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RESEARCH ARTICLE

FORMULATION AND OPTIMIZATION OF PELLETS CONTAINING ZALTOPROFEN BY EXTRUSION SPHERONIZATION TECHNIQUE

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ABSTRACT

A non-steroidal anti-inflammatory drug called Zaltoprofen has a remarkable impact on persistent post-surgical or post-traumatic inflammation. Zaltoprofen is taken three times a day in doses of 80 mg and has a shorter half-life. Zaltoprofen pellets with a sustained release have been created with the aim to get the maximum drug release possible for this study. The sustained release polymer HPMC K4M, HPMC K15M and HPMC K100M were taken at different concentrations (2.5%, 5% and 7.5%) for the preliminary trial from which HPMC K100M at 7.5% had shown enhanced release. The initial studies on the compatibility of drugs and excipients using FTIR and DSC revealed no interaction between the two. Pellets were prepared by Extrusion-Spheronization technique and evaluated for Bulk density, Tapped Density, Friability, Drug Content, Particle Size, % Yield of pellets, Scanning electron microscopy, and *in-vitro* Drug release. Controlled drug release for up to 12 hours was accomplished using the Box-Behnken design. HPMC K100M concentration (X_1), MCC concentration (X_2), and Spheronization speed (X_3) were chosen as independent factors, and the $t_{50\%}$ (Y_1) and $t_{90\%}$ (Y_2) were chosen as dependent variables. An in-vitro drug release study revealed that % CDR decreased as the amount of polymer increased. To visualize the impact of X_1 and X_2, X_1 and X_3, and X_2 and X_3 on the %CDR, contour plots and response surface

plots were created. At the concentration of independent variables X_1 (77.5%), X_2 (7.5%), and X_3 (1750 rpm), an optimal response was estimated. Different kinds of release pharmacokinetic models were used to assess the optimized batch Z13. According to ICH regulations, the optimized batch was stored for a month for a stability study at 40°C ± 2°C and 75% ± 5% RH, and it was found to be stable at the end of the study.

Keywords: Sustained release pellet, Zaltoprofen, MCC, HPMC K100 M, Spheronization speed, Box-Behnken design.

INTRODUCTION

Wide-scale research has been performed with a modified drug delivery system over the last decade. There are several benefits of modified release systems, such as better patient acceptance and consistent blood medication levels, which lead to greater potency and decreased side effects. Historically, a range of industries have used the term "pellets" to denote a range of agglomerates made from different source ingredients. The term pellets refer to spherical/semi-spherical, free-flowing solid units with a limited size distribution, with a diameter ranging from 500 and 1500 m, for use in pharmaceutical applications.[1, 2, 3, 4]

The general term "granulation" and "pelletization" shall be used synonymously, the units obtained shall be known as granules, pellets, or agglomerates without making any specific distinction between them. "Pelletization" is also referred to as a size enlargement procedure involving the production of pellets with a mean size of 0.5 to 1.5 mm. The term "spheronization" refers to the formulation of spherical units by special procedure, which involves a spheronization stage where extrudates are rounded as they tumble onto a spinning frictional base layer. [5, 6, 7]

Multiparticles get released into the gastrointestinal tract when multiple-unit systems are ingested orally, and they are less dependent on gastric emptying than single-unit systems. They can get through the pyloric sphincter because of their small size. This reduces the variance in gastrointestinal transit time within and between subjects. Additionally, due to their small size, they are simpler to distribute evenly down the digestive tract, boosting absorption and minimising the irritating effects that single-unit systems may have on the mucosal lining, especially if they have been lodged at a particular spot for an extended period of time. [8-12]

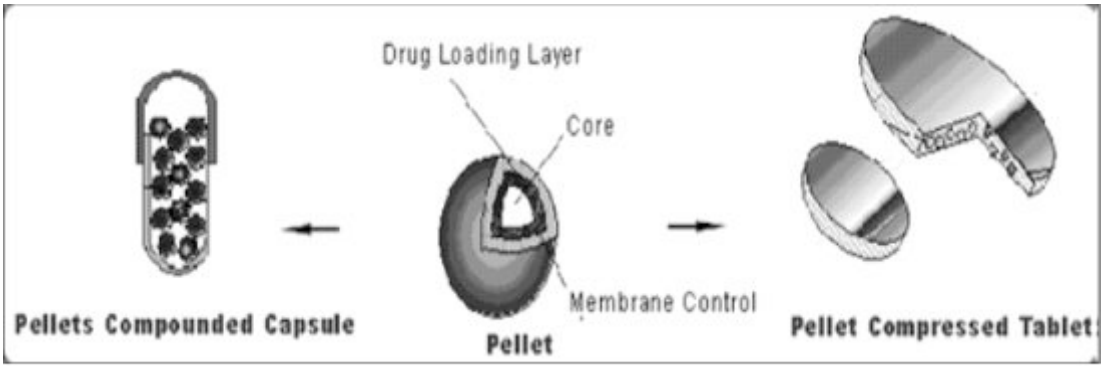

Figure 1: Schematic Representation of Pellets into Capsules and Compressed into Tablets

MATERIALS AND METHODS

Materials

Zaltoprofen was obtained from ZCL Chemicals Ltd. HPMC K4 M, HPMC K15 M, and HPMC K100 M was obtained from Colorcon Asia Pvt. Ltd. Micro Crystalline Cellulose was obtained from Chemco Fine Chemicals. Poly Vinyl Pyrrolidone K-30 was obtained from Nosch Labs Pvt. Ltd.

Study of the Drug-Excipient Compatibility using FTIR

Using an FT-IR spectrometer, the Fourier-transform infrared spectra were acquired. Zaltoprofen and other excipients were combined in a 1:1 ratio with KBr, an infrared transparent matrix. The powder was compressed in a hydraulic press for 5 minutes at a pressure of 5 tonnes to create the KBr discs. Zaltoprofen with excipients' spectra have been recorded between 400 to 4000 cm^{-1}.

Box-Behnken Design [13, 14, 15, 16]

Pellets were developed using a Box-Behnken statistical design with three factors and three levels. Constructing second-order polynomial models and studying the quadratic response surface are both possible with this design. Various dependent and independent variables along with their actual and coded levels used in this study are given in Table 1. A design matrix comprising 15 experimental runs was constructed. A multidimensional cube's midpoints and duplicated centre points are used to define the region of interest. The nonlinear quadratic model that the design produced takes the following form:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_{12}X_1X_2 + \beta_{13}X_1X_3 + \beta_{23}X_2X_3 + \beta_{11}X^2 + \beta_{22}X^2 + \beta_{33}X^2 + E$$

In which Y represents each factor level combination's measure response. β_0 is constant, β_1-β_3, linear coefficients, β_{12}, β_{13} and β_{23}, which are computed from the observed experimental value of Y from the experimental runs, and X_1, X_2, and X_3 are the coded levels of independent variables. The interaction effect is denoted by the terms X_iX_2 (i= 1, 2 and 3), whereas the

curvature effects are denoted by the terms X_1^2, X_2^2 and X_3^2. Table 1 displays the concentration range of the independent variables under research, along with their low and high levels, which were chosen based on the findings of earlier experiments.

The amount of microcrystalline cellulose (%) (X_1), amount of HPMC K100 M (%) (X_2) and Spheronization speed (rpm) (X_3) used to prepare the 15 formulations and respective observed responses were given in Table 1, 2 and 3.

Table 1: List of Dependent Variables and Independent Variables

Independent variables			Dependent variables	
X_1	X_2	X_3	Y_1	Y_2
Amount of Micro Crystalline Cellulose (%)	Amount of HPMC K100 M (%)	Spheronization Speed (rpm)	$T_{50\%}$ (hr)	$T_{90\%}$ (hr)

Table 2: Selection of Levels for Independent Variables and Coding of Variable

Levels	Coded value	Independent variables		
		Amount of Micro Crystalline Cellulose (%) X_1	Amount of HPMC K100M (%) X_2	Spheronization Speed (RPM)
Low	-1	70	5	1500
Intermediate	0	77.5	7.5	1750
High	+1	85	10	2000

Table 3: Composition of Box-Behnken Design Batches BZ1 to BZ15

Ingredients (%)	BZ1	BZ2	BZ3	BZ4	BZ5	BZ6	BZ7	BZ8	BZ9	BZ10	BZ11	BZ12	BZ13	BZ14	BZ15
Zaltoprofen	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Polyvinyl Pyrrolidone	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Micro Crystalline Cellulose	70	85	70	85	70	85	70	85	77.5	77.5	77.5	77.5	77.5	77.5	77.5
HPMC K100M	5	5	10	10	7.5	7.5	7.5	7.5	5	5	10	10	7.5	7.5	7.5
Spheronization Speed (RPM)	1750	1750	1750	1750	1500	1500	2000	2000	1500	2000	1500	2000	1750	1750	1750

Method

Preparation of Zaltoprofen Pellets by Extrusion-Spheronization Technique[17, 18, 19]

- Except for the drug, all of the solid powder components were weighed before being transferred to a clean bowl and carefully mixed. The previously mentioned powder blend was geometrically combined with a precisely weighed quantity of the drug.
- Water was gradually added to the above-mentioned powder mixture until a wet mass with suitable plasticity was formed.
- A radial piston-type extruder was then used to extrude the previously prepared wet material. The apertures were 1 mm in diameter, and the screen was 1 mm thick. Then, to obtain an extrudate size of about 1 mm in length, prepared extrudates were manually cut with a small cutter.
- The prepared extrudates were then spheronized for 15 minutes at a mentioned in the table.
- Then, for two hours, the prepared pellets were dried below 60°C.

Evaluation Parameters of Pellets [20]

Bulk Density (BD)

Weigh precisely 10 g of Pellets that have been put into a graduated cylinder after being passed through a 20# sieve. Without compacting, gently level the powder, then measure the unsettled bulk volume. Use the following formula to determine the bulk density in gm/ml:

Bulk Density = Weight of Sample / Bulk Volume

Tapped Density (TD)

Weigh precisely 10gm of pellets that have been put into a 100ml graduated cylinder after being formerly distributed through a 20# sieve. Then, using a mechanical tapped density tester that gives a fixed drop of 14±2 mm at a nominal rate of 300

drops per minute, mechanically tap the cylinder containing the sample by lifting the cylinder and letting it fall under its own weight. Measure the tapped volume to the nearest graduated units after tapping the cylinder 500 times. Then, repeat the tapping 750 times more, and calculate the tapped volume to the nearest graduated units. Use the following formula to determine the tapped density in grammes per millilitre:

Tapped Density = Weight of Sample/ Tapped Volume

Carr's Index

Carr's index is crucial in determining how the granules will flow. It is closely related to cohesiveness, particle size, and relative flow property rate. It is an easy, quick, and standard technique for estimating flow characteristics (Table 4). The following equation is used to represent Carr's index:

Carr's index (%) = [(TBD - LBD) × 100]/TBD

Table 4: Interpretation of Compressibility Index

Type of flow	Carr's index
Excellent	<10
Good	11-15
Fair	16-20
Passable	21-25
Poor	26-31
Very poor	32-37
Very Very poor	>38

Hausner's Ratio

To predict the granules' flowability, Hausner's ratio is used. This technique is comparable to Carr's index. An equation that is used to illustrate Hausner's ratio is shown below.

Hausner's Ratio = Tapped Density / Bulk Density

Angle of Repose (θ)

It is defined as the largest angle that can be made between the powder's surface and the horizontal. It employed a fixed funnel technique. Graph paper was placed on a flat, horizontal surface, and a funnel was mounted above it with the tip at a specific height (h). A funnel was used to carefully pour the powder until the funnel's tip just touched the top of the conical pile (Table

5). The following equation was then used to get the angle of repose:

$$\textbf{Angle of repose } \Theta = \tan^{-1} (h/r)$$

Where,

h = height of the pile

r = radius of the pile

Table 5: Interpretation of Angle of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair	36–40
Passable	41–45
Poor	46–55
Very poor	56–65
Very, very poor	>66

Particle Size and Size Distribution

It is possible to determine the size and size distribution of the pellets by shaking a sieve shaker for 10min using a series of standard sieves. According to the Indian Pharmacopoeia, the weight kept on each sieve is used to calculate the standard sieve aperture size.

Practical Yield (%)

The weight of dried pellets collected from each batch and the total initial dry weight of the raw material were used to calculate the percentage of production yield (wt/wt). The following is the formula for calculating % yield.

% Practical Yield = (Practical value/Theoretical value)*100

Friability

Friability was evaluated for 100 rotations at 20 rpm using the Electrolab friability instrument. 20 grammes of pellets for each test. The increase in the percentage of sampling weight attributable to pellet fragments was used to determine friability.

Surface Morphology

SEM was used to analyze the shape and pellets' surface attributes. The pellets were lightly sprinkled on a piece of double-sided adhesive tape that was attached to an aluminium stub to prepare the samples for SEM. The gold was then applied to the stub. Following a random scan of the samples, microphotographs were taken at various magnifications, and a greater magnification was employed to study the surface morphology.

Drug Content

Accurately weighed pellets equivalent to 100 mg of drug are transferred to a 100 ml volumetric flask and 5 ml methanol is added to the above flask to extract the drug from pellets. Phosphate buffer pH 6.8 was added to the flask. The flask is then sonicated for 5 min. The volume will be then made up to 100 ml with phosphate buffer pH 6.8. This solution will be filtered through Whatman paper and absorbance will be measured at 337.8 nm.

***In-vitro* Drug Release Study**

The dissolution test was carried out with Apparatus-I (basket type) at 100 revolutions per minute in 900 ml of phosphate buffer pH 6.8 for 12 hrs at 37±0.5°C. Five ml samples were taken at one hour intervals and replaced with 5 ml of fresh dissolution media each time. A UV-visible spectrophotometer set at 337.8 nm was then used to analyze the samples that had been collected.

Statistical Analysis [21]

Microsoft Excel was used to conduct a multiple regression analysis of the Box-Behnken design batches. Three factors were examined in this design, each at three levels, and experimental trials were carried out using all 15 conceivable combinations. A two-way analysis of variance (ANOVA) was performed using the design expert 10 demo version software to ascertain the influence of each element with varying levels on the response. The response surface plots, normal plots of residual, two-dimensional counterplot, three-dimensional graph, and overlay plot were produced using the design expert 10 demo version software to visually illustrate the impact of each factor on the response.

Checkpoint Analysis

The obtained polynomial equation and contour plots' predictive abilities were verified by a checkpoint analysis. Three independent variable values were taken, and by putting those values into the polynomial equation, the theoretical values of $t_{50\%}$ and $t_{90\%}$ were determined.

Optimization of Formulation [22, 23, 24]

The programme DESIGN EXPERT 10 (STAT - EASE) was used to calculate the optimized formulation. Applying constrictions (goals) to dependent (response) and independent (factors) variables led to optimized formulation. The models were assessed using R^2 values and statistically significant coefficients. To identify the ideal parameters, several grid and feasibility searches were carried out. The Design Expert software offered several 3-D response surface graphs. The optimized formulation factors were assessed for various response properties.

Stability Study [25]

To ascertain the impact of excipients on the stability of the drug as well as the physical stability of the formulation under accelerated storage situations, a stability test of the optimized formulation was conducted. The Pellets were kept in an

aluminium foil and exposed to 40 ± 2°C/ 75 ± 5% RH temperature and humidity conditions for a month.

RESULTS AND DISCUSSION

Study of the Drug-Excipient Compatibility using FTIR

Interactions between drugs and their excipients are essential for biological performance and formulation stability. The physical and chemical interactions between drugs and excipients were investigated using FTIR spectroscopy. Interpretation of Zaltoprofen and other Excipients by FT-IR was shown in Table 6. Figures 2 to 4 illustrate the typical absorption peaks that were obtained for the drug both alone and with excipients present. The principal drug peaks and peak frequencies are clearly visible in the spectra and are within the expected range. This shows that the drug and all of the excipients utilised in the formulation were compatible.

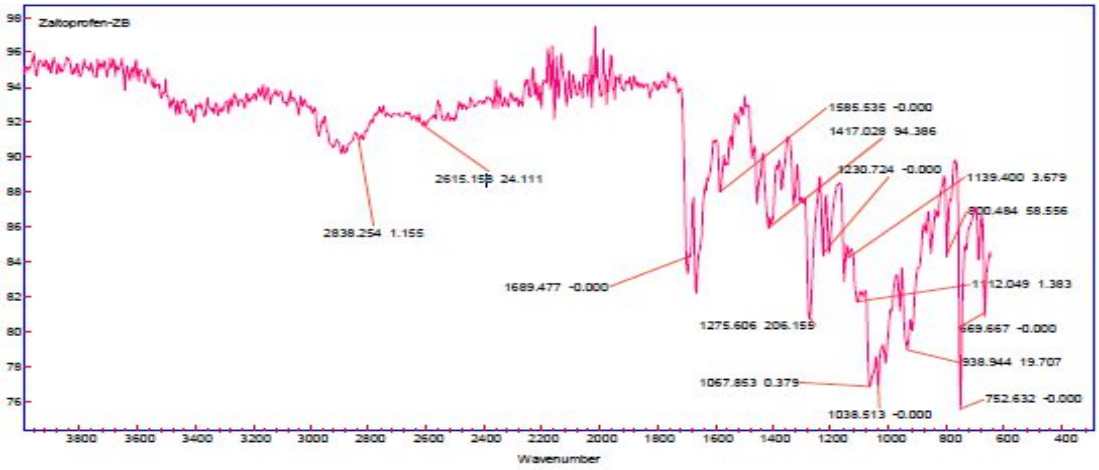

Figure 2: FT-IR Spectra of Zaltoprofen and HPMC K100M Mixture

Figure 3: FT-IR Spectra of Zaltoprofen and Micro Crystalline Cellulose Mixture

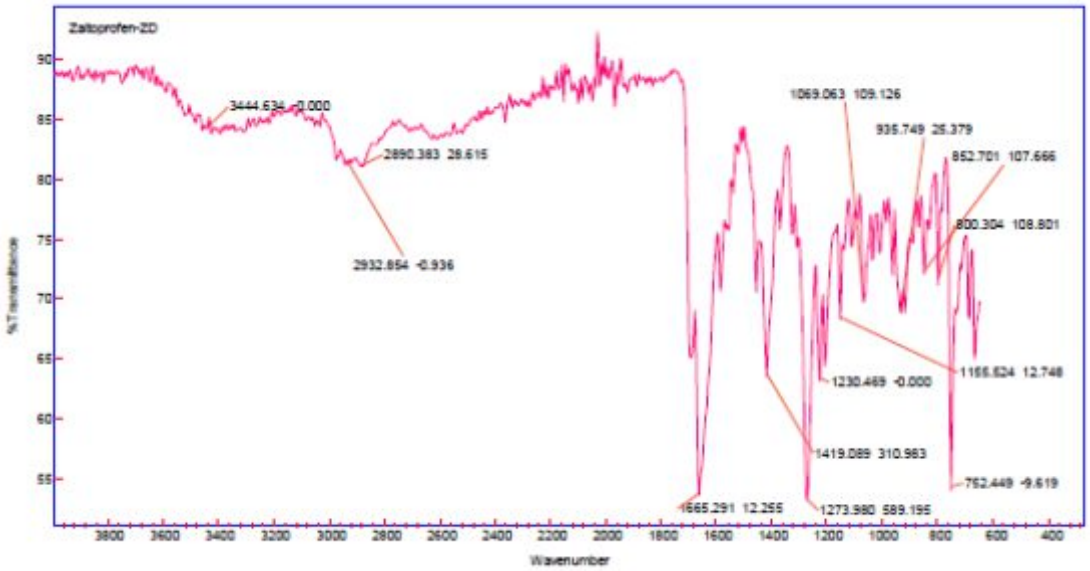

Figure 4: FT-IR Spectra of Zaltoprofen and Polyvinyl Pyrrolidone K30 Mixture

Table 6: Interpretation of Zaltoprofen and other Excipients by FT-IR

Drug + excipients mixture	Functional group wave number(cm^{-1})				
	-C-H (Aromatic) stretching	-C=O stretching	C-S-C Stretching	C-O Stretching	O-H Stretching
Zaltoprofen	2933.2	1687.900	1452.1	1286.3	1074.2
Zaltoprofen + HPMC K100M	2912.6	1689.477	1417.028	1275.606	1067.853
Zaltoprofen + MCC	2942.094	1698.646	1418.730	1275.162	1034.838
Zaltoprofen + PVP K30	2932.854	1665.291	1419.089	1273.980	1069.063

Post-Formulation Evaluation of Batches BZ1 to BZ15

Table 7: Data for Particle size, Friability, %Yield and Drug Content of Pellets

Batch No.	Mean Particle Size (µm)	Friability (%)	% Yield of Pellets	% Drug Content
BZ1	1450	0.83±0.025	93.32	95.10
BZ2	800	1.01±0.012	77.83	81.50
BZ3	950	1.23±0.023	79.23	83.55
BZ4	1100	0.92±0.031	92.87	90.32
BZ5	1050	0.85±0.035	88.87	92.75
BZ6	1300	0.81±0.027	91.76	90.85
BZ7	1000	0.96±0.025	90.90	85.12
BZ8	1050	1.02±0.018	87.41	91.82
BZ9	900	0.97±0.021	90.76	93.82
BZ10	1100	0.78±0.031	91.24	89.43
BZ11	1050	0.89±0.015	88.76	92.79
BZ12	1150	0.81±0.033	93.44	95.89
BZ13	900	0.93±0.027	91.58	92.1
BZ14	1000	0.91±0.016	90.46	89.64
BZ15	1250	1.03±0.018	95.78	91.57

Every value is presented as mean ± standard deviation, n=3

From results of mean particle size, as seen in Table 7 above, the particle size of the pellets increases with an increase in the amount of HPMC K100M as water evaporation takes longer and thus results in an increase in the particle size. The friability of the pellets decreases with a rise in the amount of HPMC K100M and

the drug content is a very significant parameter for any drug formulation. Pellets produced with HPMC K100M have a low product yield due to material loss during the spheronization process due to pellet

Table 8: Study of *In-vitro* Drug Release of Batches BZ1 to BZ15

Time (hrs)	Cumulative Drug Release (%)														
	BZ1	BZ2	BZ3	BZ4	BZ5	BZ6	BZ7	BZ8	BZ9	BZ10	BZ11	BZ12	BZ13	BZ14	BZ15
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	9.9 ± 2.34	7.9 ± 2.73	11.1 ± 3.21	14.0 ± 2.47	9.5 ± 2.18	8.1 ± 2.61	6.1 ± 4.26	11.5 ± 3.85	12.8 ± 3.89	9.5 ± 3.52	8.5 ± 3.23	5.0 ± 2.12	5.4 ± 2.21	7.5 ± 3.18	8.4 ± 2.74
2	21.1 ± 2.61	18.9 ± 2.42	28.7 ± 2.49	27.6 ± 2.54	20.8 ± 2.37	19.4 ± 2.54	13.3 ± 3.12	21.5 ± 2.75	21.9 ± 4.32	17.43 ± 2.65	15.8 ± 2.15	12.2 ± 3.17	14.6 ± 2.63	16.7 ± 2.26	19.4 ± 2.44
3	30.6 ± 2.71	30.1 ± 3.19	37.4 ± 2.54	36.3 ± 2.67	33.8 ± 2.11	28.1 ± 2.94	22.0 ± 2.32	33.0 ± 4.16	32.2 ± 3.65	26.3 ± 2.23	24.4 ± 2.65	24.2 ± 2.66	25.9 ± 3.61	25.9 ± 3.57	29.7 ± 3.26
4	40.0 ± 3.12	39.1 ± 3.24	45.1 ± 2.94	44.9 ± 3.21	49.9 ± 3.43	39.2 ± 2.37	38.3 ± 2.12	41.2 ± 2.74	40.9 ± 3.32	35.3 ± 3.41	32.2 ± 3.15	33.0 ± 3.24	36.1 ± 2.43	32.9 ± 3.16	38.6 ± 2.51
5	49.5 ± 2.51	47.4 ± 2.67	56.7 ± 3.31	58.5 ± 2.49	58.3 ± 2.67	46.9 ± 2.78	45.8 ± 3.16	49.8 ± 3.10	47.2 ± 2.25	48.0 ± 3.65	38.6 ± 2.74	44.7 ± 2.45	45.7 ± 3.51	47.4 ± 2.81	43.2 ± 2.33
6	59.3 ± 2.83	54.9 ± 2.48	69.6 ± 2.41	67.7 ± 2.16	71.4 ± 2.59	55.0 ± 3.18	51.9 ± 4.07	56.7 ± 3.65	55.6 ± 1.97	55.0 ± 2.32	48.6 ± 2.67	54.5 ± 2.89	53.8 ± 2.87	52.7 ± 3.27	52.5 ± 3.38
7	68.5 ± 3.24	64.8 ± 2.91	82.6 ± 2.19	76.2 ± 2.48	82.2 ± 2.81	68.2 ± 2.44	64.7 ± 2.36	66.4 ± 3.24	68.7 ± 3.16	61.1 ± 3.72	56.2 ± 3.41	63.0 ± 3.52	63.9 ± 3.17	62.8 ± 2.78	62.5 ± 2.19
8	75.6 ± 2.16	74.9 ± 2.77	88.9 ± 2.34	87.9 ± 2.71	91.8 ± 2.39	78.8 ± 3.24	74.3 ± 3.25	76.5 ± 4.12	77.8 ± 2.85	76.6 ± 3.56	67.5 ± 2.24	75.5 ± 3.72	70.5 ± 2.37	72.2 ± 2.48	74.4 ± 2.69
9	86.5 ± 2.49	84.0 ± 2.64	91.0 ± 2.57	91.0 ± 2.89	93.8 ± 2.77	86.6 ± 2.94	82.9 ± 2.26	89.5 ± 3.21	87.3 ± 3.12	85.6 ± 2.75	75.5 ± 3.51	87.0 ± 2.75	83.9 ± 3.41	85.0 ± 3.31	85.1 ± 2.73
10	91.3 ± 2.71	91.1 ± 3.34	93.7 ± 2.83	94.5 ± 2.79	94.4 ± 2.28	92.2 ± 2.55	91.8 ± 3.52	92.6 ± 3.52	91.8 ± 3.65	92.4 ± 2.76	83.0 ± 2.67	92.5 ± 4.16	93.4 ± 2.85	92.4 ± 3.47	91.8 ± 2.81
11	94.2 ± 3.17	94.5 ± 2.81	95.4 ± 2.65	97.0 ± 2.33	96.9 ± 3.18	94.7 ± 2.64	93.3 ± 3.65	95.7 ± 3.43	94.4 ± 2.52	94.7 ± 2.49	91.2 ± 3.34	94.9 ± 3.21	95.1 ± 2.27	94.1 ± 2.37	94.5 ± 2.62
12	97.3 ± 2.31	97.4 ± 2.27	97.6 ± 2.55	98.7 ± 3.23	97.9 ± 2.66	96.9 ± 2.33	97.8 ± 2.84	97.6 ± 2.56	98.3 ± 3.42	97.2 ± 3.13	95.6 ± 2.71	97.6 ± 2.52	98.0 ± 3.38	97.9 ± 2.14	98.4 ± 3.76

Every value is presented as mean ± standard deviation, n=3

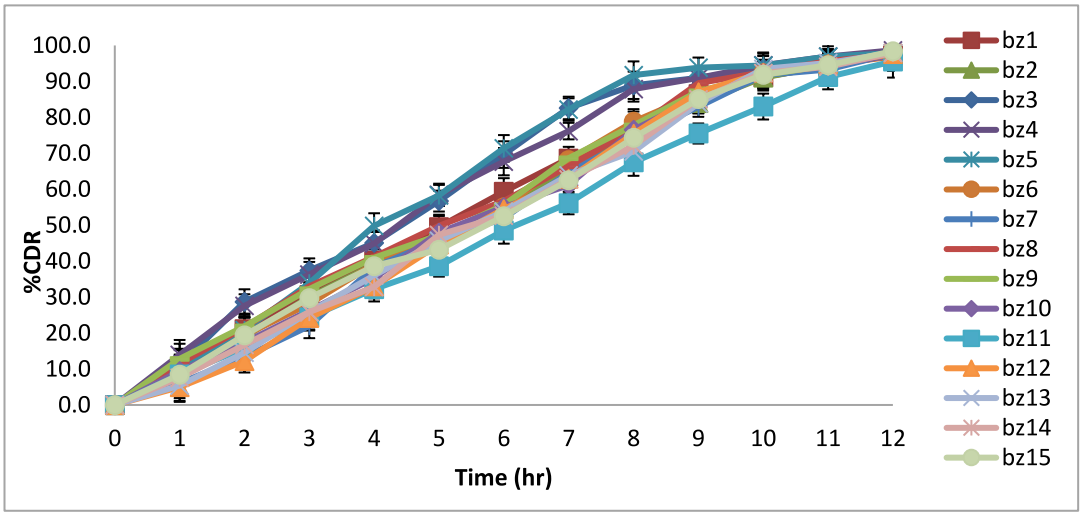

Figure 5: Comparison of Dissolution Profile of Batch BZ1-BZ15

drying and high rotational speed leads to dust formation.

Figure 5 displays the in-vitro pellet dissolving profiles, and Table 8 displays the dissolution parameter. As a result, the release rate of the drug decreases as the volume of polymer in the pellet formulation increases. Therefore, by regulating the amount of HPMC K100 M, the desired release of the drug may be attained. Due to formulation variables, t50% and t90% showed numerous differences. The time needed for the 50% ($t_{50\%}$) and 90 % ($t_{90\%}$) release of BZ1 to BZ15 formulations was found to be between 4.08 hrs and 6.26 hrs and 8.2 hrs and 10.7 hrs. Formulation BZ13 comprising 77.5% of MCC, 7.5% of HPMC K100 M and 1750 rpm of spheronization speed showed promising dissolution parameters ($t_{50\%}$ = 5.57 hr and $t_{90\%}$ = 9.6 hr) which meets the objective of work by achieving sustained drug release.

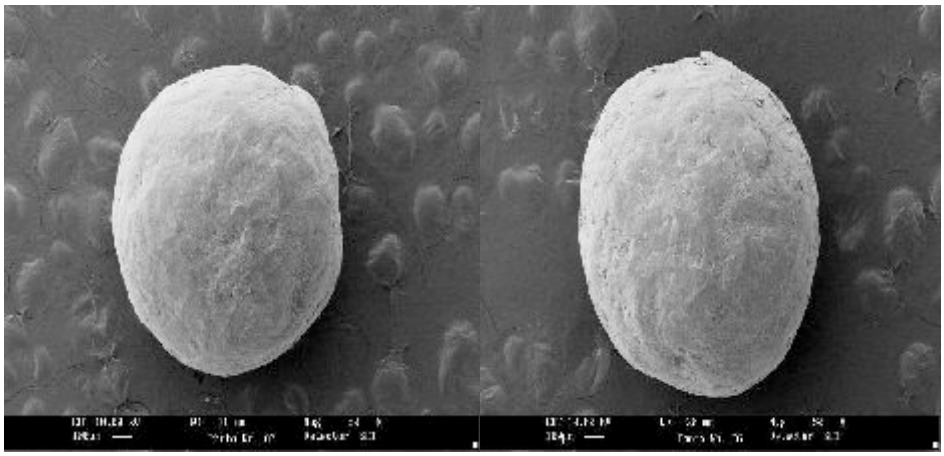

Figure 6: SEM Images (Surface Morphology) of Batch BZ13

Surface Morphology

Aspect ratio and roundness are important parameters for pellet characterization. Aspect ratio closer to 1 and roundness closer to 100% indicates spherical pellets. The BZ13 batch showed a minimal aspect ratio i.e. 1-1.03 and a minimum roundness i.e. 98.80%, which means that the BZ13 batch has spherical and uniform pellets with a smooth surface.

Statistical Analysis

The influence of the dependent variable is investigated using a 3-level and 3-factor design with 2 independent variables at 3 different levels. The 15 Batches within the experimental design were tested at 50% and 90% respectively. Dependent & Independent variables are shown in the table.

Linear, 2FI, Quadratic & Cubic Model data for dependent response was analyzed simultaneously using Design Expert Tools 10. Results of the ANOVA for response $T_{50\ \%}$ (Y_1) and $T_{90\ \%}$ (Y_2) is shown in Table 9 and 10. Following is the mathematical relationship developed for $T_{50\%}$ (Y_1) and $T_{90\%}$ (Y_2) for studied response variable amount of MCC (X_1), amount of HPMC K100M (X_2), and spheronization speed (X_3):

$$Y_1=5.59+0.18X_1-0.30X_2+0.31X_3-0.22X_1X_2-0.62X_1X_3-0.16X_2X_3-0.50X_1^2-0.015X_2^2+0.11X_3^2,\ R^2=0.9264$$

Positive signs in front of terms show a synergistic effect while negative signs show an antagonistic effect upon responses. From the equation, it may be decided that the positive sign of levels X_1, X_3 and X_3^2 had a positive effect on the response while the negative sign of X_2, X_1X_2, X_1X_3, X_2X_3, X_1^2, X_2^2 had a negative effect on the response.

$$Y_2=9.57+0.14X_1-0.40X_2+0.39X_3-0.17X_1X_2-$$

Table 9: ANOVA Response Surface Quadratic Model for Y_1

Source	SS	Df	MS	F Value	p-value prob> F
Model	4.59	9	0.51	7.00	0.0227
X_1	0.25	1	0.25	3.46	0.1220
X_2	0.71	1	0.71	9.80	0.0259
X_3	0.78	1	0.78	10.64	0.0224
X_1X_2	0.20	1	0.20	2.72	0.1602
X_1X_3	1.55	1	1.55	21.27	0.0058
X_2X_3	0.10	1	0.10	1.41	0.2891
X_1^2	0.91	1	0.91	12.54	0.0165
X_2^2	0.008	1	0.008	0.011	0.9191
X_3^2	0.045	1	0.045	0.61	0.4691
Residual	0.36	5	0.073		
Lack of Fit	0.26	3	0.086	1.62	0.4043
Pure Error	0.11	2	0.053		
Cor Total	4.95	14			

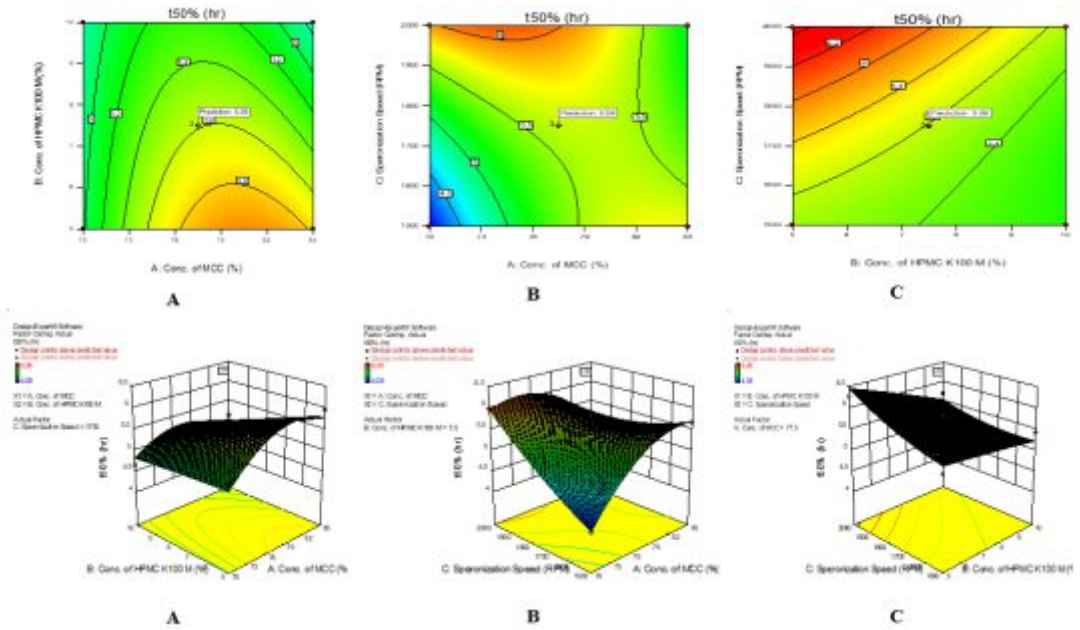

Figure 7: Two-Dimensional and 3D Contour Plot Display Effect of (A) Amount of MCC (gm) X_1 and HPMC K100M (gm) X_2, (B) Amount of MCC (gm) X_1 and Spheronization Speed (RPM) X_3, (C) Amount of HPMC K100M (gm) X_2 and Spheronization Speed (RPM) X_3on $T_{50\%}$ (Y_1)

Table 10: ANOVA Response Surface Quadratic Model for Y_2

Source	SS	Df	MS	F Value	p-value prob> F
Model	6.61	9	0.73	12.93	0.0058
X_1	0.15	1	0.15	2.66	0.1637
X_2	1.28	1	1.28	22.52	0.0051
X_3	1.20	1	1.20	21.14	0.0059
X_1X_2	0.12	1	0.12	2.16	0.2020
X_1X_3	1.44	1	1.44	25.34	0.0040
X_2X_3	0.42	1	0.42	7.43	0.0415
X_1^2	1.72	1	1.72	30.34	0.0027
X_2^2	0.013	1	0.013	0.22	0.6580
X_3^2	0.17	1	0.17	3.05	0.1412
Residual	0.28	5	0.057		
Lack of Fit	0.16	3	0.053	0.83	0.5874
Pure Error	0.13	2	0.063	-	-
Cor Total	6.90	14	-	-	-

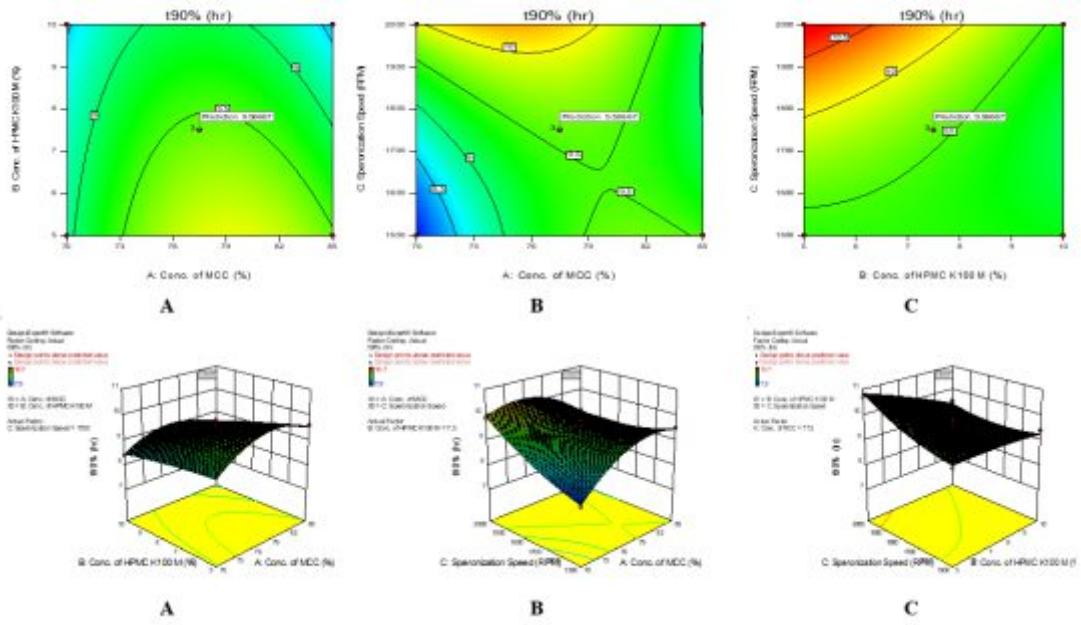

Figure 8: Two-Dimensional and 3D Contour Plot Viewing Effect of (A) Amount of MCC (gm) X_1 and HPMC K100M (gm) X_2, (B) Amount of MCC (gm) X_1 and Spheronization Speed (RPM) X_3, (C) Amount of HPMC K100M (gm) X_2 and Spheronization Speed (RPM) X_3 on $T_{90\%}$ (Y_2)

Check Point Analysis

Table 11: Checkpoint Batches with $t_{50\%}$ and $t_{90\%}$ Predicted and Measured Values

Batch Code	X_1	X_2	X_3	$t_{50\%}$		$t_{90\%}$	
				Measured	Predicted	Measured	Predicted
BZ16	-0.5	0	0.5	5.34	5.47	9.4	9.6
BZ17	0	0.5	-0.5	5.83	5.91	9.7	9.8
BZ18	0.5	-0.5	0	5.48	5.67	9.5	9.7

$$0.60X_1X_3-0.32X_2X_3-0.68X_1^2-0.058X_2^2+0.22X_3^2,\ R^2= 0.9588$$

Three checkpoint batches were prepared & evaluated for $t_{50\%}$ and $t_{90\%}$, as shown in Table 11. The differences between measured and predicted outcomes were found to be insignificant. As a result, it can be said that the attained mathematical model is true for predicted values.

Optimization of Formulation

According to specified criteria, an optimized area is produced by the overlay plot of responses. This was the most crucial element of the response surface methodology. The best drug formulation was chosen since it delivered the drug completely and under controlled conditions. The effects of the independent factors that produce the best response were identified after investigating how the independent variables affected the responses. Based on the criteria for achieving complete and controlled drug release, the best formulation was chosen. Due to better drug release rate in Batch BZ13, which contained 7.5 mg of HPMC K100M and 77.5 mg of MCC, the maximal requirements of an ideal formulation were met. The previously mentioned formulation released 50% of the drug in 5.5 hours and 90% in 9.6 hours, however, 98% of the drug was released in 12 hours, which was nearly in line with predicted values.

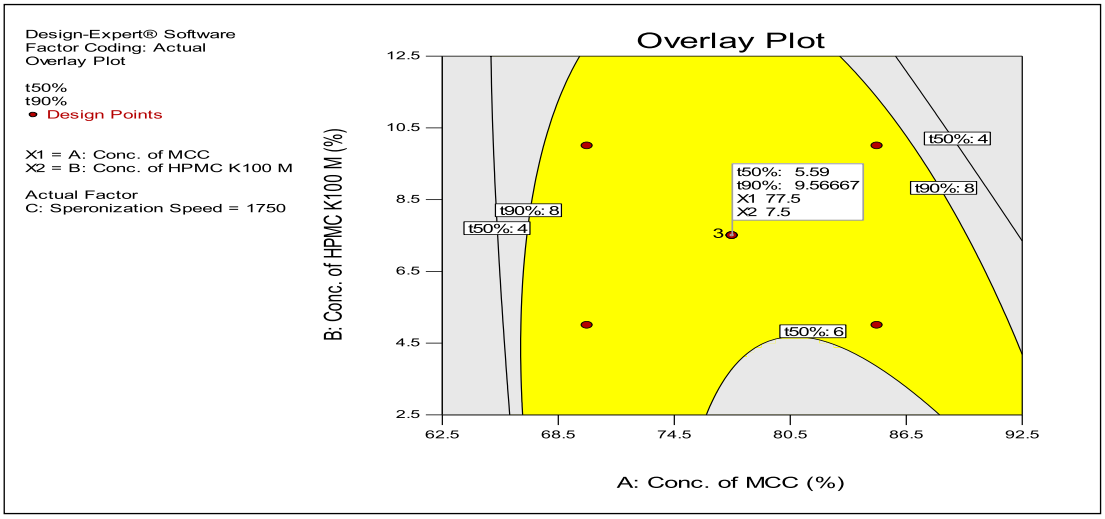

Figure 9: Overlay Plot of Batch BZ13

Stability Study

Table 12: Stability Study of Optimized Formulation (BZ13)

No. of Months	%Drug Content (n=3)	% Drug release in 12hr (n=3)
0	92.1	98
1	91.5	96.7

Zaltoprofen sustained release matrix pellets were subjected to a 1-month stability investigation under predetermined conditions. All data are cited in Table 12. The optimized formulation (BZ13) stability study reveals no appreciable changes in the physical characteristics, drug content, or rate of drug release in 12 hours when kept at 40 ± 2°C/75 ± 5% RH. The formulation was therefore considered to have good stability.

CONCLUSION

Over a longer length of time, the matrix types of pellets are probably an efficient sustained-release drug delivery system. The form and level of polymers used are essential considerations which influence the release of the drug and the physicochemical properties of the sustained release of the pellet matrix. It was done using the Box-Behnken design to produce controlled medication release for up to 12 hours. Of all the formulations produced, the formulation BZ13 containing MCC (77.5 per cent), and HPMC K100M (7.5 per cent) at Spheronization Speed (1750 rpm) showed continuous drug release for 12 hours relative to other formulations. As a result, Z13 was chosen as an optimized formulation. Drug release kinetics is accompanied by Korsemeyer-Peppas. As a result, the process was found to be non-Fickian and demonstrates continuous and consistent release of drugs over a prolonged period, a highly beneficial trait for any extended-release formulation. Stability tests were performed in conjunction with the ICH guideline, which suggests that chosen formulation was stable. From an economic point of view, it could be helpful for local pharmaceutical companies to implement such basic technology for preparation of a sustained-release product.

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