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Formulation and evaluation of sustained release micropellets of Aceclofenac

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Abstract

The objective of present work was to develop Micro pellet formulations in order to attain the instantaneous release of the active medicament in the gastrointestinal tract which would enhance gastric residence time with increased absorption from the stomach & intestine to produce sustained pharmacological responses along with reduced dosing frequency and ultimately the bioavailability would also increase. *In-vitro* release study of each formulation was carried out using pH 1.2 HCl, pH 7.0 phosphate buffers, simulated gastric and intestinal fluids. Various results were inferred i.e. Bulk density (0.742-0.753mg/ml), yield value (84%–98.8%), pellet size (189.8 µm – 290.8 µm) etc. The best drug release profiles were seen with formulation A1 at the ratio of drug: gellan gum (1:1). A 3^2 full factorial design was applied to the combination of polymers (X_1) and percentage of IPA (X_2) used as independent variables whereas particle size & drug release were chosen as selected dependent variables. The predicted value obtained at 0.986 desirability for independent variables were eg. for polymer - 3.00 gm & for IPA- 99.00% and for dependent variables i.e particle size - 189.8 µm & drug release - 88.77% .

Keywords: Micropellet, Aceclofenac, Sustained release, Factorial design, Optimization, Statistical analysis.

Introduction

Drugs that were less soluble or get degraded in the alkaline pH may be benefited from prolonged gastric retention. A prolonged gastric retention increases bioavailability, decreases the wastage and increases the solubility of drugs. Drugs, that have a narrow absorption window in the gastrointestinal tract, will have poor absorption. The Gastroretentive drug delivery system offers advantages in prolonging the gastric emptying time. [(1)] Some factors should be considered when looking to administer drugs via the oral route. In a particular, the transit time in gastrointestinal tract may vary considerably:

- Between patients and within the same patient, with the gastric residence time being the most variable.
- With the state of the dosage form (liquid dosage forms are emptied out of the stomach faster than solid dosage forms).
- With the fasted or fed state of the patient. [(2)]

Designing of oral sustained / controlled-release drug delivery system:

In essence, drug delivery by these systems usually depends on release from some type of dosage form, permeation through biological milieu and absorption through an epithelial membrane to the blood. There are a variety of both physicochemical and biological factors that come into play in the design of such system [(3)].

(a) Sustained release dosage forms:
Sustained release, sustained action, prolonged action, controlled release, extended release,

depot release etc are the terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose of the drug.

(b) Advantage of sustained release formulations includes: [4]

- Uniform release of drug substance over time.
- Reduction in frequency of intakes.
- Reduced adverse side effects.
- Better patient compliance.
- A sustained release dosage form can be treated using lipid excipients to form either a water insoluble matrix or a hydrophobic film around an active drug.

Aceclofenac belongs to non-steroidal anti inflammatory drug (NSAID) is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The drug is having a narrow therapeutic index, short biological half-life (about 4 h) as well as two third (70-80%) of the dose is excreted by renal transport and it makes aceclofenac dosing frequency more than once a day. As this dosage form would reduce the dosing frequency [5].

Micropellets: A General Overview

Traditionally, the word "Pellet" has been used to describe a variety of systematically produced, geometrically defined agglomerates obtained from diverse starting materials utilizing different processing conditions. Pelletization is an agglomeration process that converts fine powders or granules of bulk drugs and excipients into small, free flowing, spherical or semi spherical units, referred to as pellets. Pellets range in size, typically, between 0.5–1.5 mm, though other sizes could be prepared. The use of pellet, as a vehicle for a drug delivery at a controlled rate, has recently received significant attention, pellets disperse freely in the gastrointestinal tract, so they invariably maximize the drug absorption, reduce peak plasma fluctuation and minimize potential side effects without appreciably lowering drug bioavailability. The methods used for Pelletization are essentially the same as the granulation methods. The most widely used processes are extrusion & spheronization, solution or suspension layering and powder layering. Other processes with limited application in the development of pharmaceutical pelletized products include globulation, balling and compression.[6,7,8]

(a) Ideal properties of the pellets:

- Spherical shape and smooth surface.
- The particle size of pellets should be in the range of 1-1000µm.
- The quantity of the active ingredient in pellets should be maximized in order to maintain the size of pellets.

(b) Advantages: [9]

- The appearance of the product which is having fine pharmaceutical elegance.
- Pelletization offers flexibility into the dosage form design and development.
- Pellets improve the flow properties in formulation development.
- They flow freely and are easy to pack without significant difficulties (resulting in uniform and reproducible fill weight of capsules).
- Pellets are less susceptible to dose dumping.
- It reduces accumulation of drugs especially proven advantageous in the case of irritating drugs.
- It improves safety and efficacy of a drug.
- Pelletization is a convenient way to manage the separation of incompatible drugs.
- Pellets offer reduced variation in the gastric emptying rate and intestinal transit time.
- Pellets disperse freely in G.I.T. and invariably maximize drug absorption and also reduce peak plasma fluctuation
- Pelletization solves the problem of taste masking.
- Coating of pellets can be done with different drugs to enable a pellets release rate.
- The coating material may be colored with a dye material so that the beads of different coating thickness will be darker in color and distinguishable from those having fewer coats.
- In case of immediate Release Products larger surface area of pellets enables better distribution.
- Chemically incompatible products can be formed into pellets & delivered in a single dose by encapsulating them.
- In the chemical industries it is used to avoid powder dusting.

Sustained release micropellets showing a stable controlled-release of a drug without being affected by the changes in pH value etc., characterized by being produced by coating core particles with a layer containing a water-soluble drug, further forming a film layer containing a water-insoluble polymer compound and a plasticizer on the thus obtained particles, locating a water-soluble filler layer between the water soluble drug-containing layer and the film layer and having an average particle size of 300 µm or less; medicinal compositions containing these micropellets; and a process for producing the same[10]

Material and Method

Various materials i.e. drug sample, additives, reagents etc. were obtained from different reputed companies as summarized below:

Table 1: Materials and Source

S. No.	Material	Source
1	Aceclofenac	Sun pharma,Vapi,India
2	Gellan gum	Burgin and leon, Mumbai
3	Gum acacia	Sun pharma,Vapi,India
4	Gum tragacanth	Rankem, India
5	Iso propyl alcohol	R.K enterprises, Meerut
6	Microcrystalline cellulose	R.K enterprises, Meerut
7	PVP k_{30}	R.K enterprises, Meerut

Preparation of Aceclofenac Micropellets: [8]

Micropellets of aceclofenac were prepared by direct pelletization techniques: The appropriate quantity of powdered drug was mixed and moistened with the binder solution in IPA. The powder bed was set into a centrifugal motion using disc pelletizer resulting in the formation of agglomerates which became rounded to produce uniform and dense pellets. The moist pellets were subsequently dried in the tray drier and collected.

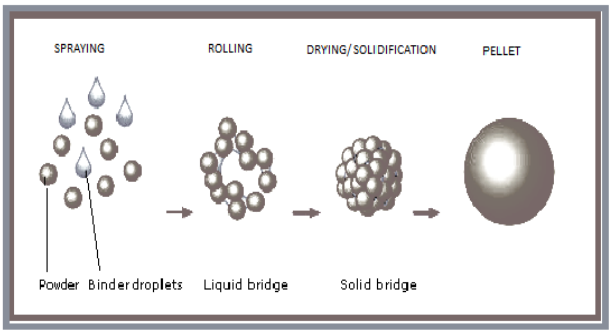

Figure 1: Schematic representation of pelletization technique
Formulation

Table 2: Formulation design of Micropellets

Ingredients	A1	A2	A3	B1	B2	B3	C1	C2	C3
Drug (gm)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Gellan gum (gm)	2.5	5	7.5	---	---	---	---	---	---
Gum acacia (gm)	---	---	---	2.5	5	7.5	---	---	---
Gum tragacanth (gm)	---	---	---	---	---	---	2.5	5	7.5
Solvent (Isopropyl alcohol: Water)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
MCC (gm)	17.5	15	12.5	17.5	15	12.5	17.5	15	12.5
$PVPk_{30}$	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
IPA %v/v	99%	95%	97%	97%	99%	95%	95%	97%	99%

Experimental design: [10]

Experimental design involves the arrangement of experiments in the design space such that the reliable and consistent information is achievable with minimum number of experiments. Experimental designs are based on the principles of randomization, replication and error control

Optimization

The runs or formulations designed based on 3^2 full factorial designs, were evaluated for the response variables. The response values were subjected to multiple regression analysis to find out the relationship between the factors used and the response values obtained.

Statistical Analysis

The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design of Experiments® 8.0.7.1 (Stat Ease, USA). The design was evaluated by quadratic model bearing the form of equation (1).

$$\mathbf{Y= b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2} \quad \textbf{..... eq-1}$$

Where y = the response variable, b_0 the constant and b_1, b_2, $b_3 \ldots b_5$ the regression coefficient. X_1 and X_2 stand for the main effect; X_1 & X_2 the interaction terms showing how response changed when two factors were simultaneously altered. X_1^2, X_2^2 were quadratic terms of the independent variables to evaluate nonlinearity. Using the regression coefficient of the factors, the polynomial equation for the response was constructed. Only significant, contributing factors were considered for the equation generation.

Desirability Details

The method made use of an objective function, D (X), called the desirability function. It reflected the desirable ranges for each response (di). The desirable ranges were from zero to one (least to most desirable respectively). The simultaneous objective function had been a geometric mean of all transformed responses.

If any of the responses or factors fell outside their desirability range, the overall function became zero. For simultaneous optimization, each response must have a low and high value assigned to each goal.

Maximum:
di = 0 if response < low value
0 ≤ di ≤ 1 as response varies from low to high
di = 1 if response > high value
Minimum:
di = 1 if response < low value
1 ≤ di ≤ 0 as response varies from low to high
di = 0 if response > high value
Target:
di = 0 if response < low value
0 ≤ di ≤ 1 as response varies from low to target
1 ≤ di ≤ 0 as response varies from target to high
di = 0 if response > high value
Range:
di = 0 if response < low value
di = 1 as response varies from low to high
di = 0 if response > high value

Stability Study: [11]

The stability study of drug loaded micropellets was carried out for a period of 30 and 90 days at 40^0±2ºC temperature and relative humidity of 75% ±5% using stability chamber. Sample was collected after 30 and 90 days and evaluated for the drug content.

Result and Discussion

Compatibility Studies

(a) TLC Method: [12]

It was also studied by thin layer chromatographic method using precoated plates of silica gel GF_{254} using mobile phase consisting of toluene : ethyl acetate : methanol : glacial acetic acid (4:6:2:0.5 v/v).

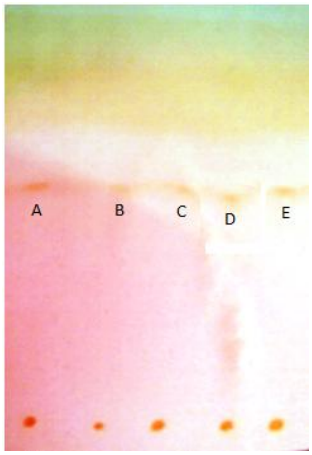

Figure 2: Representations of TLC with different drug-excipients combinations

Table 3: Rf value of TLC of different sample

S. No.	Sample	Rf value
A.	Drug	0.731
B.	Drug+gellan gum	0.730
C.	Drug+acacia gum	0.729
D.	Drug +tragacanth gum	0.728
E.	Drug in formulation blend	0.730

Evaluation parameters

a) Micropellet size analysis:

The analysis was performed for all nine batches by photomicroscope using micrometric tools. The results were as shown in table. The mean diameters of micropellet for all batches were found in the range of 189.8-290.8µm.

Table 4: Micropellet size analysis of batch A_1 - C_3

S. No.	Formulation code	Mean Particle size (µm)
1	A1	189.8
2	A2	265.8
3	A3	242.9
4	B1	230.7
5	B2	206.3
6	B3	230.3
7	C1	290.8
8	C2	260.5
9	C3	234.1

b) Surface morphology:

The surface morphology of micropellets belonging to the optimized batch, i.e. A_1, was examined by scanning electron microscopy.

SEM image of formulation A_1

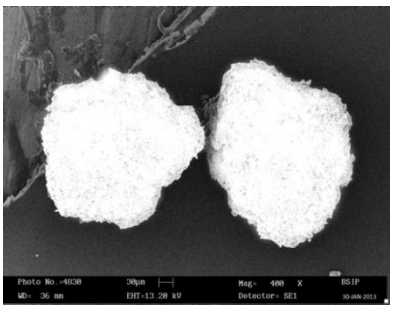

Figure 3: scanning electron microscopy of optimized formulation A_1

c) Bulk density of the Micropellets:

The Bulk density determination was performed for all nine batches by hand tapping method using measuring cylinder. Results were as shown in table no. The bulk densities for all samples were found to be in the range of 0.742 - 0.753.

Table 5: Bulk density of batch A_1 - C3

S. No.	Formulation	Bulk density (mg/ml)
1	A_1	0.742
2	A_2	0.752
3	A_3	0.750
4	B_1	0.748
5	B_2	0.745
6	B_3	0.747
7	C_1	0.753
8	C_2	0.750
9	C_3	0.748

d) Percentage yield:

The maximum percentage yield was found to be 98.8% with batch A_1 and minimum of 84% with batch A_3.

Table 6: Percentage yield of batch A_1 - C_3

Formulation	Theoretical Yield (g)	Practical Yield (g)	Percentage Yield (%)
A_1	25	24.7	98.8
A_2	25	24	96
A_3	25	21	84
B_1	25	23	92
B_2	25	23.6	94.4
B_3	25	21.3	85.2
C_1	25	21.9	87.6
C_2	25	22.1	88.4
C_3	25	22	88

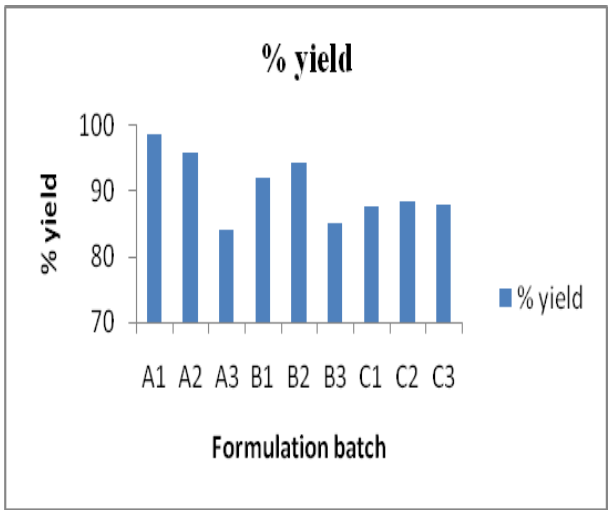

Figure 4: Graphical representation of percentage yield

d) In-vitro release kinetic

Table 7: In-vitro release kinetic values of batch A_1-C_3 with acidic (pH 1.2) and pH 7.0 phosphate buffers:

Formulation code	Zero order equation		First order equation		Higuchi's equation		Korsmeyer's equation	
	Slope	(r^2)	Slope	(r^2)	Slope	(r^2)	Slope	(r^2)
A1	0.095	0.976	0.001	0.636	2.962	0.973	0.660	0.997
A2	0.094	0.978	0.001	0.628	2.915	0.970	0.660	0.997
A3	0.087	0.958	0.001	0.616	2.756	0.980	0.655	0.997
B1	0.093	0.978	0.001	0.625	2.881	0.967	0.660	0.997
B2	0.092	0.981	0.001	0.629	2.863	0.965	0.658	0.996
B3	0.091	0.983	0.001	0.628	2.829	0.964	0.655	0.996
C1	0.095	0.979	0.001	0.618	2.960	0.971	0.661	0.997
C2	0.094	0.980	0.001	0.628	2.905	0.970	0.658	0.997
C3	0.091	0.981	0.001	0.619	2.831	0.966	0.650	0.998

All the release data were fitted into various kinetic models like zero order, first order, higuchi and korsmeyer peppas in order to find out the mechanism of drug release from micropellets in acidic pH 1.2 and pH 7.0 phosphate buffers from the release kinetics of different formulations slope & r^2 values were calculated for formulation A_1- C_3 , the r^2 = 0.998 (formulation C_3) was found to be maximum, so it followed the korsmeyer peppas kinetic model.

Table 8: In-vitro release kinetic values of batch A_1-C_3 with Simulated Gastric and Intestinal fluids

Formulation code	Zero order equation		First order equation		Higuchi's equation		Korsmeyer's equation	
	Slope	(r^2)	Slope	(r^2)	Slope	(r^2)	Slope	(r^2)
A1	0.092	0.980	0.001	0.619	2.845	0.970	0.651	0.996
A2	0.092	0.982	0.001	0.623	2.837	0.967	0.647	0.996
A3	0.091	0.985	0.001	0.629	2.801	0.965	0.639	0.998
B1	0.091	0.983	0.001	0.617	2.807	0.965	0.644	0.997
B2	0.090	0.984	0.001	0.623	2.779	0.962	0.642	0.997
B3	0.089	0.984	0.001	0.644	2.734	0.960	0.644	0.996
C1	0.092	0.983	0.001	0.640	2.842	0.966	0.653	0.996
C2	0.091	0.984	0.001	0.641	2.894	0.965	0.648	0.996
C3	0.089	0.983	0.001	0.643	2.751	0.965	0.647	0.995

All the release data were fitted into various kinetic models like zero order, first order, higuchi and korsmeyer peppas in order to find out the mechanism of drug release from micropellets in simulated gastric and intestinal fluids from the release kinetics of different formulations slope & r^2 values were calculated for formulation A_1- C_3, the $r^2 = 0.998$ (formulation A_3) was found to be maximum, so it followed the korsmeyer peppas kinetic model.

Full factorial design:

A 3^2 randomized full factorial design was used to optimize the variables in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amount (2.50, 5.00 and 7.50 gm) of polymers (X_1) and (95, 97 and 99 %) IPA (X_2), were selected as independent variables. The particle size and percentage drug release were selected as dependent variables.

Table 9: 3^2 Full Factorial Design Layouts.

Batch Code	Variable Levels in Coded Form		Particle size	Drug release
	X_1 (gm)	X_2 (%)	Particle size (µm)	Drug release (%)
A1	-1	1	189.8	89.22
A2	0	-1	265.8	87.34
A3	1	0	242.9	85.65
B1	-1	0	230.7	81.75
B2	0	1	206.3	85.24
B3	1	-1	230.3	83.87
C1	-1	-1	290.8	87.81
C2	0	0	260.5	85.98
C3	1	1	234.1	84.67

Coded values	Actual value	
	X_1	X_2
-1	2.50	95
0	5.00	97
1	7.50	99

*X_1, indicated the amount of Polymers (gm); X_2, % of IPA

Table 10: Calculations for testing the model in Portions

For Particle size					
	DF	SS	MS	F	R^2
Regression					
FM	5	7106.62	1421.32	9.90	0.9428
RM	2	6838.24	3419.12	29.34	0.9072
Error					
	FM	3	430.84	143.61	
	RM	6	699.21	116.54	
For % Drug release					
	DF	SS	MS	F	R^2
Regression					
FM	5	7106.62	1421.32	9.90	0.9428
RM	4	206.04	51.51	15.93	0.9409
Error					
	FM	3	12.89	4.30	
	RM	4	12.94	3.23	

DF indicated: degree of freedom; (SS), sum of squares; (MS), mean of squares; (F), Fischer's ratio; (R2) regression coefficient; (FM), full model; and (RM), reduced model.

Table 11: Summary of Regression Analysis Results

Variable constants: $b_0\, b_1\, b_2\, b_{12}\, b_{11}\, b_{22}$

For Particle Size						
Response	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	249.88	- 0.67	-26.12	26.20	-7.77	-8.52
RM	239.02	-	-26.12	26.20	-	-
For % Drug release						
Response	b_0	b_1	b_2	b_{12}	b_{11}	b_{22}
FM	81.62	-2.93	- 0.087	-3.95	- 4.79	4.81
RM	81.62	-2.93	-	-3.95	-4.79	4.81

*(FM), indicates full model; (RM), reduced model.

Table 12: Optimized formula obtained and their desirability

Name	Goal	Lower limit	Upper limit
Factor A	In range	2.50	7.50
Factor B	In range	95	99
Particle size	Minimize	189.8	290.8
% Drug release	Maximize	73	89.22

Table 13: Predicted Solution for optimization

Polymer	IPA	Particle Size	% Drug release	Desirability	Remarks
3.00	99.00	189.8	88.77	0.986	Selected

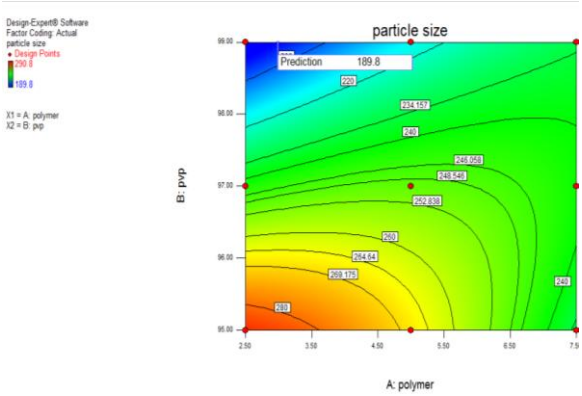

Figure 5: Contour plot showing the influence of PA and polymer concentration on particle size

Interpretation: From model graphs it could be concluded that there was a linear increase in drug release with increased amounts of polymer which accompanied decrease in particle size.

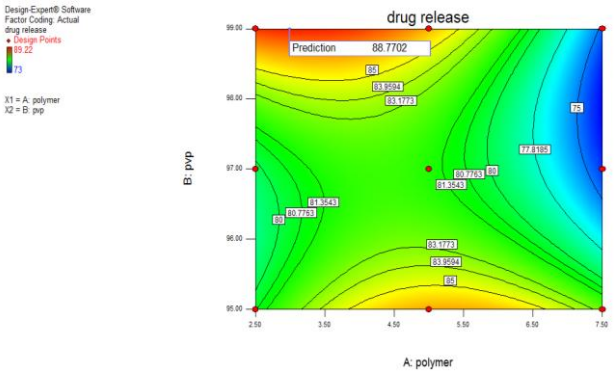

Figure 6: Contour plot showing the influence of IPA and polymer concentration on drug release

Interpretation: Particle size and drug release increased from blue to red region in contour graph, the prediction points were determined as 189.8 and 88.77.

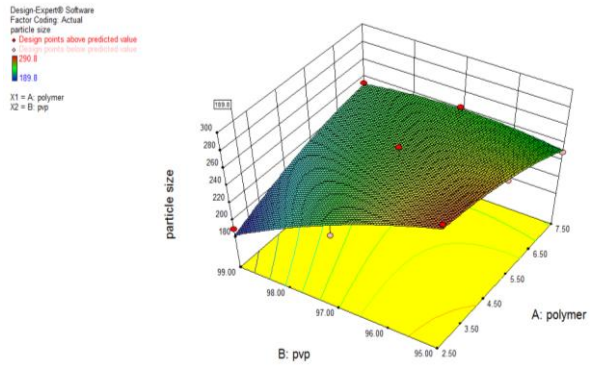

Figure 7: Response surface plot showing the influence of IPA and polymer concentration on particle size

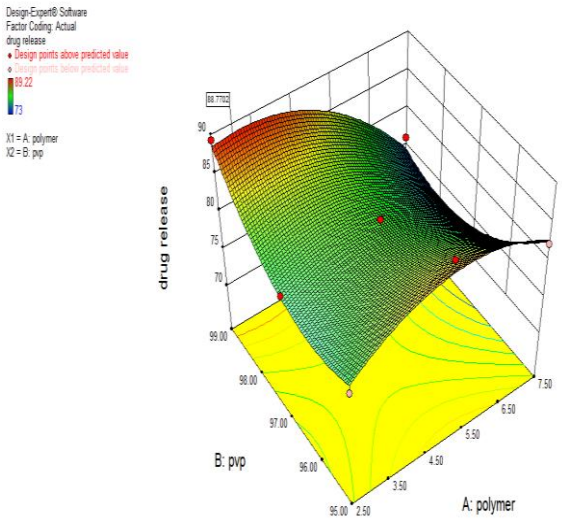

Figure 8: Response surface plot showing the influence of IPA and polymer concentration on drug release

Stability data of formulation A_1:

The stability study was performed on overall optimized batch (A_1) as per ICH guidelines at accelerated conditions (40 ± 2^0C, 75%±5 RH) which showed that the formulation was stable with no. Physicochemical changes and also there was no significant reduction in drug contents.

Table 14: Stability data of Finalized formulation

Stability Study	A_1 (Optimized Formulation)		
	0 Days	30 Days	90 Days
Physical Appearance	White	White (ok)	White (ok)
% yield	98.8	97.6	96.81
% Drug Release	89.22	88.13	86.41

Release profile of formulation A_1 on stability studies at different intervals:

Table 15: Percent release profile of batch A_1 in pH 1.2 HCl & 7.0 Phosphate buffer at different intervals (on stability)

Time (min)	% Drug Release of A_1 Formulation		
	0 Days	30 Days	90 Days
0.0	0.000	0.000	0.000
30	7.600	7.150	7.150
60	13.970	13.518	13.518
120	23.455	23.003	23.003
180	31.608	31.156	30.706
240	37.053	36.601	36.148
300	42.934	42.481	42.029
360	50.166	49.264	48.811
420	57.406	56.501	56.049
480	63.297	62.392	61.039
540	69.629	68.724	67.817
600	77.797	77.342	75.535
720	84.110	83.207	81.847
840	89.22	88.13	86.41

Release profile of formulation A_1 on stability studies at different intervals in pH 1.2 HCl & 7.0 pH buffer

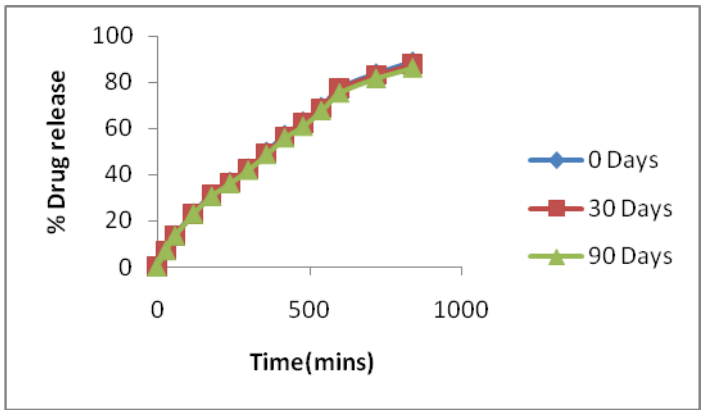

Figure 9: Stability data of A_1 formulation with pH 1.2 HCl buffer & 7.0 Phosphate buffer

Conclusion

The micropellets of aceclofenac were prepared with three polymers i.e. Gellan Gum, Gum Acacia and Gum Tragacanth. The Micropellets size determination by SEM techniques revealed that the mean particle diameter was in the range of 189.8 µm – 290.8 µm. The mean Micropellets size were in the order of $A_1 < B_2 < B_3 < B_1 < C_3 < A_3 < C_2 < A_2 < C_1$. The morphological studies were conclusive to spherical shaped pellets.

The other physicochemical parameters determined with the micropellets were bulk density (0.742–0.753mg/ml), yield value (84% – 98.8%). The in - vitro drug release in pH 1.2 HCl and pH 7.0 phosphate buffers ranged from (81.75%–89.22%) while in simulated gastric and intestinal fluids it ranged from (80.96% –84.10%) thus reflecting sustained release over a period of 12 hrs.The yield value determination revealed it was maximum with A_1 and minimum with A_3 batch.

The formulations were optimized by statistical screening design considering the concentration of combination of polymers (X_1) and percentage of IPA (X_2) used as independent variables whereas particle size & drug release as dependent variables. The statistical derivations supported the micropellets of batch A_1 as optimized one.

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Conflict of Interest

We declare that there is no conflict of interests regarding the publication of this paper.

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