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Research Article

FORMULATION, EVALUATION AND *IN-VITRO* RELEASE CHARACTERISTICS OF ZALTOPROFEN SUPPOSITORIES

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ABSTRACT

Mucosal drug delivery technique has its own advantages of bypassing the first pass metabolism and minimizing gastric irritation possibilities. In spite being a non invasive route of administration human rectum remains to be relatively unexplored route of drug delivery. The major objective of the current study was to explore the use of different suppository bases i.e. Coca butter and different grades of polyethylene glycol bases (4000 and 6000) for the successful delivery of Zaltoprofen , an novel non steroidal anti inflammatory drug through rectal route of administration. Moreover Zaltoprofen has tendency to promote gastric ulcer making it necessary to explore safer routes of its administration. Fusion method was used for the preparation of suppositories, which were further evaluated for their physicochemical properties like weight variation, liquefaction time, melting time and in-vitro release characteristics. Suppositories of PEG 4000 showed better permeation of drug with faster dissolution rate in vitro than other formulations.

Keywords: Zaltoprofen, rectal dosage forms, PEG 4000& 6000, Cocoa Butter, Suppositories.

INTRODUCTION

Zaltoprofen, (±) 2-(10-Oxo-10, 11-dihydrodibenzo [b,f]thiepin2-yl) Propanoic acid is a preferential COX-2 inhibitor, it selectively inhibits PGE2 production at the site of inflammation. It also exhibits inhibitory action on the nonciceptive responses of bradykinin. Both the actions are independent of each other. [1] Zaltoprofen is available in market in form of tablets. Zaltoprofen is rapidly absorbed, plasma half life of 4.96± 2.97h and have more than 84% bioavailability [2], but higher incidences of gastrointestinal adverse events have been reported than other propionic acid derivatives. [3] (Figure-1)

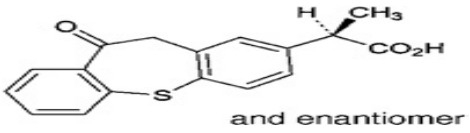

Fig. 1: chemical structure of zaltoprofen

It is mainly used for lumbago, limited shoulder movement, rheumatoid arthritis, upper respiratory tract infection, post operative pain. [3-5] Literature review lacks any information about the availability of Zaltoprofen suppositories. Using Zaltoprofen suppositories is advantageous over other routes in avoiding the gastrointestinal irritation and avoidance of its bitter taste. Suppositories of Zaltoprofen can be used in patients suffering from nausea, gastric ulcers, comatose patients, geriatrics where administration is difficult or not possible through oral route. Studies show that the release characteristics of suppositories depend on the physicochemical properties of the drug, its carrier (suppository base) and adjuvants like plasticizers and surfactants. The particle size of drug and chemical composition increase or decrease the rate of release.[6] The objective of this study was develop suppository of Zaltoprofen with a view to cover the toxic effects and produce effective dosage form and improve the solubility of poorly soluble drug.

MATERIALS AND METHODS

MATERIALS

Zaltoprofen was a gift sample fron IPCA labs Ltd, Ratlam, Madhya Pradesh and Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat. Polyethylene glycol 4000 and 6000 were purchased from Central Drug House (P) Ltd., New Delhi. Cocoa Butter (B.P. grade) was purchased from Genuine Chemicals Company, Mumbai. All other chemicals were used of analytical grade. Specially manufactured suppository moulds of 900 mg capacity were procured from Kshitij Innovations, Ambala, Haryana.

METHODS

Drug Exipient Interaction Studies

1) Differential scanning calorimetry

Differential scanning calorimetry is one of the most unique tools to determine the interaction between drug and the excipients. Reference and sample crucibles are placed on a sample carrier within a furnace of cylindric geometry which generates heat radially toward the center. Temperature is detected by thermocouples in contact with each crucible. One thermoelement is shared between the crucibles allowing the temperature difference to be measured as a voltage. First a "Baseline" is recorded. This is the response with both crucibles empty. Next a reference test, in which a sample with a well defined melting point, is tested for comparison to an experimental sample. Finally, an experimental sample is tested. The DSC curves were obtained using Shimadzu DSC-60, with temperature range 35℃- 300℃. (Figure 2&3)

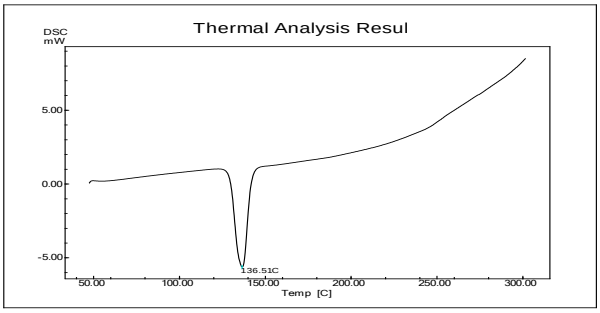

Fig. 2:DSC thermogram of pure zaltoprofen

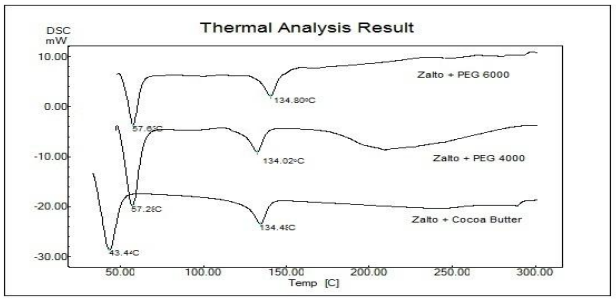

Fig. 3 :DSC thermogram of fusion mixtures

2) Infra red Spectroscopy

Zaltoprofen and its fusion mixture were also analysed using IR spectroscopy by forming KBr pellets. IR spectra didn't show any abnormality indicating any incompatibility.

Preparation of suppositories

The suppositories bases were accurately weighed and melted on water bath. Finely divided drug powder was thoroughly incorporated in the melted base with continuous stirring. The melted mass was poured in the appropriate suppository mould (0.9 gm). Suppositories were kept in refrigerator, at 4℃ to avoid the development of cracks and the exposure to room temperature was limited to less than 24h before use in *in-vitro* release studies. [6-7] (Table 1)

Table 1: Code and composition of formulations (all values are in percentage)

COMPOSITION		F1	F2	F3	F4	F5
Bases	PEG 4000	100	-	-	40	60
	PEG 6000	-	100	-	60	40
	Cocoa Butter	-	-	100	-	-
Drug	Zaltoprofen	8	8	8	8	8

Evaluation of Suppositories

Subsequently suppositories were made to undergo through some simple tests in order to ascertain their adherence to quality. These parameters should be evaluated during the storage period to determine their stability. Along with visual inspection for fissuring, pitting, fat blooming, exudation, migration of active ingredients; physical features such as length, width, weight variation, hardness (mechanical strength), breaking strength, liquefaction time, melting time, were also determined.

Visual characterization

Twenty suppositories from each batch were randomly selected, longitudinally cut and examined through naked eyes for the assessment of physical characters like absence of fissuring, pitting, fat blooming, exudation and migration of active ingredients.[8] (Table 2)

Table 2: Visual characterization of the formulations

Parameters	F1	F2	F3	F4	F5
Fissuring	No	No	No	No	No
Pitting	No	No	No	No	No
Fat blooming	No	No	No	No	No
Exudation	No	No	No	No	No
Migration of active ingredient	No	No	No	No	No

Length and width

Twenty suppositories were selected randomly from each batch, their length and width was measured using vernier callipers and screw micrometer respectively.

Fig. 4: Breaking Strength Apparatus

Breaking strength

The breaking strength is a measure of mechanical strength indicating the fragility or brittleness or elasticity of suppositories which asses the ability of suppositories to withstand mechanical shocks during transportation. An iron rod with a plastic disk on one side and pointed on the other end is used. A suppository is placed in between the pointed end of iron rod and a metallic plate. Weights are placed on the disk in increasing order till the suppository collapses, the electric circuit gets complete and the bulb lights. [9-10] (Figure 4)

Weight variation

Twenty suppositories were weighed and average weight was found out. After that each suppository was weighed individually on electronic balance (Shimadzu make). Not more than 2 individual suppositories deviate from average by 5%. [9]

Friability

Twenty suppositories were weighed and placed in the chamber of the friabilator (Electrolab EF-2). The friabilator was operated at 25 rpm for 4 min. After completion of the cycle the friability is calculated using formula

$$\frac{w_o - w_f}{w_o} \times 100$$

Where w_o is initial weight of six suppositories and w_f is the final weight of suppositories after testing. [10]

Melting point

Macro melting range test is performed with the whole suppository. A suppository from each formulation was placed in a beaker with Phosphate Buffer pH 6.8 maintained at constant temperature 37± 0.5℃. The time required by the whole suppository to melt or disperse in the media was noted. The melting time plays a crucial role in the release of active ingredient. [11-12]

Liquefaction *or softening time*

Liquefaction time was measured using a pipette having a broad opening on one side and a narrow opening on the other; suppository was pushed inside form the broad end side to reach to the narrow end. 5ml of phosphate buffer pH 6.8 was placed inside the pipette, maintained at 37± 0.5℃. A thin iron rod is placed on the top of the suppository and the time at which the iron rod just inserts into the suppository is recorded as liquefaction time. This indicates the time taken by the formulation to liquefy under similar pressures found in rectum. [10,13]

Drug Content

Drug Content was determined spectrophotometrically. Suppositories were melted individually subsequently dissolved in phosphate buffer pH 6.8. After necessary dilutions the solutions were subjected to UV spectroscopy (Shimadzu UV1800) at 338.80 nm wavelength.[14]

Dissolution study

Dissolution test was carried out in USP rotating basket dissolution apparatus (Electrolab TDT 06P). Employing the stirrer speed at 100 rpm and Phosphate buffer pH 6.8 as dissolution medium (900ml), at fixed time intervals 5 ml of the aliquot was withdrawn and same quantity was replaced by fresh buffer. The withdrawn samples were spectrophotometrically analysed at 338.80 nm on Shimadzu UV1800. [15]

RESULTS AND DISCUSSION

Zaltoprofen is a non steroidal analgesic belonging to the propionic acid derivative class used for rheumatoid arthritis, lumbago, post operative pain, etc. It is rapidly eliminated and has a half life of approx 4 hrs, which means at least the dosing frequency must be two times a day. The major problem related with the NSAIDs oral preparations are peptic ulcers due to their physiochemical nature i.e.

weak acid. Suppositories of Zaltoprofen were prepared by fusion method using different bases like PEG 4000, PEG 6000 and Cocoa butter. The results of visual and physicochemical parameters are displayed in (Table no. 2 and 3).

Table 3: Physico-chemical characterization of the formulation

Formulation	Length (cm)	Width (cm)	Weight variation (mg)	Friability (%)	Breaking strength (gm)	Liquefaction time (min)	Melting time (min
F1	1.818 ±0.016	0.890 ±0.005	896 ±0.001	0.686	455 ±7.071	2.38 ±0.43	35.20 ±0.43
F2	1.811 ±0.047	0.888 ±0.004	900 ± 0.022	0.807	492 ±3.500	2.54 ±0.21	50.40 ±0.24
F3	1.818 ±0.024	0.890 ± 0.003	721 ± 0.017	NA	338 ±9.831	1.45 ±0.05	27.56 ±0.45
F4	1.817 ±0.034	0.889 ±0.002	898 ±0.038	0.787	479 ±4.850	2.51 ±0.10	45.30 ±0.40
F5	1.814 ±0.030	0.890 ±0.002	899 ±0.087	0.713	464 ±6.567	2.47 ±0.56	39.30 ±0.25

All the formulations were found to be homogenous and uniformity in content, with sufficient mechanical strength to withstand the wear and tear during transportation and storage. The length and width of the suppositories ranged from 1.818± 0.024 to 1.811± 0.047 cm and 0.890±0.005 0.888±0.004. Weight of the formulations varied from 721 mg to 900 mg. The drug content of the formulations ranged from 95.23 to 98.98%. (Figure5). Percent cumulative drug release from formulation of the formulations varied from 18.67% to 98.64%. (Figure 6 and 7)

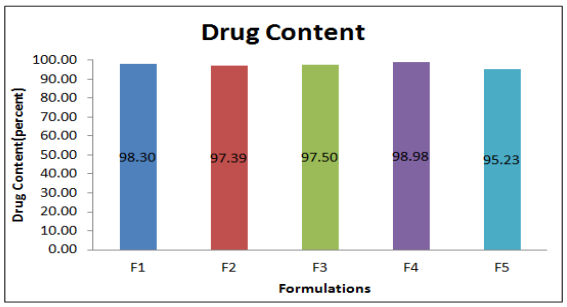

Fig. 5: drug content

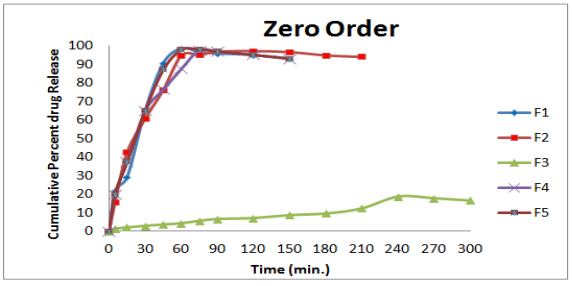

Fig. 6: Zero Order Drug Release Profile

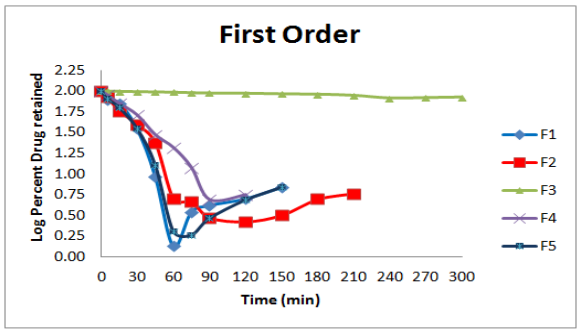

Fig. 8 : first order drug release profile

DSC analysis shows excellent compatibility between the ingredients as the peaks in curves of Drug with excipients' and peak in drugs' curve does not show any major anomaly. IR spectroscopic analysis does not indicate any incompatibility issue.

The maximum release of the drug was found to be from PEG 4000 and least with Cocoa Butter. The lower incidence of drug release from cocoa butter shows that Zaltoprofen may have a higher affinity for cocoa butter than the dissolution medium, also the insoluble nature of fatty acid base increases the dispersion time of the suppositories and drug release time period, whereas PEG bases which are easily soluble in aqueous medium, disperses rapidly and has higher rate of release.

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