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Research Article

FORMULATION, DEVELOPMENT AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE TABLET BY USING MELT GRANULATION TECHNOLOGY

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ABSTRACT

Sustained release (SR), sustained action (SA), extended release (ER, XR,OR XL), time release or timed release, controlled release (CR), modification release (MR), or continuous release (CR), is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over time. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently then immediate-release formulation of the same drug, and that they keep steadier levels of the drug in the bloodstream. The present investigation was aimed to study sustained release tablets of diclofenac sodium using Ethyl cellulose, Magnesium state, Hydroxypropyl methyl cellulose by melt granulation method. Five different formulations F1, F2, F3, F4, and F5 were prepared and compressed to form tablets. These tablets were characterized for their physicochemical properties like hardness, thickness, weight variation, disintegration time, dissolution time etc. The Weight variation was found 0.11%, angle of repose was found to be 27.23 which indicated good flow also the drug release studies showed sustained release of drug upto 12 hrs. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery.

KEYWORDS: *Sustained release drug delivery systems, Diclofenac Sodium, Melt Granulation, Hardness and Dissolution time.*

INTRODUCTION

Time release technologies, also known as sustained release (SR), sustained action(SA), extended release (ER, XR,OR XL), time release or timed release, controlled release (CR), modification release (MR), or continuous release (CR or Contin), is a mechanism used in pill tablets or capsules to dissolve slowly and release a drug over time. The advantages of sustained-release tablets or capsules are that they can often be taken less frequently then immediate-release formulation of the same drug, and that they keep steadier levels of the drug in the bloodstream.

SR formulation, the drug dissolve into the matrix, and the matrix physically swells to form a gel, allowing the drug to exit through the gels outer surface. Micro-encapsulation is also regarded as a more complete technology to produce complex dissolution profiles. Through coating an active pharmaceutical ingredient around an inert core, and layering it with insoluble substances to from a microsphere you are able to obtain more consistent an replicable dissolution rates in a convenient format you can mix and match with other instant release pharmaceutical ingredients in to any two piece gelatin capsule [1].

These are certain consideration for the formation of sustained-release formulation:

- If the active compound has a long half-life (over 6 hours), it is sustained on its own
- If the pharmacological activity of the active compound is not related to its blood levels, time releasing has no purpose.
- If the absorption of the active compound involves an active transport, the development of a time-release product may be problematic.
- Finally, if the active compound has a short half-life, it would require a large amount to maintain a prolonged effective dose.

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery.

During the last 2-3 decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Sustained release dosage forms are prepared by coating the tablets so that the rate of solubility is controlled or individually encapsulating micro particles of varying sizes so that the rate of dissolution can be controlled [2, 3].

Nart V *et al* demonstrated that carnauba wax proved to be promising excipients in melt granulation targeting the preparation of mini-tablets for sustained release of soluble drugs also Balamurugan Jeganathan *et al.* concluded Diclofenac sodium (DS) tablets and coated with polymer solution of HPMCAS and EE to achieve pH dependent and sustained-release tablets. The results of pharmacokinetic studies in rabbits showed that the formulation exhibited a delayed peak plasma concentration and marked sustained- release effect of drug in the in vivo drug release in comparison with marketed tablet and Zhang F *et al.* characterized the properties of Eudragit® FS-based granules prepared using melt extrusion process for colonic drug deliver and found granules prepared with melt extrusion demonstrated lower porosity, smaller

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pore size, and higher physical strength than those prepared with conventional compression process [4-6].

Advantages:

- Improved patient compliance due to less frequent drug administration.
- Reduced fluctuation in steady-state drug levels.
- Maximum utilization of the drug.
- Increased safety margin of potent drug.
- Reduced healthcare costs through improved therapy.
- Shorter treatment period.
- Less frequency of dosing.
- Control of drug therapy is achieved.
- Rate and extent of drug absorption can be is modified.
- Frequency of drug administration is reduced.
- Patient compliance can be improved.
- Drug administration can be made convenient.
- Maximizing the availability of drug with minimum dose.
- The safety margin of high potency drug can be increased [7].

Melt Granulation Techniques:

Melt granulation is processes by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process. This process is also called melt agglomeration and thermoplastic granulation .Principle of melt granulation:

The process of granulation consists of a combination of three phases:

I. Wetting and nucleation,
II. Coalescence step,
III. Attrition and breakage.

Wetting and nucleation step:

During the nucleation step the binder comes into contact with the powder bed and some liquid bridges are formed, leading to the formation of small agglomerates.

Two nucleation mechanisms are proposed by Schafer and Mathiesen.

I. Immersion
II. Distribution [8]

Diclofenac sodium is a benzene acetic acid derivative, designated chemically as 2-[(2, 6-dichlorophenyl) amino] benzene acetic acid, monosodium salt.

The primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of prostaglandin synthesis by inhibition of cyclooxygenase (COX). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis.

Inhibition of COX also decreases prostaglandins in the epithelium of the stomach, making it more sensitive to corrosion by gastric acid. This is also the main side effect of diclofenac. Diclofenac has a low to moderate preference to block the COX2-isoenzyme (approximately 10-fold) and is said to have, therefore, a somewhat lower incidence of gastrointestinal complaints than noted with indomethacin and aspirin [9].

METHOD AND MATERIALS

All the materials used in the formulation, evaluation and other experiments are listed below. The chemicals used were of laboratory reagents grade and were used as they were procured (Table 1).

Table No. 1: List of chemicals and reagents

S. NO.	Materials	Sources
1.	Diclofenac sodium	Kusum healthcare bhiwadi (RJ)
2.	Lactose	Central Drug House (P) Ltd, New Delhi
3.	Micro crystalline cellulose	Central Drug House (P) Ltd, New Delhi
4.	Carnauba wax	Central Drug House (P) Ltd, New Delhi
5.	Talc	Central Drug House (P) Ltd, New Delhi
6.	Magnesium stearate	Central Drug House (P) Ltd, New Delhi

Preparation of Granules by Melt- Granulation Technique

Sustained release tablets of Diclofenac sodium were prepared by melt granulation method according to the Diclofenac Sodium (100), Lactose and microcrystalline cellulose was taken in a steam incubated vessel. Steam was allowed to pass through the vessel. Carnauba wax was added and mixing was done for 5 min using planetary mixer. The mixing was done till Carnauba was melts and form granules by adhering small particles around it. The granulation was continued till al the Carnauba wax got melted. The mixer was cooled to room temperature and talc and magnesium stearate was added to gel final blend (Table 2) [10].

Table No. 2: Formulation of Sustained release Tablets

S. No.	Ingredients	Formulation				
		F1	F2	F3	F4	F5
1	Diclofenac sodium	100	100	100	100	100
2	Lactose	70	-	75	-	-
3	Micro crystalline cellulose	-	76	-	80	75
4	Carnauba wax	50	43	44	40	45
5	Talc	3	3	3	3	3
6	Magnesium stearate	2	3	3	2	2
7	Total weight	225mg	225mg	225mg	225mg	225mg

Evaluation of granules:

The flow properties of the prepared granules were evaluated by determining the bulk density, tapped density, compressibility index (Carr's index), angle of repose, Hausner's ratio.

Bulk Density: Bulk density of both loose bulk density (LBD) and tapped bulk density (TBD) was determined. The accurately weighed amount sample was taken in 50ml measuring cylinder of borosil and measured / recorded the volume of packing and tapped 50 times on plane surface and tapped volume of packing recorded and LBD and TBD calculated by following formula -

$$LBD = \frac{\text{Mass of powder}}{\text{Volume of packing}}$$

$$TBD = \frac{\text{Mass of Powder}}{\text{Tapped volume of Packing}}$$

Angle of repose: The frictional forces in loose powder or granules can be measured by the angle of repose. This is the maximum angle possible

between the surface of a pile of powders or granules and the horizontal plane.

$$\theta = \tan^{-1}(h/r)$$

Where, **h** = Height of pile; **r** = Radius of pile; **θ** = Angle of repose

The granules were allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed shown in Table No-3.

Table No. 3: Relation between Angle of repose (θ) and flow property

Angle of repose	Flow property
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Percentage compressibility (Carr's Index): Percentage Compressibility of powder mix was determined by Carr's compressibility index calculated (table No.4) by following formula [11].

$$\text{Carr's index \%} = \frac{TBD-LBD}{TBD} \times 100$$

Where, LBD=loose bulk density; TBD=Tapped bulk density

Table No. 4: Grading of the powders for their flow properties according to Carr's index

Carr's index %	Flow properties
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

Evaluation of Tablet:

Physical appearance: The entire prepared tablet was visually inspected for color, size and smoothness.

Thickness uniformity: The aim of the present study was to check the uniformity of thickness of the formulated tablets. The thickness of the tablets was measured at 3 different points using a digital caliper and average thickness of three reading was calculated. It is expressed in mm [12].

Weight Uniformity: For weight variation test, 10 tablets from each formulation were weighed individually and the average weight was calculated. The US pharmacopoeia allows a little variation in the weight of the tablet (Table No-5).

Table No. 5: Criteria for percentage deviation in weight variation

Average weight of Tablet	Percentage Deviation
130mg or less	10
More than 130 mg and less than 324mg	7.5
324 and more	5

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablet was determined using Monsanto hardness Tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the same tablet from each formulation was determined. The mean and standard deviation values were also calculated [13, 14].

Wetting Time and Water Absorption Ratio: A piece of tissue paper was folded twice and was placed in a small Petri dish containing 6 ml of water. A tablet was placed on the paper and the time required for complete wetting was then measured.

The water absorption ratio R, was determine using the following equation,

$$R = \frac{Wa-Wb}{Wb} \times 100$$

Where,

Wb is the weight of the tablet before water absorption.

Wa is the weight of the tablet of the after water absorption.

Friability studies: Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche Friabilator was used for the purpose. Pre weighed sample of ten tablets were placed in the friabilator, which was then operated for 100 revolutions. After 100 revolutions the tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight [15, 16].

Percentage Friability = (initial weight - final weight / initial weight) × 100

Disintegration studies: *In-vitro* disintegration time was perfumed by Disintegration Apparatus. 600ml distilled water was used as disintegration medium, the temperature of which was maintained at 37±2°C and the time taken for complete disintegration of the tablet with no mass remaining in the apparatus was measured in seconds.

Dissolution studies: *In vitro* release studies were carried out using tablet dissolution test apparatus. *In vitro* dissolution studies of all the formulation .The following procedure was employed throughout the study to determine in vitro dissolution rate for all the formulation (Table 6) [17, 18].

Table No. 6: Parameter for *in vitro* Dissolution studies

Dissolution medium	900ml of buffer pH 6.8
Temperature	37±2°C
Rpm	50
Drug content	Weight of Tablet equivalent to 50mg of Diclofenac sodium
Volume withdrawn	1ml
λ_{max}	278nm
Time interval	10min

RESULTS

Sustained release tablets of Diclofenac sodium were prepared by melt granulation method and were compressed to form sustained release tablet and granules and tablet both were evaluated for various parameters like Bulk Density, Tapped Density, Hausner's Ratio, % Compressibility, Angle of repose, Loss on drying, weight, hardness, friability, % drug release.

Table No. 7: Evaluation of granules

Batch	Bulk Density gm/ml	Tapped Density gm/ml	Hausner's Ratio	% Compressibility	Angle of repose	Loss on drying
F1	0.65	0.72	1.12	10.52%	28.20	1.53%
F2	0.63	0.72	1.13	11.12%	29.21	1.32%
F3	0.64	0.73	1.16	16.12%	28.43	1.45%
F4	0.60	0.75	1.15	15.16%	27.23	1.55%
F5	0.65	0.74	1.17	17.12%	27.67	1.56%

Table No. 8: Compression Parameters

Batch	Weight (mg)	Hardness (kg)	Thickness (mm)	Friability (%)
F1	225	7.8	4.02	0.28
F2	225	8.7	5.01	0.26
F3	225	10.9	4.03	0.22
F4	225	12.6	5.04	0.11
F5	225	11.8	6.05	0.24

Table No. 9: Observations for Weight Variation

S. No	Formulation	Weight variation (mean±SD)
1.	**F1**	225.50±1.9
2.	**F2**	225.20±1.7
3.	**F3**	225.80±0.8
4.	**F4**	225.05±0.5
5.	**F5**	225.70±1.5

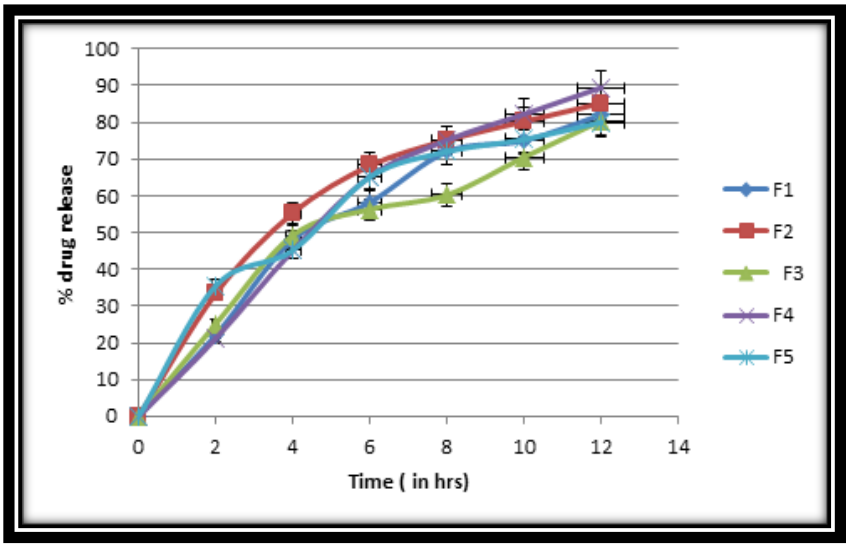

Fig. 1: *In vitro* Drug release profile

DISCUSSION

The granules were prepared using melt granulation technique and after the evaluation of granules, they were compressed into sustained release tablets. Granules and prepared sustained release tablets were subjected for evaluation on the basis of pre compression and post compression parameters.

Precompression parameter:

Angle of repose: The values were found to be in the range of 27.23-29.21 in which formulation (F4) showed the angle of repose at 27.23. It indicated that formulation F4 showed good flow property. All these remaining formulation were not selected because flow property of remaining formulation was not better than F4 formulation. (Table 7)

Bulk density and tapped density: The bulk density for all the formulation varied from 0.60-0.65 and tapped density from 0.72-0.75g/cm^3. The value obtained lies within the acceptable range and not large difference found between bulk density and tapped density. This result helps in calculating the percentage compressibility of the powder (Table 7).

Compressibility: The percent compressibility of powder mix was determined by Carr's compressibility index. Result obtained for percent compressibility for all the five formulation lies within the range of 10.52 to 17.12. All formulations showed good compressibility except F5 formulation (Table 7) [19].

Post compression parameter:

All the tablet formulations were subjected for organoleptic, physical and chemical evaluation, shape, thickness, hardness, friability, weight variation, in vitro disintegration time, wetting time, water absorption ratio; in vitro dissolution studies were carried out.

Shape and color of tablets: Randomly picked tablets from each formulation batch were examined under lens for shape and under light for colors.

Thickness of tablets: The thickness of tablets was measured by using dial calipers by picking the tablet randomly. The values are almost uniform in all the formulation. Thickness was found in the range from 4.02 nm to 6.05 nm respectively. Uniformity in the values indicates that formulations were compressed without sticking to the dies and punches. The order of thickness of tablets was found to be F1<F3<F2<F5<F4 (Table 8) [20, 21].

Hardness: It was performed by Monsanto hardness tester. Hardness was maintained to be within 7.8 to 12.6 kg/cm^2 as these are sustained release tablets. The hardness values of all the formulations were almost uniform and posses good mechanical strength with sufficient hardness. The order of hardness of all the tablets found to be F1<F2<F3<F5<F4 (Table 8) [22].

Friability: Result were found well within the range limits, which reveal that the tablets posses good mechanical strength. The order of friability of tablets is F4<F3<F5<F2<F1 (Table 8) [23].

Weight variation: All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±10%. It was found to be from 0.5 to 1.9 mg. the weight of all the tablets was found to be uniform. This was due to the good flow property and compressibility of all the formulations (Table 8) [24].

***In-vitro* dissolution studies:** *In vitro* dissolution study of all the formulations were calculated and amongst all the formulations ,F4 was the formulation which delivered maximum amount of drug up to 12 hrs in sustained manner for obtaining maximum effect for sustained period (Fig 1) [25, 26].

CONCLUSION

Sustained release dosage forms are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose. SRDDS reduced the toxicity by slowing drug absorption, improved palatability, and availability of formulation in liquid and solid SRDDS, increased stability by protecting the drug from hydrolysis or other degradative changes in the gastrointestinal tract. Today, most time-release drugs are formulated so that the active ingredient is embedded in a matrix of insoluble substances such that the dissolving drug must find its way out through the holes in the matrix. Some drugs are enclosed in polymer-based tablets with a laser-drilled hole on one side and a porous membrane on the other side. Last few years has witnessed various developments in this area. The exhaustive literature survey demonstrates that melt granulation technique for preparation of sustained release of NSAIDs is better than other granulation techniques. The main aim of preparing sustained release formulations was intended to modify and improve the drug performance by increasing the duration of drug action, decreasing the frequency of dosing, decreasing the required dose employed and providing uniform drug delivery for achieving maximum effect.

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