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FABRICATION AND OPTIMIZATION OF FLOATING TABLETS OF ANTIHYPERTENSIVE DRUG LOSARTAN

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ABSTRACT

This study developed, optimized, and evaluated floating tablets containing Losartan potassium intended to provide prolonged gastric retention for hypertensive patients. HPMC K15M was found to effectively extend drug release in a gastric pH environment. Formulations were evaluated for drug-excipient compatibility, thickness, hardness, tablet density, floating lag time, total floating time, weight variation, friability, drug content, swelling index, and stability under accelerated conditions. Preliminary findings identified HPMC K15M (X1) and MCC (X2) as independent variables in a 3² full factorial design, with friability (%F) and cumulative drug release at 12 hours (Q12) as dependent variables. Multiple linear regression, ANOVA, and contour plots generated using Design Expert were employed to analyze factor effects. In vitro release data were fitted to kinetic models, with the optimized batch exhibiting a Higuchi release profile ($r^2 = 0.993$). A checkpoint batch validated the model. Batch F7 was identified as the optimized formulation, demonstrating friability below 1 (0.80) and 95.94% cumulative drug release at 12 hours. Accelerated stability testing confirmed the stability of the optimized formulation.

Keywords: Losartan, Fabrication, Optimization, Floating tablets, Antihypertensive drug

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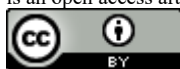
INTRODUCTION

The most popular, desired, and practical way to provide medication is orally. Because oral medications are easy to use, inexpensive, and have high patient compliance, about 90% of all medications that have systemic effects are given orally. Because of its greater versatility in dosage form formulation than other routes, the oral route has attracted a lot of interest in the pharmaceutical industry. A medicine must have good absorption throughout the gastrointestinal tract (GIT) in order for an oral drug delivery system to function effectively [1].

The entire drug delivery system stays in the stomach area for a prolonged amount of time thanks to gastro-retentive drug delivery systems (GRDDS). Compared to traditional dosing forms, this prolongs the stomach retention period and keeps the drug's minimum effective concentration in the bloodstream for

extended periods of time. Furthermore, GRDDS greatly reduces drug waste during the absorption process by increasing the solubility of medications that are less soluble at the alkaline pH of the intestine [2]. Additionally, GRDDS can administer larger drug concentrations to gastrointestinal conditions such as esophagitis, gastritis, and ulcers. Three crucial factors are necessary for the creation of oral sustained-release matrix drug delivery systems: dosage form parameters, the drug's physicochemical features, and gastrointestinal physiology. Research and development activities in both academia and industry have been greatly accelerated by the need for gastro-retentive dosage formulations. GRDDS methods include bioadhesion to gastric mucosa, expansion through swelling or unfolding to a size that permits passage through the pyloric sphincter, floating systems (low-density dosage forms that remain

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buoyant in gastric fluid), and high-density forms that remain at the bottom of the stomach. Based on their buoyancy processes, floating systems are further divided into effervescent and non-effervescent systems [3-5].

Hypertension is frequently treated with losartan potassium. In order to create gastro-retentive floating tablets that would achieve extended release in a gastric pH environment for 12 hours, this study used it as a model medication [6].

Thus, this investigation focused on enhancing floating time and prolonging the release of Losartan potassium through statistical experimental design.

MATERIALS AND METHODS

Materials

Losartan potassium was received as a generous gift sample from Mass Pharma Pvt. Ltd., Lahore. Polyvinylpyrrolidone, Sodium carboxymethyl cellulose, Microcrystalline cellulose, Camphor, HPMC K4M, HPMC 15M were purchased from SigmaAldrich, Germany. All other materials and chemicals used were of analytical grade.

Formulation of Tablets

The wet granulation process was used to make the tablets. The appropriate quantities of Losartan potassium, MCC, HPMC K4M, HPMC K15M, and NaCMC were correctly weighed and carefully mixed. A 20# sieve was used to filter the cohesive mass that resulted from granulating the mixture with a binder and solvent (PVP K-30 in IPA). The dried granules were then run through a 20# filter once more after being dried using a tray dryer. The granules were then combined with weighed quantities of talc, magnesium stearate, and camphor. Ultimately, an eight-station tablet compression machine was used to compress the granules. To allow the camphor included during formation to sublime, the produced tablets were put in a tray dryer [7, 8].

Preliminary Screening of Floating Polymers

A preliminary study was conducted on various polymers to assess their effects on the release profile of the floating formulation. The compositions of the preliminary trial batches FT-1 to FT-6.

Optimization of Variables Using Full Factorial Design

A 3² full factorial design was employed in this study. Based on preliminary results, the amounts of HPMC K15M (X1) and MCC (X2) were selected as independent variables, while Q12 and % Friability were designated as dependent variables. Multiple linear regression analysis, ANOVA, and graphical representations of the influence of factors through contour plots were conducted using the demo version of Design Expert 7.1.5 [9, 10].

Evaluation Parameters of Floating Tablets

The evaluation parameters for the floating tablets included thickness, hardness, tablet density, floating lag time, total floating time, weight variation test, % friability, drug content, and % swelling index of the formulations.

Floating Lag Time

The floating lag time refers to the duration required for the tablet to rise to the surface of the dissolution medium. This was measured at pH 1.2, with a temperature of 37±0.5°C, a paddle rotation speed of 50 rpm, and a volume of 900 ml, using a stopwatch [11].

In-vitro Dissolution Study

The rotating paddle method was used for the dissolving test, using a 50 rpm stirring rate. A 900 ml dissolving media containing 0.1 N HCl was kept at 37±0.5°C. At prearranged intervals for up to 12 hours, 5 ml samples were taken out and replaced with 5 ml of brand-new dissolving medium. A double beam UV spectrophotometer was used to detect Losartan potassium at 254 nm after the obtained samples had been suitably diluted with dissolving fluid [12].

Kinetic Modeling of Dissolution

The dissolution profile was studied using several models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas, to identify the kinetics of drug release. In particular, the mechanism of drug release was described using the Korsmeyer-Peppas approach [13-15].

TABLE 1: Composition of losartan floating tablets.

Ingredients	FT-1	FT-2	FT-3	FT-4	FT-5	FT-6
Losartan potassium	50	50	50	50	50	50
HPMC K4M	20	40	-	-	-	-
HPMC K15M	-	-	20	40	-	-
Na CMC	-	-	-	-	20	40
Camphor	15	15	15	15	15	15
MCC	65	45	65	45	65	45
PVP K30	5	5	5	5	5	5
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5

Study of Stability

For three months, the optimized tablets were kept at $45 \pm 0.5^\circ\text{C}$ and 75% relative humidity while wrapped in aluminum foil. Following this time, the tablets' in vitro release profile and drug content were examined. The similarity factor f_2 was used to compare the products' dissolving characteristics. Further details regarding the similarity factor (f_2) can be found in the US FDA draft guidance document. The two dissolution profiles are similar if the similarity factor value falls between 50 and 100 [16].

RESULTS AND DISCUSSION

Preliminary Study

The floating tablets exhibited hardness values ranging from 6.2 to 6.7 kg/cm^2 , and their density was between 0.711 and 0.773 g/cm^3 . The % friability of all batches varied from 0.08 to 0.48, while the % cumulative drug release ranged from 89.21 to 99.17. Batches FT-1 and FT-2 demonstrated a rapid drug release within 8 hours, in contrast to batches FT-3 to FT-6. According to the in-vitro dissolving tests, batches FT-3 and FT-4 outperformed batches FT-5 and FT-6. According to the preliminary study's findings, HPMC K15M or MCC by themselves were not enough to provide the intended release profile. In order to investigate their effects and optimize their concentrations for the intended release profile, additional trials were carried out with a combination of HPMC K15M and MCC [17]. Hardness, density, percentage friability, cumulative drug release after 12 hours, and floating time were all assessed for each batch (Table 2).

Full Factorial Design Batches

A 3^2 full factorial design was employed in this study, evaluating two factors at three levels each, resulting in experimental trials for all nine possible combinations. HPMC K15M creates a stronger and thicker matrix at higher concentrations, leading to a longer drug release time. Microcrystalline cellulose (MCC) was used both to bind the tablets and to achieve the desired drug release profile. An optimized combination of HPMC K15M and MCC may result in a tablet that exhibits a slow drug release at a gastric pH of 1.2 over 12 hours. Therefore, the

amounts of HPMC K15M and MCC were considered independent variables in the 3^2 full factorial design. HPMC K15M was tested at 20 mg and 40 mg, while MCC was tested at 45 and 65 mg, corresponding to levels of -1, 0, and +1, respectively.

3^2 Full Factorial Design Model Evaluation

The responses were assessed using a statistical model that included interactive and polynomial factors. The computed F values for % Friability and % CDR were 57.35 and 61.72, respectively, according to the ANOVA results. By taking into account the magnitude of the coefficients and their mathematical signs, the polynomial equation can be utilized to make inferences that all of the chosen factors had a major impact. Strong correlations between the dependent and independent variables were shown by the R^2 values for % Friability and % cumulative percentage drug release (% CDR), which were 0.988 and 0.989, respectively. Terms with $P > 0.05$ were eliminated to create reduced models for the response variables. In the simplified model, terms with $P < 0.05$ were kept since they were considered statistically significant.

Full and Reduced Model for % Friability

Statistical analysis indicated that an increase in the % Friability of the tablets corresponded with higher concentrations of MCC. MCC was incorporated into the formulation to assist the polymer in retarding drug release. When compared to HPMC K15M, the contour plot graph and regression coefficient values demonstrated that the concentration of MCC had very little impact on the percentage of cumulative drug release at 12 hours [18-20].

As HPMC K15M concentrations increased, the percentage cumulative drug release at 12 hours showed a comparable drop in drug release from the tablets. The greater concentration of HPMC K15M, which created a stronger matrix and delayed the drug's release, was blamed for this decline. In comparison to HPMC K15M, the regression coefficient values showed that MCC had a minor impact on the percentage of cumulative drug release at 12 hours, with less relevance on the percentage of CDR at this time.

TABLE 2: Evaluation of losartan potassium of floating tablets.

Ingredients	Hardness	Density	% Friability	% CDR at 12 hrs	Duration of floating
FT-1	6.2	0.722	0.08	95.37	Less than 12 hrs
FT-2	6.5	0.728	0.38	90.98	Less than 12 hrs
FT-3	6.5	0.738	0.26	89.67	Less than 12 hrs
FT-4	6.6	0.759	0.47	89.21	Less than 12 hrs
FT-5	6.4	0.711	0.48	99.17	Less than 12 hrs
FT-6	6.7	0.773	0.39	94.32	Less than 12 hrs

TABLE 3: Evaluation of stability study.

Parameters	1 st month	2 nd month	3 rd month
Thickness (mm)	2.8	2.8	2.8
Hardness (kg/cm ²)	6.2	6.3	6.2
Density (g/cm ³)	0.81	0.82	0.82
% Friability	0.54	0.49	0.55
Drug Content	98.6	97.4	97.9

Kinetic Modeling of Dissolution Data for Factorial Batches

The dissolution profile of the selected factorial batch was analyzed using various kinetic models, including zero-order, first-order, Higuchi, Korsmeyer, and Peppas, to determine the drug release kinetics. The drug release process was described using the Korsmeyer-Peppas model. The drug release mechanism from the formulation is indicated by the diffusion exponent (n). Fickian diffusion is indicated by $n < 0.5$, non-Fickian transport is suggested by $0.5 < n < 1.0$, Case II transport is indicated by $n = 1$, and super Case II transport is shown by $n > 1.0$. The medication was released through a non-Fickian transport mechanism, as all of the chosen batches had n values between 0.5 and 1.0. A correlation coefficient of 0.989, which indicates one-dimensional diffusion and insignificant edge effects under ideal sink conditions, shows that drug release may follow the Higuchi model, according to data analysis for factorial batch [21-23].

Short-Term Stress Stability Study

Batch underwent stability testing. The in-vitro release profiles at baseline and after three months were compared using the f_2 value, which was calculated to be 67.52. The minimal difference in the f_2 value indicates that the formulation remains stable [24].

CONCLUSION

The formulation containing Losartan potassium, HPMC K15M, and MCC for preparing floating tablets through the sublimation method offers a convenient option for oral administration and may enhance patient compliance by reducing the frequency of doses. Using HPMC K15M as the polymer, MCC as the binder, and camphor as a pore-forming agent during the sublimation process, floating tablets of losartan potassium were effectively created. The invention of a floating tablet that permits the gradual release of Losartan potassium in a gastric fluid environment was demonstrated in the study. A checkpoint batch was created to validate the statistical analysis of the factorial design data. The improved batch's release profile was consistent with the Higuchi model. Furthermore, the stability evaluation revealed that improved batch F7 was stable.

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