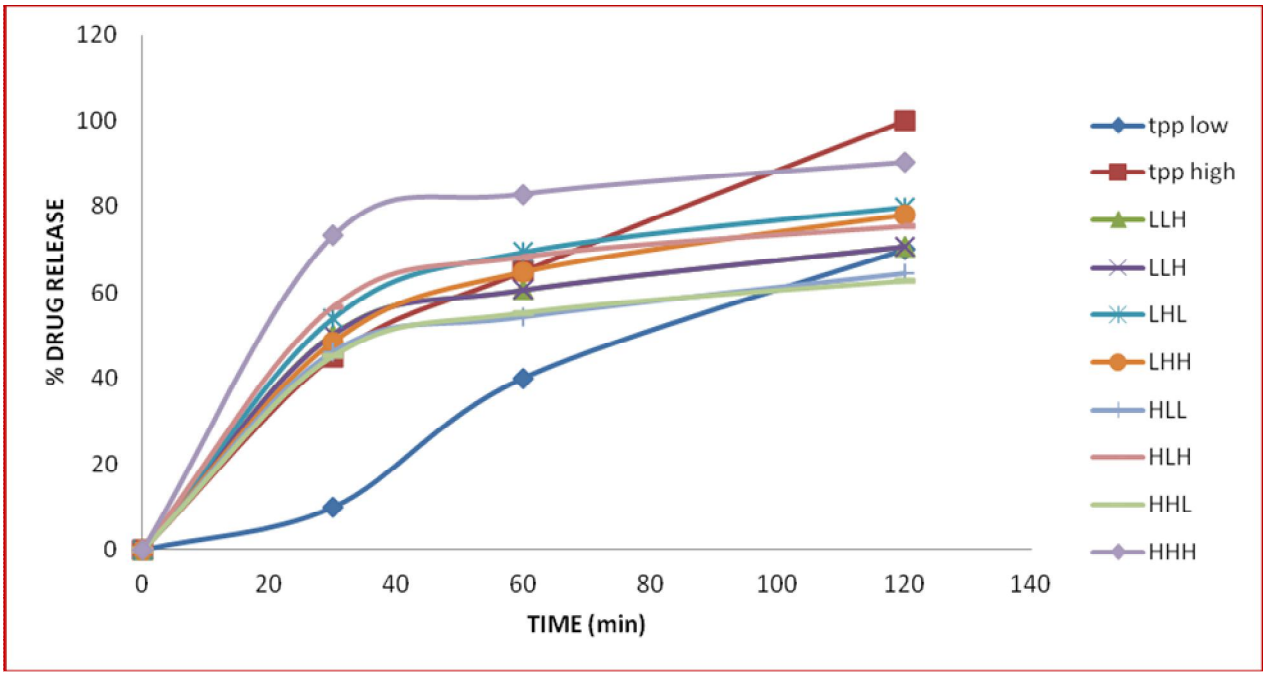

Figure 2. Dissolution profile for phenytoin sodium in water

DESIGN OF EXPERIMENT CHARTS

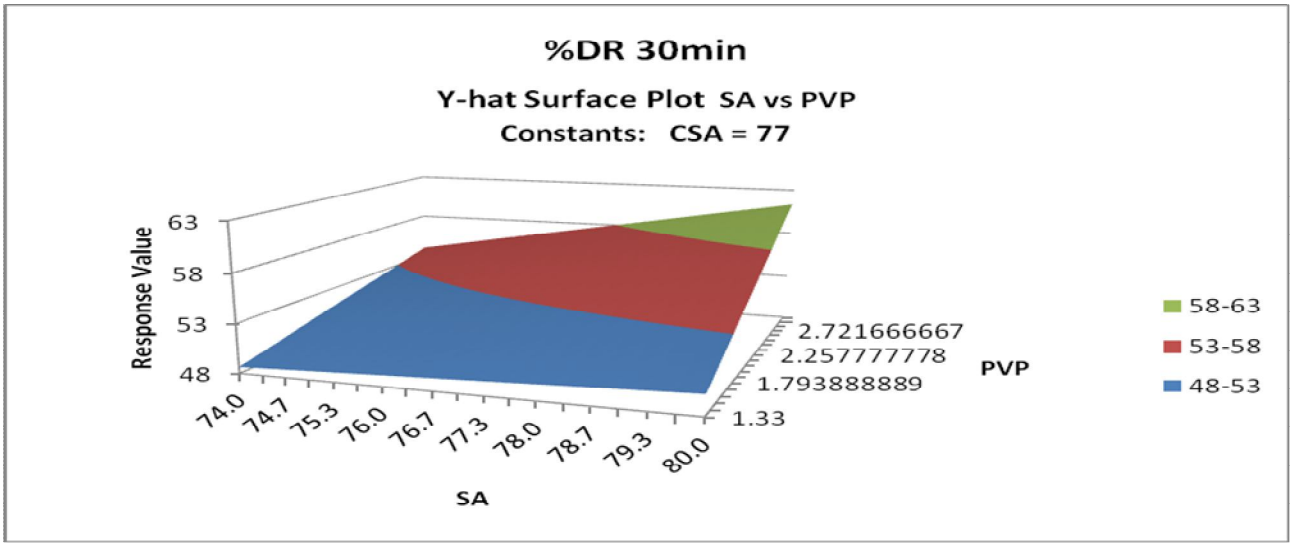

Figure 3. Y-hat surface plot stearic acid vs pvp for 30 min

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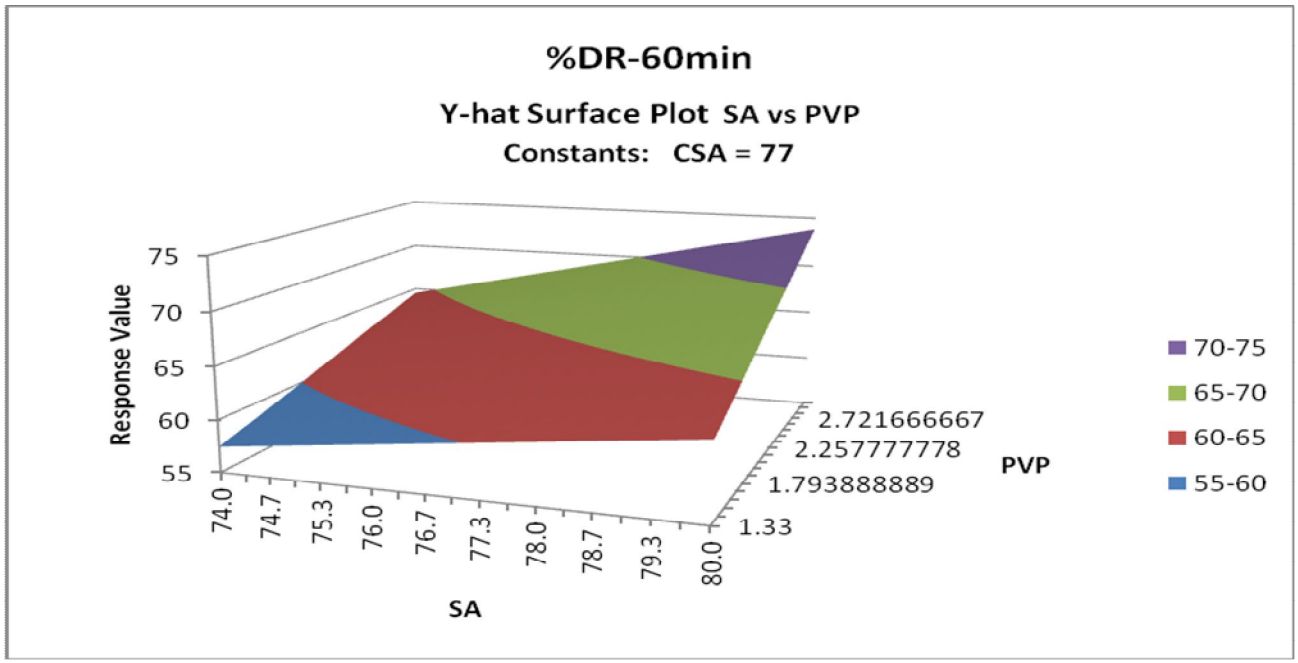

Figure 4. Y-Hat surface plot stearic acid vs pvp for 60 min

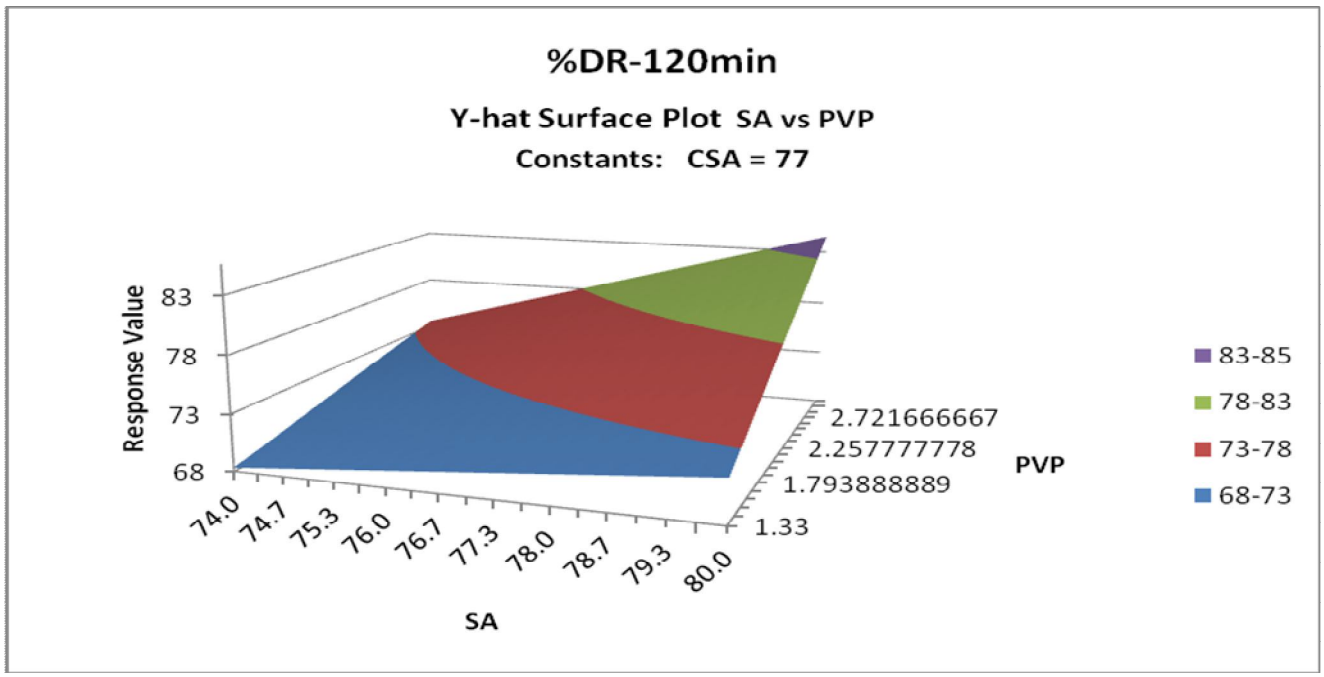

Figure 5. Y-Hat surface plot stearic acid vs pvp for 120 min

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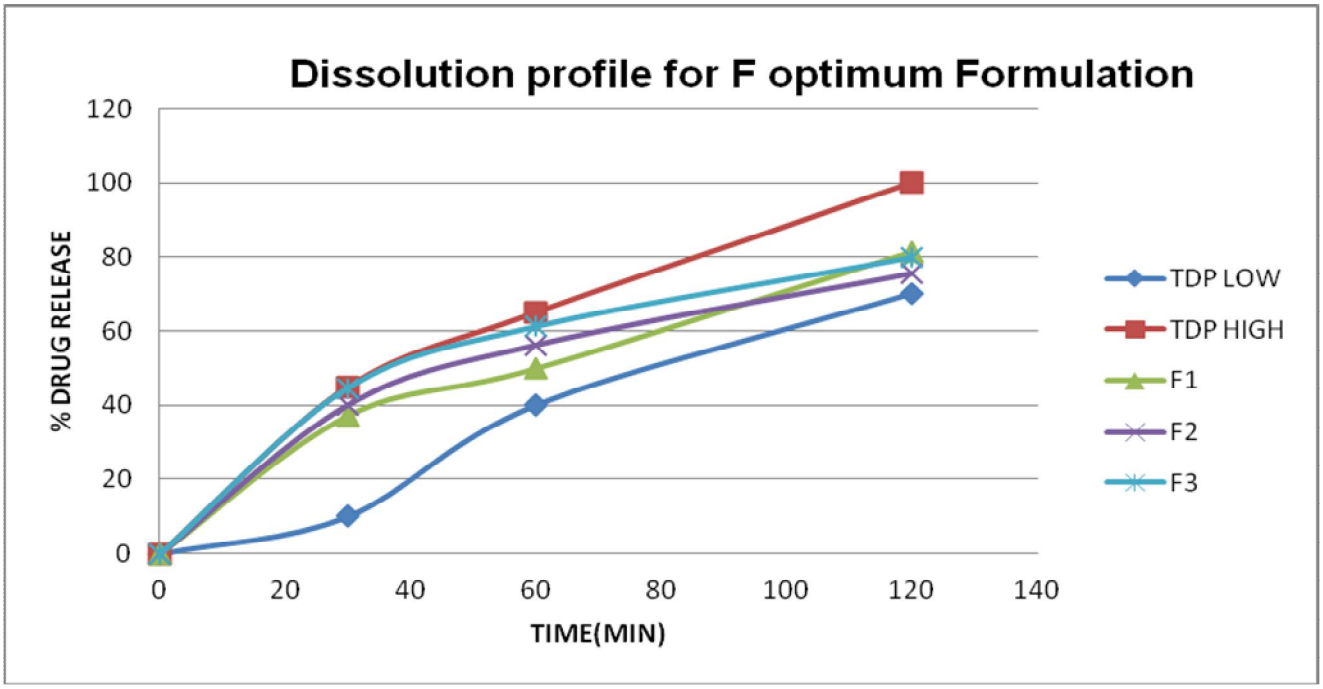

Figure 6. Dissolution profile for f optimum formulation