

## ATENOLOL MICROPARTICLES BY TWO-FACTOR TWO-LEVEL CENTRAL COMPOSITE DESIGN

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## ABSTRACT

**Objective:** The objective of this research was to formulation, optimization, and evaluation of gastric-mucoadhesive microparticles which contains selective  $\beta_1$  receptor antagonist atenolol.

**Methods:** The following chemicals were used, atenolol (Gangwal Chemicals Pvt. Ltd., Mumbai), ethyl cellulose (EC) (Loba Chemie Pvt. Ltd., Mumbai), Carbopol 940 (Loba Chemie Pvt. Ltd., Mumbai), liquid paraffin (Arora Pharmaceuticals Pvt. Ltd., New Delhi), and Span 80 (Central Drug House (P) Ltd., New Delhi). Microparticles were prepared by the emulsification solvent evaporation technique using polymers of Carbomer 934p (CP) and EC. Disc formulations were prepared by direct compression technique from microparticles. Microparticles of combined polymers were designed according to  $2^2$  factorial central composite design (CCD), taking EC concentration and surfactant concentration as the independent variables. A total of 13 batches were prepared. The dependent variables were percentage of % drug released and % entrapment efficiency.

**Results and Discussion:** All evaluation tests were done for the prepared 13 formulations, such as percentage entrapment efficiency, percentage drug release, swelling index, percentage yield, and particle size analysis. The entrapment efficiency of optimized formulation was found to be 72.02%. The entrapment efficiency increases with increase in EC concentration and stirring speed. Optimized formulation was further subjected to study of drug release kinetics based on the R2 value; it was observed that Korsmeyer Peppas release kinetic model was found to be best suited for formulation of atenolol with EC: carbopol 934 by solvent evaporation method.

**Conclusion:** The optimized formulation of microparticles containing atenolol was found to be homogeneous, good appearance and had well flow properties and better release kinetics.

**Keywords:** Selective  $\beta_1$  receptor antagonist, Entrapment efficiency, Design-Expert, Solvent evaporation, Variables, Central composite design.

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## INTRODUCTION

It is evident from the recent scientific and patient literature that an increased interest in novel dosage forms that are retained in stomach for a prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery in the gastrointestinal tract (GIT) is to control the gastric residence time (GRT), i.e., gastroretentive dosage form (GRDF or GRDS). GRDFs extend significantly the period of time over which the drugs may be released. They not only prolong dosing intervals but also increase patient compliance beyond the level of existing controlled release dosage form. Dosage form with prolonged GRT, i.e. GRDFs [1-3].

Mucoadhesive drug delivery systems contain a mucoadhesive polymer that adheres to the gastric mucosal surface and prolong its gastric retention in the GIT. The capability to adhere to the mucus gel layer makes mucoadhesive polymers very useful excipients in the GRRDs [3-5]. These polymers can be natural such as sodium alginate, gelatin, and guar gum or semi-synthetic polymers such as hydroxypropyl methylcellulose, Carbopol, and sodium carboxymethyl cellulose. The adhesion of polymers with mucous membrane may be mediated by hydration, bonding, or receptor. In hydration-mediated adhesion, the hydrophilic polymer becomes sticky and mucoadhesive on hydration. Bonding mediated involves mechanical or chemical bonding. Chemical bonds may involve ionic or covalent bonds or van der Waals forces between the polymer molecule and the mucous membrane [6,7]. Receptor-mediated adhesion takes place between certain polymers and specific receptors expressed on gastric cells [8,9].

## MATERIALS AND METHODS

## Materials

The following chemicals were used: Atenolol (Gangwal Chemicals Pvt. Ltd., Mumbai), ethyl cellulose (EC) (Loba Chemie Pvt. Ltd., Mumbai),

Carbopol 940 (Loba Chemie Pvt. Ltd., Mumbai), liquid paraffin (Arora Pharmaceuticals Pvt. Ltd., New Delhi), Span 80 (Central Drug House (P) Ltd., New Delhi), and ethanol (Loba Chemie).

## Methods

## Solubility study

The solubility study of drugs was performed in water, methanol, ethanol, acetone, 0.1 N hydrochloric acid (HCl), phosphate buffer pH 6.8, and phosphate buffer pH 7.4, individually by keeping the drug containing test tube on vortex mixture [10,11].

## Determination of melting point

All dynamic differential scanning calorimetry (DSC) studies of pure drug were carried out on DSC TA-60 Shimadzu thermal analyzer. The instrument was calibrated using high purity indium metal as standard. The scans were taken in nitrogen atmosphere at the heating rate of  $10^\circ\text{C}/\text{min}$  [12,13].

## Preparation of 0.1 N HCl

A 8.3 ml of concentrated HCl was taken and diluted with distilled water up to 1000 ml in a volumetric flask.

## Scanning of Atenolol in 0.1 N HCl

Accurately weight 100 mg of atenolol was diluted in 100 ml 0.1 N HCl solution. From this solution, 1 ml was pipette out in 100 ml volumetric flask and volume was made up to 100 ml with 0.1 N HCl (pH - 1.2) (conc.  $10 \mu\text{g}/\text{ml}$ ). The solution containing  $10 \mu\text{g}/\text{ml}$  of atenolol in 0.1 N HCl was scanned over the range of 200–400 nm against 0.1 N HCl as blank using double-beam spectrophotometer. The maximum absorbance obtained in graph was considered  $\lambda_{\text{max}}$  for pure drug [14,15].

### Standard Calibration Curve in 0.1 N HCl

Accurately weight 100 mg of atenolol was diluted in 100 ml 0.1 N HCl solution to get a solution containing 1000 µg/ml. From the above solution, 10 ml pipette out in 100 ml volumetric flask and diluted up to 100 ml to obtain a concentration of 100 µg/ml. This stock solution was used to prepare further dilution of standard solution. Aliquots (0.1–10 ml) of stock solution were transferred into a series of 10 ml volumetric flasks. The volume was made up to mark with distilled water to produce the concentration ranging from 1 to 100 µg/ml. The absorbance of each prepared solution was measured at  $\lambda_{\max}$  274 nm using double-beam spectrophotometer against 0.1 N HCl as blank [16,17].

### Fourier-Transform Infrared (FT-IR) Spectroscopy

The selected drug and polymers were characterized by FT-IR spectroscopy and the FT-IR spectra of the pure drug atenolol with used polymers such as EC and Carbopol 934 [18]. The spectrum was recorded for pure drug, physical mixture of combination of all the excipients and drug. The scanning range was 4000–500 cm<sup>-1</sup> [19,20].

### Formulation Development of Microparticles Containing Atenolol Using Central Composite Design (CCD).

The microspheres of combined polymers are designed according to 2<sup>2</sup> factorial CCD. EC concentration and surfactant concentration were the two independent variables. The selected variables with the actual and coded levels as per the design are represented in Table 1. The higher, lower, and the intermediate levels of each variable are coded as +1, -1, and 0, respectively [21,22]. Final formulation of all batches with their respective amounts is represented in Table 2.

### Preparation of Microparticles

The microparticles were prepared using solvent evaporation technique with polymers such as EC and Carbopol 934. The organic solvent system used was ethanol 20 ml. The polymers were dissolved in the organic solvent with continuous stirring using propeller type agitator. Slowly the drug was added with continuous stirring. The mixture was poured in 250 ml liquid paraffin containing 3% (w/v) Span 80 maintained at a temperature 50–60°C and subsequently stirred at a 900 rpm for 2.5 h. Continuous mixing and evaluated temperature may be employed to evaporate ethanol completely and microparticles were formed. The hardened microparticles were collected by filtration assembly and washed with small portions of n-hexane and air dried [23]. Total 13 formulation were prepared AT-1 to AT-13 (Composition shown in Table 3).

### Characterization of Formulation

#### % yield analysis

The prepared mucoadhesive microparticles were collected and weighed. The measured weight was divided by total amount of all non-volatile components, which were used for the preparation of microparticles [24]. The % yield was calculated using following formula:

$$\% \text{ yield} = \frac{\text{Actual weight of product}}{\text{Total weight of non volatile excipients and drugs}} \times 100$$

### Particle Size Analysis

Measurements of the particle size distribution of microparticles were carried out with a projection microscope stage micrometer which was used to calculate calibration factor. The particle size was calculated by multiplying the number of divisions of the ocular disc occupied by the particle with calibration factor. Fifty randomly chosen particles were taken to measure their individual size [25].

$$\% \text{ yeild} = \frac{\text{Total } \nu}{\text{Total } \nu}$$

Where,

n = number of microspheres observed

d = mean size range

### Drug Entrapment Efficiency

Microparticles (100 mg) were weighed and crushed with mortar and pestle, then were suspended in 10 ml of 0.1 N HCl. After 24 h, the solution was filtered and the filtrate was diluted up to 100 ml with 0.1 N HCl. Next, 2 ml from this solution was picked up; this filtrate was diluted up to appropriate dilution (10 ml); and the drug concentration was measured spectrophotometrically at 274 nm against 0.1 N HCl as a blank. Theoretical drug loading was determined by entire drug present in the polymer solution in the microparticles [26,27]. Entrapment efficiency was calculated by formula:

$$\text{Drug entrapment efficiency} = \frac{\text{Calculated drug concentration}}{\text{Theoretical drug concentration}} \times 100$$

### Flow Properties

#### Angle of repose

For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (h) above a piece of graph paper placed on a horizontal surface. Microparticles were poured through the funnel until the apex of the conical pile touched the tip of the funnel [28,29]. The angle of repose was calculated with the formula:

$$\theta = \tan^{-1}(h/r)$$

Where,

θ = angle of repose

h = height of the heap

r = radius of the heap

### Bulk Density

For the determination of bulk density, weight quantities of microparticles were introduced into graduated measuring cylinder and were tapped mechanically or either manually till a constant volume was obtained. The bulk density of microparticles depends on particle size

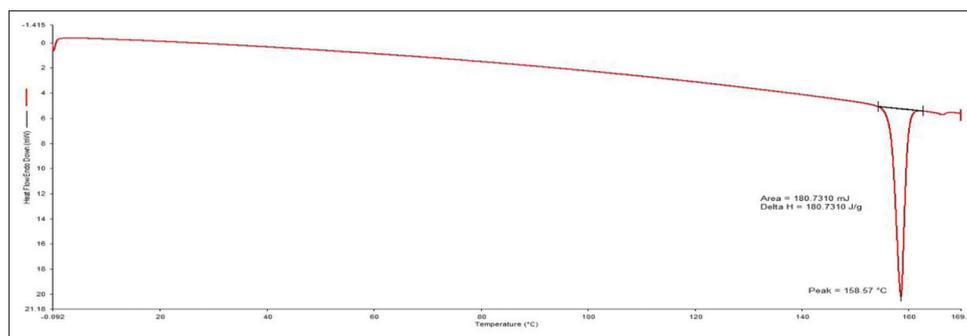


Fig. 1: Differential scanning calorimetry of atenolol

and distribution and particle shape [30,31]. Bulk density is calculated by formula:

$$\text{Bulk density} = \frac{\text{Mass of microparticles}}{\text{Bulk volume of microparticles}}$$

**Tapped Density**

The cylinder containing known amount of microparticles was given 100 taps on tap density apparatus [32]. It calculated by formula:

$$\text{Tapped density} = \frac{\text{Mass of microparticles}}{\text{Volume of microparticles after tapping}}$$

**Hausner's Ratio**

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density. Hausner value <1.25 indicates good flow, whereas greater than 1.25 indicates poor flow [33,34]. Hausner's ratio is calculated by formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

**Compressibility Index (Carr's Index)**

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property [35].

$$\% \text{ Compressibility index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

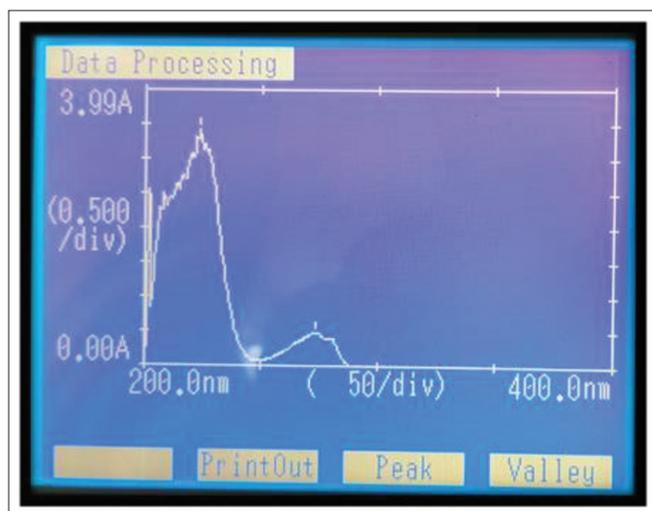


Fig. 2: λ<sub>max</sub> of atenolol in 0.1 N hydrochloric acid

**In vitro Drug Release Study**

Dissolution studies were carried out for all the formulations employing USP XXIII apparatus (paddle method) at 37±0.5°C rotated at constant speed of 50 rpm using 900 ml of 0.1 N HCl as the dissolution medium for 24 h. A sample of 100 mg of microspheres was used in each test. An aliquot of the sample was periodically withdrawn at suitable time interval and the volume was replaced with fresh dissolution medium to maintain the sink condition. The samples were suitably diluted and analyzed at 274 nm using 0.1 N HCl as blank using double-beam ultraviolet (UV)-visible spectrophotometer [36-39,15].

**Drug Release Kinetics**

In the present study, raw data obtained from *in vitro* release studies were analyzed wherein data were fitted to different equations and kinetic models to calculate the percentage drug release and release kinetics of atenolol from microparticles. Table shows the cumulative percentage drug release, log of cumulative percentage drug release, and remaining at various time points [39,28,35]. The results of *in vitro* release profile of optimized batch were fitted into four models of data treatment as follows:

- Cumulative percentage drug released versus time (zero-order kinetic model)
- Log cumulative percentage drug remaining versus time (first-order kinetics)
- Cumulative percentage drug released versus square root of time (Higuchi model)
- Log cumulative percentage drug remaining versus log time (Korsmeyer–Peppas model).

**Scanning Electron Microscopy (SEM)**

The surface morphology of the optimized drug-loaded microsphere was investigated by SEM. Studies using SEM provided a better understanding of the morphological characteristics of the microparticles [40].

**RESULTS AND DISCUSSION**

**Solubility**

Atenolol was found to be soluble in methanol, 0.1 N HCl, water, ethanol, and phosphate buffer pH 6.8.

**Melting Point**

DSC curve of atenolol showed a sharp endothermic peak near 158.57°C in Fig. 1 that is indicative of its melting temperature.

**Analytical Methodology**

*Determination of absorption maxima (λ<sub>max</sub>) of atenolol in 0.1 N HCl*

The solution of 20 µg/ml was scanned between 200 and 400 nm. The λ<sub>max</sub> was found to be 274 nm which indicates purity of sample drug atenolol. Absorption maxima of atenolol is represented in Fig. 2. The calibration curve of the drug shown in Fig. 3.

The absorbance of the drug solution was estimated at λ<sub>max</sub> 274 nm in Shimadzu UV-1700 spectrophotometer of various concentration shown in Table 4 against 0.1 N HCl (1.2 pH) as blank.

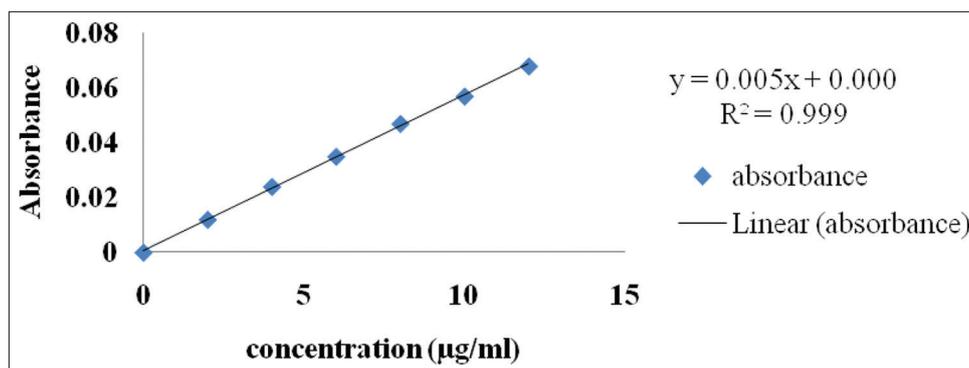


Fig. 3: Standard plot of atenolol in 0.1 N hydrochloric acid

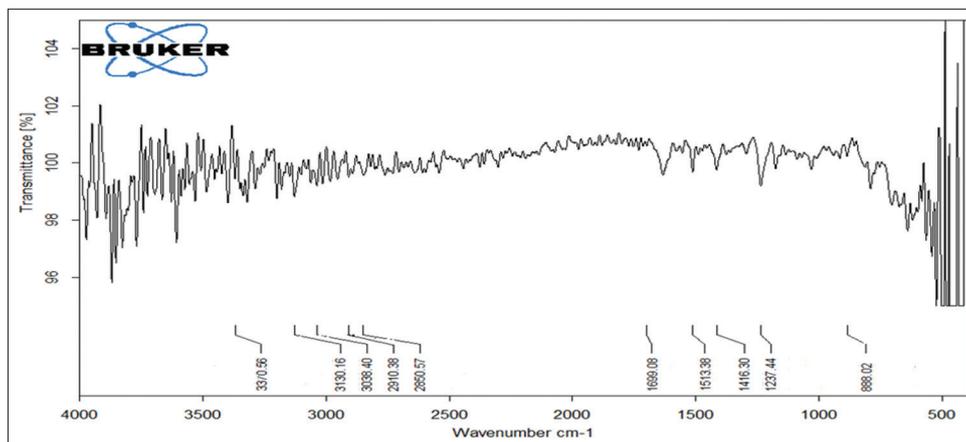


Fig. 4: Fourier transform infrared spectrum of atenolol

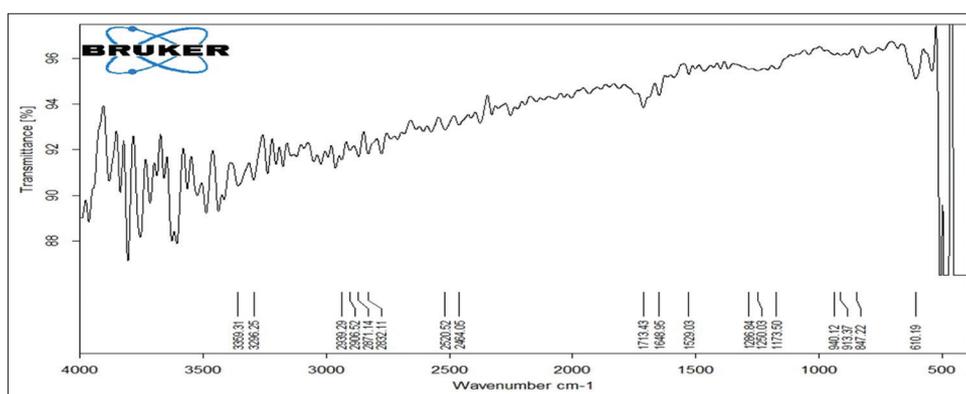


Fig. 5: Fourier transform infrared spectrum of Carbopol 940

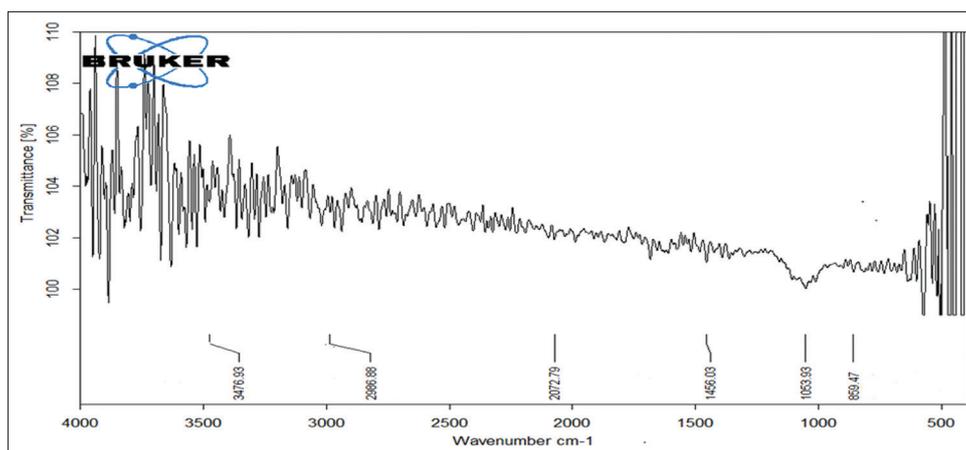


Fig. 6: Fourier transform infrared spectrum of ethyl cellulose

Table 1: Independent variables in CCD

Correlation of actual and coded value			
Factor	Coded value	Actual value	
		EC (mg) ( $X_1$ )	Surfactant conc. (%w/v) ( $X_2$ )
Low	-1	450	2
Medium	0	675	3
High	+1	900	4

CCD: Central composite design, EC: Ethyl cellulose

**FT-IR Spectral Studies of Pure Active Pharmaceutical Ingredient (API) and Physical Mixture**

The spectra obtained from FT-IR spectroscopy studied at wavelength from 4000  $\text{cm}^{-1}$  to 400  $\text{cm}^{-1}$  are shown in Figs. 4-7. FT-IR analysis revealed that there was no interaction between the drug and polymers; thus, these polymers can be conveniently used in further development of stomach specific mucoadhesive atenolol microparticles. In the present study, it has been observed that there are no chemical and physical interactions because of some bond formation between drug and polymers.

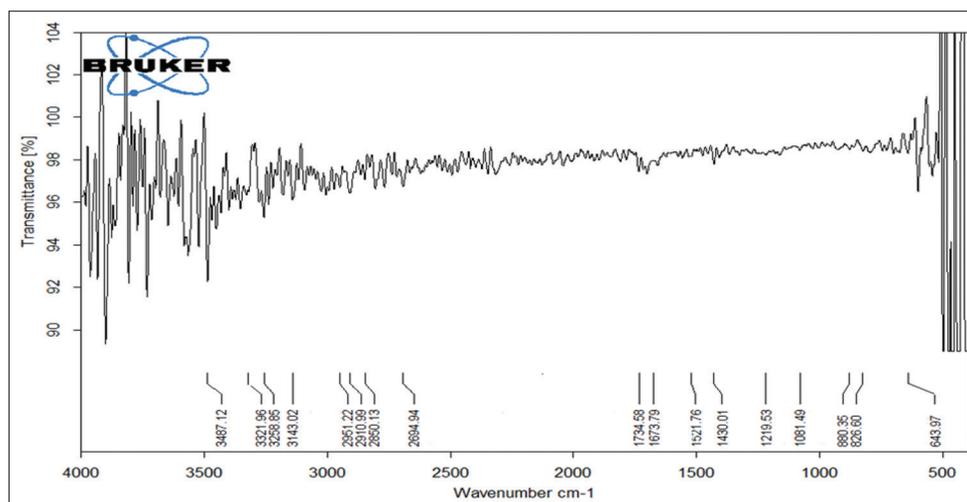


Fig. 7: Fourier transform infrared spectrum of physical mixture

Table 2: Formulation selected using CCD

S. No.	Formulation code	Independent factor	
		A: EC	B: Surfactant conc.
1.	AT-1	-1.000	-1.000
2.	AT-2	1.000	-1.000
3.	AT-3	-1.000	1.000
4.	AT-4	1.000	1.000
5.	AT-5	-1.414	0.000
6.	AT-6	1.414	0.000
7.	AT-7	0.000	-1.414
8.	AT-8	0.000	1.414
9.	AT-9	0.000	0.000
10.	AT-10	0.000	0.000
11.	AT-11	0.000	0.000
12.	AT-12	0.000	0.000
13.	AT-13	0.000	0.000

CCD: Central composite design, EC: Ethyl cellulose

### In vitro Drug Release

The release profiles of all microparticles are illustrated in Fig. 8. Initial drug release for the microparticles formulations is high. As more drugs are release from the microparticles, more channels and pores are probably produced, contributing to faster drug release rates. The reason for the burst release could be due to the presence of some atenolol particles close to the surface of the microparticles. When particles are prepared by  $O_1/O_2$  method, water-soluble drugs do not have tendency to migrate to the non-polar medium, thereby concentrating at surface of the microparticles and inducing the burst effect. Amount of drug release after 2 h shows  $29.5 \pm 0.78$ – $35 \pm 0.90$  (%) and after 24 h of different batches was in the range of  $61.32 \pm 0.99$ – $89.27 \pm 1.57$  (%).

### Particles Size Analysis

Microparticles were analyzed with calibrated optical microscope, fitted with a stage and an ocular micrometer. The particle size of microparticles was in the range of 240.7–374.1  $\mu\text{m}$ .

The microparticles size depended on the rate of polymer solidification. Deposition of polymer within droplet with the help of ethanol because ethanol is evaporated. The partitioning rate of ethanol from emulsion to external phase could be the main factor controlling the deposition rate of the polymers.

### Responses Analysis of Optimization

Statistical validation of polynomial equation generated (Table 5) by Design-Expert at R11 was established on the basis of ANOVA provision

in the software. A total of 13 run (AT-1 to AT-13) were generated. The 3-D response surface plots were obtained using this software. The resultant experiment data of response properties were compared with that of the predicted values.

### Evaluation of Results

The observed value of responses (% drug entrapment efficiency Fig. 9 and % drug release) Fig. 8 was further analyzed statistically to evaluate effect of various factors and interaction of factors using design of experiments. The optimized formulation was selected using statistical screening.

### Optimization Data Analysis

For the design, linear regression analysis method was applied using the Design-Expert software to the full polynomial equation with added interaction terms.

Polynomial equation:

$$\text{Response 1; Drug release} = + 141.28913 - 0.092751A - 14.54967B + 0.018933AB$$

$$\text{Response 2; Entrapment efficiency} = + 0.212944 + 0.189249A + 7.49470B - 0.000089AB - 0.000127A^2 - 1.74500B^2$$

### Optimization formulation

#### Final Optimized Formulation Prepared

Final batch of atenolol microparticles was prepared by emulsion-solvent evaporation method. Optimized formulation was prepared by taking 520 mg EC and 2.36 mg surfactant and was evaluated (Fig. 10).

#### Evaluation of Optimized Batch

Predicted and obtained values of responses of drug release % and Entrapment efficiency % given in Table 6. The obtained value is same as predicted value.

#### Compression of Microparticles into Disc

Disc formulations were prepared by direct compression technique from microparticles. Each disc contained 100 mg of atenolol microparticles. The disc round and flat with an average diameter of 9.4 mm and disc were compressed with a constant compression force (3.5 tones). Disc form of microparticles of atenolol shown in Fig. 11.

#### Evaluation of Optimized Batch

##### Drug entrapment efficiency

The percentage entrapment efficiency was found to be 72.02%. This shows that 72.02% of the drug is entrapped into the microparticles.

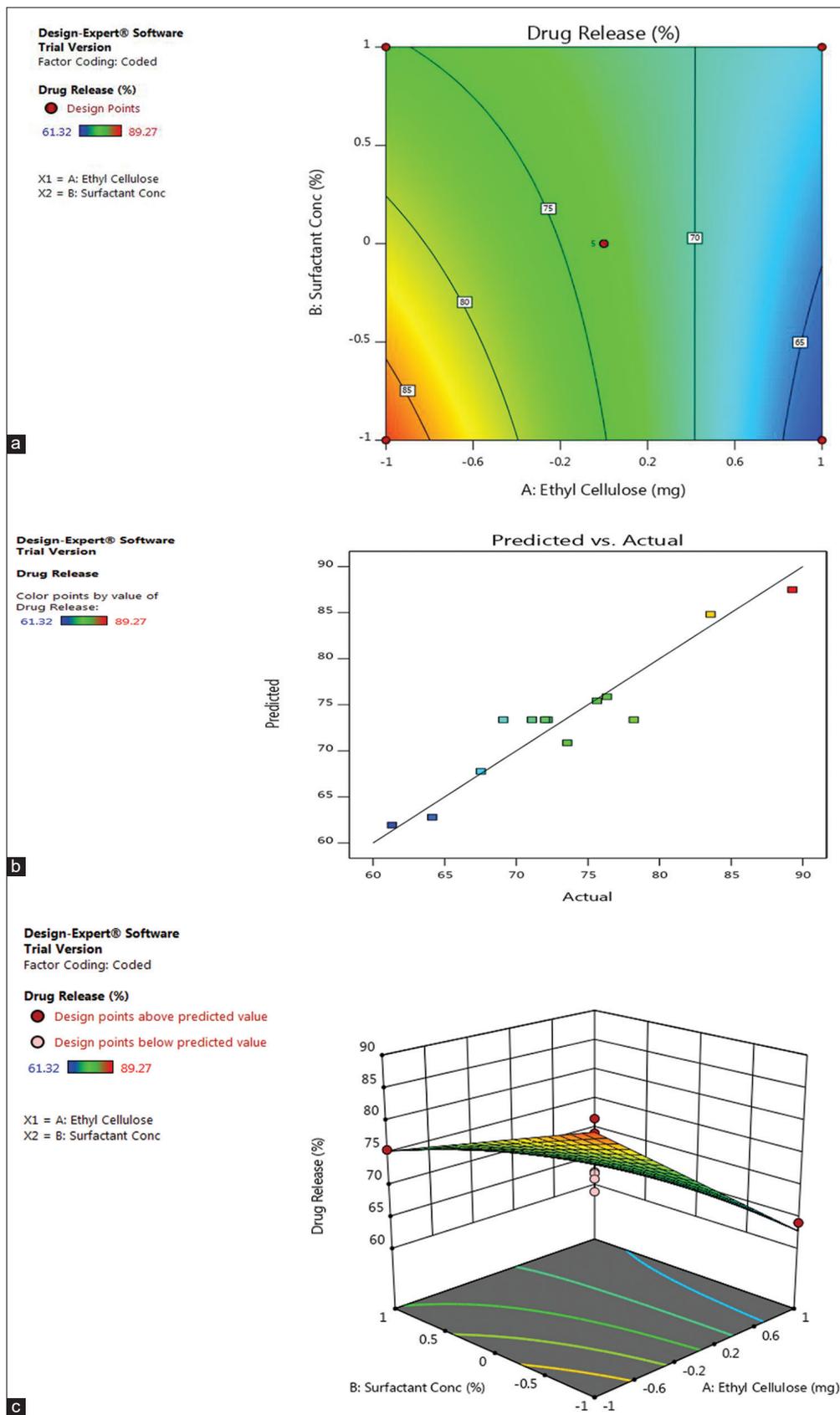


Fig. 8: Various plots showing influence of surfactant conc. and ethyl cellulose on % drug release (a) contour plot, (b) predicted versus actual, (c) response surface plot

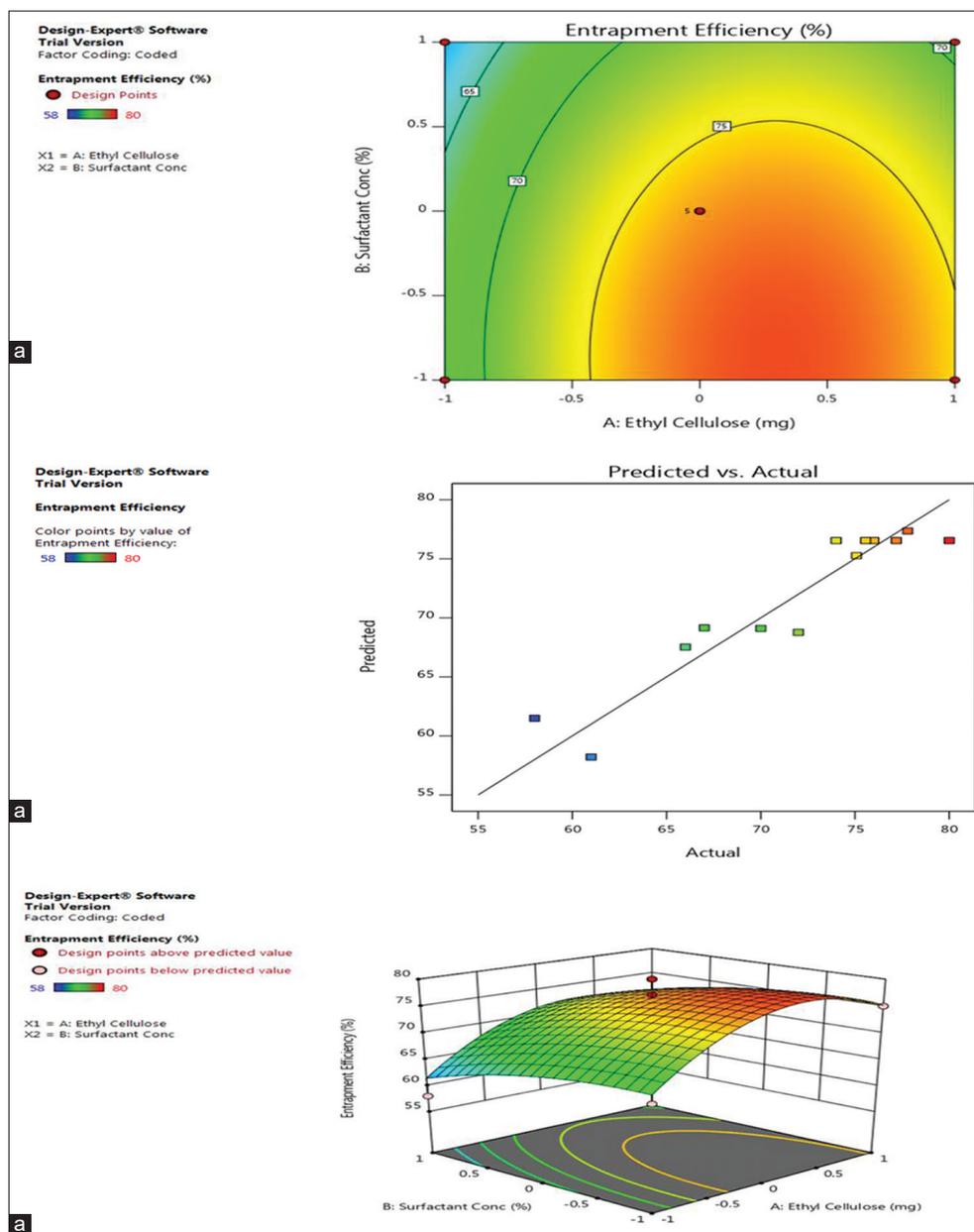


Fig. 9: Various plots showing influence of surfactant conc. and ethyl cellulose on % entrapment efficiency (a) contour plot, (b) predicted versus actual, (c) response surface plot

Table 3: Composition of different microparticles formulations with code using CCD

Formulation code	Drug (mg)	EC (mg)	Carbopol 934 (mg)	Liquid paraffin (ml)	Ethanol (ml)	Span 80 (% w/v)
AT-1	50	450	225	125	20	2
AT-2	50	900	225	125	20	2
AT-3	50	450	225	125	20	4
AT-4	50	900	225	125	20	4
AT-5	50	356.80	225	125	20	3
AT-6	50	993.20	225	125	20	3
AT-7	50	675	225	125	20	1.59
AT-8	50	675	225	125	20	4.41
AT-9	50	675	225	125	20	3
AT-10	50	675	225	125	20	3
AT-11	50	675	225	125	20	3
AT-12	50	675	225	125	20	3
AT-13	50	675	225	125	20	3

CCD: Central composite design, EC: Ethyl cellulose

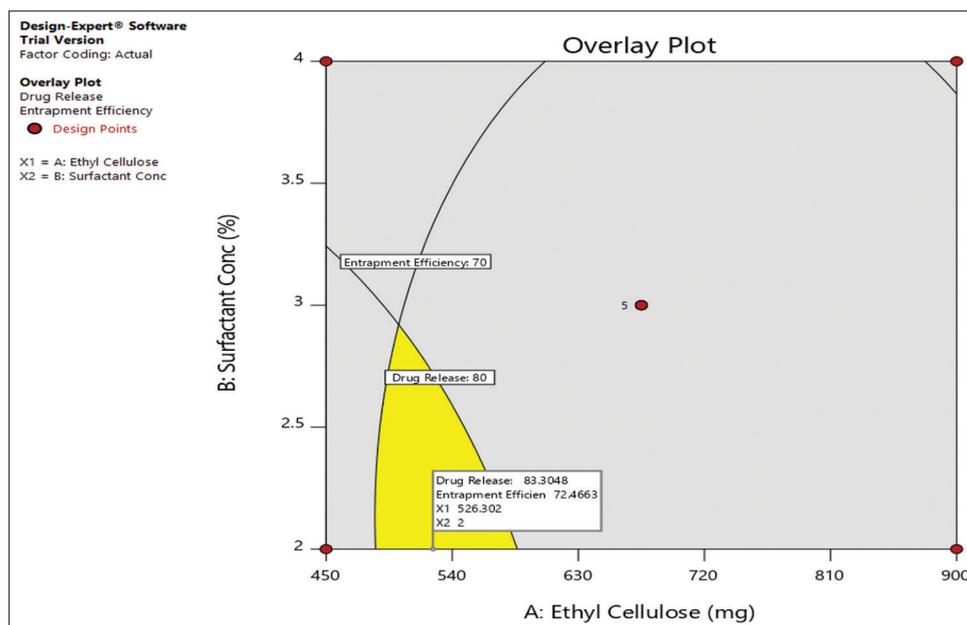


Fig. 10: Optimized formulation solution with desirability

Table 4: Concentration and corresponding absorbance in HCl

S. No.	Concentration (µg/ml)	Absorbance at 274 nm±SD
1.	0	0
2.	2	0.012±0.001
3.	4	0.024±0.002
4.	6	0.035±0.004
5.	8	0.047±0.006
6.	10	0.057±0.005
7.	12	0.068±0.007

HCl: Hydrochloric acid

Table 5: The composition and observed response from randomized runs in CCD

Run	Factor 1 A: EC Mg	Factor 2 B: Surfactant conc. %	Response 1 Drug release %	Response 2 Entrapment efficiency %
1.	0.000	0.000	71.09	80
2.	0.000	0.000	69.08	75.56
3.	0.000	0.000	72	74
4.	-1.000	1.000	75.63	58
5.	0.000	0.000	78.2	77.19
6.	1.414	0.000	61.32	70
7.	0.000	1.414	73.55	72
8.	-1.414	0.000	83.56	61
9.	1.000	1.000	67.52	67
10.	0.000	-1.414	76.32	77.8
11.	1.000	-1.000	64.12	75.08
12.	0.000	0.000	72.19	76
13.	-1.000	-1.000	89.27	66

CCD: Central composite design, EC: Ethyl cellulose

Table 6: Predicted and obtained values of responses

Response	Predicted	Obtained
Drug release %	81.95	81.94
Entrapment efficiency %	72.07	72.07

Table 7: Kinetics of drug release of atenolol microparticles

Plot	R <sup>2</sup>
Zero order	0.696
First order	0.774
Higuchi	0.837
Peppas	0.989

*% yield*

The percentage yield of atenolol microparticles was found to be 94.26%.

*Particle size*

The particle size yield of atenolol microparticles was found to be 292.5 µm.

*Swelling index*

The swelling index of atenolol microparticles was found to be 95.6%.

*Angle of repose*

The angle of repose of atenolol microparticles was found to be 18.25°θ. It indicates the good flow property for microparticles.

*Bulk density*

Bulk density of optimized batch was found to be 0.131 g/cm<sup>3</sup>.

*True density*

True density of optimized batch was found to be 0.156 g/cm<sup>3</sup>.

*Carr's index*

Carr's index was found to be 16.02%. This was <20 indicating good flow characterizes.

*Hausner's ratio*

Hausner's ratio was found to be 1.19.

**In vitro Dissolution Study and Kinetic Modeling of Drug Release Studies**

The optimized batch prepared mucoadhesive microparticles of atenolol were subjected to *in vitro* release studies, these studies were carried



Fig. 11: Disc form of microparticles of atenolol (side and top view)

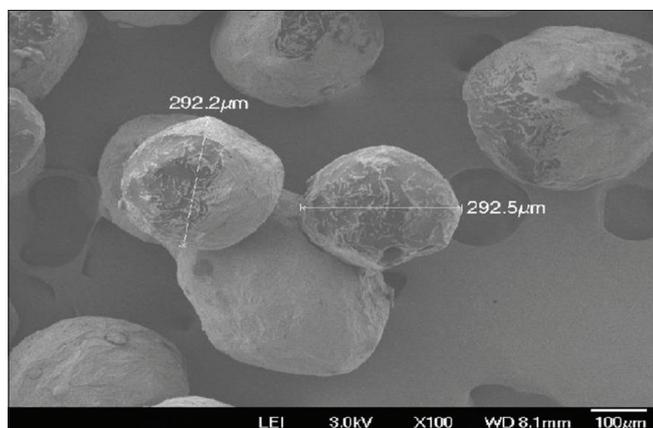


Fig. 12: Scanning electron microscopic picture of atenolol microparticles

out using Shimadzu, dissolution apparatus with 0.1 N HCl (pH 1.2) of dissolution media. The kinetic values obtained for formulation are shown in Table 7. The values of *in vitro* release were attempted to fit into various mathematical models.

The data obtained for *in vitro* release were fitted into equations for zero-order, first-order, Higuchi, and Korsmeyer–Peppas release models. The interpretation of data was based on the value of the resulting regression coefficients.

From these values, it was observed that the Korsmeyer–Peppas release model was found to be best suited with  $R^2=0.989$ .

#### SEM

Scanning electron photomicrographs of optimized drug-loaded mucoadhesive microparticles are shown in Fig. 12. The surface morphology of prepared microparticles shows spherical shape with a slightly rough surface which may be because of surface-associated drug crystals.

#### CONCLUSION

The objective of this project was formulation and evaluation of microparticles containing atenolol. Atenolol was selected for the formulation of oral mucoadhesive drug delivery system. Antihypertensive drugs are predominantly used to treat hypertension and prevent complications of high blood pressure, such as stroke and myocardial infarction.

To formulate optimize mucoadhesive microparticles containing atenolol as API, CCD was employed using EC polymer and Span 80 as surfactant (independent variables) and other excipients Carbopol 934, liquid paraffin, ethanol, and n-hexane. The percentage drug entrapment efficiency and percentage drug release were selected as dependent variables and the best formulation was selected by the Design–Expert version 11. The optimized formulation of microparticles containing atenolol was found to be homogeneous, good appearance and had well flow properties and better release kinetics.

Thus, it may be concluded that atenolol is believed to be a widely used medication for antihypertensive activity. Further studies (such as animal testing) can be conducted to make it viable for commercial product.

#### ACKNOWLEDGMENT

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#### AUTHORS' CONTRIBUTIONS

All the authors have contributed equally.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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