Formulation and Evaluation of Sustained Release Matrix Tablets of Prazosin Hydrochloride

[1]Patel Vijay, [2]Raval Anil
[1]Student, [2]Assistant Professor
[1]Department of Pharmaceutics,
[1]Sharda School of Pharmacy, Pethapur, Gandhinagar, India

Abstract*:* The aim of present investigation was formulation and development of Prazosin HCl Sustained Release Matrix Tablets. Study started from the preformulation study of the drug. Drug having good solubility in both dissolution mediums. The flow of API is low so directly compressible excipient used for tablet preparation. While studying IR spectrum, we can conclude that there is no interaction between drug and other excipients. Initially feasibility trials were taken using HPMC K4M and K100M. Tablets were found acceptable in physical parameters evaluation. During drug release evaluation amount of HPMC K4M increases the drug release for long period of time. In contrast less amount of HPMC K100M helps in drug release. So role of polymer concentration is very important in this formulation. Based on that F3 batch found satisfactory and considering for further factorial screening. 3^2 factorial design applied by taking HPMC K4M and PVP K-30 as independent factors. Factorial batch P1-P9 prepared by using direct compression method. Physical and chemical evaluation was done for all batches. PVP K-30 and HPMC K4M significantly impact on Drug release and hence the model found significant. Finally the optimized batch P12 taken based on Contour plot and evaluation done. Batch P12 load for stability for 1 month and found stable. Hence the batch P12 was optimized batch.

Key Words: Prazosin HCl, Matrix Tablets, Sustained Release.

I. INTRODUCTION

The delivery of accurate drug concentration to the site of action in order to achieve appropriate therapeutic effect or response in the body is the key objective of the drug delivery systems. There are two types of delivery systems which are generally used. Conventional drug delivery systems or the immediate release drug delivery systems and modified release drug delivery systems. Modified release drug delivery systems include: Targeted drug delivery systems, delay or repeated drug delivery systems and prolonged or extended drug delivery systems (Controlled release, Sustained release and long-acting dosage forms).

Sustained Release Formulation: Sustained release tablets and capsules are commonly taken only once or twice daily, as compared with counterpart conventional forms that may have to be taken three or four times daily to attain the same therapeutic effect. Sustained-release formulations provide an immediate release of drug that produces the desired therapeutic effect, followed by a gradual release of additional amounts of drug to maintain this effect over a predetermined period. The oral administration is the most popular route used for sustained release delivery due to ease of administration, convenience, greater flexibility in dosage form design, ease of production and low cost of production of such a system.

Matrix Tablets: Matrix tablets can be defined as the oral solid dosage forms in which the drug is homogeneously dispersed or dissolved within the hydrophilic or hydrophobic polymeric matrices. The preparation of sustained release matrix tablets involves the direct compression of blend powder mixture of drug, retardant material and other additives to formulate a tablet in which the drug is dispersed in a matrix of the retardant. Alternatively, drug, retardant blend and other additives may be granulated prior to compression. These systems release the drug in a continuous manner by dissolution-controlled and diffusion-controlled mechanisms.

Prazosin is a selective α-1-adrenergic receptor antagonist. It is well-absorbed from gastrointestinal tract and its bioavailability is variable (50 to 85%). Prazosin acts by inhibiting the postsynaptic alpha(1)-adrenoceptors on vascular smooth muscle. This inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation. Prazosin is used treatment of hypertension, symptomatic benign prostatic hyperplasia, and severe congestive heart failure. May also be used alone or in combination with β-blockers in the preoperative management of signs and symptoms of pheochromocytoma.

The objective of the present study is to formulate and evaluate a sustained release matrix tablets with better stability, better patient compliance and reduce dose frequency.

II. CHARACTERIZATION

2.1 Characterization of Prazosin HCl

Characterization of Prazosin HCl was performed. Prazosin HCl was characterized for different micromeritics properties such as bulk density, tapped density, compressibility index, Hausner's ratio and Angle of repose. Prazosin HCl was characterized for description, solubility in different solvent media and melting point determination.

2.2 Selection of Excipients and Drug Excipients Compatibility Studies

Drug excipient compatibility study of Prazosin HCl with different excipients was performed to assess their interactions with the drug and to select suitable excipients which will ensure the development of a stable, safe and therapeutically effective dosage form. FTIR studies were carried out to determine the compatibility of excipients with the drug. Selection of excipients was carried out based on the compatibility study.

III. EXPERIMENTAL WORK

3.1 Materials

Prazosin HCl was received as a gift sample Zydus Research Centre, Ahmedabad. Hydroxy propyl Methyl Cellulose (HPMC K4M and HPMC K100M), Polyvinylpyrrolidone (PVP K-30), Lactose DCL 11, Microcrystalline cellulose (MCC), Colloidal silicone dioxide and Magnesium stearate was obtained ACS Chemicals, Ahmedabad.

3.2 Preformulation study

Preformulation studies are the first step in the rational development of dosage form of a drug substance. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product. Followings studies performed for in the Preformulation study: Description, Solubility, Melting point determination, Bulk density, Tapped density, Compressibility index, Hausner's ratio and Angle of repose.

3.3 Calibration curve of Prazosin HCl

Standard stock solution of Prazosin HCl (100 µg/ml) was prepared by dissolving 10 mg of Prazosin HCl in 100 ml using 0.1 N HCl to get a concentration of 100 µg/ml. Appropriate volumes of this solution were further diluted to obtain final concentrations in the range of 1 to 10 µg/ml. The spectrum of this solution was recorded from 200 nm to 400 nm using Shimadzu UV-VIS Spectrophotometer. Same process repeated for 6.8 phosphate buffer.

3.4 Drug excipients compatibility study

FTIR studies were carried out to determine the compatibility of excipients with the drug. Pure drug sample and physical mixture of excipients with drug compared by FTIR and check the compatibility.

3.5 Dose Calculation

Optimum release profile for twice daily Sustained Release formulation was calculated by the below equation using available pharmacokinetic data.

$$Dt = Dose\ (1+ 0.693 \times t / t\ ½) \quad (1)$$

3.6 Formulation of Sustained release matrix tablets of Prazosin HCl

Sustained Release Matrix Tablets of Prazosin HCl was prepared by using Direct Compression Method. The tablets were prepared using polymers like HPMC K4M and HPMC K100 along with other additives. All excipients except Magnesium stearate were passed through 40# sieve and Magnesium stearate was passed through 60# sieve. Drug, polymer, binder, diluent and glidant were mixed and blended for 10 minutes. Then Magnesium stearate was added and lubricated for 2 minutes. The tablet powder was compressed into tablets on tablet punching machine.

In formulations prepared, the drug release controlling polymers were hydroxyl propyl methylcellulose (HPMC K4M, HPMC K100). PVP K-30 was used as binder. Microcrystalline cellulose (MCC) and Lactose (DCL 11) were used as diluent. Colloidal silicon dioxide was used as glidant. Magnesium stearate was used as lubricant.

Table 1 Trial batch formulation F1-F7

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7
Prazosin HCl	3.8	3.8	**3.8**	3.8	3.8	3.8	3.8
Microcrystalline Cellulose (Avicel pH 102)	62.2	52.2	**42.2**	62.2	52.2	42.2	42.2
Lactose (DCL 11)	90	90	**90**	90	90	90	90
PVP K-30	10	10	**10**	10	10	10	10
HPMC K4M	30	40	**50**	-	-	-	25
HPMC K100M	-	-	**-**	30	40	50	25
Colloidal silicon dioxide	2.0	2.0	**2.0**	2.0	2.0	2.0	2.0
Magnesium Stearate	2.0	2.0	**2.0**	2.0	2.0	2.0	2.0
Total	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	**200.0**	200.0

Based on feasibility trial results, F3 batch which contains 50.0 mg of HPMC K4M gives satisfactory drug release up to 12 hours. Hence F3 batch composition selected for factorial design. Design and formulation of factorial batches are given below.

Table 2 Design of experiment

Design	3^2	**Level**		
Level	3			
Factor	2			
Factors		**Low**	**Medium**	**High**
X1=Amount of HPMC K4M (mg)		45	50	55
X2=Amount of PVP K-30 (mg)		5	7.5	10
Dependent Factors				
Y1	% Drug release at 2 hours			
Y2	% Drug release at 8 hours			

Table 3 Formulation table for factorial batches

Ingredients (mg)	P1	P2	P3	P4	P5	P6	P7	P8	P9
Prazosin HCl	3.8								
Lactose (DCL 11)	90								
Microcrystalline Cellulose (Avicel pH 102)	52.2	47.2	42.2	49.7	44.7	39.7	**47.2**	42.2	37.2
PVP K-30	5	5	5	7.5	7.5	7.5	**10**	10	10
HPMC K4M	45	50	55	45	50	55	**45**	50	55
Colloidal silicon dioxide	2.0								
Magnesium Stearate	2.0								
Total	**200.0**								

3.7 Evaluation of Pre Compression Parameters

3.7.1 Loose Bulk Density

Weigh accurately powder blend and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume (V_0). Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = Weight of powder / Bulk Volume

3.7.2 Tapped bulk density

Weigh accurately powder blend and transfer in 100 ml graduated cylinder. Then tap the cylinder containing the sample manually. Tap the cylinder for approximately 100 times initially and measure the tapped volume (V).

Tapped Density = Weight of powder / Tapped Volume

3.7.3 Carr's Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x 100] / TD

3.7.4 Hausner's Ratio

The Hausner's ratio is a number that is correlated to the flow ability of a powder or granular material.

Hausner's ratio = TD/BD

Table 4 Effect of Carr's Index and Hausner's Ratio on flow property

Carr's Index (%)	Flow Character	Hausner's Ratio
$\leq$ 10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34

26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

3.7.5 Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following formula.

$\tan \theta = h / r$

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

Table 5 Effect of Angle of repose (ϕ) on Flow property

Angle of Repose (Φ)	Type of Flow
< 20	Excellent
20-30	Good
30-34	Passable
>35	Very poor

3.8 Post Compression Parameters

3.8.1 Weight variation

The weight variation test was conducted by weighing 10 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 7.5 % (As per IP, BP and USP).

3.8.2 Thickness

The thickness was measured by using digital vernier caliper.

3.8.3 Hardness

The hardness of the tablets was determined by diametric compression using a Hardness testing apparatus. Determinations were made in triplicate.

3.8.4 Friability

The friability of the tablets was measured in a Roche friabilator. Tablets of a known weight (W_0) de dusted in a drum for a fixed time (100 revolutions) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in formula as below. The weight loss should not be more than 1 %.

$\%\ \text{Friability} = (W_0 - W / W_0) \times 100$

3.8.5 Drug Content

Tablets were individually finely ground in a mortar. Accurately weighed quantity of the powder tablet equivalent to 3.8 mg of the drug was transferred to 100 ml volumetric flask dissolve in 100 ml 0.1 N HCl Aliquots were filtered and assayed spectrophotometrically (by UV) at 246 nm for drug content.

3.8.6 In-vitro dissolution study

In vitro release studies were carried out for all the formulations as per USP-II tablet dissolution tester employing rotating paddle at 50 rpm using 900 ml 0.1 N HCl of pH 1.2 for first two hours and phosphate buffer of pH 6.8 for 10 hours as dissolution medium. About 5 ml aliquot samples were collected at 1 hour interval up to 4 hours and at 2 hours interval up to 12 hours. The samples were replaced with fresh dissolution medium of same quantity. Absorbance of these solutions was measured at 246 nm using a UV spectrophotometer.

3.8.7 Drug Release Kinetics

In vitro drug release can be explained through various pharmacokinetic models to describe the drug release kinetics. Five types of models have come into existence for the study.

Zero order model: The models explain that the rate of drug release is independent of the concentration.

First order model: The model explains the rate of drug release with dependence on concentration.

Higuchi model: The model explains the release of drug based on the fickian diffusion as a square root of time dependent process from the swellable insoluble matrix.

Korsmeyer-Peppas model: The model explains the drug release from a polymeric system and the type of release mechanism can be studied.

Hixon-Crowell cubic root law model: The model explains the release of drug from the systems by erosion or dissolution resulting in a change in surface area of particles.

3.8.8 Stability study

Prazosin HCl sustained release tablets (optimized batch) was kept for one month and the stability of the tablets monitored up to 1 month at accelerated stability conditions (40 ºC temperature and 75 ± 5% RH). Samples will be removed and characterized by appearance, drug content and in-vitro drug release study.

IV. RESULTS AND DISCUSSION

4.1 Prazosin HCl Characterization

4.1.1 Description

White to off white crystalline powder.

4.1.2 Solubility

Freely soluble in water, 0.1N HCl and pH 6.8 Phosphate buffer.

Table 6 Result of Preformulation study of Prazosin HCl

Drug	Angle of Repose (ϕ)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner's Ratio
Prazosin HCl	27.34	0.375	0.516	27.32	1.376

4.1.3 Melting Point

Melting point of the drug Prazosin HCl measured by capillary melting method and found 279 °C which gives the identity and purity of the drug.

From the Results of Preformulation studies of the Prazosin HCl, It was concluded that Prazosin HCl has poor flow property and compressibility. So, to improve the flow and compressibility, it was beneficial to use the directly compressible grade components in the formulation of tablet.

4.2 Drug Excipient Compatibility Study

The Results of compatibility study were given in below figure. There is no any change observed in initial and physical mixture sample.

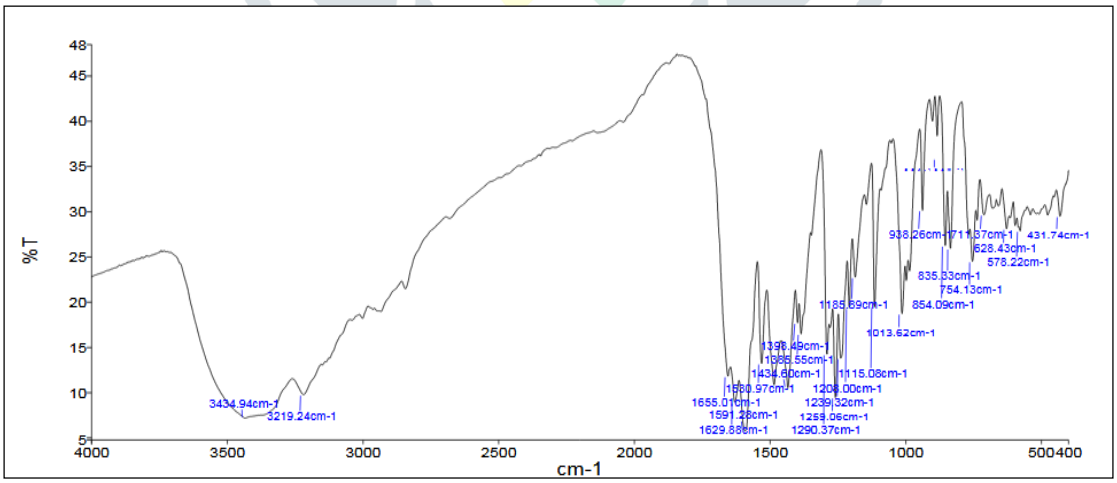

Figure 1 FTIR Spectra of Pure Drug Prazosin Hydrochloride

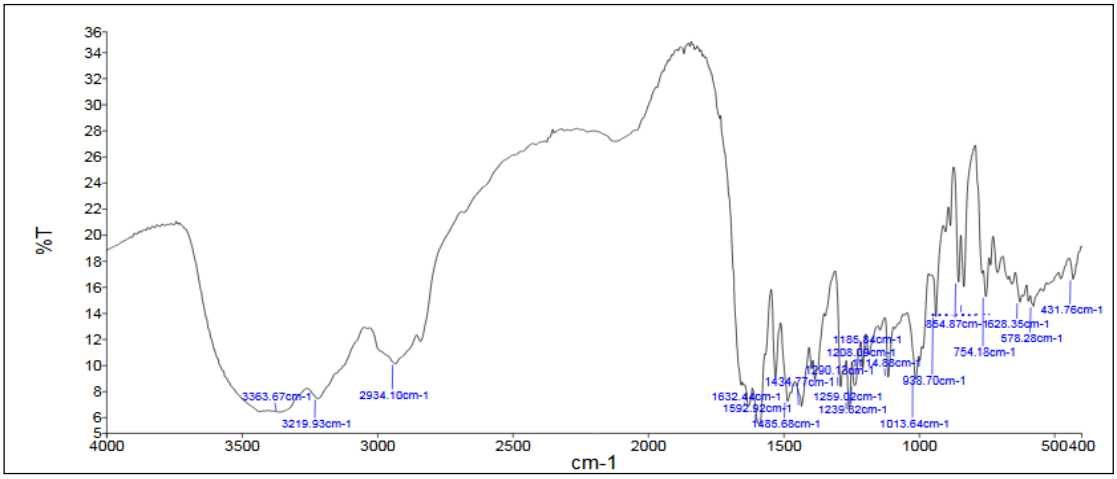

Figure 2 FTIR Spectra of Physical Mixture

From the above FTIR Study, it was concluded that there was no significant Drug- Excipient interaction was observed. So we can conclude that drug and other excipients are compatible which each other.

4.3 Calibration curve of Prazosin Hydrochloride

The calibration curve of Prazosin Hydrochloride was found to over a concentration range 1-10 µg/ml. (R^2=0.9998) the data for calibration curve is given below.

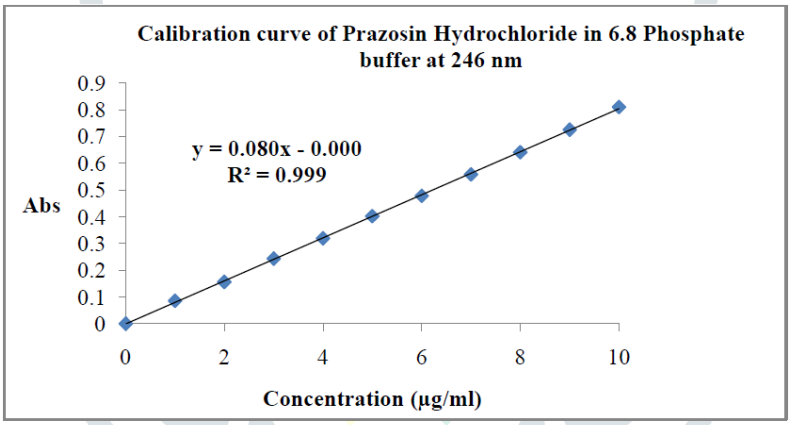

Figure 3 Calibration curve of Prazosin Hydrochloride in 6.8 Phosphate buffer at 246 nm

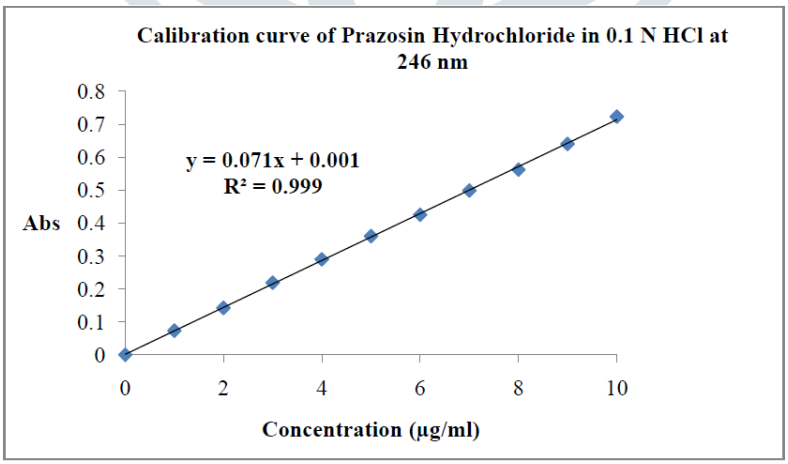

Figure 4 Calibration curve of Prazosin Hydrochloride in 0.1 N HCl at 246 nm

4.4 Analysis of factorial batches

4.4.1 Precompression and Post compression parameters

The results of Precompression and Post compression parameters of factorial batches P1-P9 given below:

Table 7 Pre compression and Post compression parameters of batches P1 to P9

Batch	Bulk density (gm/ml)	Tapped Density (gm/ml)	Carr's Index (%)	Hausner Ratio	Angle of Repose (ϕ)	Weight Variation (mg) (n=10)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	% Friability	% Drug Content (n=10)
P1	0.43±0.01	0.49±0.02	12.24±0.05	1.14±0.05	33.50±0.07	199 ± 0.58	3.50 ± 0.16	6.5 ± 1.20	0.55	99.5 ± 0.65
P2	0.42±0.02	0.47±0.03	10.64±0.06	1.11±0.04	34.12±0.03	200 ± 0.68	3.45 ± 0.34	7.0 ± 0.89	0.60	98.3 ± 0.60
P3	0.40±0.01	0.51±0.04	21.57±0.04	1.28±0.07	42.33±0.05	198 ± 0.98	3.49 ± 0.47	6.8 ± 0.55	0.62	99.4 ± 0.87
P4	0.41±0.03	0.50±0.02	18.00±0.09	1.22±0.03	39.41±0.04	197 ± 0.47	3.53 ± 0.31	7.2 ± 0.89	0.40	97.9 ± 0.36
P5	0.43±0.01	0.49±0.01	12.24±0.03	1.14±0.05	33.92±0.05	200 ± 0.23	3.64 ± 0.18	6.9 ± 1.20	0.45	98.6 ± 0.47
P6	0.42±0.02	0.49±0.03	14.29±0.02	1.17±0.03	38.63±0.03	197 ± 0.34	3.35 ± 0.37	6.4 ± 0.98	0.49	99.2 ± 0.35
P7	0.40±0.01	0.53±0.01	24.53±0.07	1.33±0.07	41.52±0.07	200 ± 0.65	3.86 ± 0.34	7.1 ± 1.20	0.52	98.7 ± 0.79
P8	0.41±0.03	0.48±0.03	14.58±0.05	1.17±0.02	37.61±0.06	201 ± 0.78	3.36 ± 0.15	6.4 ± 0.98	0.35	97.3 ± 0.15
P9	0.43±0.02	0.50±0.01	14.00±0.03	1.16±0.02	38.43±0.09	202 ± 0.85	3.45 ± 0.25	6.9 ± 0.98	0.47	98.1 ± 0.50

Factorial batches P1-P9 evaluated for Precompression parameters before compression. Most of the batches have a good to passable flow in nature. Additionally the flow of all batches blend was enough for compression operation.

Based on above table of post compression parameters, it seems that the weight variation in all batches found well within acceptable limit. Further the thickness found within range as per desired parameters. Hardness was good enough to give a proper mechanical strength to tablets and hence the friability was observed below 1 %.

4.4.2 Drug release study

Drug release study of factorial batches P1-P9 were performed and the data of drug release shown below.

Drug release study shows the impact of HPMC K4M in formulation. Higher the amount of HPMC retards the drug release and vice versa. It also seems that the amount of PVP K-30 which was used as dry binder also impact on drug release. The actual impacts of both factors analyzed by using factorial design regression study. From the results of drug release study, P7 batch which contains 45 mg HPMC K4M and 10 mg PVP K-30 shows good drug release up to 12 hours which also match the profile with theoretical drug release profile.

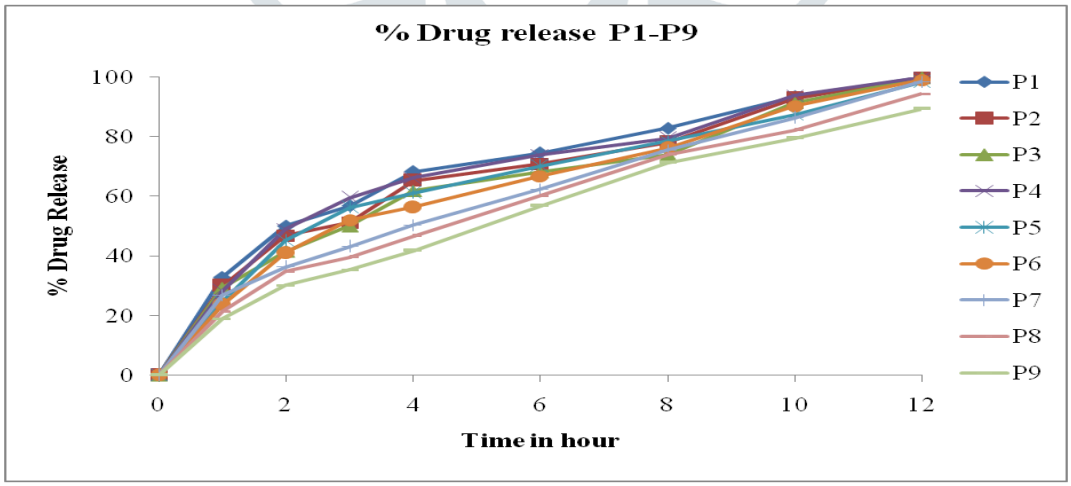

Figure 5 Drug release study of factorial batches P1 to P9

4.4.3 Drug release kinetic study

To establish the order and mechanism of drug release, dissolution data of the optimized batch (P7) were fitted to different kinetic models, namely, Zero order model, first order model, Hixon crowell, Higuchi model and Korsmeyer peppas model.

Table 8 Drug release kinetic study of P7 batch

Formulation Code	R^2				
	Zero Order	First Order	Higuchi model	Korsmeyer Peppas model	Hixon crowell
P7	**0.998**	0.975	0.994	0.997	0.925

From the results of data fitting to various models, it was found that the optimized batch P7 showed zero order drug release.

4.5 Regression Analysis of Factorial Design

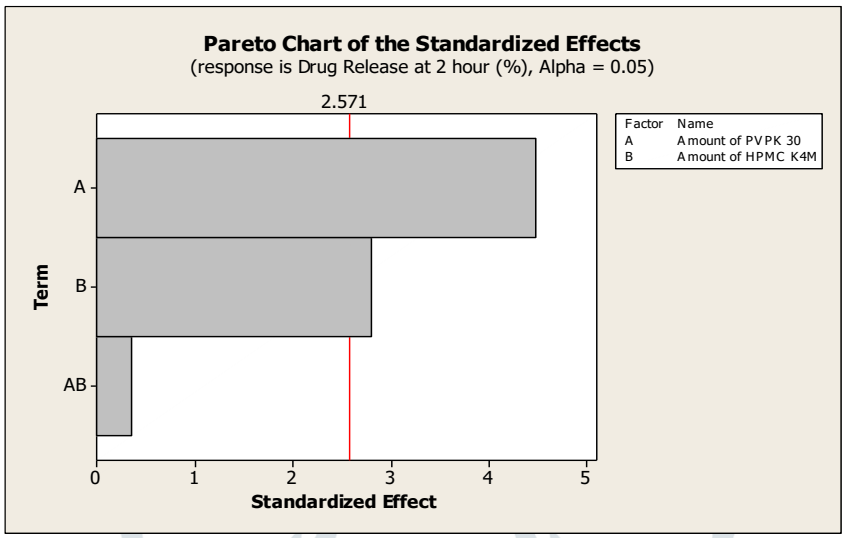

Figure 6 Pareto Chart for Drug release at 2 hours

Based on Pareto Chart, it shows that PVP K-30 having a more effect as compare to HPMC K4M on % Drug release at 2 hours.

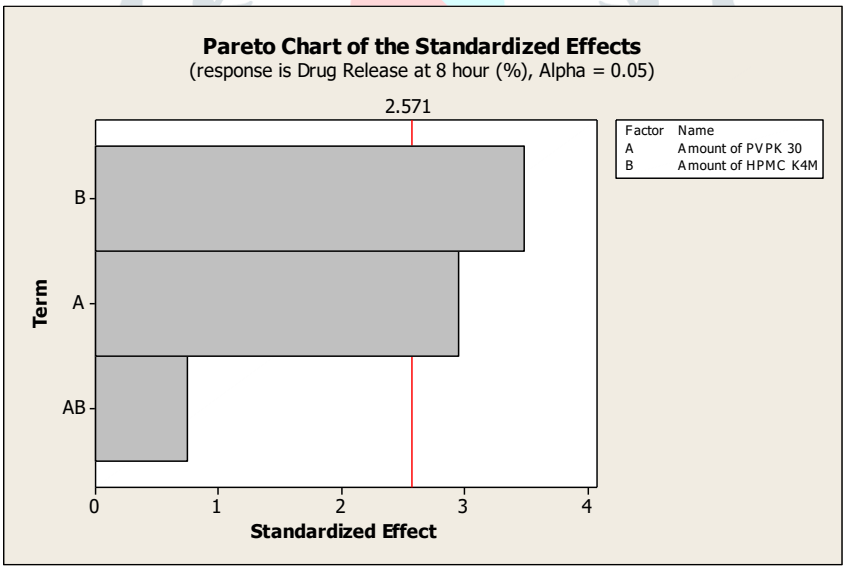

Figure 7 Pareto Chart for Drug release at 8 hours

Based on Pareto Chart, it shows that HPMC K4M having a more effect as compare to PVP K-30 on % Drug release at 8 hours.

Optimized Batch

Based on Factorial Design data, final optimized batch selected from the Contour plot to achieve desired drug release. Complete analysis of this batch done and recorded below.

Table 9 Formulation table for optimized batch P12

Ingredients (mg)	P12
Prazosin HCl	3.8
Lactose (DCL 11)	90
Microcrystalline Cellulose (Avicel pH 102)	38

PVP K-30	9.8
HPMC K4M	54.4
Colloidal silicon dioxide	2.0
Magnesium Stearate	2.0
Total	**200.0**

Table 10 Results of Optimized batch P12

Parameter	**Results**	
Appearance	White colored round shape tablet plain on both side	
Average weight (mg)	200±0.8	
Thickness (mm)	3.75 ± 0.6	
Hardness (kg/cm^2)	6.9 ± 0.9	
Friability (%)	0.45	
Drug content (%)	99.3 ± 0.8	
% Drug Release	**Time (hour)**	**%Drug Release**
	0	0
	1	25.7 ± 0.4
	2	33.1 ± 1.7
	3	40.1 ± 1.1
	4	47.0 ± 2.1
	6	60.8 ± 0.4
	8	72.9 ± 0.9
	10	86.8 ± 1.2
	12	99.5± 1.9

4.6 Stability Study

Stability study on optimized batch P12 carried out and the results were recorded in below table. Formulation found stable and no any critical observation seen during stability.

Table 11 Results of Stability study

Physical parameter	**Initial**	**1 Month**
Appearance	White colored, round tablet	White colored, round tablet
Average Weight (mg)	200 ± 0.8	199 ± 1.5
Thickness (mm)	3.75 ± 0.6	3.75 ± 0.9
Hardness (kg/cm^2)	6.9 ± 0.9	7.0 ± 0.6
Friability (%)	0.45	0.49
% Drug Content	99.3 ± 0.8	99.1 ± 0.5
% Drug release after 12 hours	99.5 ± 1.9	98.9 ± 2.6

4.7 Conclusion

Factorial batch P1-P9 prepared by using direct compression method. Physical and chemical evaluation was done for all batches. Drug release study for P1-P9 batch shows the significant impact of both factors. PVP K-30 and HPMC K4M significantly impact on Drug release and hence the model found significant. Finally the optimized batch P12 taken based on Contour plot and evaluation done. Batch P12 load for stability for 1 month and found stable. Hence the batch P12 was optimized batch.

REFERENCES

[1] Aulton ME. Pharmaceutics. The Science of Dosage Form Design. 2nd Edn Churchill Livingstone, London: Harcourt Publ Limited; 2005. pp. 296-298.
[2] Pundir S, Badola A, Sharma D. "Sustained release matrix technology and recent advance in matrix drug delivery system: A review." *Int J Drug Res Tech*, **2013,** 3, 12-20.
[3] Brahmankar DM, JaiswalSB. Biopharmaceutics and Pharmacokinetics: Pharmacokinetics. 2nd Edn. Delhi: Vallabh Prakashan; 2009. pp. 399-401.
[4] Chandra S, Jaikumar R, Harish K, Suresh R, Sangeetha S, Tamilselvan A, "Formulation and Evaluation of Rosuvastatin Sustained Release Matrix Tablet", *Int J Adv Pharm Sci*, **2018**,01-38.
[5] Prasanna K, Vaishnavi G, Divya K, Lakshmi U, "An Overview on Preformulation Studies", *IAJPS*, **2015**, 2 (10), 1399-1407.

[6] Srinivasa R, Ratnam B, "Formulation and Optimization of Sustained Release Tablets of Rosuvastatin Using HPMC K4M, HPMC K100M and Carrageenan", *Int J Chem Tech Res*, **2018**, 11(05), 376-386.