AMERICAN JOURNAL OF PHARMTECH RESEARCH

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Formulation, Evaluation and Optimization of Ibuprofen Micropellets using 3^2 full factorial design

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ABSTRACT

This study was focused over the designing of sustained release HPMC K100M micropellet dosage form for Ibuprofen which is an anti-inflammatory agent and broadly used for treating mild and severe pains. The approach of this study was to make a comparative evaluation among polymers & excipients and to assess the effect of physicochemical nature of the active ingredients on the drug release profile. The prototype micropellets were obtained using drum pelletizer at 300 rpm. Percentage of water in binding liquid, i.e. IPA, is varied from 95 to 99% and the effect over various parameters, such as particle size, entrapment, bulk density and particle shape, were observed. Concerning the results of prototype preparation of Ibuprofen micropellets were prepared using HPMC K100M, as release retardant, in three different concentrations i.e. 16.7%, 33.3% & 50%. Formulated micropellets showed particle size in the range of 275-284µm, bulk density (0.74-0.82 g/ml), % yield (25.9 -58.3%) & % entrapment (32.8-34.3%). Formulations showed the maximum desirability 0.996. Dry suspension formulation parameters such as pH (5.15), Viscosity (450 cps), Redispersibility (5) & Sedimentation volume (0.46 ml), was found in range. Formulation PIH were selected as the best optimized formulation and evaluated for In-vivo parameters, results inferred good sustainability with $p>0.0001$. 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: Ibuprofen, micropellets, factorial design, HPMC K100M, pelletizer, NDDS

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Please cite this article in press as: Mittal A. *et al.*, Formulation, Evaluation and Optimization of Ibuprofen Micropellets using 3^2 full factorial design. American Journal of PharmTech Research 2013.

Received 24 September 2013, Accepted 12 October 2013

INTRODUCTION

Micropellets are of great interest to the pharmaceutical industry for a variety of reasons.[1-8]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 Ibuprofenmicropellets for sustained therapeutic effect.

MATERIALS AND METHODS

MATERIALS

Ibuprofen 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

DRUG POLYMER COMPATIBILITY STUDY:[14,15]

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 K100M (gm)	DCP (gm)	PVP K30 (gm)	Isopropyl alcohol %v/v
H1	5	2.5	7.5	2.5	95
H2	5	2.5	7.5	2.5	97
H3	5	2.5	7.5	2.5	99
H4	5	5	5	2.5	95
H5	5	5	5	2.5	97
H6	5	5	5	2.5	99
H7	5	7.5	2.5	2.5	95
H8	5	7.5	2.5	2.5	97
H9	5	7.5	2.5	2.5	99

PREPARATION OF IBUPROFEN 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.

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 ratio of weight and volume 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.

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

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 Ibuprofen 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 at predetermined λ_{max} using HPLC.

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; Particle size in µm 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 $40^0 \pm 2^oC$ temperature and relative humidity of 75% ±5%. Samples were collected 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 color, Sodium Benzoate and SCMC were blended. Then flavor 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 [21-24]

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:

Redispersibility:

The redispersibility was determined was determined by studying number of strokes to redisperse the formed sediment at the end of 7th 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 was stored in air tight amber colored glass bottles at 45°C & RT and then evaluated after 6th and 12th hour of reconstitution.

RESULTS AND DISCUSSION

Ibuprofen micropellets formulated using HPMC K100M, as 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.

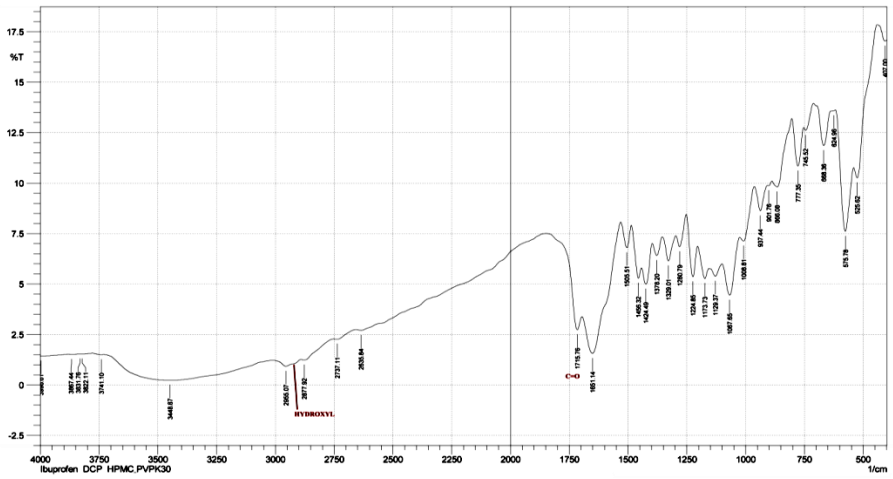

Fig 1: FTIR spectra of formulation blend

Micropellet Evaluation:

Ibuprofen Micropellets were evaluated for various physiochemical parameters viz. Percent yield, Bulk density, Entrapment efficiency and particle size. Particle size ranges from 257-284 µm. The bulk densities for all samples were found to be in the range of 0.74 - 0.82 g/ml. The maximum percentage yield was found to be 52.4% with batch IH6 and minimum of 21.3% with batch IH5. The maximum percentage entrapment was found to be 34.3 % with batch IH8 and minimum of 32.8% with batch IH5. The Results were shown in Table 3, Figure 2,3,4,5.

Table No. 3: Tabular data representation of Micropellets evaluation of IH1-IH9.

HPMC K100 M Micropellet containing Ibuprofen									
Code	**IH1**	**IH2**	**IH3**	**IH4**	**IH5**	**IH6**	**IH7**	**IH8**	**IH9**
Size (µm)	266	260	249	271	266	256	289	282	277
BD g/ml	0.77	0.75	0.77	0.81	0.77	0.79	0.74	0.71	0.815
% yield	43.4	49.2	44	48.7	52.4	55.9	58.3	25.9	26.2
%Entrapment	34.1	33.3	34.2	33.1	32.8	32.9	34.0	34.3	33.3

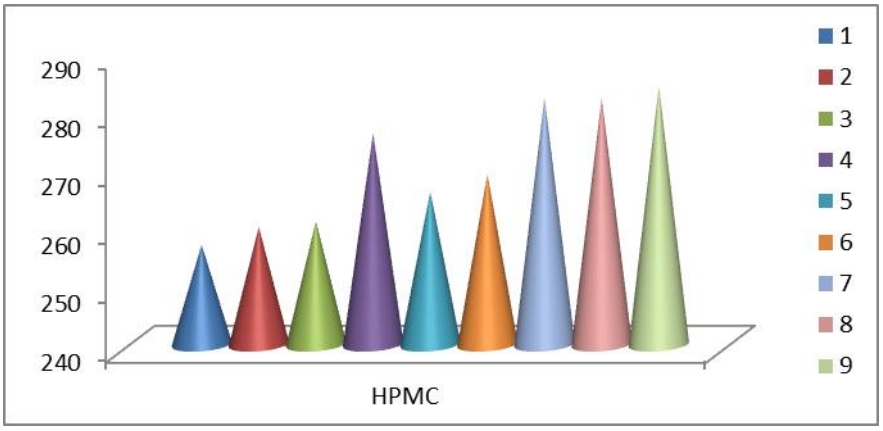

Fig. 2: Graphical representation of micropelletssize range of IH1-IH9.

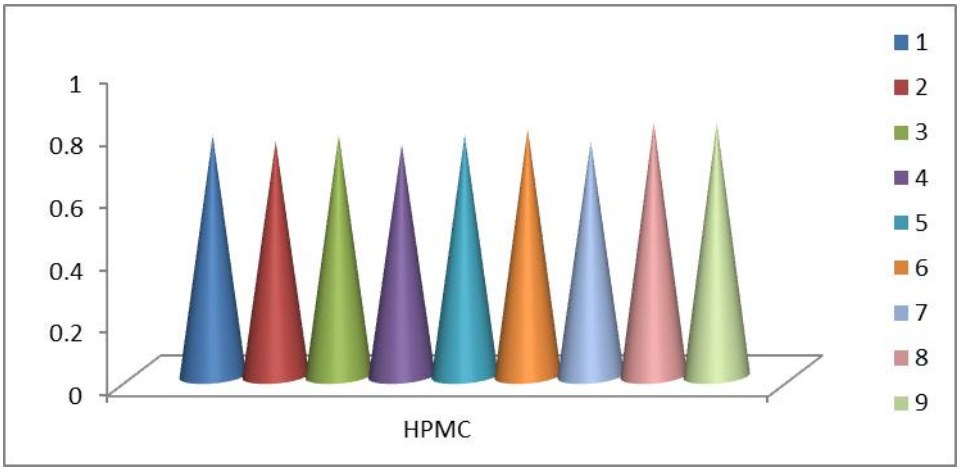

Fig. 3: Graphical representation of bulk density of IH1-IH9.

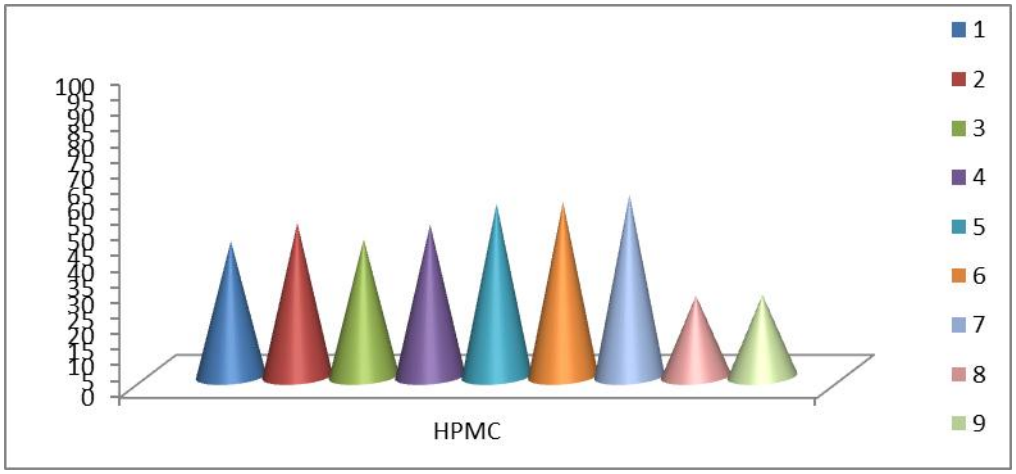

Fig. 4: Graphical representation of percentage yield of IH1-IH9.

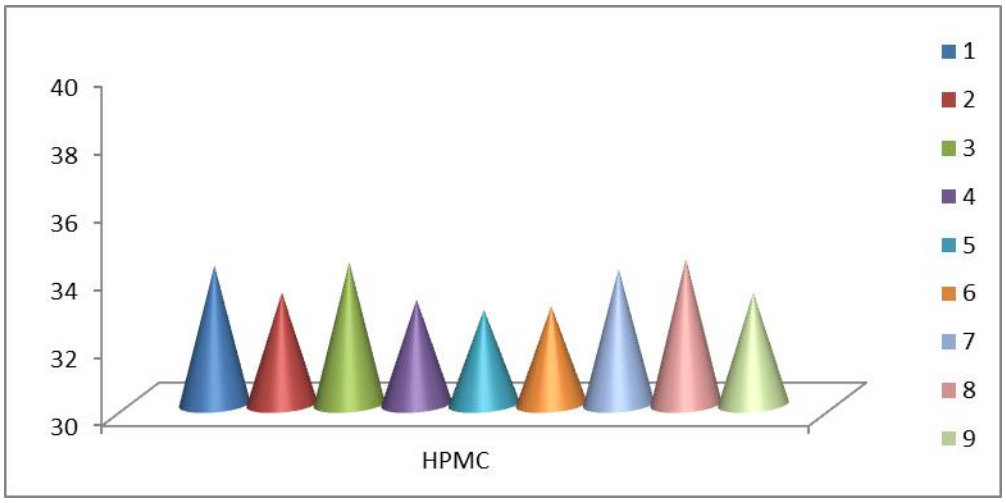

Fig. 5: Graphical representation of percentage entrapment of IH1-IH9.

Surface morphology:

The surface morphology of micropellets belonging to optimized batch i.e. IH1 was examined by scanning electron microscopy. The micropellets were semi-spherical and in the size range with

rough surface, as shown in Figure 6.

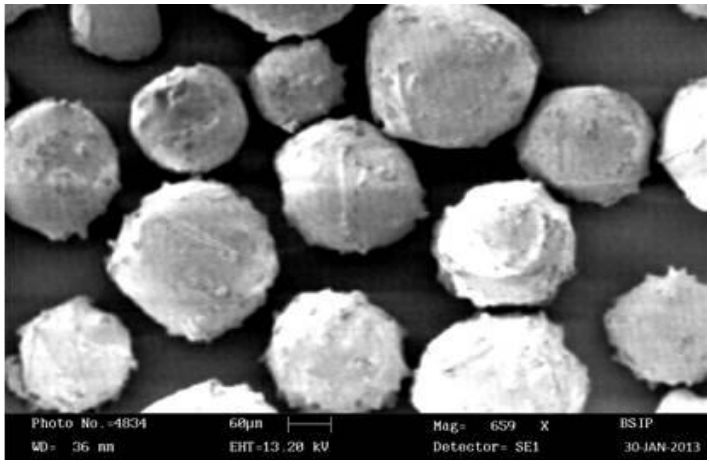

Fig. 6: SEM image of formulation IH1

IN-VITRO DISSOLUTION STUDIES:

In-vitro dissolution profile of formulation IH1-IH9 showed maximum release in 24 Hr study. Results were shown in Table 4 Figure 7.

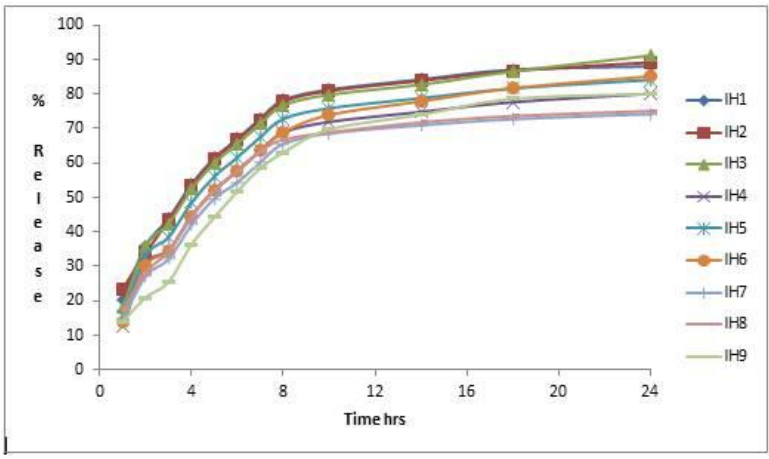

Fig. 7: Drug release of batch IH1-IH9 in pH 1.2 HCl and pH 7.0 phosphate buffers.

Table 4: Release kinetic data of batch IH1-IH9 in pH 1.2 HCl and pH 7.0 phosphate buffers.

TIME (hrs)	H1	H2	H3	H4	H5	H6	H7	H8	H9
1	20.4	23.5	18.1	12.6	15.8	13.8	14.9	17.2	14
2	36	33.9	35.7	30.8	33	30.2	27.1	28.2	21
3	43.9	43.5	42.5	34.6	38.6	34.6	32.2	34.5	25.5
4	53.9	53.5	52.4	44.6	48.5	44.6	42.1	44.4	36.4
5	61.5	61.1	60	52.2	56.1	52.2	49.7	52	44.3
6	67.1	66.7	65.6	57.7	61.7	57.8	54.4	57.6	51.8
7	72.9	72.5	71.4	63.6	67.5	63.6	60.3	63.5	58.5
8	78.2	77.8	76.7	68.9	72.8	68.9	65.6	66.8	63
10	81.3	80.9	79.8	71.9	75.9	74	68.6	68.9	69.7
14	84.3	83.9	82.8	74.9	78.8	77.9	71	71.8	74.1
18	87.1	86.7	86.6	77.7	81.6	81.7	72.8	73.6	78.6
24	88.1	89.2	91.2	80.1	84.1	85.2	74.2	75.1	80.1

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 ofIH1-IH9

Predicted Solution					
Polymer	% IPA	Particle size	% Drug release	Desirability	Remarks
2.5	99	249.31	91.29	0.996	Selected

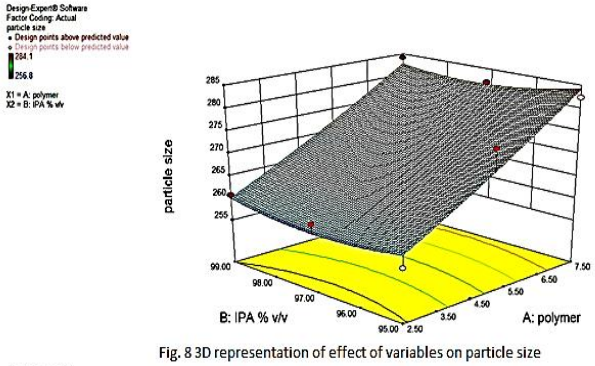

Fig. 8 3D representation of effect of variables on particle size

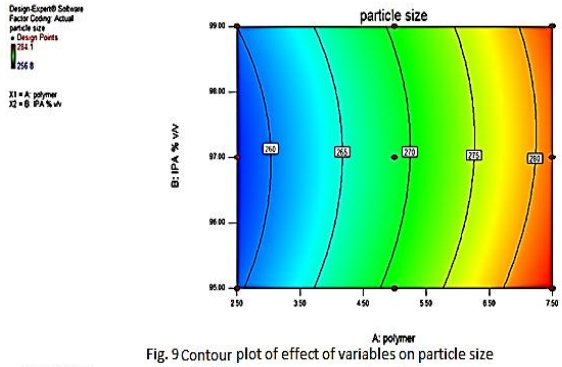

Fig. 9 Contour plot of effect of variables on particle size

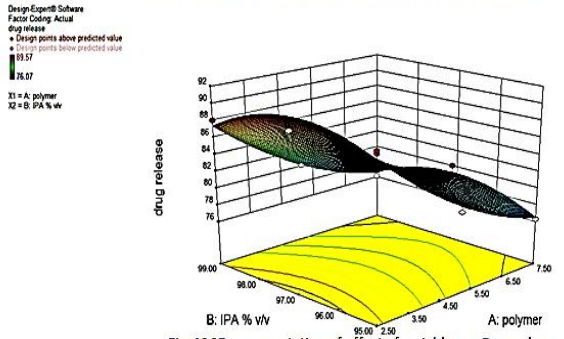

Fig. 10 3D representation of effect of variables on Drug release

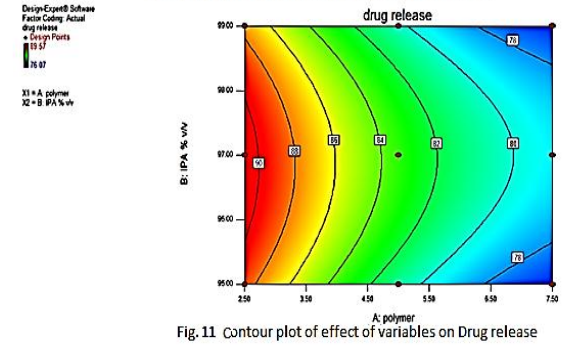

Fig. 11 Contour plot of effect of variables on Drug release

In-vitro dissolution profile of optimized formulation FIH1, in buffer media and simulated fluids:

The comparative In-vitro study of **PIH**, 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 PIH in buffer & simulated fluids.

Time	PIH	PIHS
1	20.35	15.95
2	35.99	31.46
3	43.9	38.53
4	53.88	47.57
5	61.5	55.42
6	67.06	61.14
7	72.9	67.18
8	78.22	72.65
10	83.31	79.82
14	87.27	85.86
18	90.09	88.75
24	91.47	91.31

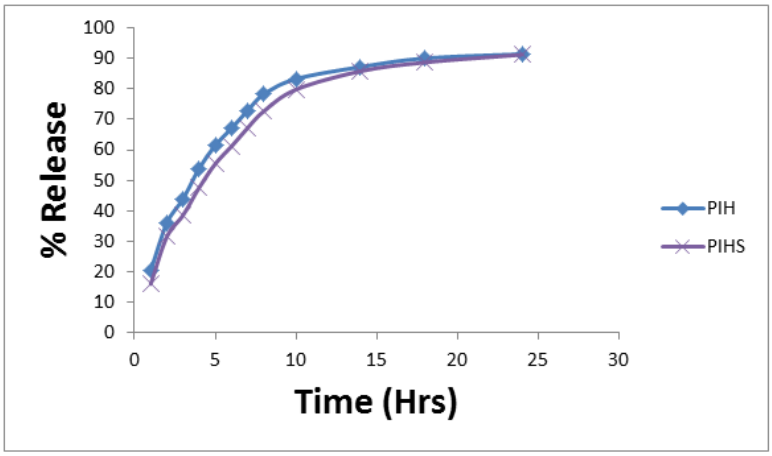

Fig. 12: Graphical representation of comparative study of FIH1 release profile in buffer and simulated fluids

Stability data of Micropellets PIH:

The stability study was performed on overall optimized batch (PIH) as per 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.

Table 7: Stability data of Finalized formulation

Batch	**PIH**			
Time	**0D**	**1M**	**2M**	**3M**
Drug Release	92.62	91.33	91.16	90.23

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	5.15	450	5	0.46

Stability data of Dry Suspension Formulation.

The stability study was performed as per ICH guidelines at accelerated condition (40±2^{0}C) 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 Ibuprofen 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 IH1 containing HPMC K100M 2.5 g and 99% v/v IPA showed best sustained release profile.

ACKNOWLEDGEMENT:

The authors are grateful to TeerthankerMahaveer College of Pharmacy providing requisite facilities to complete my research work within time and BirbalSahni Institute of Paleontology, Lucknow, providing SEM facility.

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