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Research Article

A Novel Approach for the Treatment of Hypertension: Gastroretentive Microballoons of Atenolol

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ABSTRACT

The formulation of atenolol-loaded microballoons involved the use of Eudragit RS 100, HPMC K4 M as a polymer, and span 80 as a surfactant. The microballoons were prepared by an emulsion solvent diffusion (non-aqueous) using liquid paraffin, methanol, and dichloromethane as a processing medium. The Box-Behnken design was utilized to get optimized formulation using a concentration of HPMC K4 M (A), Concentration of Eudragit RS 100 (B), Concentration of surfactant (C), and stirring speed (D) as an independent parameter while, Particle size (Y1), entrapment efficiency (Y2) and %buoyancy (Y3) using as a dependent parameter. For the optimised formulation, the mean particle size was 85.878 ± 1.063 µm, entrapment efficiency was 92.26 ± 1.65%, and buoyancy was 89.19 ± 1.48% found. An image of the formulation taken using a scanning electron microscope (SEM) reveals discrete particles with a smooth surface texture, a hollow interior, a spherical shape, and a particle size of less than 200 µm. The FTIR study confirms there was no interaction between the drug and excipients. The *in-vitro* drug release study found that atenolol-loaded microballoons released the drug for up to 12 hours as compared to the pure drug. This was due to increasing the gastric residence time and absorption area in the stomach. The drug release kinetic study reveals that it follows the Higuchi model and the drug release mechanism was type II transport which was obtained from the Korsmeyer Peppas model. The stability study shows that there is no significant change in the optimized microballoons for 30 days as per ICH guidelines.

Introduction

In the medical field, more than 60% of the drugs are orally[1] administered while having the most beneficial route for application of offer drugs in a solid form like a tablet, capsule, or powder and also for liquid products like suspension, emulsion, etc. for therapeutic as well as local action. Because the oral route provides ease of administration, different dose of the drugs can be administered and also provides high patient compatibility. Drugs that are easily absorbed from the GI tract and have a shorter half-life are eliminated quickly from systemic circulation. Frequent dosing of these drugs is thus required to achieve suitable therapeutic activity. So to avoid these limitations, modified oral sustained controlled-release formulations have been developed based on many decades of research. Gastro retentive drug delivery system (GRDDS) is an orally controlled drug release system and a novel approach. GRDDS works by increasing the retention time of a drug for a longer period in the stomach. [2,3]

Microballoons are a type of floating drug delivery system (FDDS) that is a part of the GRDDS. A non-effervescent approach prepares microballoons. In a general sense, microballoons are strictly spherical-shaped particles with a hollow core. They are characteristically free-flowing powders composed of proteins or synthetic polymers with a size <200 µm. Microballoons are considered one of the most favourable and unique buoyant systems in the multiple-unit system because the floating property of the microballoons is due to the hollow core or hollow space inside the matrix system.[4,5]

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After the administration of the microballoons, they come in contact with the GI fluid. The air trapped by the swollen polymer lowers the density and confers buoyancy to the microballoons. The colloidal gel barrier controls the rate of fluid penetration into the matrix system and is also responsible for drug release. As the exterior surface of the dosage form dissolves, the gel layer is maintained by the hydration of the adjacent hydrocolloid layer. However, to obtain the buoyancy of the dosage form minimum quantity of the gastric content or gastric fluid is necessary.[6,7] The drug release and better-floating properties mainly depend upon the type of polymer, plasticizer, and solvents employed for the formulation. For example, natural polymers like guar gum, chitosan, xanthan gum, gellan gum, sodium alginate, etc., and also semi-synthetic or synthetic polymers like HPMC (Methocel), Eudragit (Polymeric methacrylate), ethyl cellulose, etc. Here HPMC K4M acts as a buoyancy enhancer and Eudragit RS 100 acts as a matrix system because various grades of Eudragit like Eudragit RL, RS, NE 30D, NE 40D, and NM30D are used to form water-insoluble film coats for sustained release products and when they are mixed with any other polymer, the rate of permeability can be changed/controlled which can directly affect the rate of drug release from the complex matrix system.[8,9]

Risk factors for causing hypertension are family history, age, high salt intake, low potassium intake, obesity, smoking, excess alcohol consumption, stress, etc.[10] Atenolol is an anti-hypertensive drug used for the treatment of hypertension. It belongs to the BCS class III which has high solubility and low permeability. The protein binding of atenolol is around 6 to 16% with a half-life of about 6 to 7 hours. The conventional dose of atenolol is 50 and 100 mg.[11]

The main aim of this research work is to develop atenolol-loaded microballoons for the treatment of hypertension by increasing the gastric residence time of atenolol in the stomach. The 50% of the bioavailability of the drug is due to less drug available for therapeutic action in the body due to poor absorption and high excretion rate of atenolol through the renal route.[12] From the various research work related to microballoons, it was concluded that they can improve the gastric residence time (GRT) in the stomach by providing the floating property which enables the microballoons to float over the gastric content for a longer period while continuously releasing the drug in a controlled manner for a longer period without causing any irritation in the stomach. They improve the drug stability from various environmental factors like light, heat, and moisture, can reduce the frequency of dosing, and improves patient compliance.[13] By formulating the microballoons we can solve both major problems of less gastric residence time and less absorption of the drug from the stomach so that we may be able to improve the BA of the drug by ensuring the optimum therapeutic effects while improving patient compliance. [14]

Materials And Methods

Materials

Atenolol was obtained as a gift sample from Cadila Pharmaceuticals, Ahmedabad, India. Synthetic and semi-synthetic polymers like Ethylcellulose, HPMC K4 M, Eudragit RS 100, and Eudragit L 100 were obtained from ChemDyes Corporation. Natural polymers like Xanthan gum from ChemDyes Corporation, guar gum from Oxford Laboratory Reagent, and chitosan from AnaChem Laboratories were obtained. Solvents like chloroform, dichloromethane (DCM), acetone, and acetonitrile were obtained from ChemDyes Corporation and also methanol was obtained from the RANKEM laboratory agent. Surfactants like Span 80 and Tween 80 from ChemDyes Corporation. Liquid paraffin as a processing medium was obtained from ChemDyes Corporation.

Methods

Solubility of Drug in Different Solvents

Solubility of the drug in different solvents was done by the qualitative method. The excess amount of the drug was dissolved in 10 mL of the solvent. The solvents were sonicated for 10 minutes. The mixtures were shaken for 48 hours in an orbital shaker. The saturated solution was centrifuged at 6000 rpm for 10 minutes. The supernatant was collected, dissolved 1-mL of supernatant in 10 mL methanol and analyzed by UV-visible spectrophotometry at 226 nm. [14,15]

Selection of Excipient by Solubility Method

Solubility of various polymers in different solvents was also done by the quantitative method. The solubility determination of various polymers in various solvents was performed by adding various polymers in increments of 1-mg until they failed to dissolve further in the fixed 10 mL solvent. The amount of the polymers soluble or insoluble in solvents was determined.[9,16]

Compatibility of Drug and Excipients by FTIR

The compatibility of the drug and excipients can be done by fourier-transformed infrared spectroscopy (FTIR). In this method, the KBr pellet is grounded in a powder and mixed with the sample by using the KBr pellet press and the spectrum was taken using FTIR. FTIR spectrum of atenolol was compared with the spectrum mixture of HPMC K4M + Eudragit RS 100 + span 80 + atenolol. The disappearance of the atenolol peak or shifting of any peak of the spectra was studied.[16,17]

Formulation and Development

Method of preparation of atenolol loaded microballoons by non-aqueous emulsion solvent diffusion method.**[18,19]** In this method, all the polymers and drugs are accurately weighed and added in a solvent mixture of methanol and

Table 1: Optimization factors with different levels

Factors	*Levels*		
Independent Variables	*Low (%) (-1)*	*Medium (%) (0)*	*High (%) (+1)*
(A) Concentration of HPMC K4 M (mg)	100	300	500
(B) Concentration of Eudragit RS 100 (mg)	100	300	500
(C) Concentration of surfactant (%)	0.5	0.75	1.0
(D) Stirring speed (rpm)	500	600	700
Dependent variables	Response		
Y1	Particle size (μm)		
Y2	%Entrapment Efficiency		
Y3	%Buoyancy		

dichloromethane in the ratio of 1:1 to prepare a drug + polymer + solvent containing organic phase. Liquid paraffin was taken in a different beaker with a different concentration of Span 80 as a surfactant for the preparation of the oily phase. The oil phase was placed under constant stirring on a mechanical stirrer at different rpm speeds and maintained 40°C temperature after the constant temperature the organic phase was added drop by drop. The stirring was continued for 4 hours while continuously maintaining the 40°C temperature of the oily phase. The organic solvents will evaporate during this process and the formation of microballoons takes place. To obtain the microballoons, microballoons were separated from the liquid paraffin, washed with petroleum ether, and dried at room temperature.

Optimization of the Formulation Parameters[20]

The Box- Behnken design was used to obtain an optimized formulation using a minimum number of trial runs. Start-Ease Design Expert V10.0.0 was used for formulation optimization. A complete Box-Behnken design was utilized to study the effects of the independent variable on the dependent variables in the formulation of microballoons. The independent variables and dependent variables for design was shown in Table 1.

Interaction between the Factors

Analysis of variance (ANOVA) was used to statistically evaluate all of the collected data using DoE software. The effect of several independent factors on particle size, %EE, and %buoyancy were revealed by the ANOVA (*p-value*) results. A comprehensive polynomial model was developed after regression analysis of all formulations. The effects of independent factors on dependent variables are represented by this equation.

Preparation of Optimised Formulation based on the Desirability Function

Optimization was carried out to ascertain the level of independent variables (A, B, C, and D) that would provide data for Y1, Y2, and Y3. At the time of developing the formulation, the response has been united to design the product of the required attribute. The main function of the desirability was to join every response in a single experiment and provide the probability of perfecting the highest level for independent variables. The last optimized formulation suggested by the software was prepared and parameters were compared to the value given by the software.

Evaluation of Atenolol Loaded Optimised Microballoons [13,21-23]

Particle Size

The particle size of the microballoons was measured with a digital microscope equipped with a camera, and the mean microballoons size was determined by measuring 100 particles with a digital microscope.

Percentage Yield (%)

The percentage yield of floating microballoons was determined by dividing the product's actual weight by the total value of all non-volatile components used in the preparation of floating microballoons, as represented by the following formula:

$$\%\ \textbf{Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of drug and excipients}} * 100$$

Drug Entrapment Efficiency (%)

Microballoons, equivalent to 10 mg drug, crushed in a glass mortar. Volume was then made up to 10 mL with methanol in a volumetric flask. The solution was dissolved and filtered; the absorbance was noted at 226 nm. The amount of drug entrapped in the microballoons was calculated using the following formula:

$$\textbf{Concentration}\%\ \textbf{Entrapment Efficiency} = \frac{\text{Calculated Drug Concentraion}}{\text{Theoritical Drug Concentration}} * 100$$

In-vitro Buoyancy (%)

Microballoons (100 mg) were dispersed in USP dissolution apparatus containing simulated gastric fluid (SGF 900 mL, pH 1.2, 37°C) or 0.1 N HCL. It was stirred with a paddle at 100 rpm at 37 ± 0.5°C. After a predetermined time, the layer of floating particles was separated from the settled particle. Both fractions of particles were dried in vacuum desiccators. Both the fractions of microballoons were weighed and buoyancy was determined by using the formula:

$$Buoyancy(\%) = \frac{weight\ of\ the\ Floating\ Microballoons}{Initial\ weight\ of\ the\ Microballoons} * 100$$

In-vitro Drug Release Study (%)

The USP dissolution test apparatus II (paddle type) with the whole assembly was used to conduct an *in-vitro* drug release study. In this study microballoons containing the drug dose are applied to 900 mL of 0.1 N HCL as a dissolution medium, with stirring of 100 rpm at 37 ± 0.5°C. Samples are collected at regular intervals and analyzed at 224 nm using any appropriate analytical process, such as UV spectroscopy.

Pharmacokinetic Drug Release Modelling[24]

Various models were developed by using the *in-vitro* drug release data and some of them are:

- *Zero Order Model*

From the *in-vitro* drug release studies, the graph was plotted as the cumulative amount of drug released versus time.

$$Qt = K_0 .t$$

Where, Qt = percentage of drug released at time t and K_0 = release rate constant

- *First Order Model*

The data obtained are plotted as a cumulative log percentage of drug remaining versus time, yielding a straight line with a slope of -K/2.303.

$$Ln\ (100 - Qt) = \ln 100 - K_1 t$$

Here, K_1 = first order release rate constant.

- *Higuchi's Model*

The data obtained were plotted as cumulative percentage drug release versus square root of time.

$$Qt = K_H \cdot t\ 1/2$$

Where K_H = Higuchi release rate constant.

- *Hixson-Crowell Model*

To study the release kinetics, data obtained from *in-vitro* drug release studies were plotted as the cube root of drug percentage remaining in the matrix versus time.

$$W0\ 1/3 - W11/3 = K_{HC}.t$$

Where K_{HC}= Hixson-Crowell rate constant.

- *Korsmeyer Peppas Model*

Korsmeyer *et al*. (1983) derived a simple relationship that described drug release from a polymeric system equation

$$Qt/Q\infty = KKp.tn$$

Where, Qt/Q∞ = fraction of drug released at time t, KK_P = Korsmeyer-Peppas rate constant compromising the structural and geometric characteristics of the device, n = release exponent, which is indicative of the mechanism of drug release. Log the cumulative %drug release in matrix versus time for this model graph plotted. Various exponent values and their drug transport mechanism with their release rate as a function of time are explained in Table 2.

Characterization of Optimise Microballoons [17-18], [25-27]

FTIR Study of Microballoons

It is necessary to identify the interaction that may occur during the manufacturing process of the microballoons. The IR spectrum of formulated microballoons was measured by FT-IR spectrometer. In this process, a sample of microballoons was mixed with KBr, compressed to form a thin pellet, and then used for testing. The recording range for the measurement was 4000 to 400 cm^{-1}.

Scanning Electron Microscopy (SEM)

The external morphology of the microballoons is examined using a SEM. The SEM samples were produced by gently sprinkling microballoons powder on a double adhesive tape applied to a stub. The stubs were then coated with platinum in an argon atmosphere using a gold sputter module in a high vacuum evaporator. The samples were then randomly scanned, and photomicrographs with higher magnification were taken for surface morphology.

Stability Study

The optimised formulation was sealed in aluminium packaging that was polyethylene-coated on the inside. For three months, the samples were kept in a stability chamber (Frontline electronic and machinery Pvt. Ltd)

Table 2: Interpretation of diffusional release mechanism from polymeric film

Release exponent (n)	*Drug transport mechanism*	*Rate as a function of time*
0.5	Fickian diffusion	t-0.5
0.45 < n = 0.89	Non-Fickian transport	tn-1
0.89	Case II transport	Zero Order release
Higher than 0.89	Super case II transport	tn-1

Table 3: Composition and optimization of microballoon formulation

		Independent Variables				*Dependent variables*		
Batch No:	*Drug (mg)*	*Concentration Of HPMC K4m (mg) (A)*	*Concentration Of Eudragit RS 100 (mg) (B)*	*Surfactant Concentration (%) (C)*	*Stirring Speed (rpm) (D)*	*Particle size (μm) (Y1)*	*Entrapment Efficiency (%) (Y2)*	*In-vitro Buoyancy (%) (Y3)*
MB 1	100	100	100	0.75	600	65.71 ± 0.74	49.87 ± 1.90	71.86 ± 1.33
MB 2	100	500	100	0.75	600	47.71 ± 1.12	78.36 ± 1.54	87.73 ± 0.89
MB 3	100	100	500	0.75	600	72.77 ± 1.71	68.96 ± 1.70	60.69 ± 1.06
MB 4	100	500	500	0.75	600	72.44 ± 1.30	65.41 ± 1.02	77.82 ± 1.01
MB 5	100	300	300	0.5	500	82.48 ± 1.64	70.45 ± 1.43	81.83 ± 0.61
MB 6	100	300	300	1	500	80.82 ± 2.29	65.27 ± 1.08	69.82 ± 0.80
MB 7	100	300	300	0.5	700	56.81 ± 2.59	78.62 ± 2.05	85.01 ± 0.94
MB 8	100	300	300	1	700	79.59 ± 1.32	83.74 ± 1.41	64.96 ± 1.53
MB 9	100	100	300	0.75	500	78.84 ± 2.01	73.79 ± 2.04	79.34 ± 0.72
MB 10	100	500	300	0.75	500	82.44 ± 2.05	71.12 ± 2.02	80.22 ± 0.32
MB 11	100	100	300	0.75	700	57.74 ± 1.80	69.18 ± 0.79	73.11 ± 0.60
MB 12	100	500	300	0.75	700	59.76 ± 1.40	84.29 ± 1.66	76.96 ± 1.38
MB 13	100	300	100	0.5	600	61.28 ± 1.95	72.41 ± 0.75	92.56 ± 1.16
MB 14	100	300	500	0.5	600	79.28 ± 0.83	87.05 ± 1.60	85.23 ± 0.48
MB 15	100	300	100	1	600	64.31 ± 2.07	75.24 ± 1.75	65.21 ± 0.99
MB 16	100	300	500	1	600	75.47 ± 0.67	85.9 ± 1.82	62.59 ± 0.80
MB 17	100	100	300	0.5	600	72.96 ± 1.64	60.46 ± 0.83	86.01 ± 0.70
MB 18	100	500	300	0.5	600	77.54 ± 0.96	86.09 ± 0.98	86.23 ± 1.35
MB 19	100	100	300	1	600	71.12 ± 0.83	79.45 ± 1.20	68.96 ± 1.17
MB 20	100	500	300	1	600	71.55 ± 1.59	68.42 ± 1.23	71.08 ± 0.71
MB 21	100	300	100	0.75	500	73.16 ± 0.91	73.16 ± 0.91	82.31 ± 1.04
MB 22	100	300	500	0.75	500	91.89 ± 0.9	91.89 ± 0.9	82.41 ± 0.82
MB 23	100	300	100	0.75	700	81.41 ± 0.73	81.41 ± 0.73	79.96 ± 0.85
MB 24	100	300	500	0.75	700	88.76 ± 1.06	88.76 ± 1.06	78.42 ± 0.81
MB 25	100	300	300	0.75	600	85.31 ± 0.85	85.31 ± 0.85	77.94 ± 0.28

Mean ± SD, n = 3

at 40°C and 75% (RH) Relative humidity. After the studies, samples were examined for physical appearance and drug entrapment efficiency.

Results and Discussion

Solubility of Drug in Different Solvents

The solubility of atenolol was done by the qualitative method. The amount of drug dissolved in solvents like DCM, methanol, acetone, chloroform, acetonitrile, and isopropyl alcohol was observed. Atenolol shows the highest amount of solubility in the methanol compared with all the other solvents but DCM shows the second highest solubility compared with other solvents. So methanol was selected after the solubility study.

Solubility of Drug in Different Excipients

Solubility of various polymers in different solvents was done by quantitative method. The amount of synthetic or semi-synthetic polymers like Eudragit RS 100, Eudragit L 100, HPMC K100M, HPMC K4 M, ethyl cellulose, and natural polymers like xanthan gum, tragacanth gum, guar gum, and chitosan was dissolved in solvents like DCM, methanol, acetone, and chloroform. All the remaining polymers are either insoluble or slightly soluble in their respective solvents. From the results of the polymer solubility study, it can conclude that HPMC K4 M and Eudragit RS 100 are soluble in methanol and DCM. So, HPMC K4 M and Eudragit RS 100 were selected.

Compatibility of Drug and Excipients by FTIR

The drug and excipients compatibility study were checked by comparing the pure drug spectra with the physical mixture of drug and excipients. In case of pure drug C-H stretching was at 2870 cm^{-1}, C=C stretching was at 1584.24 cm^{-1}, O=C-NH_2 stretching was at 1649.8 cm^{-1} and AR-O-R group was at 1242 cm^{-1} observed. From the spectrum Figs. 1 and 2 it can be concluded that no major changes

Table 4: Pharmacokinetics model's R2 value

S. no.	*Type of Kinetic Model*	*R2 value*
1	Zero Order	0.9525
2	First order	0.9037
3	Huguchi model	0.9837
4	Hixson-Crowell	0.9718
5	Korsmeyer-Peppas	0.9837 with exponent value (n) = 0.98

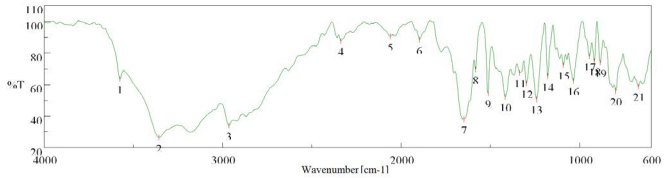


Fig. 1: FTIR spectra of pure drug ATL

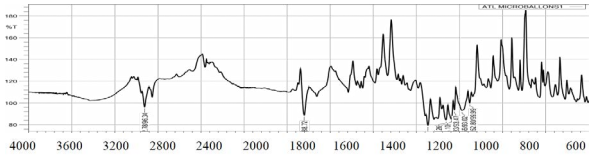
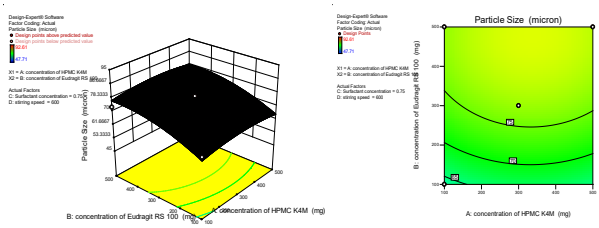


Fig. 2: FTIR Spectra of physical mixture of drug and excipients



(A) (B)

Fig. 3: (A) 3D Response surface plot, (B) Contour plot for particle size

were observed in the peak of the drug and physical mixtures of drug and excipients.

Formulation and Development

Optimization of Formulation Parameters

To obtain an optimized formulation using a minimum number of trial runs, the Box- Behnken design was used by using Start-Ease Design Expert V10.0.0. Table 3 shows that particle size varies from 47.71 ± 1.12 to 92.61 ± 1.53 µm and %EE varies from 49.87 ± 1.90% to 91.89 ± 0.9 and %buoyancy varies from 60.69 ± 1.06% to 92.56 ± 1.16%. With the help of ANOVA and constructing a polynomial equation, variation in the particle size, %EE and %buoyancy evaluated

- Y1 (Particle Size): 77.0006 + 0.7779* A + 6.59627* B + (-1.28789)* C + (-12.3788)* D + 0.0588004* AB + (-1.0375)* AC + (-0.414901)* AD + (-1.71)* BC + (-0.740099)* BD + (-1.89882)* CD + (-2.33766)* A^2 + (-3.76141)* B^2 + (-3.14267)* C^2 + (-5.18116)* D^2
- Y2 (%EE): +81.91+3.59* A +5.54* B -1.25* C +2.43* D -5.77* AB -9.17* AC +3.72* AD -0.99* BC -2.12* BD +7.06* CD -10.65* A^2 -2.77* B^2 -0.075* C^2 +0.67* D^2
- Y3 (% Buoyancy): 75.8293 + 2.93727* A + (-2.30394)* B + (-10.548* C + -2.13456)* D + 1.52069* AB + 0.475* AC + 1.8839* AD + 1.1775* BC + (-1.5514)* BD + 1.07155* CD + (-1.02783)* A^2 + (-0.180327)* B^2 + 1.05079* C^2 + 3.52201* D^2

The F-value for particle size, %EE and %buoyancy was found to be 55.31, 2.90 and 4.18, respectively, indicating the model is significant. There is only a 0.01% chance that a "Model F-value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In the case of particle size, the factors B, D, for %EE factors B, AC, A^2 and, for %buoyancy only factors C were significant model terms. Values greater than 0.1000 indicate that the model terms are not significant.

Interaction between Factors

Effects of Independent Parameters on Dependent Parameters

Change in independent variables such as increasing the concentration of Eudragit RS 100 shows a significant positive influence on particle size and %EE shown in Figs. 3 and 4 respectively, while it shows a negative influence on %Buoyancy shown in Fig. 5; in the case of HPMC K4M increasing the concentration of HPMC K4M shows only positive influence on particle size, %EE and, %buoyancy shown in Figs. 3-5 While in case of stirring speed and surfactant concentration, increasing the stirring speed *and* surfactant concentration shows only negative influence on particle size Fig. 6.

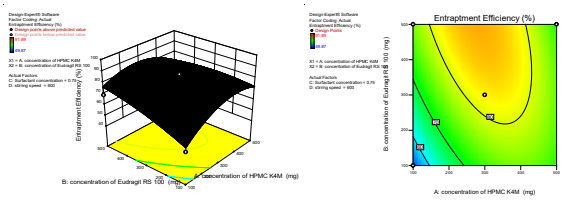
Preparation of Optimized Batch based on Desirability Function

During the optimization of the formulation, all the responses were considered to find out the desirability characteristic of the formulation. The concentration of HPMC K4M (242.90 mg), concentration of Eudragit RS 100 (500 mg), surfactant concentration (0.52%), stirring Speed (500 rpm), with Desirability (0.947) obtained from Box-Behnken design.

Table 5: Stability study

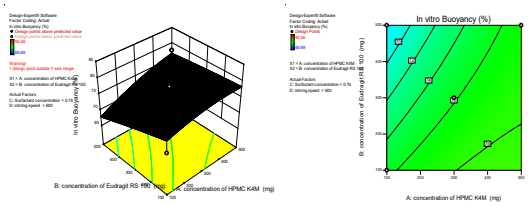
Storage condition	*Particle size (µm)*	*%EE*	*%Buoyancy*
At the time of preparation	85.87 ± 1.063	93.26 ± 1.65	89.19 ± 1.48
Initial 40 ± 2°C temperature and 75% ± 5 %RH (for 15 days)	85.68 ± 0.456	93.19 ± 0.431	89.11 ± 0.384
Initial 40 ± 2°C temperature and 75% ± 5 %RH (for 30 days)	85.62 ± 0.712	93.11 ± 0.231	88.91 ± 0.645

Mean ± SD, n = 3



(A) (B)

Fig. 4: (A) 3D Response Plot, (B) Contour Plot for %EE



(A) (B)

Fig. 5: (A) 3D Response surface plot, (B) Contour plot for %Buoyancy

Evaluation of Atenolol Loaded Optimized Microballoons

Particle size, %EE and %Buoyancy

The optimized formulation shows particle size 85.878 ± 1.063 µm, the %EE was 92.26 ± 1.65% and, the %Buoyancy was 89.19 ± 1.48% observed, which is near to the predicted value given by the software. so, it can be concluded that the model developed by the software was significant and reliable. As shown in Figs. 7 and 8 microballoons possessed discrete particle sizes with smooth surface texture with hollow space which is responsible for the increase in buoyancy and leads to increases in gastric retention time and better therapeutic effect.

Percentage (%) Yield

The %yield of atenolol-loaded microballoons of the optimized batch was found to be 94.90 ± 1.026%.

In-vitro Drug Release Study

The USP dissolution test apparatus II (paddle type) with the whole assembly was used to conduct an *in-vitro* drug release investigation of atenolol-loaded microballoons and pure drug in a conventional tablet form. During the *in-vitro* drug release investigation, it was discovered that the pure drug in its conventional dosage form releases the drug in 1 to 2 hours, whereas the atenolol-loaded microballoons

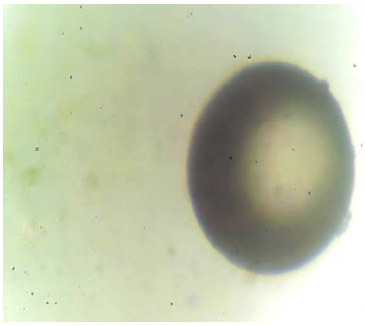


Fig. 7: Microscope image

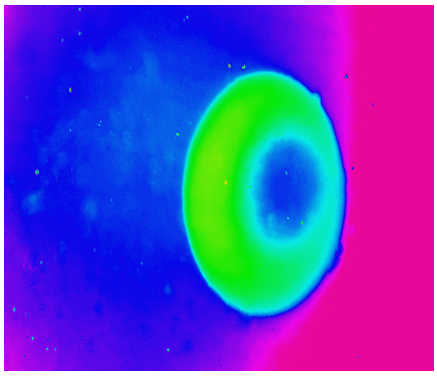
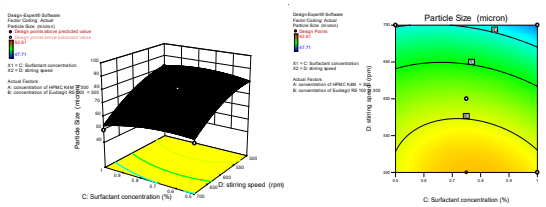


Fig. 8: Digital microscope image

release the drugs for up to 12 hours. Because of its floating/buoyancy characteristic, the microballoons dosage form releases the drug for a longer period and also improves drug absorption by enhancing the surface area for the drugs to be absorbed in the stomach. The results obtained from *in-vitro* data revealed that the prepared microballoons had good buoyancy and better drug release shown in Fig. 9.

Pharmacokinetic Drug Release Modelling

From the *in-vitro* drug release study of ATL-MBs Pharmacokinetics models were developed to know the type of mechanism involved in the release of the drug. Various pharmacokinetic models with their R^2 value shown in Table 4. ATL-MBs following the Higuchi model were shown in Fig. 10 and which describes the drug release from the matrix system and the mechanism involved in the release of the drug release was super case type II



(A) (B)

Fig. 6: Effect of stirring speed *and* surfactant concentration on Particle Size in (A) 3D Response surface plot, (B) Contour plot

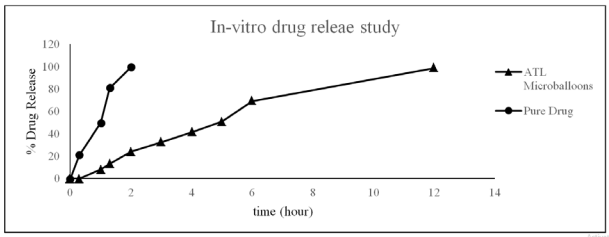


Fig. 9: Graphical Representation of in-vitro drug release comparison between ATL-MBs and pure drug

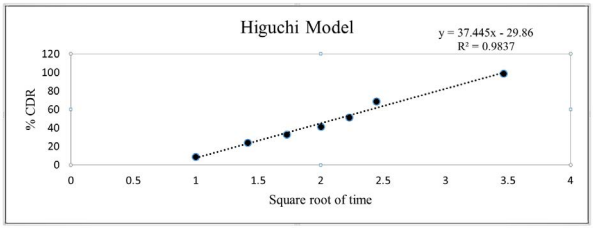


Fig. 10: P'cokinetics Higuchi Model

transport which was obtained from Korsmeyer Peppas model's release exponent value which was shown in Fig. 11

Characterization of Optimised Microballoons

FTIR Study of Optimized Atenolol-loaded Microballoons

FTIR spectrum of ATL-MBs shown in Fig. 12. From the result, it can be observed that in the atenolol-loaded microballoons, no significant changes in the frequencies of the functional group compared with the FTIR spectra of pure drug were observed.

SEM

The morphological characteristics of microballoons were shown in the following Fig. 13. SEM image describes the discrete particle size and the smooth surface of microballoons with their spherical shape without the aggregation of the micro-sized particles. Also, the particle size with a range < 200 µm confirms the particle size of the microballoons.

Stability Study

A stability study was performed to provide conclusive evidence that the formulation remains stable for a specific period. Stability study data is shown in Table 5. Which shows the measured particle size, %EE, and %buoyancy of the microballoons to ensure that the product remains unchanged. And the stability chamber was maintained for about 40 ± 2°C temperature and relative humidity at about 75 ± 5% RH for 15 days and 30 days as per ICH guidelines. But after the study, a slight change was observed in their particle size, %EE, and %buoyancy properties which were shown in Table 5. Based on the stability, we can conclude that there was no significant change in microballoons of the optimized formulation after 30 days of storage at 40 ± 2°C temperature and 75 ± 5% RH.

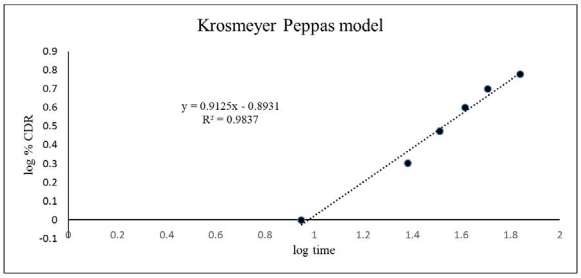


Fig. 11: P'cokinetics Korsmeyer Peppas model

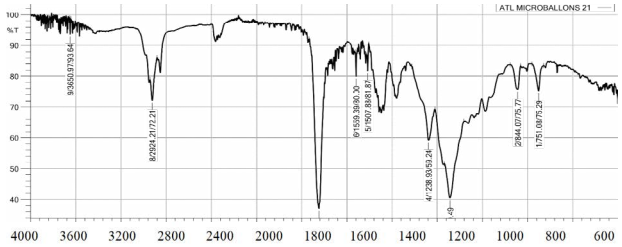


Fig. 12: FTIR Spectra of Prepared Batch of ATL-MBs

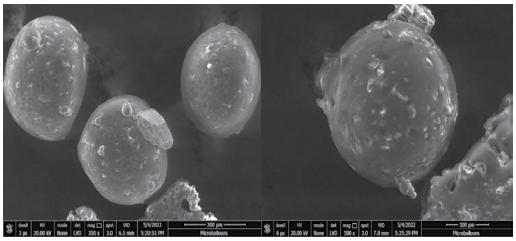


Fig. 13: SEM Image Shows Range of Microballoons Particle Size with Their Smooth Surface

Conclusion

The current study successfully formulated the ATL-loaded microballoons by the non-aqueous solvent emulsion diffusion method. The independent variables like the concentration of HPMC K4M, the concentration of Eudragit RS 100, the concentration of surfactant (Span 80), and stirring speed plays a crucial role in the formation of microballoons and also affects the dependent variable like particles size, drug entrapment efficiency, and *in-vitro* drug buoyancy. The formulation was optimized by the Box-Behnken design. The optimized batch shows 85.878 ± 1.063 µm particle size, 93.26 ± 1.65% EE, and 89.19 ± 1.48% buoyancy. FTIR study shows no incompatibility between the drug and excipients. SEM study shows smooth texture and a spherical shape of the microballoons with particle size < 200 µm and the space between the microparticle can be confirmed with the help of a digital microscope and compound microscope. The *in-vitro* drug release shows an improved drug release compared to the pure drug because of an increase in the gastric residence time. The pharmacokinetic model shows ATL-MBs release the drug in a controlled manner with a mechanism involved was super case type II transport. The stability study shows no significant change in microballoons of the optimized formulation after 30 days of storage as per ICH guidelines. Hence, we can conclude that microballoons drug delivery can be used for gastric retention in the stomach which may improve patient compliance by reducing the dosage frequency and increasing the gastric emptying time.

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References

1. Zhong H, Chan G, Hu Y, Hu H, Ouyang D. A comprehensive map of FDA-approved pharmaceutical products. Pharmaceutics. 2018; 4:263.
2. Streubel A, Siepmann J, Bodmeier R. Gastroretentive drug delivery systems. Expert Opinion on Drug Delivery. 2006; 2:217-33.
3. Saeed A, Adnan S, Farooq M, Masood Z, Mahmood A, Ranjha NM, Saeed S, Hassan S. Development and optimization of atenolol loaded polymeric microspheres: in vitro attributes. Latin American Journal of Pharmacy. 2020; 4:707-16.
4. Sadhu PK, Baji AA, Shah NV, Seth AK, Dash DK, 2020CJ, Kumari M. An Approaches and Patents on Controlled Release Gastroretentive Drug Delivery System–A Review. International Journal of Pharmaceutical Research.2020; 2:2047-2059.
5. Patel S, Aundhia C, Seth A, Shah N, Gohil D, Ramani V. Design, Development, Evaluation and Optimization of Microballoons of Telmisartan. 2018; 70-89.
6. Kawashima Y, Niwa T, Takeuchi H, Hino T, Itoh Y. Hollow microspheres for use as a floating controlled drug delivery system in the stomach. Journal of Pharmaceutical Sciences. 1992; 2:135-140.
7. Sharma AR, Khan A. Gastroretentive drug delivery system: an approach to enhance gastric retention for prolonged drug release. International Journal of Pharmaceutical Sciences and Research. 2014; 4:1095.
8. Yang Z, Song B, Li Q, Fan H, Ouyang F. Preparation of microspheres with microballoons inside for floating drug-delivery systems. Journal of Applied Polymer Science. 2004; 1:197-202.
9. Zubedi SS, Mohammed S. Floating tablets and its polymers. Journal of Drug Delivery and Therapeutics. 2018; 8:16-24.
10. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Dominic AF, Grassi G, Jordan J, Poulter NR, Rodgers A, Whelton PK. Hypertension. Nature reviews. Disease primers, 4, 18014.
11. Drug bank "Atenolol" March 2023. From: https://go.drugbank.com/drugs/DB00335
12. HV G, Balamuralidhara V, Kumar P. Formulation and in vitro evaluation of gastric floating tablets of atenolol. Journal of Pharmacy Research. 2010; 6:1450-5.
13. Hajare PP, Rachh PR. Gastroretentive microballoons: a novel approach for drug delivery. International Journal of Pharmaceutical Sciences and Research. 2020; 3:1075-83.
14. Alanazi A, Alshehri S, Altamimi M, Shakeel F. Solubility determination and three dimensional Hansen solubility parameters of Gefitinib in different organic solvents: Experimental and computational approaches. Journal of Molecular Liquids. 2020; 299:112211.
15. Bari S, Sather S, Jain P, Susana S. Spectrophotometric method for simultaneous estimation of atenolol in combination with losartan potassium and hydrochlorothiazide in bulk and tablet formulation. Journal of Biomedical and Pharmaceutical Sciences. 2010; 4:372.
16. Liltorp K, Larsen TG, Willum Sen B, Holm R. Solid state compatibility studies with tablet excipients using non thermal methods. Journal of Pharmaceutical and Biomedical Analysis. 2011; 3:424-8.
17. Chadha R, Bhandari S. Drug–excipient compatibility screening—role of thermoanalytical and spectroscopic techniques. Journal of Pharmaceutical and Biomedical Analysis. 2014; 87:82-97.
18. Krishna SR, Ramus A, Vidyadhara S. Study of Inf luence of Formulation and process Variables on entrapment efficiency and particle size of Floating microballoons of Clopidogrel bisulphate by DoE. Research Journal of Pharmacy and Technology 2020; 9:4373-80.
19. Srivastava A, Shukla R, Sharma K, Jain H, Meshram DB. Microballoons: a gastro retentive drug delivery system. Journal of Drug Delivery and Therapeutics. 2019; 4-s:625-30.
20. Varshosaz J, Tabbakhian M, Zahrooni M. Development and characterization of floating microballoons for oral delivery of cinnarizine by a factorial design. Journal of Microencapsulation. 2007; 3:253-62.
21. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vitro evaluation of floating and drug releasing behaviours of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. European Journal of Pharmaceutics and Biopharmaceutics. 2004; 2:235-43.
22. Havaldar VD, Kulkarni AS, Dias RJ, Aloorkar NH, Mali KK. Floating matrix tablets of atenolol: Formulation and in vitro evaluation. Asian Journal of Pharmaceutics. 2014; 4.
23. Kate BA. Formulation and Evaluation of Floating Microspheres of Atenolol. Journal of Medical and Pharmaceutical Innovation. 2015; 11.
24. Polli JE, Rekhi GS, Augsburger LL, Shah VP. Methods to compare dissolut ion prof iles and a rat ionale for w ide dissolut ion specifications for metoprolol tartrate tablets. Journal of Pharmaceutical Sciences 1997; 6:690-700.
25. Segall AI. Preformulation: The use of FTIR in compatibility studies. Journal of applied pharmaceutical science. 2019.
26. Mahdavi SA, Jafari SM, Assadpour E, Ghorbani M. Storage stability of encapsulated barberry's anthocyanin and its application in jelly formulation. Journal of food engineering. 2016 Jul 1;181:59-66.
27. Tolun A, Artik N, Altintas Z. Effect of different microencapsulating materials and relat ive humidit ies on storage st abilit y of microencapsulated grape pomace extract. Food Chemistry. 2020; 302:125347.

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