International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 8, Issue 4, 2016

Original Article

DEVELOPMENT OFRIZATRIPTAN BENZOATE MICROSPHERES FOR NOSE TO BRAIN TARGETING

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Received: 25 Aug 2016, Revised and Accepted: 28 Sep 2016

ABSTRACT

Objective: Oral administration of rizatriptan benzoate shows poor bioavailability due to first pass metabolism, which can be avoided by nasal administration of drugs. Additionally, the nasal administration provides faster onset of action, which is desired to get relief from the intense pain of a migraine. The present research work was emphasised on design, development and evaluation of mucoadhesive microspheres for nasal delivery of rizatriptan benzoate through a systematic approach.

Methods: The microspheres of rizatriptan benzoate were prepared by the w/o/w double emulsion solvent diffusion method using the non-aqueous medium. Critical formulation and process parameters were identified through preliminary trial batches and 2[4-1] fractional factorial design was employed using polymer concentration (X_1:2-5%), drug to polymer ratio (X_2:1:2-1:6), amount of liquid paraffin (X_3:100-200 ml) and the amount of magnesium stearate (X_4:100-150 mg) as independent variables.

Results: Design batches were evaluated for percent yield (50-78%), percent entrapment efficiency (62-85%), drug loading (7.5-30%), % mucoadhesion (47-75%) and drug release at 6 h (44-78%). Scanning electron microscopic (SEM) study showed that microspheres were of 50 µm in size and spherical in shape with a smooth surface. The optimised batch (D10) showed 85% entrapment efficiency and 66.6% drug release within 6 h. The developed microspheres could be used to deliver rizatriptan benzoate through nasal administration for treatment of a migraine.

Conclusion: The developed microspheres can be considered as a promising system for nasal delivery system of rizatriptan benzoate

Keywords: Rizatriptan benzoate, Ethylcellulose, Mucoadhesive microspheres, Nasal route

DOI: http://dx.doi.org/10.22159/ijap.2016v8i4.14883

INTRODUCTION

A migraine is a most common disease affecting more in women as compared to men amongst the victim population. The goal of managing migraine is to reduce its occurrence. The migraine attack can be controlled by changing lifestyle as well as by drug therapy. Several drugs are utilised in the management of a migraine which includes beta-blocking agents, Ca channel blockers, tricyclic antidepressants and anticonvulsants. Over-the-counter analgesics and prescription drugs are available in the market for the painful condition of a migraine [1].

The drugs used in the treatment of migraine are generally administered by the peripheral route. Although the oral route of administration is most popular and stands on the top of all other routes, but it also has a few limitations like first pass metabolism and drug degradation at various pH conditions of GIT. However, now a day's other routes like transdermal, pulmonary, nasal, etc. are gaining popularity to deliver challenging molecules to its site of action. Among all, nasal route now being watched as the preferred route of administration for brain targeting. Nasal route protects drugs and biomolecules from susceptible enzymatic or acidic degradation, can deliver drugs directly to the brain via olfactory lobe and eliminate first pass metabolism. Nasal cavity also has highly vascularized epithelial layer and enough absorption area. Brain targeting further can reduce the dose and dose-related side effects. The various pathways responsible for drug transport in the nasal mucosa include carriers mediated transport, passive diffusion, transcytosis and transport through tight junctions. Due to the direct delivery of drug to brain via olfactory region, the nasal route provides faster onset of action which is very essential for getting relief from an intense migraine headache [2-6].

The microsphere is an important particulate drug delivery system due to their small size and efficient carrier function. Microspheres provide several advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience [7]. Ethyl cellulose (EC) is a water-insoluble polymer with the excellent safety profile and wide acceptance. [8]. It is a low viscosity grade polymer used to control drug release by coating compressed tablets or microspheres [9].

Rizatriptan benzoate is an orally active serotonin 5-HT receptor agonist that selectively binds to the 5-HT receptor. It is available in the market as 5 mg and 10 mg orally disintegrating tablet. It is considered as a serious prospect for development of mucoadhesive nasal microspheres due to its short plasma half-life of 4 h and low oral bioavailability (40%) due to extensive first pass metabolism by hepatic enzymes [10-12]. Currently, it is available in tablet form, and we have explored the nasal route to overcome above mentioned challenges.

The purpose of the present research work was to develop and optimise the ethyl cellulose based microspheres for nasal administration of rizatriptan benzoate. The systematic approach was utilised for the development of microspheres by the w/o/w double emulsion method and for its detailed *in vitro* evaluation. This system may achieve a therapeutic effective concentration of drug in the systemic circulation over an extended period of time with better patient compliance [13].

MATERIALS AND METHODS

Materials

Rizatriptan benzoate was obtained as a gift sample from the Torrent Research Center, Ahmedabad (India). Ethyl cellulose (45 cp) was obtained as a gift sample from the Cadila Healthcare Ltd., Ahmedabad (India). Light liquid paraffin was purchased from Finar Ltd., Ahmedabad (India) and Pectin from Hi-media Ltd., Mumbai (India). All the other chemicals and reagents used in this study were of analytical grade.

Methods

Preparation of rizatriptan benzoate microspheres

Microspheres were prepared by the w/o/w double emulsion method. 1062.5 mg of ethylcellulose (45 cp) was dissolved in a blend of light liquid paraffin and n-hexane. Then212.5 mg of rizatriptan benzoate

was added to the above ethyl cellulose solution slowly with stirring and emulsified with an aqueous medium containing a magnesium stearate (100 mg) as a stabiliser. The mixture was stirred for 3-4 h in order to remove organic solvents. The resulting dispersion was filtered, and microspheres were washed twice with distilled water. Finally, microspheres were air dried for 24 h and then stored in a tightly closed container until further use [14, 15].

Optimisation using experimental design

Based on various trial batches, polymer concentration, a drug to polymer ratio, the volume of liquid paraffin and amount of magnesium stearate was considered as important variables affecting formulation parameters. The design of experiments (DOE) approach was used to study the relationship between the process variables and output. A 2[4-1] fractional factorial experimental design was employed to study interactions among the variables. The independent variables were polymer concentration 1 to 3% (X_1), drug to polymer ratio 1:2 to 1:6 (X_2), volume of liquid paraffin 100 to 200 ml (X_3) and the amount of magnesium stearate 100 to 150 mg (X_4)(as shown in table 1) and the dependent variables were % practical yield, particle size, % mucoadhesion, %entrapment efficiency and % drug loading [16].

Table 1: Transformed values for 2^{4-1} factorial design batches

Batch No	Transformed factors			
	X1	**X2**	**X3**	**X4**
D1	-1	-1	-1	-1
D2	+1	+1	-1	-1
D3	+1	-1	+1	-1
D4	-1	+1	+1	-1
D5	+1	-1	-1	+1
D6	-1	+1	-1	+1
D7	-1	-1	+1	+1
D8	+1	+1	+1	+1
	Actual value			
Levels	**X1**	**X2**	**X3**	**X4**
(-1)	2 %	1:2	100	100
(+1)	5 %	1:6	200	150

Data analysis, statistical optimisation and model validation

Analysis of variance (ANOVA) was utilised for statistical validation of polynomial equations generated by Design expert software (Stat-Ease Inc., ver. 8.0.1, Minneapolis, USA). An overlay plot was used to generate design space and select optimised batch. Three-dimensional response surface plots were generated to validate the model [17].

Characterization microspheres

Production yield

The percent yield of microsphere was calculated based on the amount of drug and polymer used for the formulation of microspheres. The yield was calculated by using the following equation [18].

$$\text{Percent yield} = \frac{W1}{W2} * 10$$

Where W1 = weight of dried microspheres

W2 = weight of rizatriptan benzoate and ethyl cellulose

Particle sizes analysis

Particle size analysis of rizatriptan benzoate is loaded ethyl cellulose microspheres was determined by an optical microscope (Unico, IP 730, NJ, USA). A little amount of dry microspheres was dispersed in cyclohexane (5 cc) (cyclohexane was selected due to insolubility of polymer and drug in it). Then the suspension was sonicated for 5 s. A small drop of suspension, thus obtained was placed on a clean glass slide. The slide containing ethyl cellulose microspheres was mounted on the stage of the microscope, and the diameter of molecules was evaluated utilising a calibrated ocular micrometre. [19, 20].

***In vitro* mucoadhesion studies**

The mucoadhesive property of microspheres was determined by mucoadhesion apparatus (fabricated in the laboratory). For study purposes, the sheep nasal mucosa was isolated by cutting nose bone with the help of a bone cutting tool. Then mucosal portion was separated slowly from bone by using blunt forceps within 2 h of sacrifice and washed with isotonic saline solution. Accurately weighed the quantity of microspheres was placed on the mucous membrane, which was confiscated over a plate and phosphate buffer pH 6.6 (37 °C) was appended at a rate of 2 ml/min and flow was regulated by means of the burette. The percent mucoadhesion was determined by looking at the amount of microspheres adhered to the mucosa and total amount of microspheres initially applied to mucous. The percent mucoadhesion was calculated utilising the following equation after 2 h [21].

$$\% \text{ Mucoadhesion} = \frac{\text{Amount of microsheres adhered to mucosa}}{\text{Total amount of microspheres applied to mucosa}} * 100$$

Drug loading and entrapment efficiency

Fifty mg of microspheres was taken and crushed in a glass mortar and pestle. The resulting powdered microspheres were suspended in 50 ml phosphate buffer (pH 6.6). The mixture was stirred using the magnetic stirrer for 24 h. The solution was strained and the filtrate was analysed spectrophotometrically (UV 1800, Shimadzu, Japan) at 278 nm. The drug loading and entrapment efficiency (%) was calculated by applying the following equations [22, 23].

$$\text{Drug loading} = \frac{\text{Amount of drug in microspheres}}{\text{Amount of microspheres formed}} * 100$$

$$\text{Entrapment Efficiency} = \frac{\text{Amount of drug in microspheres}}{\text{Amount of drug used in formulation}} * 100$$

Scanning electron microscopy (SEM)

The surface characteristic of the optimised batch (D10) was analysed by scanning electron microscope (SEM). The microspheres were placed on double-sided tape that had previously been secured on aluminium stubs, and the microspheres were observed by scanning electron microscope (JSM 6510 LV, JEOL DATUM Ltd., Japan) operated at a voltage of 10 kV and magnification of 3000x [24].

Differential scanning calorimetry (DSC)

The thermal nature of rizatriptan, blank microspheres and rizatriptan-loaded microspheres (Batch D10) was determined using differential scanning calorimeter (DSC 4000, Perkin Elmer, USA). Five mg of rizatriptan microspheres was accurately weighed and hermetically sealed in aluminium pans. Thermograms were obtained by heating samples at a constant rate of 10 °C/min and the over the temperature interval of 30–300 °C under a nitrogen purge of 20 ml/min [25].

***In vitro* diffusion study**

Multiple Franz's diffusion cell (12 ml capacity; 10.17 cm^2 area) (Orchid scientific, FDC-06, India) was used to study the *in vitro*

diffusion of the optimised microsphere batch (D10) across the sheep nasal mucosa (thickness: ~100 µ) as a permeation barrier. The microspheres equivalent to 5 mg of rizatriptan benzoate was spreaded over the membrane into donor compartment already containing 3 ml simulated nasal fluid (monosodium phosphate anhydrous (7.5 mmol), disodium phosphate anhydrous (3 mmol), sodium chloride (150 mmol), potassium chloride (40 mmol) and calcium chloride (5 mmol)) [26] and receptor compartment was filled with phosphate buffer solution pH 6.6 (12 ml) (pH same as that of nasal cavity). The temperature was maintained at 37±0.5 ℃ with the aid of a circulating water bath. Samples were periodically withdrawn at 5 min, 15 min, 1 h, 2 h, 4 h, and 6 h and replaced with the same quantity of fresh buffer solution. The samples were filtered and examined using a spectrophotometer at 278 nm [27].

RESULTS AND DISCUSSION

Holding in mind industrial preference, microspheres was developed using water as an external phase by a solvent evaporation method in preliminary work. As rizatriptan benzoate is hydrophilic in nature, it is likely to partition into the aqueous medium, leading to low entrapment efficiency (<20%) even after optimisation of process and formulation parameters. Hence, the effort was made to encapsulate rizatriptan benzoate with sufficiently high entrapment efficiency by a W/O/W double emulsion method using a non-aqueous processing medium. It is a simple and rapid method for fabrication of microspheres.

Various formulation factors like polymer concentration, a drug to polymer ratio, the concentration of stabiliser as well as process parameters like stirring speed, stirring time and volume of external phase were studied during preliminary trials (Data not shown). It is reported that magnesium stearate can be utilised as a stabiliser and it may cause an impingement on the size as well as drug release from microspheres [28]. It was likewise discovered that polymer concentration, a drug to polymer ratio and concentration of stabiliser were found equally significant components of product characteristics. Hence, these four factors were selected for optimisation using 2^{4-1} fractional factorial design.

Preparation of microspheres

Eight batches were prepared by the W/O/W double emulsion method as per factorial design, in which polymer concentration (X_1:2-5%), drug to polymer ratio (X_2:1:2-1:6), amount of liquid paraffin (X_3:100-200 ml), amount of magnesium stearate (X_4:100-150 mg) were selected as independent variables and % practical yield (Y1), particle size (Y2), % mucoadhesion (Y3), % entrapment efficiency (Y4) and % drug loading (Y5) of the microspheres were taken as the dependent variables (table1 and 2). Amongst all the responses, percent entrapment efficiency, % mucoadhesion and drug diffusion at 6 h were treated using design expert software.

Characterization of microspheres

Production yield

The yield of production was in the range 50-78 %. The production yield depends on the quantity of drug loaded into the microspheres.

Particle size

The mean particle size of microspheres ranged from 42 to 50 µm (table 2), indicated narrow particle size distribution. The narrow particle size distribution was considered as a prerequisite for nasal administration. It has been reported that particles smaller than 1 mm directly pass the nasal cavities with the inspired air, whereas particles larger than 10 µm deposits at the anterior parts of the nose [24].

In vitro mucoadhesion

In vitro mucoadhesion studies give information about adhesive properties of the developed formulation at the site of absorption. The results showed that the microspheres remained adhered on the nasal mucosa for required time. The proportion of the adhered microspheres was expressed as percentage mucoadhesion. For optimised batch D10, percentage mucoadhesion was found to be 67%. Increase in concentration of ethyl cellulose further increased the mucoadhesion. Most of the studies showed that most important condition for a good mucoadhesion is the high flexibility of polymer structure and presence of polar functional groups. The cross-linked microspheres are more rigid as compared to non-cross-linked microspheres. *In vitro* mucoadhesion studies cannot mimic *in vivo* condition but *in vitro–in vivo* correlation can be established. [29].

Drug loading and entrapment efficiency

The encapsulation efficiency determines the percentage of encapsulated drug with respect to the total drug introduced into the polymer solution. The concentration of polymer showed a significant difference in encapsulation efficiency.

The encapsulation efficiency was in the range of 62.55 to 95.77 (table 2). The study showed that increase in the polymer concentration resulted into higher encapsulation efficiency. This might be due to the higher viscosity of the polymer solutions reduced the escaping of drug into the external phase, which resulted into higher drug entrapment. The entrapment efficiency of batch D10 was 84.66% [2].

Drug loading was found to be between 7 to 30 %, is inversely proportional to polymer concentration and also to the drug to polymer ratio (table 2).

Scanning electron microscopy

The surface morphology of optimised formulation was examined by scanning electron microscopy as shown in fig. 1.

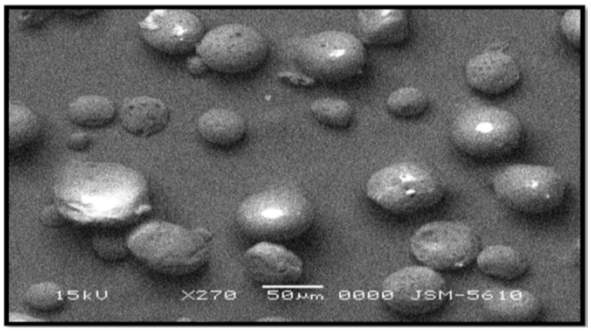

Fig. 1: SEM image of optimised batch

Microspheres were spherical in shape and possessed a smooth surface; such morphology shows a good deposition pattern in the nasal cavity. The further majority of particles were having a particle size less than 50 µm, which is the requisite of the nasal formulation.

Table 2: Evaluation results of microspheres

Batch No	% Production yield	Particle size	% Mucoadhesion	PEE	% Drug loading
D1	55.12±4.1	42.87±0.88	47±2.31	68.09±0.25	25.91±0.78
D2	50.58±5.3	49.10±0.33	68±1.75	86.18±0.23	12.27±0.65
D3	78.00±4.3	47.05±1.45	75±1.02	90.21±0.85	27.84±1.03
D4	76.47±3.3	44.76±.0.55	52±0.89	66.68±0.56	7.50±0.89
D5	54.56±4.2	46.70±0.25	70±2.22	95.77±0.73	30.31±0.75
D6	68.91±2.3	43.68±0.18	55±2.14	70.85±0.69	8.65±0.58
D7	64.12±3.5	41.63±1.25	51±1.81	62.65±0.65	17.35±1.02
D8	70.04±4.9	48.56±2.10	72±1.85	80.17±0.35	10.82±2.41

Differential scanning calorimetry

The thermogram of rizatriptan benzoate exhibited a sharp endothermic peak at 196.05 °C, signifying its melting point which was reported in the literature fig.2a. Characteristic peaks of rizatriptan benzoate were disappeared in the drug-loaded microspheres. This indicates that rizatriptan benzoate was uniformly dispersed and encapsulated in the polymeric microspheres show an ever peak of ethyl cellulose was observed at 183.63 °C fig. 2b.

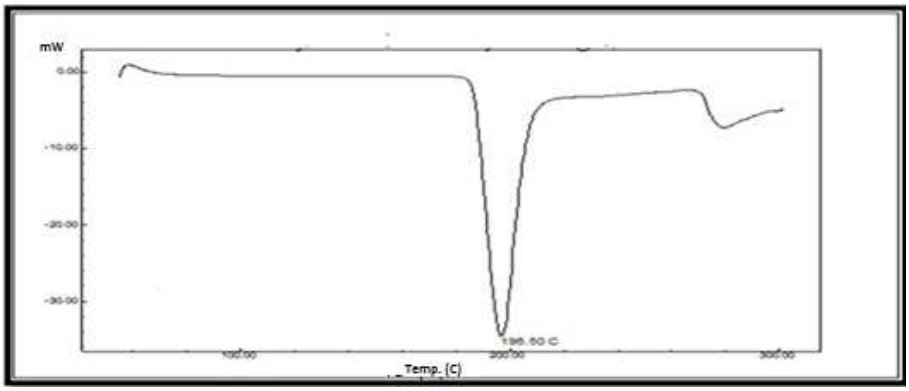

Fig. 2a: DSC spectra of rizatriptan benzoate

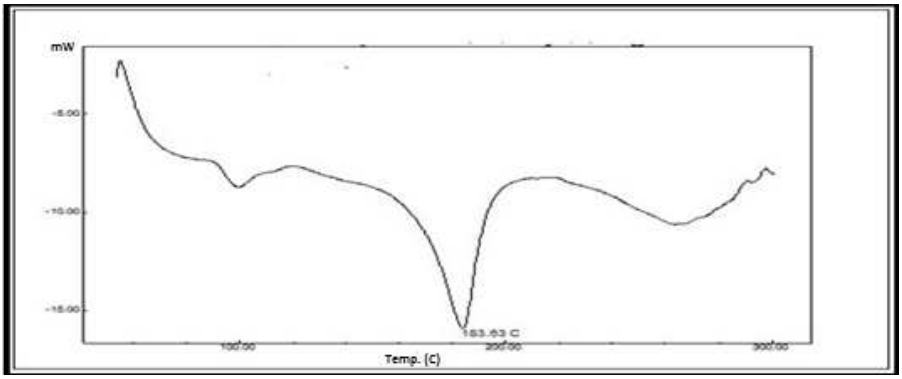

Fig. 2b: DSC spectra of rizatriptan benzoate loaded microspheres

***In vitro* diffusion**

The *in vitro* diffusion study of a batch D10 of rizatriptan benzoate loaded microspheres was carried out using the sheep nasal mucosa. The result of *in vitro* diffusion study is represented in fig. 3.

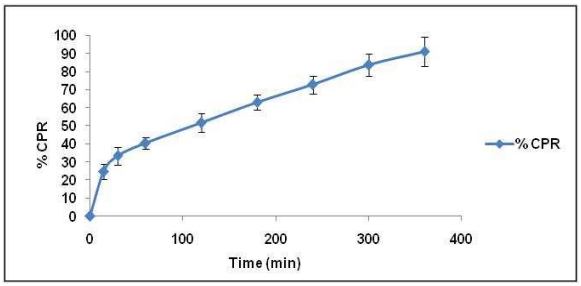

Fig. 3: *In vitro* diffusion study of optimised batch (D10) (n=3)

The percent drug permeated at 6 h was 66.6% which indicate incomplete drug diffusion. The absorption will depend on the retention of microspheres in the nasal cavity.

Statistical Interpretation

A) For percent entrapment efficiency (PEE)

The polynomial equation for PEE was generated using multiple linear regression analysis. The equation was derived as follows:

$$PPE = 77.55 + 10.58 * X1 - 1.53 * X2 - 2.67 * X3 - 0.24 * X4 - 3.33 * X1X3 + 10.17 * X1X3 + 0.18 * X1X4$$

The results indicated that the concentration of polymer has a high positive impact on entrapment of the drug. Therefore with increased in concentration of polymer, PEE was also increased (fig. 4). The drug to polymer ratio had shown the negative impact on PEE; it may be due to a higher proportion of the drug in comparison with the polymer. The volume of light liquid paraffin, as well as the amount of stabilizer also, has shown negative effects on PEE. Further, the regression statistics showed that the R^2value 0.9998, which indicates a good fit.

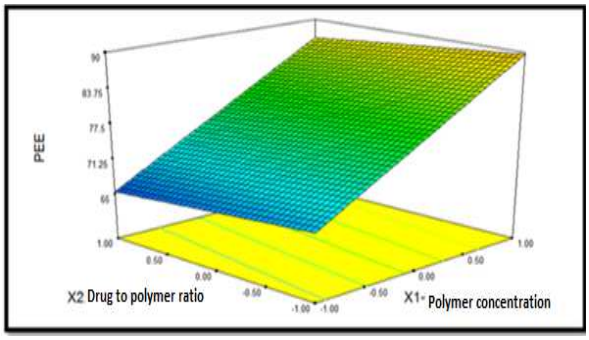

Fig. 4: 3D-surface graph for percentage entrapment efficiency

B) % CPR for 6 h

The polynomial equation for drug release was also generated using multiple linear regression analysis as under:

$$\% \text{ CPR} = 77.81 - 18.31 * X1 - 2.13 * X2 + 1.75 * X3 - 5.93 * X4 - 2.59 * X1X2 + 1.65 * X1X3 + 3.70\ X1X4$$

The concentration of polymer had a negative significant effect on % CPR after 6hdue to release retarding nature of polymer (fig. 5). Further increased in the proportion of drug with respect to polymer also reduced the release rate of rizatriptan benzoate. Hydrophobicity of magnesium stearate might also be responsible for retardation in drug release indicated by negative signs of the coefficient. The volume of liquid paraffin had a positive effect on drug release which might be due to larger volume available for the dispersion, resulted into a smaller size of microspheres with higher surface area. Further, the regression statistics showed that the R^2value was 0.9424, which indicated a good fit.

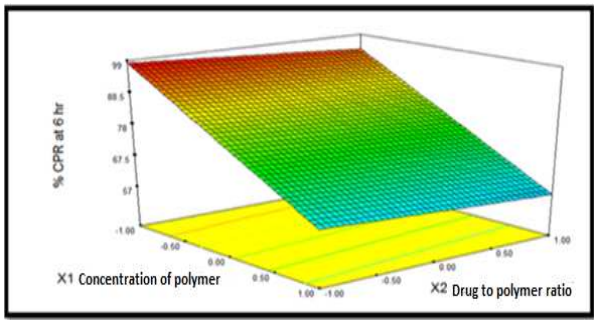

Fig. 5: 3D-surface graph of % CPR at 6thh

C) Percent mucoadhesion (% MA)

The polynomial equation was generated for mucoadhesion using multiple linear regression analysis. Full model equation was as follows:

$$\% \text{ MA} = +61.25 + 10.00 * X1 + 0.50 * X2 + 1.25 * X3 + 0.75 * X4 - 1.75 * X1X2 + 1.00 * X1X3 - 1.00\ X1X4$$

The results indicated that the concentration of polymer had a significant positive impact on % mucoadhesion (fig. 6). Hence, an increase in the concentration of polymer had resulted into higher mucoadhesion. The remaining three factors showed the little positive effect on mucoadhesion indicated by a small value of the coefficients. Further regression statistics had shown that the R^2value was 0.9814, which signifies a good fit.

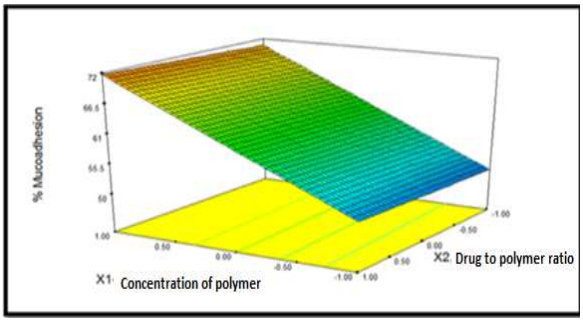

Fig. 6: 3D-surface graph for % mucoadhesion

FDA recommends the use of a systematic approach for formulation development and hence, the output can help to justify minor post-approval changes in the formulation if required. Hence, to identify the design space, overlay curve was drawn considering percent entrapment efficiency at least above 80%, drug release at 6 h from 65% to 75% and more than 60% mucoadhesion as required, responses as shown in fig. 7.

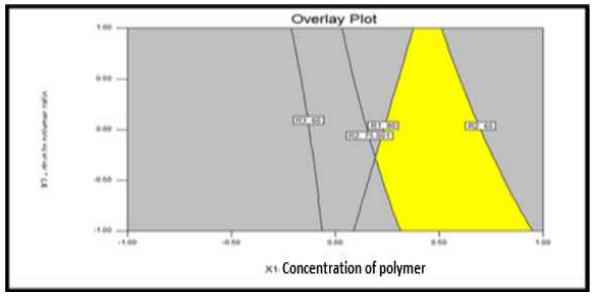

Fig. 7: Overlay plot

This curve indicates that the concentration of a polymer in the range of 2.25% to 2.75% and drug to polymer ratio in the range of 1:2 to 1:6, low level of volume of liquid paraffin and magnesium stearate, resulted into the fulfilment of all set criteria.

Two checkpoint batches suggested by design of experiment approach were prepared and evaluated. The results of the batches were predicted from polynomial equations generated from the coefficients of 2^{4-1} fractional factorial design. Predicted responses were compared with practically calculated responses (table 3). Predicted responses were similar to practical values which further validated the derived mathematical models. Batch D10 was selected as optimised batch as it was well within generated design space and showed good percentage entrapment and mucoadhesion which is desired for nasal drug delivery.

Table 3: Evaluation of checkpoint batches

Batch no	Composition				Predicted values			Observed value		
	Code value		Actual value							
	X1	X2	X1	X2	PEE	% CPRAt 6 h	% Muco	PEE	% CPRAt 6 h	% Muco
D9	-0.5	-0.5	2.75	1:3	73.02	88.02	56.0	70.46	85.05	54
D10	+0.5	+0.5	4.25	1:5	82.07	67.59	66.5	84.66	66.61	67

The developed microspheres can be delivered through powder insufflators, or microspheres can further be converted into either spray or in situ gel to facilitate delivery via the nasal route. This shall be followed by the studies using a suitable animal model to claim brain targeting.

CONCLUSION

The article demonstrated the systematic approach for the development of microspheres containing rizatriptan benzoate using ethyl cellulose as a polymer. By selecting and evaluating the process and product parameters at the appropriate level, it is possible to prepare microspheres with desired properties; such as uniform particle size distribution, high entrapment efficiency and improved surface properties. The most prominent advantage of the microspheres is that it is a free flowing powder suitable for nasal administration using powder, insufflators; this feature is useful for the convenience of administration for patients and maintaining the accuracy of drug dosing. This study concludes that the developed microspheres can be considered as a promising nasal delivery system for the administration of rizatriptan benzoate.

ACKNOWLEDGEMENT

All authors Shital Butani, Tora Shah, Kunal Parmar, and Amarjitsing Rajput declared that they have no conflict of interest. This article does not contain any studies with human and animal subjects performed by any of the authors. Authors are thankful to Dr. Ruchi Sawhney, Publication officer, Nirma University for language editing.

CONFLICT OF INTERESTS

Declare none

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How to cite this article

- Shital Butani, Tora Shah, Kunal Parmar, Amarjitsing Rajput. Development of rizatriptan benzoate micro spheres for the nose to brain targeting. Int J Appl Pharm 2016;8(4):69-74.