RESEARCH ARTICLE

Development and Optimization of Eperisone Hydrochloride Microcapsule

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Received: 15th October, 2023; Revised: 20th December, 2023; Accepted: 10th February, 2024; Available Online: 25th March, 2024

ABSTRACT

The main objective of the work is to develop the microcapsule of eperisone hydrochloride. In the investigation, a 2^3-factorial design were was employed for the optimization process and to investigate the effect of Eudragit® RS100 concentration in the coating solution (X1), the speed of rotation (X2) and the concentration of plasticizer (PEG 400) (X3) on the release rate of the drug from the microcapsules. The extent of coating (Y1), and the percentage of drug released at 1 (Y2), 6 (Y3) and 12 hours (Y4) were selected as dependent variables. Optimized microcapsules of eperisone hydrochloride follow the zero-order kinetics that a promising controlled release of the highly water soluble drug and was successfully designed for further formulation.

Keywords: Eperisone HCl, Ion exchange resins, Amberchrom, Factorial design, Optimization.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.1.34

How to cite this article: Sharma V, Singh C, Gupta AK, Yashwant. Development and Optimization of Eperisone Hydrochloride Microcapsule. International Journal of Drug Delivery Technology. 2024;14(1):230-235.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

The oral pathway has proven to be the most accessible and widely used method of medicament administration. The kind of drug delivery approaches, quality of medicine, ailment being treated, patient, and length of therapy are all considerations to be considered.[1] Matrix tablets, osmotic pumps, microspheres, and microcapsules are all examples of oral controlled drug delivery. Coated granules, pellets or seeds, micro spherules, and spansules are all words used to describe microcapsules.[2,3]

Ion exchange resins are found as cross-linked polymers attached with a water-insoluble functional group.[4] Drug resin complexes are created as a consequence of the drug and resin exchanging process.[5] IER has now been explored mostly in the advancement of NDDS. Because of its (IER) drug holding capabilities and avoidance of dose missing, ion exchanger is utilized for improvement in novel prolonged releasing methods.[6] According to research conducted last few years, ion exchange resin is suited for the delivery of medicament as a taste mask, for DDS through outer surface, DDS *via* nostril route, and for the controlled release of drugs.[7]

Eperisone HCl is classified as a BCS class I medication, which means it may be used as both an antispasmodic and a muscle relaxant.[8] Eperisone HCl is mostly used for the treatment of lower back pain, headache, and cervical spondylosis.[9,10] Eperisone hydrochloride was found a brief half-life ranging from 1.6 to 1.8 hours.[11] Eperisone HCl acts as a vasodilators, enhancing muscle blood flow. The recommended dosage for this medication is to take it three times per day. EpeH is formulated as an extended-release dosage form because it has a short half-life and the dosing frequency is three times a day.[11,12] The purpose of our study are to work toward the development of microcapsules containing a chosen drug for controlled releases (Eperisone hydrochloride) by using a variety of cation exchanger resins

MATERIALS AND METHODS

Eperisone hydrochloride, a model drug, was obtained from the SNA laboratories Ltd. Mumbai Ion-exchange resins (Amberchrom50wx4; 50-100), and Alkind Pharma provided Eudragit RS 100. light liquid paraffin, Span-80, magnesium stearate, benzene methanol, acetone and other excipients were available at the laboratory.

Methods

Eperisone hydrochloride microcapsule was prepared using o/o microencapsulation method and evaluated various parameters like extent coating and *in-vitro* drug release by employing factorial design.

Preparation of coated eperisone hydrochloride–resinate beads using O/O microencapsulation techniques

The DRC of eperisone hydrochloride was chosen because they exhibited the highest sustained drug release. The required

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controlled drug release pattern with a 12-hour duration has been achieved by encapsulating eperisone resinate beads in Eudragit RS100 utilizing solvent evaporation techniques.[13]

Initially, 20 g of Eudragit RS 100 was added to 100 mL acetone to make 20% w/v Eudragit RS 100 solution. The eperisone-resinate particulates were dispersed in 10 mL of Eudragit RS100 Solution (20% w/v). Afterward, emulsification is performed by employing a propeller agitator at 500 rpm rotational speed into 100 mL liquid-paraffin light containing span 80 at 1% w/v in addition of 0.1% w/v magnesium stearate. Magnesium stearates were utilized like a droplet stabilizer's compound to resolve problems regarding solvent evaporation-induced coalescence. The microcapsules were separated by vacuum filtration after the entire evaporation of the acetone (about 1-hour), rinsed three times with n-hexane (75 mL), and after that permitted to 12-hour drying period in the open air.[14]

Optimization of EpeH–resinate microcapsules employing 2^3 factorial design

A 2^3 factorial method has been employed to formulate EpeH-resin microcapsules.[15] The 2^3-factorial designs are employed to explore the overall impact of factors (variables) and experimental situations on each other. In this approach, three factors are investigated, every at two levels, which are given in Table 1. Furthermore, practical runs are investigated using the entire eight different configurations. The concentration of Eudragit RS100(X1) was first independent variable, followed by the rotational speed (X2), and finally PEG-400 concentration (X3) . As the dependent variables, it was decided to use the microcapsules' extent of coating (Y1), drug released percentage after one hour (Y2), drug released percentage after six hours (Y3), and drug released percentage after 12 hours (Y4). Table 1 show the 2^3 Factorial design run.

Evaluation of drug resin microcapsules[13]

The evaluation of drug resin microcapsules of eperisone hydrochloride as follows:

- *Determination of extent of coating of the microcapsules*

First, 500 mg of EpeH–resin microcapsules were carefully weighed, and after that acetone was used three times to eliminate the polymer coating from the EpeH–resin microcapsules. The leftover EpeH microcapsules were kept to 50°C over 12 hours to dry them off, and then they were weighed.[13,14]

The following formula was used to determine the coating's extent:

$$\text{Extent coating} = \frac{\text{EpeH–resin microcapsules weight–dried EpeH resin beads weight}}{\text{EpeH–resin microcapsules weight}} \times 100$$

- *In-vitro drug released from the prepared microcapsules*

The procedure for releasing the drug from the different eperisone resinate microcapsules has been conducted utilizing USP-II dissolution unit. About 900 mL of distilled water kept at 37° ± 1°C as the dissolving media. It rotated at a rate of 50 rpm. As the solution is stirred up with the paddle, a specific weight of an eperisone hydrochloride resinate microcapsule that is equal to 100 mg of drug (Eperisone hydrochloride) has been introduced. A 1-mL mixture solution is taken out and updated at suitable intervals by adding fresh solution. Using an ultraviolet spectrophotometer set to 261 nm, the obtained sample's absorbance was determined.[15]

Table 1: 2^3Factorial design Run

Factors (Independent variables)	Level used	
	(-) Low level	(+) High level
X1 = EudragitRS100 concentrations	5%	20%
X2 = Speed of Rotation	500	1500
X3 = PEG 400 Concentration	0%	10%

Table 2: Extent coating of formulation

Formulation	*Weight of Microcapsules (mg)*	*Weight of dried EpeH resinate beads (mg)*	*Weight of extent coating (mg)*	*% extent coating*
F1	500	452	48	9.6
F2	500	408	92	18.4
F3	500	436	64	12.8
F4	500	397	103	20.6
F5	500	476	24	4.8
F6	500	462	38	7.6
F7	500	468	32	6.4
F8	500	449	51	10.2

RESULTS

We employed a factorial design for developing and optimizing trial runs. Extent coating of microcapsule and *in-vitro* dissolution studies was performed.

Determination of Extent Coating

Extent coating was calculated using the formula given in materials and method, and the results are reported in Table 2. Extent coating was found between 4.8 to 20.6%.

In-vitro Dissolution Study of Prepared Microcapsules

The results of a 12 hours *in-vitro* release study from formulations F1 to F8, are depicted in Table 3.

Kinetic Analysis of *In-vitro* Release of EpeH from Different Microcapsules

The data obtained after dissolution were treated with different mathematical equations to find out the release mechanism and drug release kinetics. The result obtained after treatment are shown in Table 4.

The above table shows the results of the kinetic investigations of the *In-vitro* EpeH-release findings via EpeH-microcapsules. As per the correlation coefficients (R^2), finding from *in-vitro* releases supported Koresmeyer-Peppas release kinetics. (for formulations F5, F6). First-order release kinetics (for formulations F7) and kinetics of zero-order (for F1; F2; F3; F4 or F8 formulations).

Table 3: Dissolution profile of different formulations of microcapsule (O/O Method)

Time (min.)	*Cumulative %drug release*							
	F1	*F2*	*F3*	*F4*	*F5*	*F6*	*F7*	*F8*
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	8.25	3.75	6.75	2.25	10.50	5.25	7.50	4.50
120	12.76	7.50	10.51	7.50	14.26	10.51	16.51	12.76
180	18.02	9.01	12.77	12.01	19.53	15.02	21.78	16.52
240	23.29	14.27	19.53	16.52	25.55	21.78	27.05	21.79
300	30.07	19.54	25.56	19.54	33.08	28.56	34.58	27.06
360	34.60	28.56	28.58	23.31	41.36	36.09	39.87	30.09
420	41.39	34.59	37.62	28.59	44.41	41.38	46.66	34.63
480	46.69	37.63	46.66	34.62	48.96	45.93	52.72	39.91
540	55.74	43.67	52.71	37.66	59.51	52.73	58.02	43.71
600	60.24	46.67	57.96	41.41	64.76	55.73	59.52	50.46
660	63.37	48.27	61.83	45.25	68.65	61.85	63.40	54.31
720	66.44	52.08	64.90	48.30	72.48	63.42	68.72	57.37

Table 4: *In-vitro* release kinetics of drug from different microcapsules

Formulations	*Zero order*		*First order*		*Higuchi*		*Korsemeyer peppas*		
	K_0	R^2	K_1	R^2	K_H	R^2	K_P	R^2	*'n'*
F1	0.102	0.995	0.0185	0.981	1.882	0.927	1.0772	0.991	0.892
F2	0.0703	0.983	0.0189	0.981	1.3669	0.895	1.0489	0.982	1.135
F3	0.0901	0.99	0.0187	0.97	1.7042	0.894	1.0574	0.987	0.992
F4	0.065	0.997	0.0191	0.991	1.2617	0.916	1.0467	0.985	1.178
F5	0.1137	0.995	0.0183	0.975	2.0692	0.927	1.0808	0.997	0.8419
F6	0.0926	0.993	0.0186	0.989	1.762	0.926	1.0659	0.996	1.0398
F7	0.1176	0.985	0.0184	0.994	2.0484	0.959	1.0873	0.992	0.8751
F8	0.0858	0.995	0.0188	0.989	1.6028	0.939	1.0709	0.986	0.9679

Table 5: Experimental runs, independent variables and measured responses of the 2^3 factorial experimental design.

Formulations	X_1	X_2	X_3	*Responses*			
				Y_1	Y_2	Y_3	Y_4
F1	5	500	0	9.6	8.25	34.6	66.44
F2	20	500	0	18.4	3.75	28.56	52.07
F3	5	500	10	12.8	6.75	25.58	64.89
F4	20	500	10	20.6	2.25	23.32	48.3
F5	5	1500	0	4.8	10.5	41.37	72.47
F6	20	1500	0	7.6	5.25	36.09	63.42
F7	5	1500	10	6.4	7.5	39.86	68.73
F8	20	1500	10	10.2	4.5	30.09	57.37

Table 6: Regression results of the measured responses (coded value)

Coefficient	Y_1	Y_2	Y_3	Y_4
X1	5.8	-4.31	-5.84	-12.84
X2	-8.1	1.68	8.84	7.57
X3	2.4	-1.68	-5.44	-3.77
X1X2	-2.5	0.19	-1.69	2.64
X1X3	1.2	0.56	-0.18	-1.13
X2X3	-0.3	-0.19	1.69	-1.12
$X_1X_2X_3$	0.5	0.56	-2.07	0.03

Analysis of Factorial Design

We employed a factorial design, the popular statistical method for developing and optimizing trial runs. The 2^3 complete factorial designs make up the utilized model. The results of the experimental runs , reported in Table 5, including the measured responses and independent variables, were compiled and are displayed in the table beneath. With statistical analysis utilising complete factorial design, experts In Software Trial version 13.0, the truly independent variables and response factors were connected by employing the polynomial equation. The measured responses' regression outcomes are shown in Table 6. The coefficient values for X1, X2, and X3 determine the impact of these factors on the responses. A positive coefficient sign shows a synergistic influence on the response, whereas opposed effect is indicated through the minus coefficient sign. A greater coefficient indicates that such an independent factor has a stronger effect upon the response. The following version of a polynomial equation may be fitted to the data obtained from an experiment using experimental design with two level.

This contains the following:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{123}X_1X_2X_3$$

Where Y represents the dependent-variable, b_0 represents intercept, then b_1, b_2, b_3 represent coefficients for said variables X_1,X_2,X_3 as well as their interaction terms.

By creating a Pareto chart using design expert software, the standardized influence of such independent variables including interactions between them on the dependent-variables was examined. These were used to illustrate the impacts of independent variables as well as interactions among them with dependent-variables.

Where

Y_1 = extent coating, Y_2= % EpeH released after 1 hour.

Y_3=% EpeH released after 6 hours, Y_4=% EpeH released after 12 hours

The effect of formulation and process variables on the extent of coating of EpeH loaded microcapsules using a 2^3 factorial design

A pareto chart (Figure 1) illustrates the correlation between the EudragitRS100 concentrations, the rotating speed, and the PEG-400 concentration upon the coating's extent. As the EudragitRS100 and PEG-400 concentrations were raised, the coating's extent was also raised. Accelerating the rotating speed greatly reduced the coating's extent. Microcapsule's coating extent was shown to be significantly influenced by EudragitRS100 percentage into coating mixture. The coating's thickness suggested by a upbeat coefficient (+5.8) greatly raised when the Eudragit RS100 concentration was raised from low level (5%) to high level (20%). The microcapsule's coating extent was also highly influenced by rotating speeds. Coating's extent was drastically reduced when rotating speeds was raised from low 500 rpm to high 1500 rpm, suggesting downbeat coefficient (-8.1). The polymer may not have been deposited evenly on the core because the solution evaporated too quickly due to the fast rotational speed. The microcapsule's coating thickness increased dramatically with a upbeat coefficient (+2.4) when the PEG-400 concentration was raised.

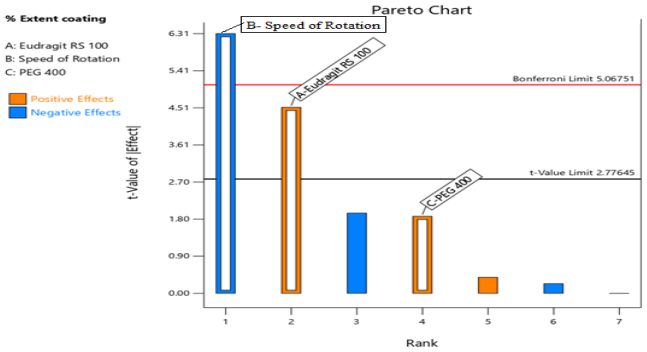

Figure 1: Pareto chart of the effect of Eudragit RS 100 concentration, speed of rotation and concentration of plasticizer PEG 400 on the extent of coating

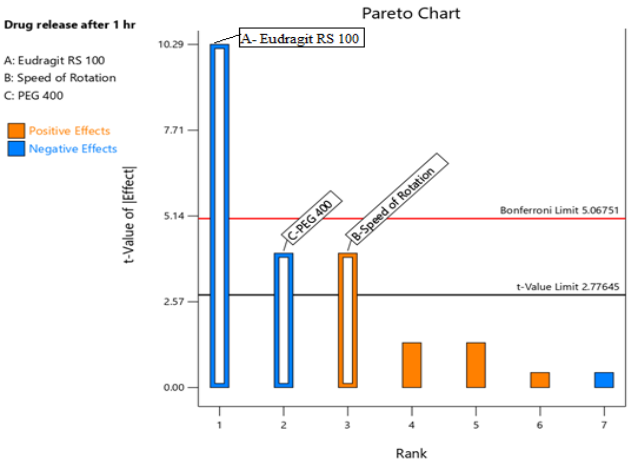

Figure 2: Pareto chart of the effect of Eudragit RS 100 concentration, speed of rotation and concentration of plasticizer PEG 400 on the *in-vitro* release after 1 hour

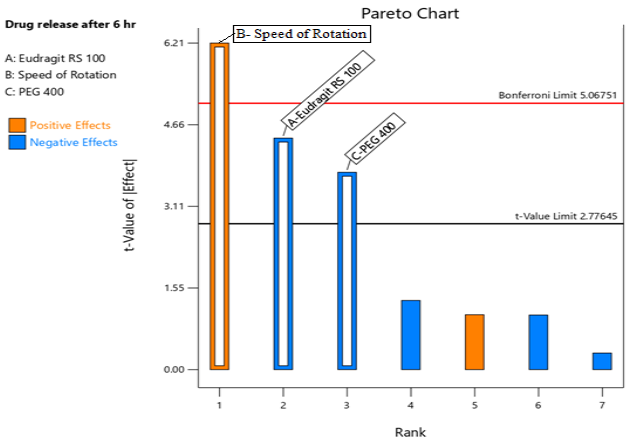

Figure 3: Pareto chart of the effect of Eudragit RS 100 concentration, speed of rotation and concentration of plasticizer PEG 400 on the *in-vitro* release after 6 hours

Table 7: Optimized formulation process and response variables

Code	*Solution*							
	Process variables			*Response variables*			*Error*	*Desirability*
	X1	*X2*	*X3*		*Predicted value*	*Observed value*		
O	5.5	1201.67	6.27	Y1	7.27	7.28	-0.01	1.00
				Y2	8.23	8.1	0.13	
				Y3	36.47	35.35	1.12	
				Y4	68.25	67.94	0.31	

The effect of formulation and process variables on the in-vitro release of EpeH from EpeH loaded microcapsules using 2^3 factorial designs.

Pareto charts illustrating the correlation between the EudragitRS-100 concentrations, the rotating speed, and the PEG-400 concentrations upon the invitro %EpeH-release after 1 hour. (Figure 2), then 6 hours. (Figure 3) and next 12 hours. (Figure 4) from eperisone hydrochloride microcapsules. It has

Table 8: *In-vitro* release kinetics of drug from optimized microcapsules

Formulations	*Zero order*		*First order*		*Higuchi*		*Korsemeyer peppas*		
	K_0	r^2	K_1	r^2	K_H	r^2	K_P	r^2	'n'
O	0.102	0.998	0.0185	0.984	1.889	0.932	1.0735	0.993	0.9025

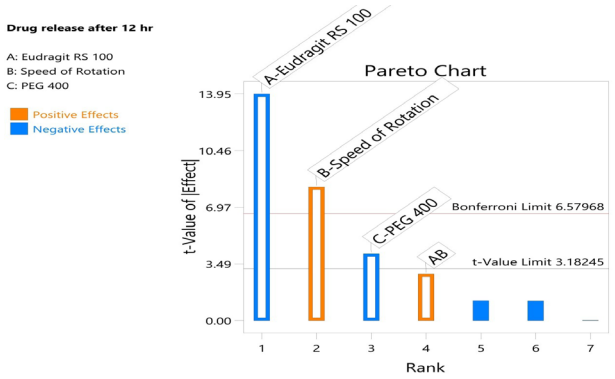

Figure 4: Pareto chart of the effect of Eudragit RS 100 concentration, speed of rotation and concentration of plasticizer PEG 400 on the *in-vitro* release after 12 hours

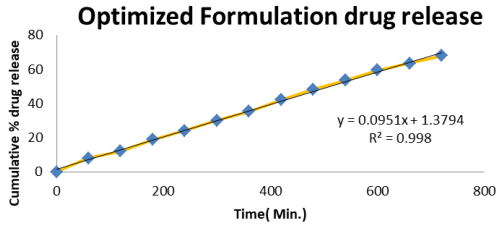

Figure 5: *In-vitro* drug release of optimized formulation (O)

been discovered that the Eudragit RS100 concentrations has a substantial effect on medicament releases. After 1, 6, and 12 hours, the proportion of EpeH released was significantly reduced when the Eudragit RS100 concentrations was raised from low level (5%) to high level (20%) with a considerable rise in the coating's extent. A higher Eudragit RS100 concentrations creates an extended diffusion way, which slows down the EpeH release. As a consequence of Eudragit RS100's limited permeability, medicament release was slowed even more. The findings are in agreement with those regarding the amount to which the microcapsules were coated, showing that a higher Eudragit-RS100 concentrations led to a thicker coating upon microcapsule and a slower release of the medicament.

Similarly, the rotating speed has been discovered to have a noticeable influence upon the releasing of medicament. The proportion of EpeH releasing has been risen exponentially after 1, 6, and 12 hours when the rotating speed was changed from low level-500 to high level-1500 rev/m. A possible explanation is that the microcapsule resinate experienced uneven polymeric membrane deposition. Such findings further show a strong correlation with the findings concerning microcapsule coating's extent; specifically, raising the rotating speeds led to a lowering in the microcapsules coating's extent, resulting in an enhanced EpeH-releasing percentages.

Only in the last phases of the medicament release, when EpeH-release is controlled, PEG-400 concentrations are significant. Raising the PEG-400 concentrations significantly affects the % of medicament release. A considerable reduction in EpeH release rate was seen after PEG400 administration.

Optimized Formulation

The optimal settings of the formulation variables (factors), as predicted by the design expert software, were numerical, as shown in Table 7.

In vitro dissolution study of optimized formulation

In vitro dissolution resulting data was the construction of plots representing the cumulative percentage of drug released over time for the optimized formulation which are shown in Figure 5.

Kinetic analysis of in-vitro release of EpeH from optimized microcapsule

The data obtained after dissolution were treated with different mathematical equation to find out the release mechanism and drug release kinetics. The result obtained after treatment are shown in the Table 8.

The above table shows the results of the kinetic investigations of the *in-vitro* EpeH-release findings *via* optimized EpeH-microcapsules. As per the correlation coefficients (R2), findings from *in-vitro* releases supported zero-order kinetics. After applying optimization (numerical) by Design expert software, predicted process variables and response variables were obtained. Microcapsules were prepared and evaluated.

CONCLUSION

The main objective of this research was to develop and optimize the microcapsule of eperisone hydrochloride by using a 2^3 factorial design. Creating a Pareto chart using design expert software examined the standardized influence of such independent variables, including interactions between them on the dependent variables. Optimized microcapsules of eperisone hydrochloride follow the zero order kinetics of a promising controlled release of the highly water soluble drug and was successfully designed for further formulate into the suspension containing different suspending agents for geriatric patients.

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