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Formulation design of Aceclofenac sustained release tablets prepared by melt granulation technique

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ABSTRACT

The objective of present study was to prepare and characterize aceclofenac sustained release tablets prepared by melt granulation technique. The granules were prepared by hydrophilic meltable binder PEG 4000. Compared to ordinary conventional technique, this method does not employ any organic solvent or water and hence reduces drying step because dried granules were obtained by cooling them. And moreover it is less time consuming process. This method can be used for granulating water sensitive material and for producing sustained release granules. Melt granulation technique fulfill today's pharmaceutical industry need because it is simple, continuous and efficient. Different formulation trials of aceclofenac tablets were prepared using PEG 4000 and among the various prepared trials, the best formulation is chosen. The best judged formulation were found to be effective in sustaining the drug release up to 10 hours.

INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAID) are widely prescribed medications for treating arthritis. NSAIDs are used to relieve pain and reduce inflammation when administered alone or in combination with other classes of drug. NSAIDs work by counteracting cyclooxygenase enzyme which in turn prevents prostaglandins synthesis responsible for pain. Aceclofenac is a non-steroidal anti-inflammatory drug. It is used for the relief of pain in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase, which is involved in the production of prostaglandins. The drug inhibits synthesis of the inflammatory cytokines interleukin (IL). Aceclofenac is a derivative of phenyl acetic acid and is well absorbed orally. The plasma elimination half-life of the drug is approximately 4 hours.

Polyethylene glycol polymers (PEG) are commonly known as Carbowaxes/ polyglycols/ macrogols and it is made from ethylene glycol. It is available in a range of molecular weights. Higher molecular weight PEGs are waxy, white solids with melting points proportional to their molecular weights to an upper limit of about 67 °C[1]. PEG is an excellent excipient used in pharmacy mainly because of its inert and non toxic nature. It is an FDA approved polymer for use as an excipients or as a carrier in different pharmaceutical formulations[2].

Melt granulation technique [3-5] is widely used granulation technique in the field of pharmacy nowadays. Today melt granulation technology represents an efficient pathway for manufacture of variety of drug delivery systems. The physical state of the drug can be modified with help of various polymers and also the use of this process. Thereby the drug release can be sustained for prolonged period of time. The granules of aceclofenac were prepared by using polyethylene glycol (PEG) 4000 as a melting binder which is in solid state at room temperature but preferably melts in the temperature range of 50°C 80°C[6]. The granules were characterized for different pharmaceutical parameters.

MATERIALS AND METHODS

Aceclofenac was purchased from Chennai Drug House. PEG, Magnesium Stearate and Talc were obtained from General Drug House Pvt.Ltd, Bombay. Micro Crystalline Cellulose was procured from Merck, Mumbai. Other materials used were of analytical grade.

Method for preparation

Preparation of Granules [7]:

The granulation procedure was standardized on the basis of preliminary trials. Polyethylene glycol 4000 was exactly weighed as per formulation design and then melted in porcelain dish on a water bath maintained at 75°C for three minutes. Aceclofenac was exactly weighed and it was sifted through sieve no 16. Gradually Aceclofenac was added to melted compound with

continuous stirring when it is about to solidify and it should be added at a temperature slightly more than the melting point of PEG and the contents were transferred to a glazed tile by spreading them out in thin layers. The molten mixture was then allowed to solidify at room temperature. The solidified mass was crushed in mortar and passed through a 10 mesh sieve. The granules were evaluated [8 - 10] for bulk density, tap density, angle of repose, Carr's index and Hausner's ratio. The results were discussed in the table no.1.

Preparation of Tablets:

Tablet formulation was prepared by melt granulation technique. A non-aqueous granulation process adopted to prepare Aceclofenac tablets. The dried granules were mixed with MCC and finally lubricated with magnesium stearate and talc for one minute. The granules were compressed into a flatfaced tablet using rotary tablet punching machine equipped with concave punches. Tablet weight was kept constant i.e. 500mg. Sustained release tablets of aceclofenac prepared with polyethylene glycol were denoted by formulation code F1, F2, F3, F4, F5 and F6.

All the formulated tablets were evaluated for weight variation, friability, hardness, uniformity drug content and in-vitro drug release characteristics. Table no.2 gives over view of the formulation compositions evaluated during this study.

RESULTS

Sustained release tablets of aceclofenac was prepared by melt granulation method and evaluated various physicochemical parameter. Melt granules F5 and F6 was found to show excellent flow properties compared to other trials. Hardness range was 4.5 - 6.8 kg/cm^2. friability of all batch were in range of 0.66 to 0.99%.and assay values in range of 93.32-99.51%. The *in-vitro* drug release was performed using USP type II apparatus using 900 ml of phosphate buffer of pH 6.8 at the rotations of 50 rpm at 37± 5°C. The samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analyzed at 273 nm by UVspectrophotometer. The content of drug and cumulative percentage drug release was calculated using calibration curve. The Aceclofenac containing PEG 4000 gives the nearly 85% drug release after 10 hr [Figure 1].

Table 1: Technological characterization of Granules

Parameters	Formulation Code					
	F1	F2	F3	F4	F5	F6
Bulk density (g/ml)	0.5600	0.4113	0.4444	0.4503	0.5800	0.5000
Tap density(g/ml)	0.8120	0.5800	0.6000	0.5900	0.6032	0.5500
Carr's index (%)	31.0344	29.0862	25.9333	23.6779	3.8461	9.0909
Hausner's ratio	1.45	1.41	1.35	1.31	1.04	1.10
Angle of repose	47°35'	39°42'	37°21'	32°30'	28°25'	26°24'

Table 2: Characterization of tablets for various formulation trials

Parameters	Formulation Code					
	F1	F2	F3	F4	F5	F6
Weight Variation (mg)	500	500.5	500.4	500.3	500.2	500.1
Hardness (kg/sq.cm)	4.52	3.32	6.14	6.54	6.86	6.54
Friability (%)	0.66	0.99	0.97	0.65	0.66	0.99
Drug Content (%)	95.15	93.32	96.46	97.54	98.26	99.51
Cumulative Drug Release after 10 hours	62.04	68.34	72.68	78.05	79.85	83.33

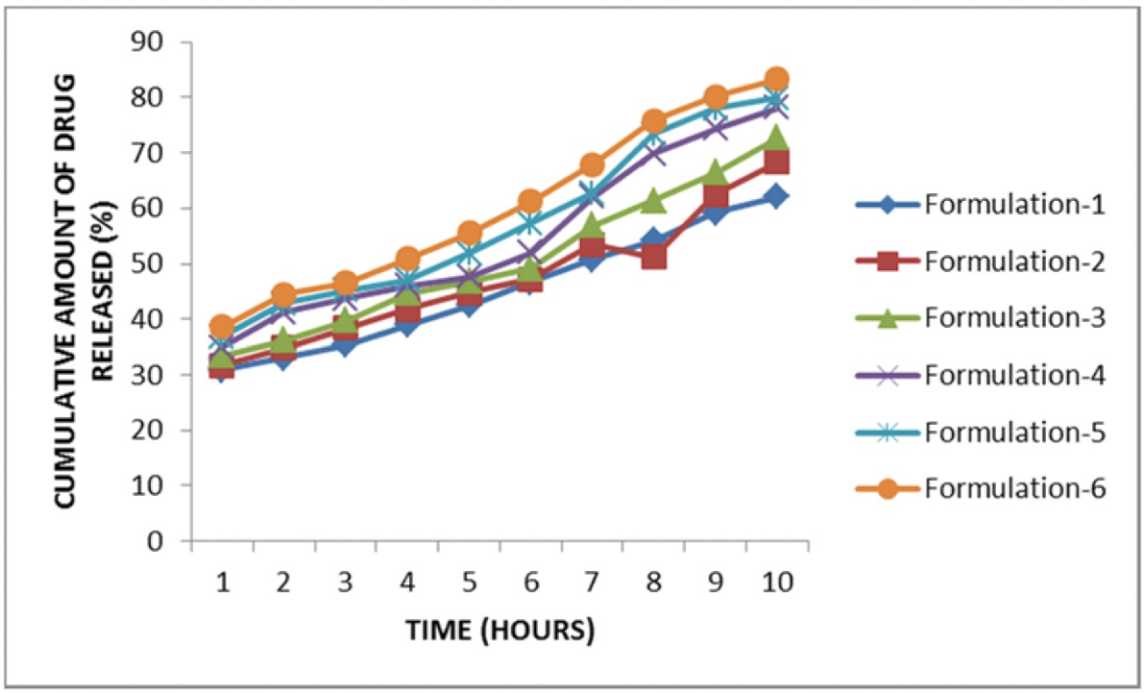

Figure 1: Cumulative Drug Release after 10 hours Vs Time Profile

DISCUSSION

Aceclofenac sustained release tablets was successfully developed by melt granulation method. Melt granulation usually produces bigger and irregular shaped granules which may account for the lower packing of these granules upon tapping. Since the solidified mass was crushed in mortar and passed through a 10 mesh sieve. Granules were almost completely packed upon tapping. According to the literature, powders with a Compressibility Index (CI) between 5 to 15%, Hausner ratio below 1.25 and angle of repose below 30 shows good flowability. The prepared melt granules (Table 1) possess a CI between 3 and 9% (F5 and F6 trials), Hausner ratio was below 1.10 and angle of repose were below 30.The prepared aceclofenac melt granules significantly improves the flow properties of drug. This improvement in the flowability of agglomerates could be attributed to the significant reduction in inter-particle friction, due to their size enlargement and a lower static electric charge.

From the above observation it was concluded that all melted granules shows the drug content value in the range of nearly 93-99%.Hardness and friability results were also good and within the limits for formulation F5 and F6.

The *in vitro* dissolution profiles of the granules prepared by melt granulation were compared with that of pure drug. The results were evaluated for 10hours. The dissolution rate of pure aceclofenac was good, with the amount of drug dissolved in 30 min being 59-63%. As per the results of dissolution study formulations F1, F2, F3, F4, F5 and F6 showed 62.04,68.34, 72.68,78.05,79.85 and 83.33% respectively. Slow and sustained release was obtained for the formulation code F5 and F6. Hence these formulations were considered to be best among all other formulations. The *in vitro* dissolution rate of all prepared granules was lower as compared to the pure drug. In the case of granules, the drug with meltable polymer PEG decreases the dissolution rate and helped to prolonged the drug release as compared to drug alone. The decrease in dissolution rate could be attributed to the waxy nature of the polymer. These results show that melt granulation can be a useful technique to sustain the dissolution rate of aceclofenac.

CONCLUSION

Melt granulation technique is one of the effective approach to sustain a drug using PEG as a meltable binder, without using any solvents. The dissolution profiles of aceclofenac sustained release tablets exhibited a sustained action with a drug release of nearly 85% after 10 hrs. The results confirmed that the carrier PEG more effectively sustained the release of aceclofenac from the tablet. From the present investigation, it was concluded that the concentrations of PEG 4000 as a melt binder have more sustaining effect compared to that of pure drug. With future development of technology, melt granulation technique will continue to enable novel approach in drug delivery and solve problems like solubility, wettability and dissolution rate of poorly soluble and wettable drugs.

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