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Original Article

FORMULATION OPTIMIZATION OF PROMETHAZINE THEOCLATE IMMEDIATE RELEASE PELLETS BY USING EXTRUSION-SPHERONIZATION TECHNIQUE

SHELAR VISHWAS S.[a], SHIROLKAR SATISH V.[a], KALE RUPALI N.[a*]

[a]Department of Pharmaceutics, Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research Centre, Pimpri, Pune 411018
Email: rupalikale07@gmail.com

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ABSTRACT

Objective: Promethazine theoclate is a BCS Class II drug having anti-histaminic property and mainly used for the treatment of motion sickness and postoperative emesis. The main objective of the research work was to formulate and optimize immediate release pellets of promethazine theoclate by using the extrusion-spheronization technique to offer immediate release dosage form suitable for treatment of nausea and vomiting associated with motion sickness and post-operative conditions.

Methods: Immediate release pellets of promethazine theoclate were prepared by using microcrystalline cellulose (MCC) and corn starch as filler and disintegrant respectively along with other excipients. Pellet formulation was further optimized for bulk density, disintegration time and percent drug release after 10 min. using 3^2 factorial design. Formulations were also characterized for drug-polymer interactions using Differential Scanning Calorimetry (DSC), surface morphology by Scanning Electron Microscopy (SEM) and other physicochemical properties.

Results: Optimised pellet formulation contains 2.5:4.5:1 ratio of MCC: Corn Starch: Drug and spheronization time of 60 seconds showing highest percent yield of 78% and immediate drug release of 100.52±0.65% after 10 min.

Conclusion: Promethazine theoclate pellets formulated in this study can serve as an alternative to tablet dosage form which can give immediate drug release for treatment of motion sickness and postoperative emesis.

Keywords: Promethazine theoclate, Immediate release pellets, Multiparticulate drug delivery, Extrusion-spheronisation, Factorial design

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INTRODUCTION

Promethazine theoclate is BCS Class II, H_1 antihistaminic drug mainly used in the treatment of motion sickness and postoperative emesis [1, 2]. It has 25% bioavailability due to its poor aqueous solubility which is the major limiting factor for its absorption and delayed onset of action [3]. Promethazine theoclate tablets are available in the market as immediate release single-unit dosage form for oral administration. Formulation development of transdermal patch, SLN, suppository and gel for promethazine theoclate are also explored in research for different routes of administration [4-6].

Pellets formulation as multiple-unit dosage forms are preferred over single-unit dosage forms due to stable plasma profiles, free dispersion in GI tract maximizing GI absorption and minimizing local mucosal side effects. Among the various types of multiple-unit dosage forms, pellets have attracted more attention due to their unique clinical and technical advantages. Pellet drug delivery system offers various therapeutic advantages such as dose tailoring as well as it helps in reducing inter and intrapatient variability by reducing fluctuations in peak plasma concentrations with no significant reduction in bioavailability [7, 8].

Microcrystalline cellulose (MCC) and Corn starch are most common excipients utilized for the production of pellets via extrusion spheronisation technique. It has ideal rheological properties well suited for the process [9, 10]. In case of a drug having low solubility, MCC alone can give prolonged drug release profile [11] due to the lack of disintegration of MCC-based pellets. It may also show drug adsorption onto the surface of MCC core [12, 13] which can be minimized by using Corn starch in combination with MCC [14] to get an immediate release of the drug.

The objective of this study was to formulate promethazine theoclate immediate release pellets using MCC and Corn starch and optimize the formula using 3^2 factorial design.

MATERIALS AND METHODS

Materials

Promethazine theoclate was obtained as a gift sample from Mehta Pharmaceutical Pvt. Ltd., Mumbai. Microcrystalline cellulose (Avicel PH101) was purchased from Research Lab, Mumbai. Corn starch, sodium starch glycolate, lactose (monohydrate), isopropyl alcohol and HCl were purchased from Loba Chemie, Mumbai. Polyvinylpyrrolidone (PVP) K-30 was purchased from Himedia Laboratories Pvt. Ltd., Mumbai.

Methods

Construction of calibration curve of promethazine theoclate in 0.1 N HCl

Accurately weighed 10 mg of the promethazine theoclate was dissolved in 10 ml methanol and diluted to 100 ml with 0.1N HCl. The prepared stock solution was subsequently diluted to get the concentrations of 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 and 55 µg/ml of promethazine theoclate respectively. The absorbance of these solutions was measured at 278 nm using UV/Visible spectrophotometer (Shimadzu). Calibration curve was plotted as shown in fig. 1.

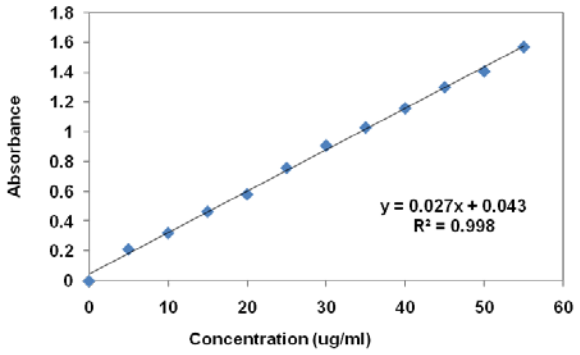

Fig. 1: Calibration curve of promethazine theoclate in 0.1N HCl

Drug-excipient compatibility study

Investigation of the potential interaction of promethazine theoclate and other excipients was done by recording and analysing

thermograms using DSC (DSC 60 Shimadzu, Japan) for pure drug and physical mixture of the drug with excipients. Samples were heated at a heating rate of 10 °C/min. in the range of 25–400 °C using standard aluminium sample pans. DSC thermograms were observed for potential interactions.

Preparation of pellet formulation by extrusion-spheronization technique

Preliminary screening of excipients

Preliminary screening for selection of binder, other excipients and instrument parameters was done by visual inspection and flow properties of the pellets obtained from the initial studies. It was observed that PVP K30, as a binder, gave acceptable spherical pellets with good yield, low friability and satisfactory flow properties. Based on the observations, 7% of PVP K30, 8% of SSG and speed of 800rpm with 5 mm friction plate were selected as formulation and process parameters.

Preparation of drug-loaded pellets

Pellets were prepared by following steps using lab scale spheronizer (Shakti Pharmatech).

Preparation of wet mass

The powder mixture was prepared by homogenous blending of microcrystalline cellulose, corn starch, PVP K-30 and sodium starch glycolate. Binder solution containing PVP K30 in a mixture of purified water and isopropyl alcohol was added separately to dry mixture with kneading. Successive pauses were taken for the addition of the liquid components for proper kneading to obtain a damp mass of appropriate consistency for the extrusion process [10, 11].

Extrusion

Prepared wet mass was immediately extruded through sieve number 14 (B. S. S.) to get compact cylindrical extrudates of uniform diameter.

Spheronization

The extrudates were spheronised using lab Spheronizer (Shakti Pharmatech) at 800 rpm with 5 mm friction plate to get spherical pellets. Wet pellets were dried in Fluid Bed Dryer (FBD) for 10 min keeping product temperature below 65 °C.

Formula optimization

Preliminary studies showed a significant effect of concentration of MCC and Corn starch on bulk density, disintegration time and percent drug release of pellets. These two parameters were selected as Independent variables for the formulation optimization of promethazine theoclate loaded pellets using 3^2 factorial design. Nine batches were prepared at levels of-1, 0,+1 of independent variables as shown in table 1.

Table 1: Composition of promethazine theoclate pellets for factorial design

Batch code	MCC (g)	Corn starch (g)	Lactose (g)	SSG (g)	PVP K-30 (g)	Drug (g)
I	3	7	4.25	2	1.75	2
II	3	8	3.25	2	1.75	2
III	3	9	2.25	2	1.75	2
IV	4	7	3.25	2	1.75	2
V	4	8	2.25	2	1.75	2
VI	4	9	1.25	2	1.75	2
VII	5	7	2.25	2	1.75	2
VIII	5	8	1.25	2	1.75	2
IX	5	9	0.25	2	1.75	2

All batches were evaluated for response variables, bulk density, disintegration time and percent drug release. The data obtained was analyzed using Design Expert 7.0.0 software to generate polynomial equation, contour plots and design space.

Characterization of drug loaded pellets

Developed formulations of pellets were characterized for the following properties.

Particle size

Photomicrograph of pellets was taken and analysed using Image J software to determine its particle size.

Morphology

The surface morphology of pellets was examined using the scanning electron microscope (FEI Nova NanoSEM 450) which was operated at 3.0 kV and 5.0kV at magnifications of 103X, 250X, 1000X and 5000X.

Bulk density

Apparent bulk density is determined by pouring a weighed quantity of pellets into a graduated cylinder and measuring the volume and weight. Bulk density is calculated using the following formula:

$$\text{Bulk density} = \frac{\text{Weight of pellets}}{\text{Bulk volume of pellets}}$$

Hardness

The hardness of pellets was measured by using a digital pellet hardness tester (Veego).

Friability [16]

Friability of pellets was checked by using Friability test apparatus (Roche Friabilator) at 25 rpm for 4 min. Percent friability was calculated by the equation below after removing fines from sieve no.36.

$$\text{Friability (\%)} = \frac{W1 - W2}{W1} \times 100$$

Where,

W1= Initial weight of pellets

W2= Final weight of pellets after removing fines.

Disintegration time

The disintegration time of pellets was checked by putting 250 mg of pellets in 50 ml distilled water with continuous shaking in water bath shaker at 37 °C till complete disintegration.

Drug content

About 250 mg of the pellets were taken and crushed in a mortar to obtain a fine powder. 25 mg powder was taken and dissolved in 10 ml methanol and diluted up to 50 ml with 0.1N HCl, sonicated for 5 min and volume was made up to 100 ml with 0.1N HCl. The absorbance of the resulting solution was measured at 278 nm using the UV/Visible spectrophotometer.

The concentration of drug in solution was calculated using calibration curve.

Drug content (%) was calculated using following formula:

$$\text{Drug content (\%)} = \frac{\text{Actual amount of Promethazine theoclate found in pellets}}{\text{Theoretical amount of Promethazine theoclate in pellets}} \times 100$$

In vitro dissolution studies

In vitro dissolution studies were performed using USP type 1 apparatus (basket). An accurately weighed sample of pellets containing an equivalent amount of 25 mg of promethazine theoclate was filled into gelatine capsules and dissolution studies were carried out into 900 ml of 0.1N HCl, maintained at a temperature of 37 °C±0.5 °C at 100 rpm. At different time intervals, 10 ml aliquot of the sample was withdrawn and the volume was replaced with an equivalent amount of dissolution medium kept at 37 °C. The collected samples were filtered and the absorbance was measured at 278 nm. Percent drug release was compared with drug release from marketed formulation (Avomine tablet; Promethazine theoclate 25 mg; Mfg. by: sanofi aventis).

Stability studies of optimized batch

Stability studies of the optimized formulations were performed using gelatin capsules filled with developed promethazine theoclate pellets at accelerated conditions of 40 °C temperature and 75 % RH for 30 d as per the International Conference on Harmonization (ICH) guidelines

Samples were withdrawn after 30 d and subjected to analysis for specified parameters.

RESULTS AND DISCUSSION

Drug-excipient compatibility studies for promethazine theoclate along with the excipients used in the formulation was checked using DSC technique. As shown in fig. 2, DSC thermogram of pure promethazine theoclate and physical mixture of the drug with excipients showed sharp endothermic peaks at 180.1 °C and 178.9 °C respectively, indicating no significant difference in peak position and compatibility of the drug with excipients.

The flow properties of pellets were evaluated by checking the angle of repose. An angle of repose (θ)<30 ° indicates free-flowing material and >40° indicates poor flow. Values for the angle of repose (θ), for all factorial batches of pellets, were found to be in the range of 20.55 °±0.02 to 28.35 °±0.02 indicating free-flowing pellets which can be easily filled into capsules.

Percent friability of prepared pellets was found to be within 0.32±0.35 to 0.80±0.19 which was acceptable as the standard limit for percent friability which is <1%. It indicates sufficient mechanical integrity, strength and hardness. The particle size of all factorial batches was found within 0.87±0.42 to 1.41±0.18 mm. Data of evaluation of promethazine theoclate loaded pellets is shown in table 2.

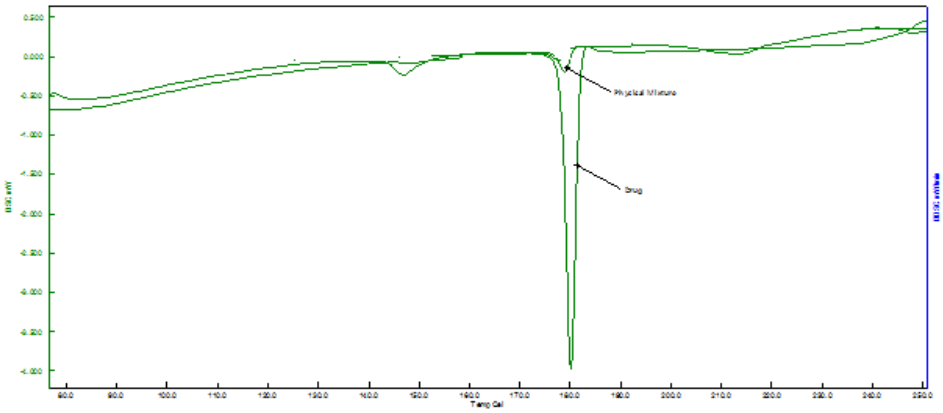

Fig. 2: Overlay of DSC thermogram of promethazine theoclate and physical mixture with excipients

Table 2: Evaluation of promethazine theoclate loaded pellets

Batch code	Angle of repose (θ)*	Friability (%) **	Particle size (mm)$	Disintegration time (sec) (Y_1)	% Drug release after 10 min(Y_2)#	Bulk density (g/ml)* (Y_3)
I	28.35±0.02	0.57±0.24	1.41±0.18	33.89	101.71±0.34	0.71±0.02
II	24.87±0.03	0.42±0.02	1.31±0.23	24.30	93.67±0.27	0.68±0.03
III	23.96±0.02	0.72±0.40	1.32±0.22	23.20	93.82±0.45	0.71±0.02
IV	20.55±0.02	0.62±0.16	1.34±0.24	56.25	85.94±0.40	0.72±0.02
V	25.42±0.01	0.37±0.09	1.29±0.22	40.21	82.05±0.45	0.63±0.01
VI	28.07±0.01	0.32±0.35	1.11±0.24	28.88	85.14±0.59	0.66±0.01
VII	23.80±0.01	0.43±0.42	0.87±0.42	59.00	77.43±0.79	0.65±0.01
VIII	23.90±0.01	0.80±0.19	1.01±0.19	53.08	87.75±0.65	0.59±0.01
IX	24.56±0.02	0.58±0.35	1.29±0.37	21.05	100.52±0.65	0.58±0.02

Values are expressed as mean±SD, *n = 3, # n = 3, ** n=2, $n=200

Disintegration time and percent drug release after 10 min. are the important parameters to be optimized as far as drug release from immediate release pellets is concerned. Bulk density plays a critical role when pellets need to be filled in capsules in order to get correct dose to be delivered.

Disintegration time, percent drug release and bulk density were found to vary with changing concentration of MCC and Corn starch.

To estimate the effect of concentration MCC and Corn starch on disintegration time, percent drug release and bulk density, 3^2 factorial design was investigated. Statistical analysis of data by ANOVA suggested linear model significant for disintegration time with p-value 0.0102 and quadratic model significant for percent drug release after 10 min. and bulk density with p values 0.0353 and 0.0167 respectively.

Polynomial equations generated by design expert software are explained herewith for its interpretation of effect on response parameters.

$$\text{Disintegration time } (Y_1) = 37.76+8.62*X_1-12.67*X_2 \ldots\ldots\ldots (1)$$

Positive coefficient of X_1 in equation (1) indicated increase in the disintegration time (Y_1) with increase concentration of MCC up to

certain concentration, and negative coefficient of X_2 indicates decrease in its response (Y_1) with increase in concentration of Corn starch up to certain concentration since Corn starch acts as disintegrating agent, and thereby reduces disintegration time of pellets. The response plot and counterplots in fig. 3A and 3B respectively are indicative of the relative effect of concentration of MCC and Corn starch on disintegration time of promethazine theoclate loaded pellets.

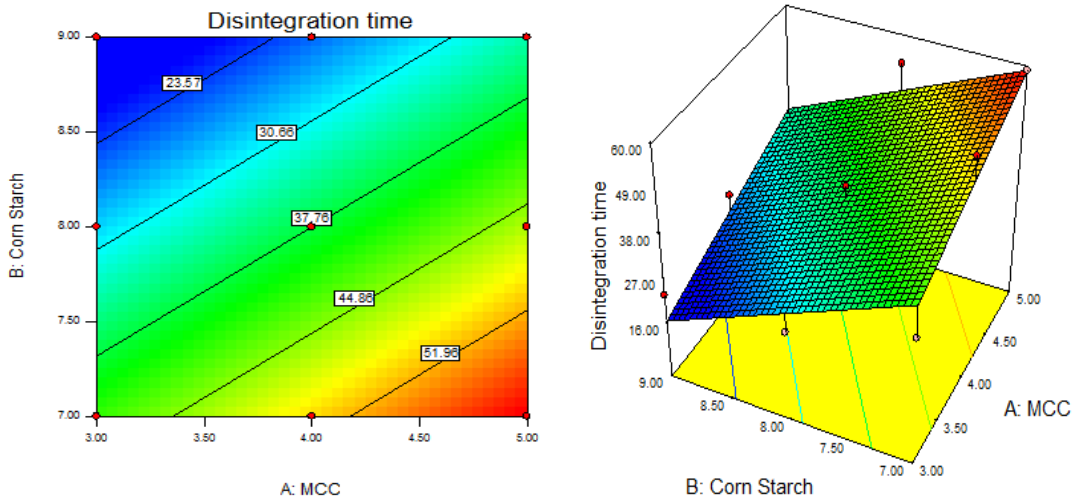

Fig. 3: Different plots showing effect of independent variables on Disintegration time of pellets, (A) Counterplot showing the relationship between various levels of two independent variables, (B) Response surface plot showing the influence of the concentration of MCC and Corn Starch on the Disintegration time

Percent drug release after 10 min (Y_2) = 82.42-3.92*X_1+2.40*X_2+7.75*X_1*X_2+8.11*X_1^2+2.94*X_2^2... (2)

From equation (2), it is observed that negative coefficient of X_1 indicates a decrease in percent drug release after 10 min (Y_2) with an increase in the concentration of MCC whereas the positive coefficient of X_2 indicates an increase in percent drug release after 10 min with an increase in the concentration of Corn starch till certain concentration level. Increase in Corn starch might be increasing disintegration of pellets leading to faster drug release. The 3D response plot and counterplots indicating the relative effect of concentration of MCC and Corn starch on percent drug release after 10 min of promethazine theoclate loaded pellets are shown in fig. 4A and 4B respectively.

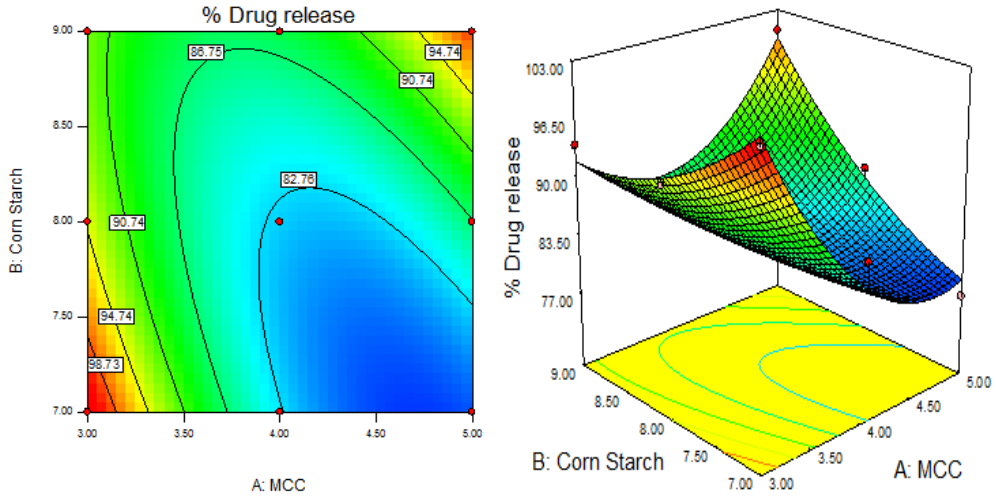

Fig. 4: Different plots showing the effect of independent variables on % drug release of pellets after 10 min, (A) Counterplot showing the relationship between various levels of two independent variables, (B) Response surface plot showing the influence of the concentration of MCC and Corn Starch on the % drug release of pellets after 10 min

Bulk density (Y_3)= 0.64-0.047*X_1-0.020*X_2-0.018*X_1*X_2-0.018*X_1^2+0.037*X_2^2.... (3)

Equation (3), indicated a decrease in the bulk density (Y_3) with an increase in the concentration of MCC and decrease in bulk density with increase in the concentration of Corn starch up to certain concentration level, might be due to a reduction in the total content of excipients.

The response plot and counterplots are shown in fig. 6A and 6B respectively which are indicative of a relative effect of concentration of MCC and Corn starch on the bulk density of promethazine theoclate loaded pellets.

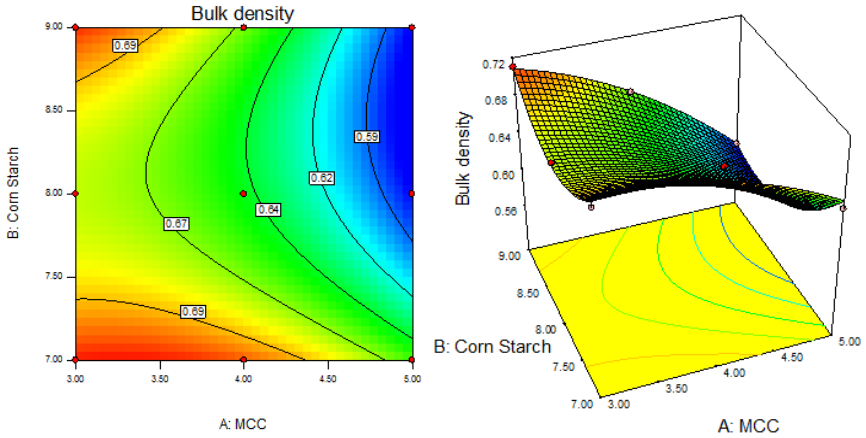

Fig. 6: Different plots showing the effect of independent variables on the bulk density of pellets, (A) Counterplot showing the relationship between various levels of two independent variables, (B) Response surface plot showing the influence of the concentration of MCC and corn Starch on the bulk density of pellets

Though excipients are considered as inactive ingredients, they have a significant impact on functional properties of the formulation. It is known that MCC when extruded to get the dense material, it tends to disintegrate very slowly with the absence of disintegrating agent as well as an increase in the concentration of MCC increases compatibility of powder mixture leading to lower disintegration time [17].

Considering these facts, here increase in the concentration of MCC decreases disintegration time, a decrease in bulk density of pellets. Due to reduced disintegration time, it further leads to decrease in percent drug release. On the contrary, Corn starch being a disintegrant, cause disintegration of pellets by swelling action [18] and thereby enhancing the drug release from pellets.

With reference to the graphical and mathematical analysis of data by experimental design formulation composition of batch IX of promethazine, theoclate was found to give desired results at higher concentrations of MCC, 5% and Corn starch 9%.

Optimized formulation was further characterized by SEM analysis to evaluate the morphology of pellets such as pellet shape and surface characteristics.

It was found to have a spherical shape and smooth surface with minimal pores, indicating uniformity in pellets as shown in fig. 7.

The observed values of optimized batch during the response variables are compared with the predicted values. From the results observed (table 3), it was found that mathematical models generated were statistically significant and valid for predicting values of response parameters at selected levels of formulation variables

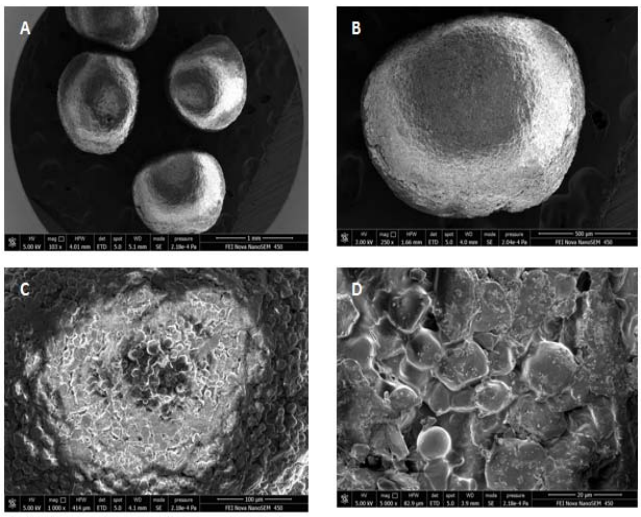

Fig. 7: SEM images of optimized formulation batch IX; A) at 103X, B) at 250X, C) at 1000X, and D) at 5000 X

Table 3: Validation of optimised formulation (Batch code: IX)

Parameters	Predicted value	Actual (experimental) value
Bulk density (g/ml)	0.58	0.59
Angle of repose(°)	24.65	24.56
Yield (%)	71.88	78.00
Particle size (mm)	1.285	1.21
Hardness (kg/cm^2)	0.07	0.08
Friability (%)	0.55	0.58
Drug release after 10 min. (%)	99.69	100.52

An optimized batch of promethazine theoclate pellets (IX) was filled into capsule shell equivalent to a required dose of the drug and it's percent release was compared with the marketed formulation of promethazine theoclate tablet (Avomine tablet). Both formulations showed the comparative release of > 85% within 30 min. which indicates immediate drug release.

The comparative release profile is shown in fig. 8.

Stability studies of optimized formulation indicated no significant change in the appearance of pellets, its assay, and disintegration time and percentage drug release after 30 d of storage at accelerated conditions.

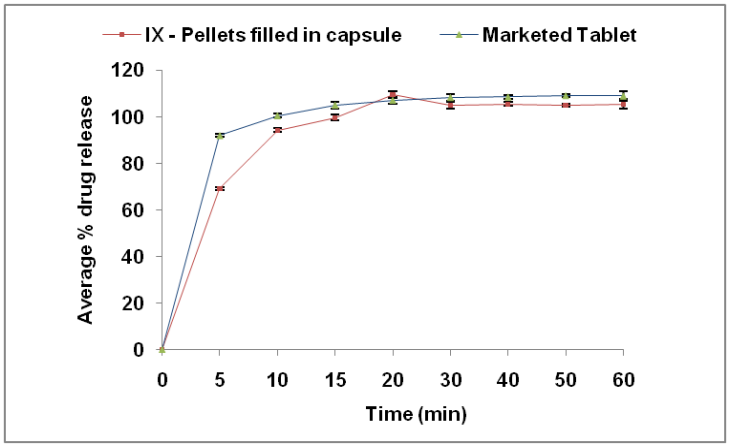

Fig. 8: Comparative percent release profile of optimized formulation of pellets filled in a capsule with the marketed product (Avomine tablet; sanofi aventis)

CONCLUSION

In the present study, systematic efforts were made to develop and optimize promethazine theoclate loaded immediate release pellets as multiparticulate drug delivery system which can be delivered after filling into a gelatin capsule.

Optimization of the formulation was demonstrated by using 3^2 full factorial design and investigation using polynomial equations, surface response plots and counterplots generated during the investigation. Optimised formulation (IX) was found to show highest percent yield of 91.4, the bulk density of 0.58±0.02 g/ml with good flow properties having a 24.56±0.02 °angle of repose, 0.58±0.35 % friability, and disintegration time of 21.05 seconds. The particle size of optimized formulation was found to be 1.29±0.37 mm with 100.52±0.65 % drug release after 10 min. Promethazine theoclate loaded pellets showed the significant effect of independent variables i.e. concentration of MCC and Corn starch on dependent variables i.e. bulk density, disintegration time and percent drug release after 10 min which are critical parameters in terms of dosage, disintegration and drug release respectively when pellets are to be delivered into the capsule. Percent drug release of optimized formulation (IX) was found to be comparable with marketed formulation (Avomine Tablet). Optimized formulation (IX) was found to be stable at 40 °C and 75%RH after 30 d of storage.

Promethazine theoclate pellets formulated in this study can be used as an alternative to tablet dosage form which can give immediate drug release for treatment of motion sickness and post-operative emesis.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICTS OF INTERESTS

All authors have none to declare

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