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Research Article

Polyethylene matrix tablet Metoprolol

Design and Optimization of a Polyethylene Oxide-Based Matrix Tablet of Metoprolol Succinate Using Design Expert Software

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Abstract: Hypertension is a common lifestyle disorder, the prevalence of which advances with age. In the case of antihypertensive therapy, patient compliance is hampered, especially in geriatric patients, if the dose is b.i.d or more, as it is difficult for the patient to remember and take medicine at a scheduled time. The present study involves the fabrication of a sustained-release matrix-designed tablet using a combination of polyethylene oxide (PEO) polymers and metoprolol succinate as the model drug. The tablet is optimized and evaluated for its *in-vitro* release using the Design expert software. Polyethylene oxide is a non-ionic hydrophilic polymer which is directly compressible. Polyox WSR 301 and 303 grades have been used in the study to get the desired sustained release of 12 h. The formulations were analysed for various pre-compression and post-compression characteristics. The polymers Polyox WSR 301 and 303 influence drug release are measured using a 3^2 factorial design where the concentration of drug released at various time points has been analysed statistically as a response. Response surface plots demonstrate and depict the effect of the variables, thus aiding in optimization. All the formulated batches exhibited acceptable pre and post-compression characteristics. The optimized formulation M05 showed a sustained drug release up to a 12 h period. Thus polyethylene oxide can be used as an excellent sustained-release matrix polymer due to its ability to gel and prolong drug release from a matrix. Due to their molecular weight, a combination of two grades of polyethylene oxide helps reinforce the drug release.

Keywords: Metoprolol succinate, PEO WSR 301, PEO WSR 303, sustained release, design expert

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1. INTRODUCTION

Hypertension is a common lifestyle disorder, the prevalence of which advances with age.[1] Mortality rate associated with stroke and heart disease is enhanced with elevated blood pressure.[2] Non-adherence to antihypertensive medication is the major cause of morbidity associated with a cardiovascular disorder.[3] Patient compliance in the case of antihypertensive therapy is hampered, especially in geriatric patients if the dose is b.i.d or more, as it is difficult for the patient to remember and take medicine at scheduled times.[4] Present study aims to design a sustained-release matrix tablet of metoprolol succinate drug as the model drug widely used and prescribed for hypertension. Metoprolol has been included to combat hypertension since 1975. It is a selective β 1 adrenergic antagonist and is a time-tested drug to reduce cardiovascular complications arising from hypertension.[5,6] As the half-life of the drug is 4-6 h. Therefore, it is a suitable candidate for extended-release formulation to extend drug action and improve patient compliance.[7] Extended-release formulation has been efficacious in increasing the plasma concentration of drug to achieve sustained therapeutic level, thus reducing concentration-related adverse effects and enhancing patient compliance due to the once-daily schedule.[8,9] Researchers have discovered different ways to design and develop sustained and controlled release of active molecules in the body. The design and development of new polymers, drug and dosage form optimization and novel matrix have facilitated this.[10,11] Hydrophilic polymer matrices are a popular and widely accepted method for developing sustained-release formulations.[12] Hydrophilic matrix oral dosage form is one of the cost-effective and economical methods to design sustained-release dosage forms.[13] Polyethylene oxide (PEO) is an accepted hydrophilic polymer extensively used to formulate sustained-release tablets.[14] PEO polymers have excellent swelling properties, solubility, non-irritant and non-toxic nature. In addition, it hydrates and has the excellent gelling ability, thus making it suitable for oral sustained release matrix systems. [15,16] In the current study, the effect of various grades of PEO, namely Polyethylene oxide Polyox WSR 301 and Polyethylene oxide Polyox WSR 303 were used as independent variables and their combination and its effect on the sustained release of the drug was studied using the Design expert software, trial version 13.

2. MATERIALS AND METHODS

Metoprolol succinate as a gift sample by Dr Reddys Ltd. Hyderabad. Polyethylene oxide Polyox WSR 301 and Polyethylene oxide Polyox WSR 303 was provided as gift sample by Colorcon Asia Pvt. Ltd. Goa.

2.1 Formulation Using 3^2 Factorial Design

The effect of the concentration of Polyox WSR 303 and Polyox WSR 301 in the matrix tablet was analysed using a 3^2-full factorial design containing two factors at three levels. The responses analysed were the percentage of drug released at 2, 6 and 10 h as dependent variables. Table 1 depicts the experimental design set by the design expert software trial version 13.[17]

Table 1: Experimental design as per design expert

Coded values	Actual value	
	X_1	X_2
	The concentration of Polyox WSR 303 per tablet (mg)	The concentration of Polyox WSR 301 per tablet (mg)
-1	25	0
0	50	25
+1	75	50

The matrix tablets containing metoprolol succinate and PEO polymers were prepared by a direct compression method. Nine batches with varying concentrations of PEO as per table 2 were compressed by mixing the drug with Polyox WSR 303 and Polyox WSR 301 in ratios as obtained from the experimental design using design expert software using a laboratory scale blender for 10 min after which microcrystalline cellulose was blended into for the next 10 mins. Finally, magnesium stearate was added and blended, and tablets were compressed using the Karnavati Rimek tablet compression machine with a weight of 210 mg for each tablet. Precompression analysis of all blends was carried out.[18,19]

Table 2: Formulations of PEO Matrix Blends of Metoprolol Succinate

Ingredients (mg)	M1	M2	M3	M4	M5	M6	M7	M8	M9
Metoprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Polyox WSR 303	25	50	75	25	50	75	25	50	75
Polyox WSR 301	0	0	0	25	25	25	50	50	50
Microcrystalline cellulose (MCC pH 102)	136	111	86	111	86	61	86	61	36
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total tablet weight **(mg)**	**210**	**210**	**210**	**210**	**210**	**210**	**210**	**210**	**210**

Table 2 illustrates the blends prepared using a combination of Polyox polymer grades as per the experimental design obtained from the design expert.

2.2 Evaluation

The sustained-release tablet was characterized for various tests. The chemical integrity of the drug and incompatibilities were ascertained by DSC and FTIR studies.[20,21] Pharmacopeia procedures were employed to test the formulations for hardness, weight variation, hardness, drug content and friability.

2.2.1 *In-vitro* drug release

The dissolution profile was estimated using a USP type II paddle apparatus with 900 mL phosphate buffer pH 7.2 at 37±0.5°C and rpm 50 for a 12 h period. Sampling was carried out every two hours for a total 12 h period and analyzed on a UV-Visible spectrophotometer at 222 nm.[22] The outcome of the independent variables (concentration of Polyox polymers) on the response, that is, drug release Q2 (at 2 h), Q6 (at 6 h) and Q10 (10 h), were depicted through contour plots and response surface plots. Statistical analysis and stability studies were carried out on the optimized batch.[23,24]

2.2.2 *Stability studies*

A stability study per ICH guidelines was carried out on the optimized batch of formulated matrix tablets using a stability chamber (Patel Scientific Instruments) for three months. In addition, further physical attributes of the tablets, content uniformity and in vitro drug release profiles were evaluated.

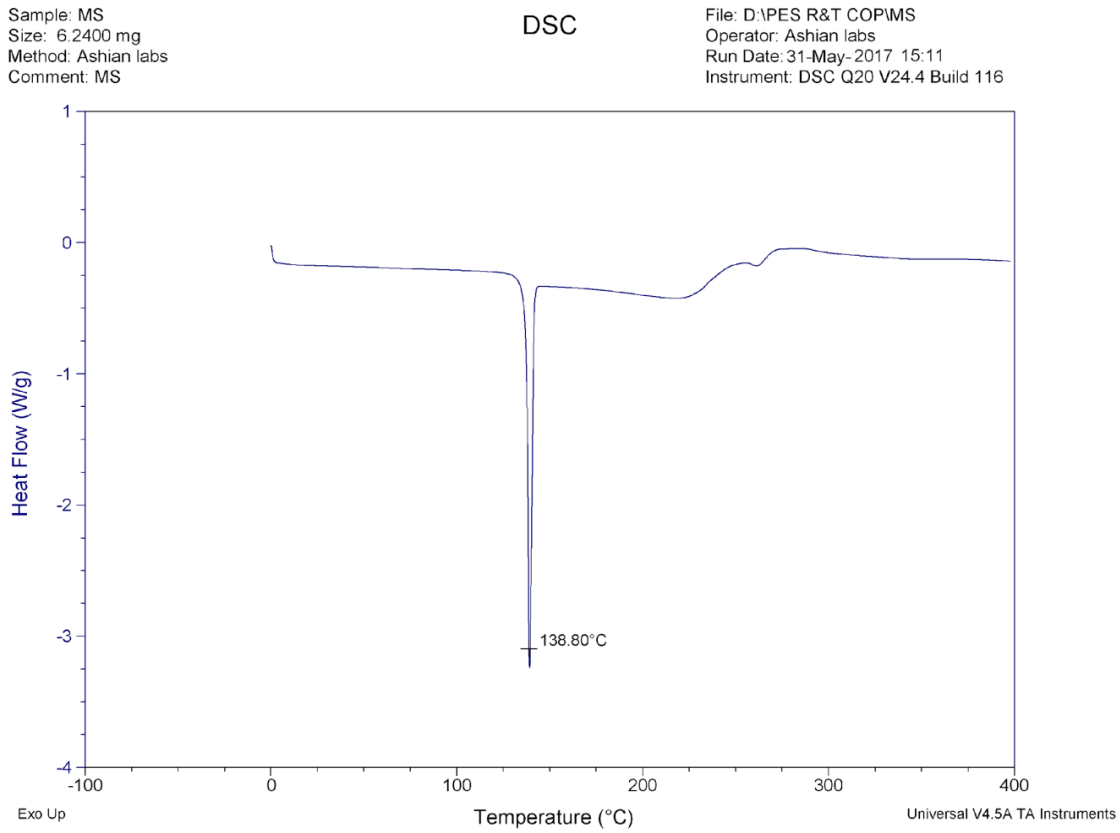
3 RESULTS AND DISCUSSION

The pre-compression and post-compression characteristics indicated ideal formulation characteristics. All the parameters such as hardness, friability, weight variation, friability etc. met the pharmacopoeia standards.

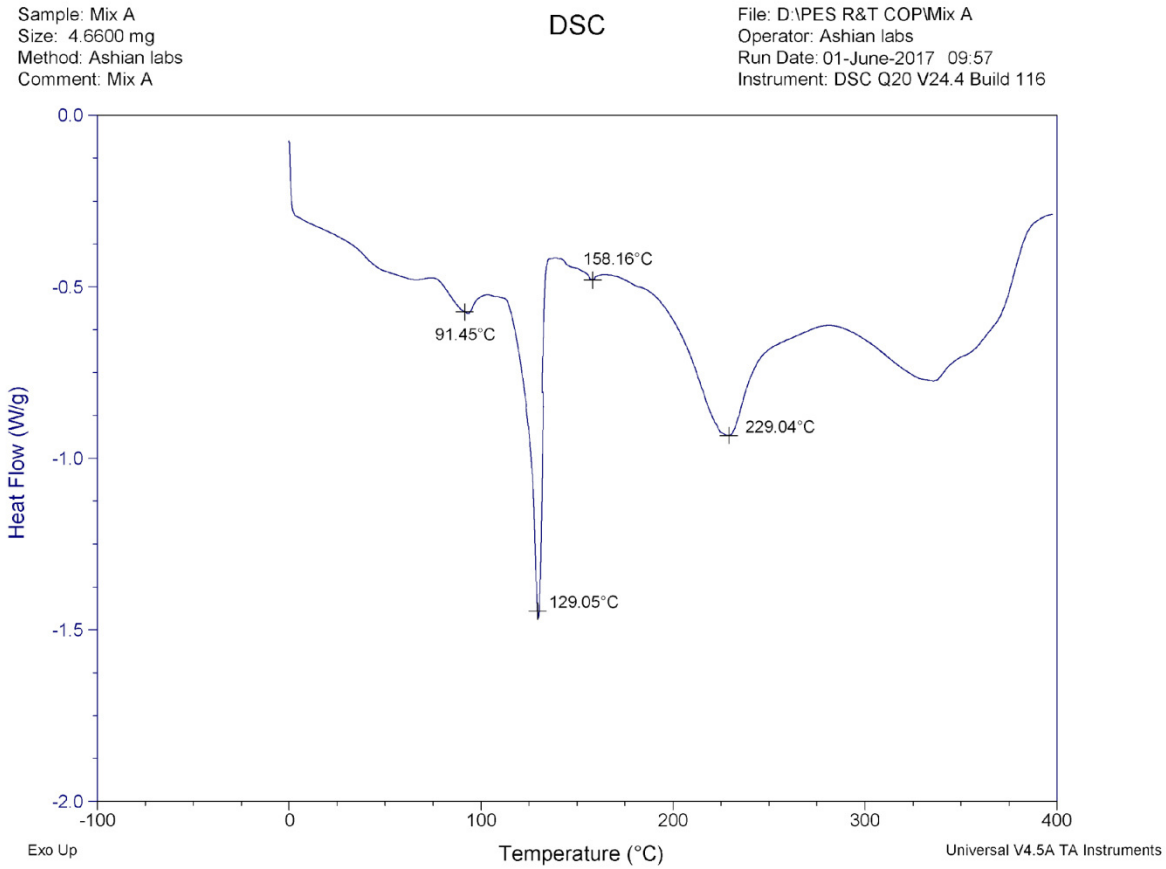
3.1 *Drug Excipient Compatibility*

3.1.1 *DSC studies*

The thermograph of the pure drug showed the melting point to be 138 °C, as reported in the literature. On the other hand, the thermograph of drug and excipient mixtures does not reveal a significant change in the melting points, thus ruling out incompatibilities as depicted in figure 1.



DSC thermogram of Metoprolol succinate pure drug

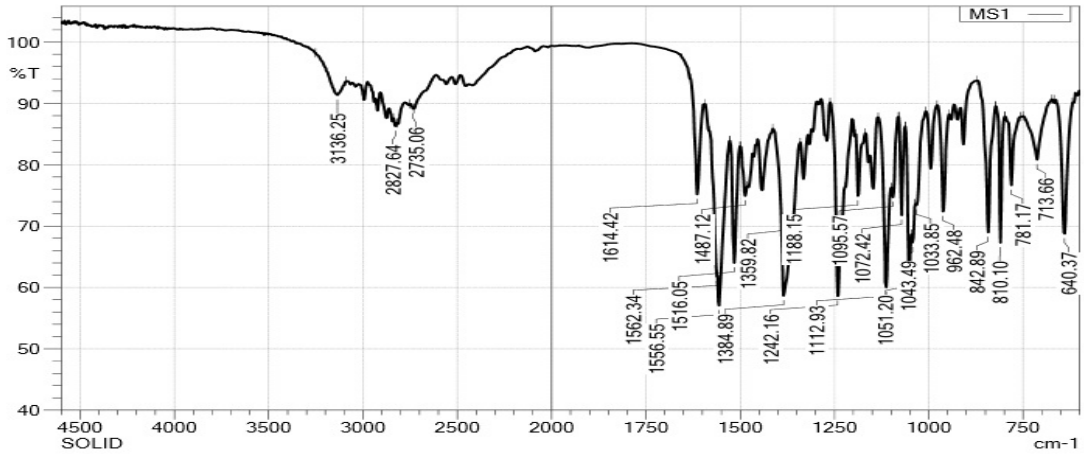


DSC thermogram of Metoprolol succinate with excipients

Fig 1: Compatibility studies of drugs and excipients using DSC

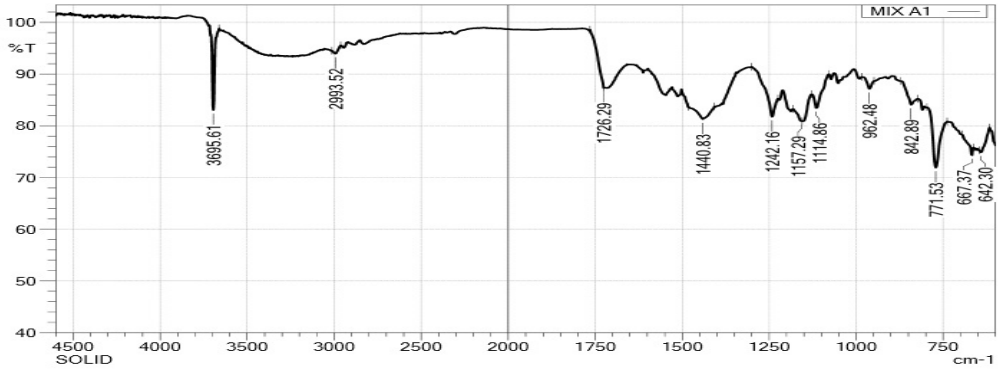
3.1.2 FTIR studies

IR spectra of pure drug Metoprolol succinate show characteristic peaks of NH stretch at 3136.25cm^{-1}, aliphatic C-H stretch at 2827.64 cm^{-1} and C-O stretch at 1051.20cm^{-1} as depicted in Figure 2. The characteristic peaks of the mixture of metoprolol with excipients are also observed in the IR spectra. Therefore, per Figure 2, there is no interaction between the drug and excipients.



	Item	Value
2	Sample name	MS
3	Sample ID	SOLID
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	16
10	Resolution	4 cm-1

FTIR of pure drug Metoprolol succinate



	Item	Value
2	Sample name	MIX A
3	Sample ID	SOLID
4	Option	
5	Intensity Mode	%Transmittance
6	Apodization	Happ-Genzel
9	No. of Scans	16
10	Resolution	4 cm-1

FTIR of drug Metoprolol succinate + excipients

Fig 2: Drug excipient compatibility studies by FTIR

3.2 *In-Vitro* Drug Release

The drug release from the nine batches is given in figure 3. All the factorial batches showed sustained drug release between 8 -12 hours depending on the polyox concentration. As observed from the release profile, the formulation comprising only Polyox WSR 303 (M01) could sustain the release for up to 8 hours. It also exhibited a high release of 35% at 2 hours. This might be attributed to the high swellability of the hydrophilic polymer. The batches with a combination of two grades of polyox WSR 303 and 301 showed better ability to control the drug release, wherein formulation M05 could efficiently prolong the release up to 12 hours. The difference in polymer molecular weights helps the gel matrix regulate the drug release for a prolonged time. As described by Maggi *et al*., higher molecular weight PEO swells to a greater extent and tends to form, upon hydration, a stronger gel, thus regulating drug release. [14]

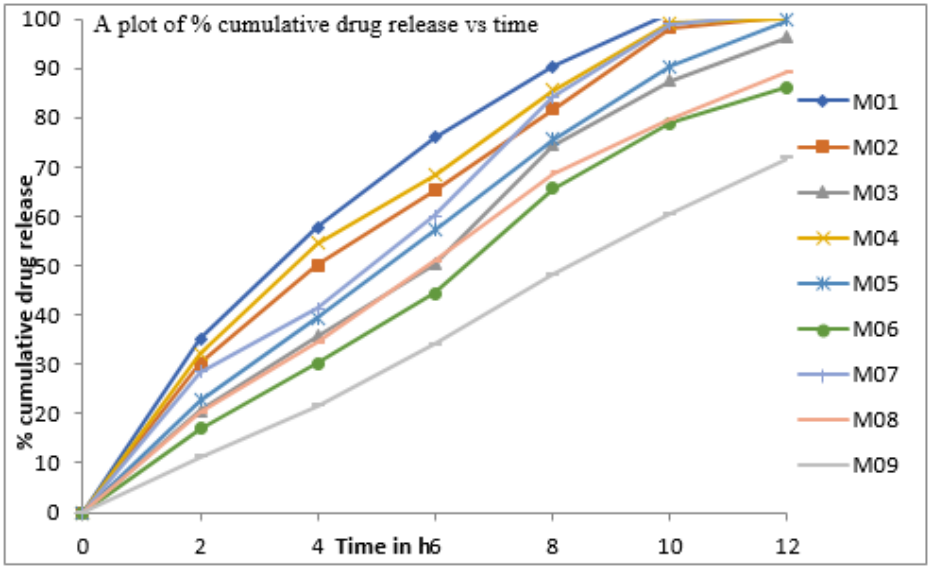


Fig 3: Cumulative drug release profiles of metoprolol succinate sustained-release batches

3.2.1 *Diffusion of drug from hydrogel matrices*

At 2 h (Q2), as described in the response surface plot in figure 4, the amount of drug released is controlled as the concentration of Polyox polymers increases. As the concentration of Polyox WSR 303 increases from 25 mg to 75 mg per tablet, the drug released at 2 hours is controlled. A similar phenomenon was observed with Polyox WSR 301 in retarding the drug release. The formulation with the single polymer of Polyox releases the drug faster at 2 hours. Polyox WSR 303 exerts a more significant effect due to its higher concentration and molecular weight, as described by Shojaee *et* al. [15]. At 6 and 10 hours, a similar phenomenon was observed. As the concentration of the Polyox polymers increases, the drug release rate is controlled, as depicted in figures 5 and 6. Again, the combination of the two grades exhibited a more efficient effect in controlling the release.

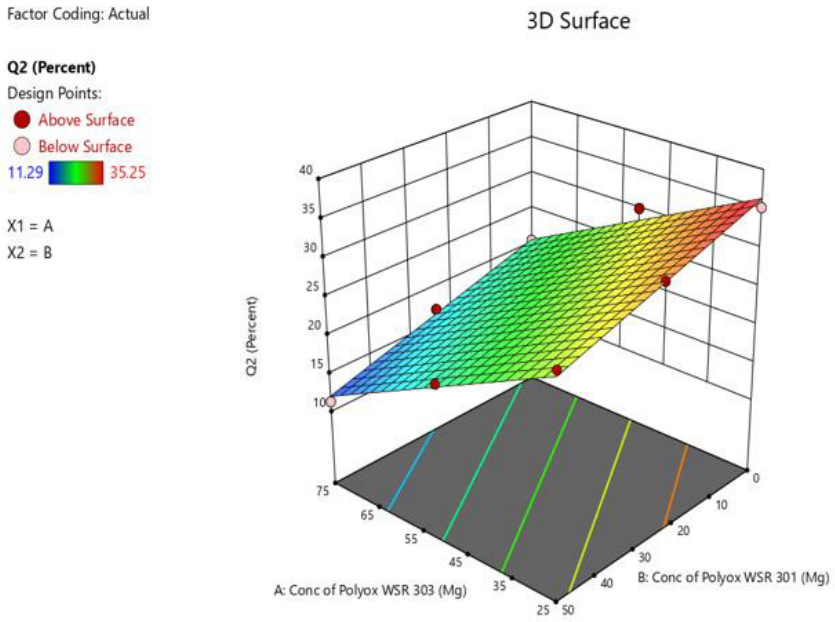


Fig 4: Response surface plot for drug release at 2 h (Q2)

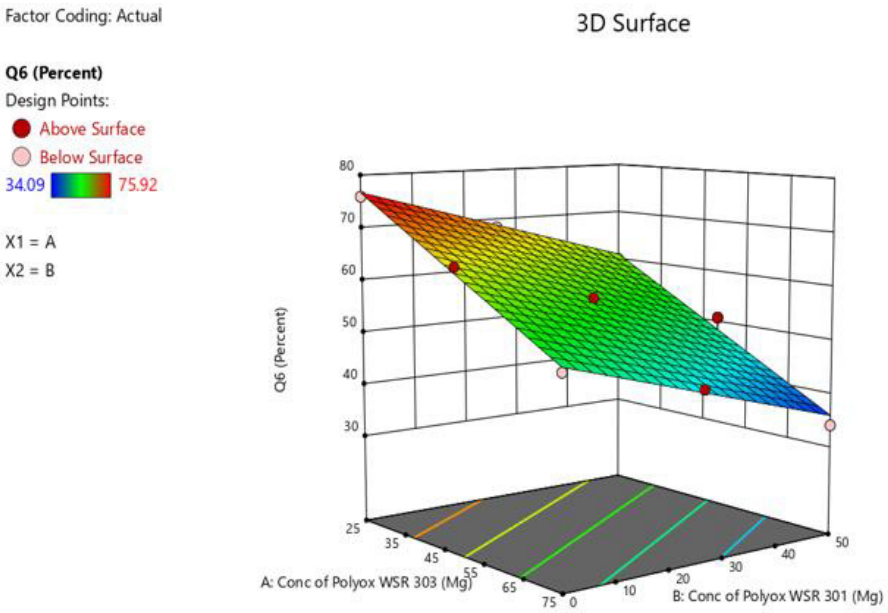


Fig 5: Response surface plot for drug release at 6 h (Q6)

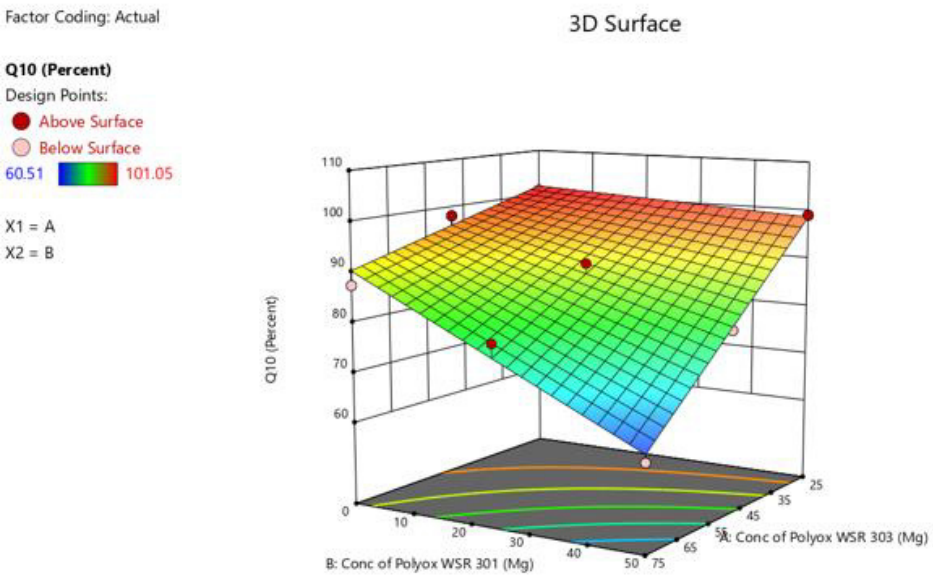


Fig 6: Response surface plot for drug release at 10 h (Q10)

The ANOVA result for the model is shown in table 3. It can be concluded that Polyox WSR 303 (X1) has a significant effect on all responses Q2, Q6 and Q10, reinforcing that it controls the drug release up to 12 h. At two hours, however, the coefficient has a comparatively lesser value as a completely swollen gel matrix still needs to be formed. This is also depicted by the swelling index measured and reported in figure 7. It was also seen that the second grade of Polyox WSR 301 forms a cohesive matrix with Polyox WSR 303. This can be ascertained because the batch devoid of Polyox WSR 301 released the drug much faster than the batches having a combination. This could be attributed and ascertained by the fact that Metoprolol succinate, a highly soluble drug, oozes out from the polymer matric faster. A combination of polymers helps build a synergistic gel matrix, thereby controlling the release rate more efficiently, which justifies using the combination of polymers. Formulation M05, which contains 50 mg of Polyox WSR 303 and 25 mg of Polyox WSR 301, was found to match the solutions obtained from the software and was considered the optimized batch to obtain a 12 h sustained release. A good degree of correlation between experimental and predicted responses was observed.

Table 3: ANOVA influence of formulation variables

Regression model	R^2	Adjusted R^2	Predicted R^2	Model P value
Q2= +24.21-7.85X1 -4.32 X2	0.9810	0.9789	0.9661	< 0.0001
Q6 = +56.31 -12.58 X1 -7.77 X2	0.9892	0.9856	0.9737	< 0.0001
Q10 = + 88.27 - 12.07X1 -7.90 X2 -6.22 X1*X2	0.9792	0.9667	0.8885	0.0001

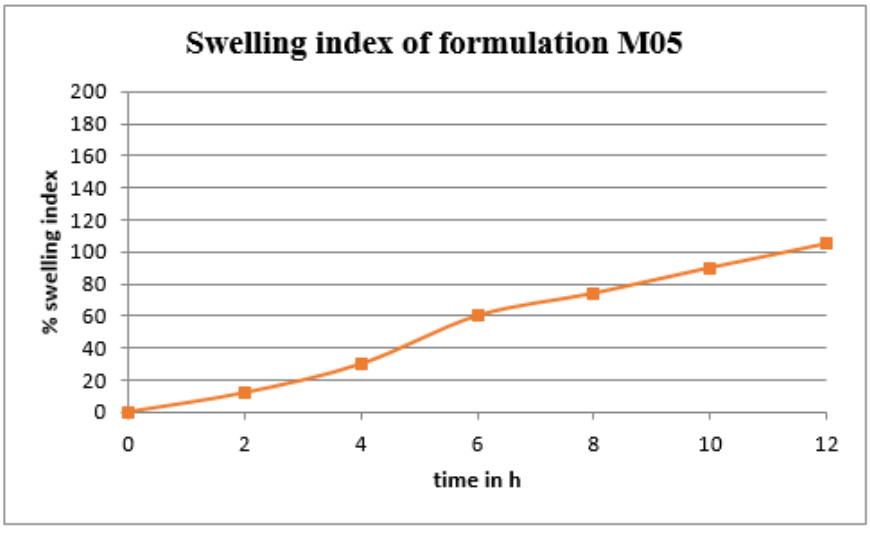


Fig 7: Swelling index of formulation M05

As depicted in figure 8, it was observed that the swelling index increases at various time points as the concentration of the polyethylene oxide polymer increases. The combination of polymers exhibits a higher swelling index, thus envisaging the existence of a cohesive gel matrix. As described by Apicella *et al*., wherein drug release using different molecular weights of PEO was investigated, it interpreted that drug release from the high molecular weight poly(ethylene oxide) is principally

related to the material swelling rather than polymer dissolution, and the drug release from the low molecular weight poly (ethylene oxide) is strictly related to the polymer dissolution mechanism, that helps achieve stationary conditions, in which the rate of swelling equals the rate of dissolution hence ensures a constant release rate. [16]

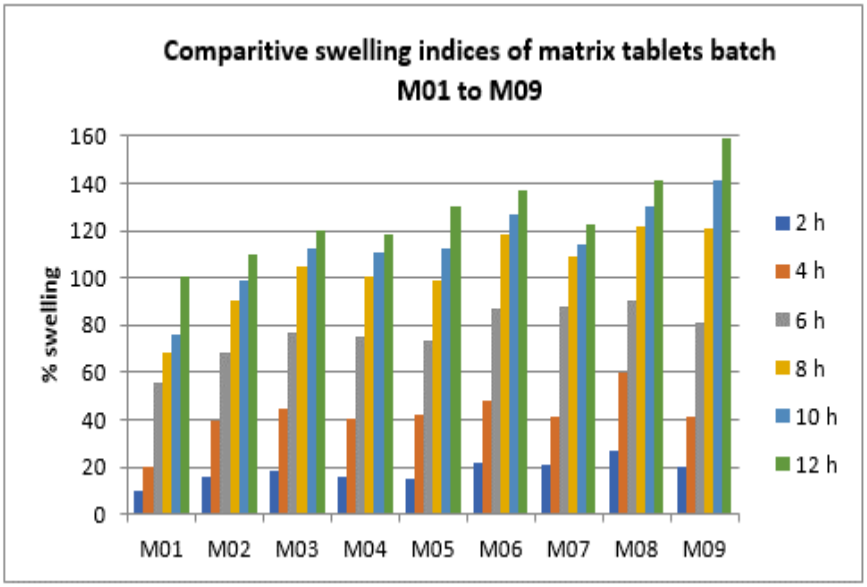


Fig 8: Comparative swelling index of formulations M01 to M09

The *in vitro* release data analyzed with kinetic equations describe that *in vitro* release profile[25] was expressed best by the Higuchi equation as in Table 4, which indicates drug release by diffusion from the matrix and which holds for BCS class I drugs like metoprolol that is highly water soluble. Further, the 'n' value in the Korsmeyers Peppas plot indicates drug release by diffusion and erosion, as depicted in figure 9 and as described by Chime *et al*. [25]

Table 4: Correlation coefficients of different pharmacokinetic models for release

Formulation	Zero-order r^2	First order r^2	Higuchi r^2	Peppas (n)	Hixon crowel r^2
M01	0.8424	0.7591	0.8476	0.7569	0.8973
M02	0.8975	0.8671	0.9974	0.7436	0.8891
M03	0.9351	0.8871	0.9921	0.7546	0.9621
M04	0.6217	0.6497	0.8457	0.7331	0.7757
M05	0.9457	0.8639	0.9979	0.7656	0.8113
M06	0.9595	0.9691	0.9908	0.7546	0.9621
M07	0.8279	0.9142	0.9625	0.766	0.9379
M08	0.9483	0.8374	0.9924	0.7848	0.8128
M09	0.9814	0.9266	0.9617	0.8069	0.9617

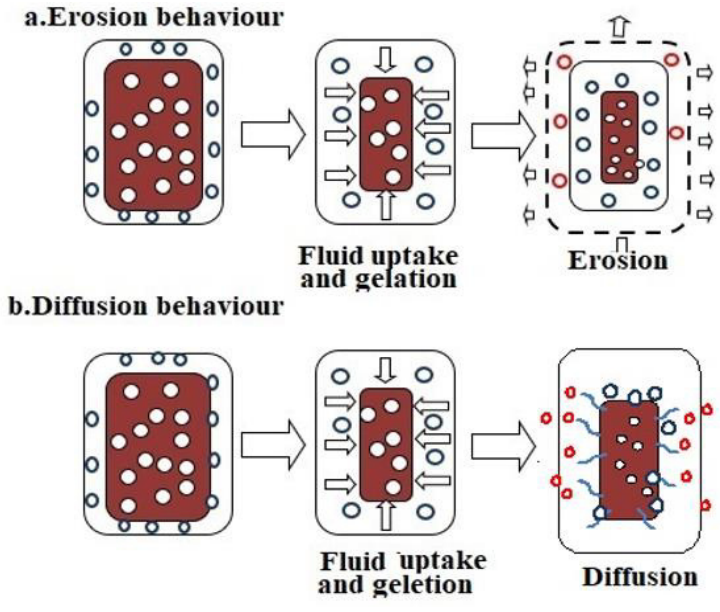


Fig 9: Drug release mechanism from matrix formulations

The formulations on evaluation post-stability studies indicate no change in characteristics, thus affirming the chemical integrity of the drug and the formulation.

4 CONCLUSION

In the present research, a sustained-release tablet of metoprolol succinate using a combination of polyethylene oxide polymers Polyox WSR 303 and Polyox WSR 301 was developed and optimized using the design expert software, which predicted the influence of both polymers on drug release was determined. The optimized formulation M05 showed a sustained drug release up to a 12 h period. Polyox polymers, due to various advantages and the ability to control the drug release by forming the gel matrix, can be used as an alternative to other polymers like HPMC in controlling drug release.

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5 ACKNOWLEDGEMENTS

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6. AUTHORS CONTRIBUTION STATEMENT

Dr Pearl Dighe conceptualized the matrix tablets' design, formulation and methodology. Dr Mangirish Deshpande helped analyze the results from design expert software and prepared the manuscript.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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