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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.

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

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.

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

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 spectrophotometrically at predetermined λ_{max} using dissolution media (pH 1.2 HCl, 7.0 phosphate Buffer, SGF & SIF, respectively) as blank.

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

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.

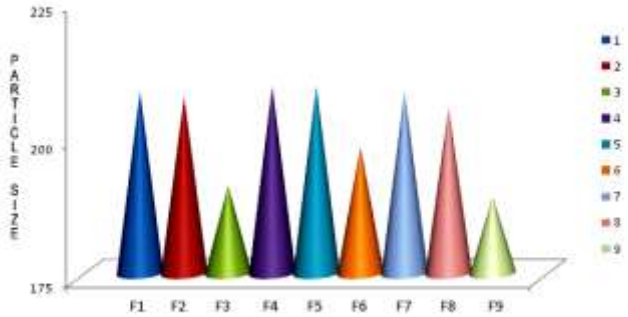
Diclofenac Micropellets were evaluated for various physiochemical parameters viz. Percent yield, Bulk density, Entrapment efficiency and particle size.

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 189-208µm.

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



8. Rajesh. N, Siddaramaiah, 2010. Design and evaluation of controlled release of piroxicam from the pellets of microcrystalline cellulose and hydroxypropylmethyl cellulose blends. Int. J. Pharmtech Res. 2(2), 1465-1473.
9. Kumar Vikash, Mishra Santosh Kumar, Lather Amit, Vikas,Singh Ranjit, Multiple unit dosage form-pellet and pelletizationtechnique an overview,IJRAP,2011,2(1) 121-125
10. Rahman. A. M., Ahuja. A., Baboota. S., Bhavna. Bali. V., Saigal. N., and Ali. J., 2009. Recent advances in pelletization technique for oral drug delivery: A review. Curr. Drug Del. 6(1):122-129.
11. Sharma A., Chaurasia S., 2013. Multiparticulate drug delivery system: pelletization through extrusion and spheronisation. Int. Res. J. Pharm. 4(2), 6-9.
12. Padhy K. K., Swain K. and Chowdary K. A., 2010. Influence of organic acids on drug release pattern of verapamil hydrochloride pellets. J. .Adv. Pharm. Res. 1, 65-73.
13. Kammili L., Senthil V., 2011. Pelletization technology: A quick review. Int. J. Pharm. Sci. Res. 2(6), 1337-1355.
14. Abbaspour M.R., Sadeghi F., 2005. Preparation and characterization of ibuprofen pellets based on eudragit RS PO and RL PO or their combination. Int. J. Pharm. 3(3), 88-94.
15. Seo S., Baeg C., Composition and pharmaceutical dosage form for colonic drug delivery using polysaccharide. United State Patent/6413494.
16. Tayade P. T., Kale R. K. D, 2004. Encapsulation of water-insoluble drug by a cross-linking technique: effect of process and formulation variables on encapsulation efficiency, particle size, and in vitro dissolution rate. AAPS Pharm. Sci. 6(1), 1-8.
17. Ghosh A., Nayak U. K., Rout P., Nag T. and Roy P., 2008. Preparation, evaluation and in vitro- in vivo correlation (ivivc) study of lamivudine loaded microspheres. Res. J. Pharm. and Tech. 1(4), 353-356.
18. Alfred M., James S., A text book of physical pharmacy. 513- 515.
19. Paulo C., Jose M. S. L., 2001. Modeling and comparison of dissolution profiles. Eu. J. Pharm. Sci.13, 123–133.
20. Jain D.K., Darwhekar G.N., and Choudhary N., 2011. Formulation and evaluation of reconstitutable oral suspension of Ambroxol HCl and Azithromycin. Int. J. Pharmtech Res. 3(2), 741-746.
21. Shanbhag P. P., Bhalerao S. S., 2010. Development and evaluation of oral

reconstitutable systems of cephalexin. Int. J. Pharmtech Res. 2(1), 502-506.

22. Raju K.N., Venkatanarayana B., Eswaraiah M. C., 2012. Formulation and evaluation of sustained release Diclofenac Table ts. Int. Res J Pharm. App Sci. 2(6), 85-89.

23. Mor J., Nanda A., 2011. Formulation and evaluation of a colon targeted drug delivery system using ibuprofen as a model drug. T. Ph. Res. 5(1), 176-183.