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FORMULATION, EVALUATION AND OPTIMIZATION USING FULL FACTORIAL DESIGN OF DICLOFENAC SUSTAINED RELEASE MICROPELLETS

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ABSTRACT

Micropellets are small, free flowing, semi-spherical solid units, typically from about 0.1mm to 0.5mm and are intended for oral administration. The study was undertaken with an aim to develop sustained release micropellet dosage form for Diclofenac which is an anti-inflammatory agent and is one of the most widely used drugs for treating mild and severe pains. The approach of this study was to make a comparative evaluation among polymers and excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype formulations of micropellets were prepared using drum pelletizer at 300 rpm. Percentage of water in binding liquid, i.e. IPA, is varied from 95 to 99% and the effect on various parameters, such as particle size, entrapment, bulk density and particle shape, were observed. Concerning the results of prototype preparation of Diclofenac micropellets were prepared using HPMC K 100 M, as release retardant, in three different concentrations i.e. 16.7%, 33.3% & 50%. Formulated micropellet showed sustained in-vitro dissolution rate, due to optimized polymer concentration. The micropellets were stable at 40°C±2°C/75%±5% RH as per ICH guidelines, after 3 months.

Keywords: Micropellets, Diclofenac, HPMC K100M, Full Factorial Design

INTRODUCTION

Micropellets are of great interest to the pharmaceutical industry for a variety of reasons.[1-5] Pelletized products not only offer flexibility in dosage form design and development, but are also utilized to improve the safety and efficacy of bioactive agents.[5-6] When pellets

containing API are administered in-vivo as suspensions, capsules or disintegrating Tablets, they offer significant therapeutic effect over single unit dosage forms[5], since pellets disperse freely in the GIT, they invariably maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering drug bioavailability.[7-9]

In case of oral products micropellets solve difficult taste-masking problems while maintaining a high degree of bioavailability due to their high surface area.[10] As compared to normal pellets which have diameters in the millimeter range, these are much smaller in size (10 - 600 μm) furthermore, because of the special design of the manufacturing process, dust fractions (representing uncoated fragments which could cause taste problems) are absent in micropellets. Pellets also reduce variations in the gastric emptying rate and overall transit time, thus, intra- and inter subject variability of plasma profiles which are common with single unit regimens, are minimized.[11]

Another advantage of pellets over single-unit dosage forms is that high local concentrations of bioactive agents which may inherently be irritative or anesthetic, can be avoided[9] when formulated as modified release dosage forms; pellets are less prone to dose clearance than the reservoir-type single unit formulations.[12-13]

The objective of this research is to formulate a dry suspension formulation containing Diclofenac micropellets for sustained therapeutic effect.

MATERIALS AND METHODS

MATERIALS

Diclofenac was obtained as gift sample from Best Laboratories, Delhi. All other ingredients, HPMC K100M, Di Calcium Phosphate and PVP K30, used were of analytical grade.

METHODS

Preparation of Standard Calibration & Regression Curve in different media: [14]

A sample solution of (100 μg/ml) was scanned at a range of 200-400 nm to access the λmax value of the drug which was reproduced and confirmed by obtaining the overlain UV spectra. The standard calibration & Regression curve was obtained with the aliquots of different concentrations by plotting absorbance vs concentration graph in different media, separately.

DRUG POLYMER COMPATIBILITY STUDY:[15]

FTIR analysis:

The drug-polymer compatibility was studied by FTIR (Shimadzu IR Affinity-1) spectrophotometry. Various samples were prepared in KBr discs (2mg sample in 200 mg KBr) with hydrostatic press at a force

of 5.2τ cm^{-2} for three times. The scanning range was 450 – 4000 cm^{-1} and at resolution 4 cm^{-1}. The characteristic peaks were recorded.

FORMULATION DESIGN:

The formulation was divided into nine batches prepared with different ratios of suitably chosen polymers as depicted in the Table -1:

Table 1: Formulation design of Micropellets:

Ingredients / Code	Drug (gm)	HPMC K 100M (gm)	DCP (gm)	PVP K30 (gm)	Isopropyl alcohol %v/v
DH1	5	2.5	7	0.5	95
DH2	5	2.5	7	0.5	97
DH3	5	2.5	7	0.5	99
DH4	5	5	4.5	0.5	95
DH5	5	5	4.5	0.5	97
DH6	5	5	4.5	0.5	99
DH7	5	7.5	2	0.5	95
DH8	5	7.5	2	0.5	97
DH9	5	7.5	2	0.5	99

PREPARATION OF DICLOFENAC MICROPELLETS:[16]

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 drum 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.

EVALUATION OF MICROPELLETS:

Percentage yield (% yield): [17]

The percentage yield was determined on the basis of method as reported by **Amitava et al.** The yield was calculated as the weight of the micropellets recovered from each batch divided by total weight of drug and polymer used in the preparation of the particular batch.

$$\text{Percentage yield} = \frac{\text{practical yield}}{\text{theoretical yield}} \times 100$$

Micropellet size analysis:

The analysis of pellet size was carried out using a photomicroscope (QUASMO, Quality Scientific, Ambala) fitted with micrometric tools (Winzoe). The size distribution was determined and the average diameter was calculated for each batch of micropellets.

Bulk density: [18]

Bulk density was calculated by manual tapping method introducing micropellets in 10 ml graduated cylinder & calculated by the given formula.

$$B.D = \frac{\text{wt.of micropellets}}{\text{vol.of micropellets}}$$

Drug entrapment

Accurately weighed micropellets were taken, thoroughly triturated and suspended in a minimal amount of solvent. The suspension was filtered with 0.22µ nylon filter to separate excipients. Drug contents were analyzed and % Drug entrapment is calculated by using following equation.

$$\%\ \text{Drug Entrapment} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Surface Morphology: [19]

The morphology and surface characteristics of micropellets were studied by Scanning electron microscopy. The dried micropellets were coated with gold foil (100 A°) under an argon atmosphere in a gold coating unit and micrographs were obtained at both higher and lower resolutions.

In-Vitro Release Studies: [17, 21]

In-vitro drug release studies were carried out for all batches by using USP (TDT 06L) type I dissolution test apparatus. The sample of Micropellets containing 100 mg of the pure Diclofenac was used for the study in pH 1.2 HCl buffer for two hours and then in pH 7.0 buffer for next twelve hours 5 ml sample were withdrawn at predetermined time interval, diluted suitably and analyzed for the drug content using HPLC method at predetermined λ_{max} using dissolution media (pH 1.2 HCl, 7.0 phosphate Buffer, SGF & SIF, respectively).

OPTIMIZATION

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

1. Particle size in µm
2. percentage drug release in %.

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 (StatEase, USA).

Stability Study: [15]

The stability study of drug loaded micropellets was carried out for a period of

30, 60 and 90 days at 40^0±2ºC temperature and relative humidity of 75% ±5% using stability chamber. Sample was collected after 30, 60 and 90 days and evaluated for drug release.

DRY SUSPENSION FORMULATION METHOD

All the ingredients were passed from sieve # 12 to remove coarse particle. Sieved ingredients then mixed and blended in specified order. At first colour, Sodium Benzoate and SCMC were blended. Then flavour was added continued with drug micropellets. This mixture was blended for 10 minutes to get homogenous blend. In the homogenized blend sodium citrate and citric acid followed by Sucrose was blended. The homogenized blend then collected and packed. Formulation is depicted in Table -2.

Table 2: Dry Suspension Formulation

	DS
Pellets %	3.125
Sodium Citrate %	1
Citric Acid %	1
SCMC %	1
Flavour %	0.55
Colour %	0.25
Sod. Benzoate %	0.2
Sucrose %	QS to 100

Formulation Evaluation [21-23]

pH:

pH of reconstituted dry suspension was determined by using digital pH meter.

Viscosity:

The rheological behavior of the suspension was determined by using Brookfield viscometer.

Sedimentation behavior:

1) Redispersibility:

The redispersibility was determined was determined by studying number of strokes to redisperse the formed sediment at the end of 7^{th} day of storage of reconstituted formulations.

2) Sedimentation Volume Ratio (SVR):

During the seventh day study sedimentation behavior of formulations was studied for sedimentation volume (F).

Stability study of Dry Suspension:

The reconstituted suspension were stored in air tight amber coloured glass bottles for 15 days at 45°C and then evaluated after 6th and 12th hours of reconstitution.

RESULTS AND DISCUSSION

Diclofenac micropellets formulated using HPMCK100M, release retardant, in various concentrations and pelletized with the help

of drum pelletizer.

Under Preformulation study, FTIR analysis between the drug and excipients mixture showed no unaccountable extra peaks which confirms the absence of chemical interaction between ingredients.

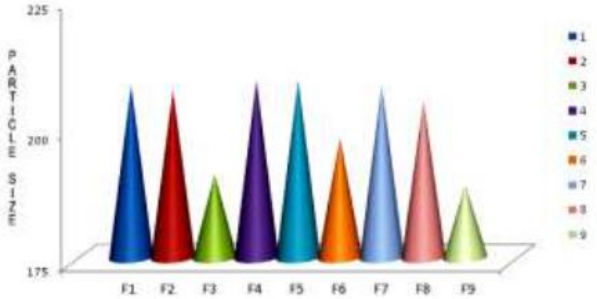
Diclofenac Micropellets were evaluated for various physiochemical parameters viz. Percent yield, Bulk density, Entrapment efficiency and particle size.

Particle Size Analysis

The analysis was performed for all nine batches by photomicroscope using micrometric tools. The Results were shown in Table 3. The mean diameters of micropellet for all batches were found in the range of 189-219µm.

Table 3: micropellet size analysis of batch DH1-DX9.

HPMC K100 M Micropellet containing Diclofenac potassium									
Formulation code	**DH1**	**DH2**	**DH3**	**DH4**	**DH5**	**DH6**	**DH7**	**DH8**	**DH9**
mean size (µm)	207	203	191	219	216	198	208	205	189
BD g/ml	0.80	0.78	0.74	0.81	0.8	0.78	0.79	0.80	0.78
% yield	26.3	44.6	52.2	36.4	34.6	29.3	40.4	40.7	47.7
% Entrapment	32.1	33.6	34.0	34.3	33.4	32.4	32.1	33.8	33.6

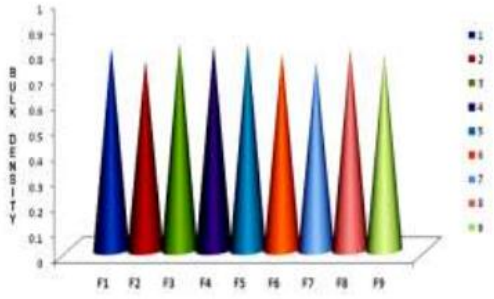


Surface morphology:

The surface morphology of micropellets belonging to optimized batch i.e. DH3 was examined by scanning electron microscopy. The micropellets were semi-spherical and in the size range with rough surface, as shown in Figure 3.

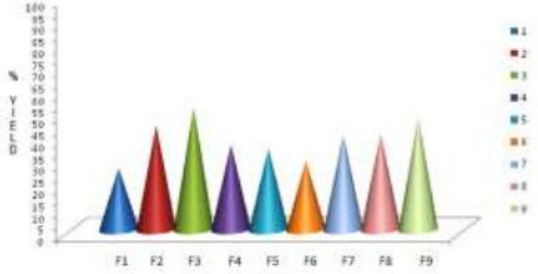
Bulk density of the Micropellets:

The Bulk density determination was performed for all nine batches by hand tapping method using measuring cylinder. The bulk densities for all samples were found to be in the range of 0.74 - 0.81 g/ml. Results were shown in Table 3, Figure 4.



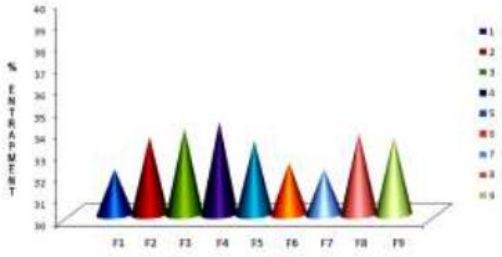
Percentage yield:

The maximum percentage yield was found to be 52.2% with batch DH3 and minimum of 26.3% with batch DH1. Results were shown in Table 3, Figure 5.



Percentage Entrapment:

The maximum percentage entrapment was found to be 52.2% with batch DH3 and minimum of 26.3% with batch DH1. Results were shown in Table 3, Figure 6.

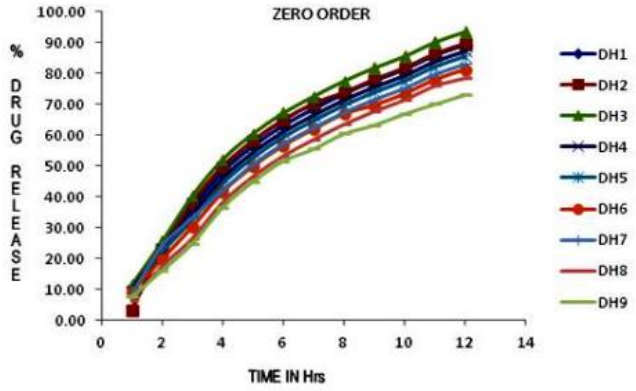


IN-VITRO DISSOLUTION STUDIES:

In-vitro dissolution profile of formulation DH1-DH9 in pH 1.2 HCl and pH 7.0 phosphate buffers represented that the micropellet formulations are susceptible to provide sustained release effect. Formulations DH3 showed maximum release in 24 Hr study. Results were shown in Table 7, 8, 9 Figure 7.

Table 4: Release kinetic data of batch DH1-DH9 in pH 1.2 HCl and pH 7.0 phosphate buffers.

TIME (hrs)	DH1	DH2	DH3	DH4	DH5	DH6	DH7	DH8	DH9
1	10.72	3.25	11.44	9.63	9.27	9.15	8.19	6.38	7.71
2	23.86	22.73	25.48	23.30	21.95	19.70	23.82	17.55	16.22
3	36.17	37.90	40.36	34.34	32.55	30.15	33.16	26.58	24.95
4	47.91	49.65	52.11	46.06	44.28	41.44	42.03	38.30	36.67
5	56.29	58.05	60.51	54.44	52.66	49.82	50.39	46.66	45.03
6	63.02	64.79	67.24	61.16	59.37	56.53	56.08	53.37	57.74
7	68.36	70.15	72.60	66.49	64.70	61.85	60.38	58.69	64.63
8	73.30	73.68	77.55	70.42	69.63	66.78	64.29	63.61	70.54
9	79.55	79.94	83.82	73.67	73.87	71.60	67.51	68.84	75.35
10	83.26	84.66	87.54	75.37	77.57	75.29	70.19	72.53	79.02
11	81.84	89.24	91.13	77.94	79.14	78.84	72.73	75.09	81.14
12	89.20	91.60	93.50	79.40	80.50	82.30	73.10	78.60	82.50



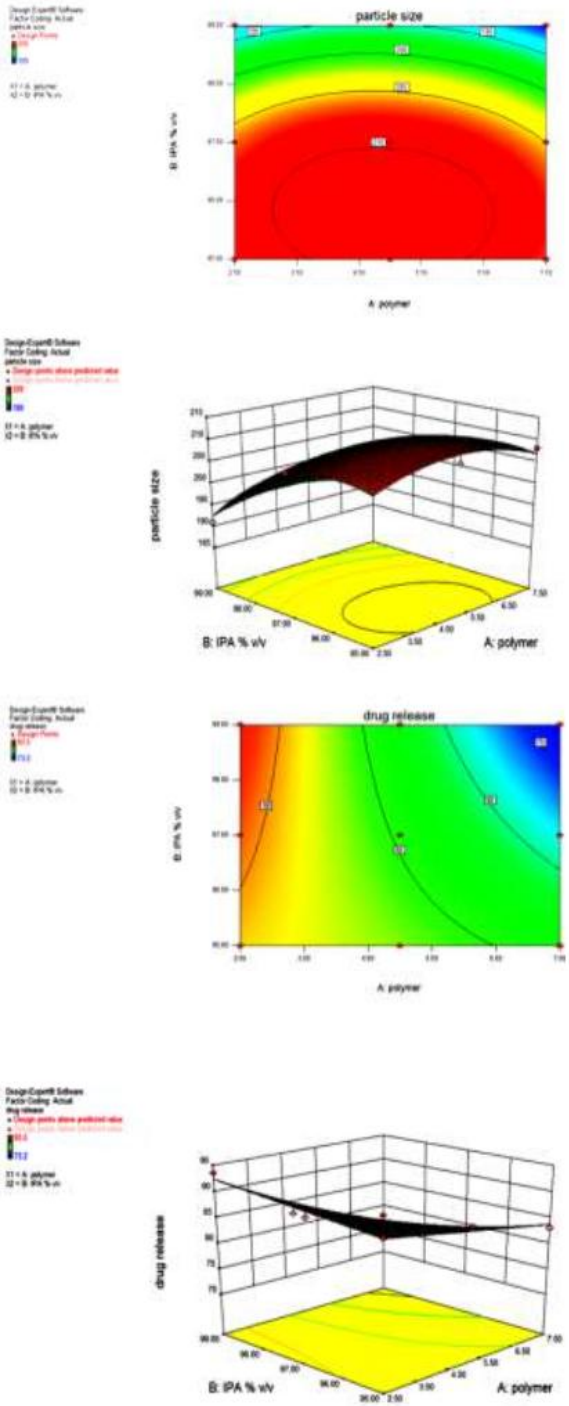
Full factorial design:

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. The desirability data & predicted formula was determined from factorial composite design. Results were shown in Table 5, Figure 8, 9, 10, 11.

Table 5: Predicted value for full factorial design of DH1-DH9

Predicted Solution

polymer	% IPA	particle size	% drug release	desirability
2.5	99	189.75	92.84	0.971

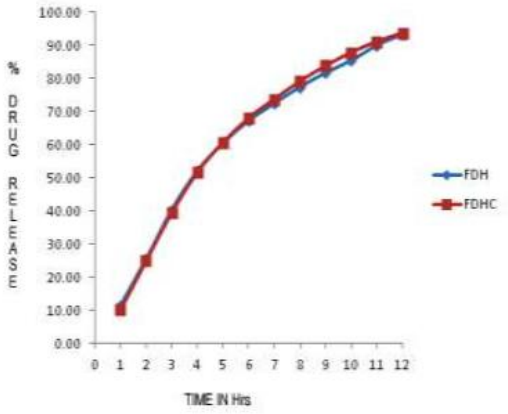


In-vitro dissolution profile of optimized formulation PDH, in buffer media and simulated fluids:

The comparative In-vitro study of PDH, in buffer and simulated fluids showed that there was significant reduction in simulated fluid drug release percentage might be due to protein binding or increased ingredient load. Results were shown in Table 6, Figure 12.

Table 6: Release kinetic data of batch PDH in buffer & simulated fluids.

Time	PDH	PDHS
1	11.44	10.16
2	25.47	24.95
3	40.34	39.51
4	52.09	51.70
5	60.49	60.79
6	67.23	68.12
7	72.44	73.81
8	77.40	79.20
9	82.66	83.84
10	86.39	87.88
11	90.98	90.17
12	92.34	91.75

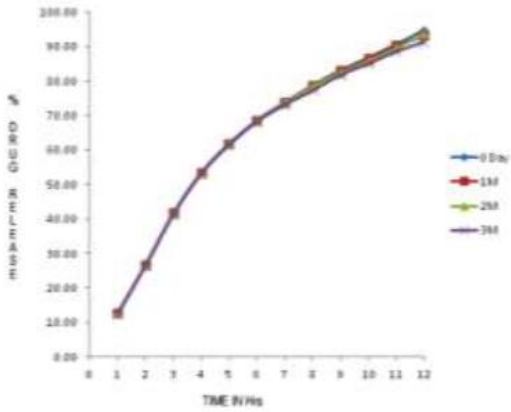


The stability study was performed on overall optimized batch FDH(PDH) as ICH guidelines at accelerated condition (40±2^{0}C, 75%±5 RH) which showed that the formulation was stable with no physicochemical changes and also there was no significant reduction in drug contents. Results were shown in Table 7, Figure 13.

Stability data of Micropellets PDH :

Table 7: Stability data of Finalized formulation

Batch	**PDH**			
Time	**0D**	**1M**	**2M**	**3M**
Drug Release	96.98	96.29	95.22	93.13



Evaluation of Dry Syrup:

pH of the dry suspension formulations was within the range of 5.0- 6.0. Viscosity of formulations was good enough to pour out from package as well as provided sufficient suspensibility. The redispersibility was determined by studying number of strokes to redisperse the formed sediment at the end of 7th day of storage of reconstituted formulations. Low redispersibility showed that the reconstituted suspension was more stable and flocculated. Low Sedimentation Volume Ratio (SVR) showed good suspensibility. Results were shown in Table 8.

Table 8: Evaluation data of Dry Suspension formulation

Formulation	**pH**	**Viscosity cps**	**Redispersibility (no. of strokes)**	**Sedimentation volume**
DS	5.0	460	5	0.41

Stability data of Dry Suspension Formulation.

The stability study was performed as per ICH guidelines at accelerated condition (40 ± 2^0C) which showed that the formulation was stable and also there was no significant reduction in drug contents.

CONCLUSION

The study was undertaken with an aim to develop sustained release micropellet & dry suspension dosage form for Diclofenac which is an Anti-inflammatory & is one of the most widely used drug for treating mild and severe pain. Based on the Drug-Excipient compatibility data & factorial design, the formula that found to be giving the maximum drug release pattern within stipulated time was considered as the optimized formulation. By the observations made, it was concluded that the formulation PDH containing HPMC K100M 2.5 g and 99% v/v IPA showed best sustained release profile.

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