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Formulation and In Vitro Characterization of Zaltoprofen Suppositories Using Bases and Different Concentration of Plasticizer.

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ABSTRACT

The objective of the current study was to explore the use of different suppository bases i.e. Cocoa butter and different grades of polyethylene glycol bases (4000 and 6000) and to observe the effect of plasticizers incorporated in the suppositories for the successful delivery of Zaltoprofen, an novel non steroidal anti inflammatory drug through rectal route of administration. Moreover, Zaltoprofen has tendency to cause 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 visual characteristics, physicochemical properties like dimensions, weight variation, liquefaction time, melting time, disintegration time, drug content and *in-vitro* release characteristics. Suppositories of PEG 4000 showed best drug release in vitro than other bases. Addition of plasticizer (PEG 400) at 30% concentration reduces the dissolution time in both grades of PEG suppositories.

Keywords: Zaltoprofen, PEG 4000, PEG 6000, PEG 400, Suppositories, Cocoa butter.

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INTRODUCTION

A suppository is a medicated solid dosage form generally intended for use in the rectum, vagina, and to lesser extent, the urethra. Rectal and urethral suppositories usually employs a vehicles that melt of soften at body temperature, whereas vaginal suppositories sometimes called pessaries are also made as compressed tablets that disintegrate in the body fluids [1]. Bases acts as the vehicles or carriers of drugs. A variety of substances has been as suppository bases from the commencement of the history of suppository. Their use was governed by the factor of their availability rather than scientific approach. These bases play an important role in release of medication they hold and therefore availability of drug.

Suppositories are being used from as early as 1500 B.C. by the Egyptian civilization for the local treatment of hemorrhoids and constipation. Studies show that some of the active agents like indomethacin, aspirin, diazepam and propanolol when administered by both oral route and rectal route exhibits greater bioavailability. In spite of being slowly absorbed on rectal administration Pentobarbital exhibits bioequivalence with oral dosing. Due to the absence of first pass metabolism, the solution form of some active principles show at par bioavailability with oral dose. Sustain release formulations of suppositories have a superiority over the oral sustained release formulations as a new suppository is inserted after defecation of the older suppository, therefore avoiding overdosing [2].

Zaltoprofen is an analgesic and non steroidal anti-inflammatory drug usually employed in rheumatic disorder. It has a plasma half life of 4.96 hrs and to maintain the therapeutic plasma levels the drug must be administered at least twice a day. In the usual oral administration of NSAIDs, the tablets and capsules have led to peptic ulceration and anorexia. As it is a weak acid, on coming in contact with gastric contents it cause gastric mucosal irritation. Administration of NSAIDs through rectal route can be a good alternative route for patients with peptic ulcer, children and old age patients. In comparison to oral route 3/4th of the intact drug can be absorbed into blood circulation without passing liver in suppositories form. The purpose of the study was to prepare suppositories of Zaltoprofen using different suppository bases. Effect of plasticizer at their different concentrations on suppositories was also studied. Addition of plasticizers may decrease the dissolution time [3,4].

MATERIAL AND METHOD

Materials

Zaltoprofen was obtained as gift sample from IPCA Labs Ltd, Ratlam. Cocoa Butter was purchased from Genuine Chemical Company, Mumbai. PEG 4000, PEG 6000 was obtained from CDH Pvt. Ltd, New Delhi. PEG 400 was obtained from Fischer Scientific, Mumbai. All the ingredient used were of analytical grade.

Drug polymer interaction studies

The drug and polymer compatibility studies were carried out to check the compatibility between drug and various bases. It was necessary to confirm that drug was not interacting with bases and plasticizer under experimental conditions and shelf life.

UV analysis: The aqueous solutions of the pure drug and the suppositories containing Zaltoprofen were filtered through whatmann filter paper and scanned for UV absorption between 200 and 400 nm.

FT-IR: Fourier Transform InfraRed is the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed through (transmitted). The resulting spectrum represents the molecular absorption and transmission, creating a molecular fingerprint of the sample. Like a fingerprint no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. *Sample*

Scanning: The samples were scanned in 400-4000 wave number range, using KBr pellet technique [5].

Differential Scanning Calorimetry: Differential Scanning Calorimetry (DSC) measures the temperatures and heat flows associated with transitions in materials as a function of time and temperature in a controlled atmosphere. These measurements provide quantitative and qualitative information about physical and chemical changes that involve endothermic or exothermic processes, or changes in heat capacity. Differential scanning calorimetry (DSC) monitors heat effects associated with phase transitions and chemical reactions as a function of temperature [6]. DSC was carried out on Shimadzu DSC-60 at Temp range-35^0C-300^0 C; Rate – 20^0C per min; Atmosphere-Air.

Formulation of Suppositories

Hot Fusion method: It involves first melting the suppository base, and then dispersing or dissolving the drug in the melted base. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them. Suppositories are generally made from solid ingredients and drugs which are measured by weight. When they are mixed, melted, and poured into suppository mold cavities, they occupy a volume – the volume of the mold cavity. Since the components are measured by weight but compounded by volume, density calculations and mold calibrations are required to provide accurate doses (Table 1) [7-9].

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Table 1: Trial Formulation batches of Zaltoprofen suppositories

Composition/Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	8	8	8	8	8	8	8	8	8
Cocoa Butter	-	-	92	-	-	-	-	82	62
PEG 4000	92	-	-	82	62	-	-	-	-
PEG 6000	-	92	-	-	-	82	62	-	-
PEG 400	-	-	-	10	30	10	30	10	30

Method of Evaluation of Suppositories:

Weight Variation: 20 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% [1].

Friability: Six suppositories were weighed and placed in the chamber of the Roche 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

$$\frac{w_o - w_f}{w_o} \times 10$$

Where w_o is initial weight of six suppositories and w_f is the final weight of suppositories after testing. [10-12]

Breaking Point (Hardness): 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. [1, 12]

Liquefaction 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 of 30gm 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 [11, 13].

Melting time & range: 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 [14].

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Disintegration time: Disintegration test is carried out using 6 suppositories in normal disintegration test apparatus and noting the normal time taken by a suppository to disintegrate in phosphate buffer pH 6.8. Disintegration was evaluated according to BP 2002 [15, 16].

Drug content: Randomly selected suppository from each formulation was melted in a volumetric flask containing 100ml phosphate buffer pH 6.8; the solution was continuously stirred by using glass magnetic beads. After necessary dilutions and filtration using 0.45µm filter solutions were subjected to UV spectroscopy (Shimadzu UV1800) at 338.80 nm wavelength [17,18].

***In-Vitro* dissolution profile:** Dissolution test was carried out in USP rotating basket dissolution apparatus (Electrolab TDT 06P). Each suppository was placed in vessel and the stirrer was lowered to a height 1-2mm from the bottom off the vessel. Employing the stirrer speed at 50 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 replaced by fresh buffer. The withdrawn samples were spectrophotometrically analysed at 338.80 nm on Shimadzu UV1800 [17,19].

RESULTS AND DISCUSSIONS

Analysis of Drug

The identity of the compound was confirmed by comparison with an authentic sample and verifying the presence of functional groups in an unknown molecule was done by IR spectra. The IR spectrum was analyzed for important chromophoric groups. The FTIR spectra showed peaks at 2978, 2716, 2685, 1710, 1670 and 1281 cm^{-1}. The peaks are shown in figure 1 and DSC thermogram of Zaltoprofen showed a sharp peak at 136.5^{0}C (Figure 1 and Figure 2).

Figure 1: Prepared Suppositories (Fusion molding)

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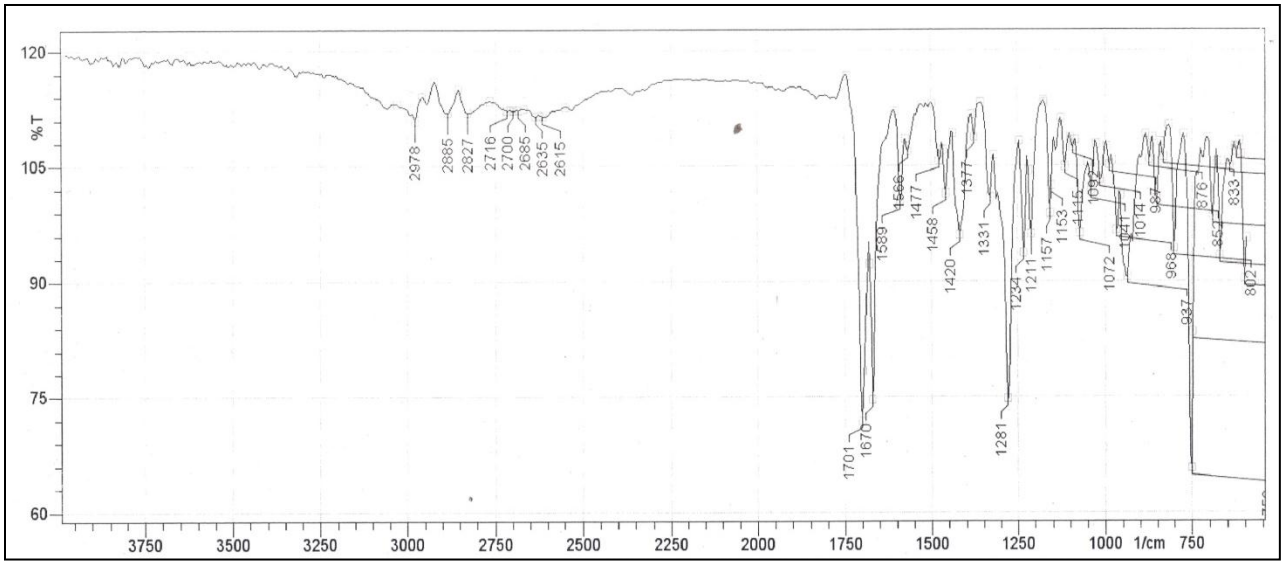

Figure 1: FT-IR of Pure Zaltoprofen

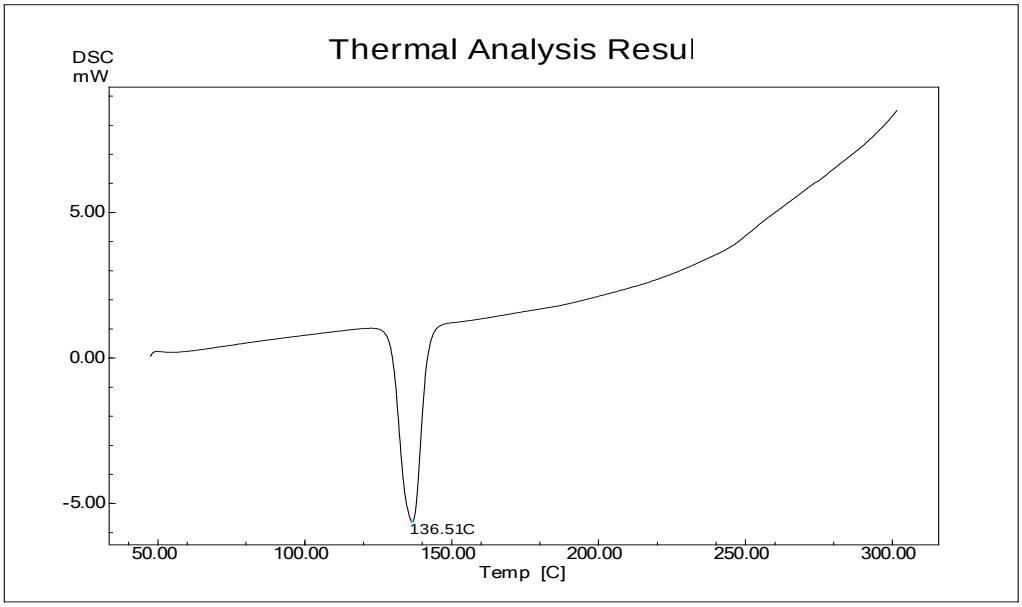

Figure 2: DSC of Pure Zaltoprofen

Drug excipient compatibility study

Compatilibility of drug and excipient was determined by FT-IR of fusion mixtures of the respective drug and bases and plasticizer. It was found that there was no significant interaction between the drug and the excipient (Figure 3-5).

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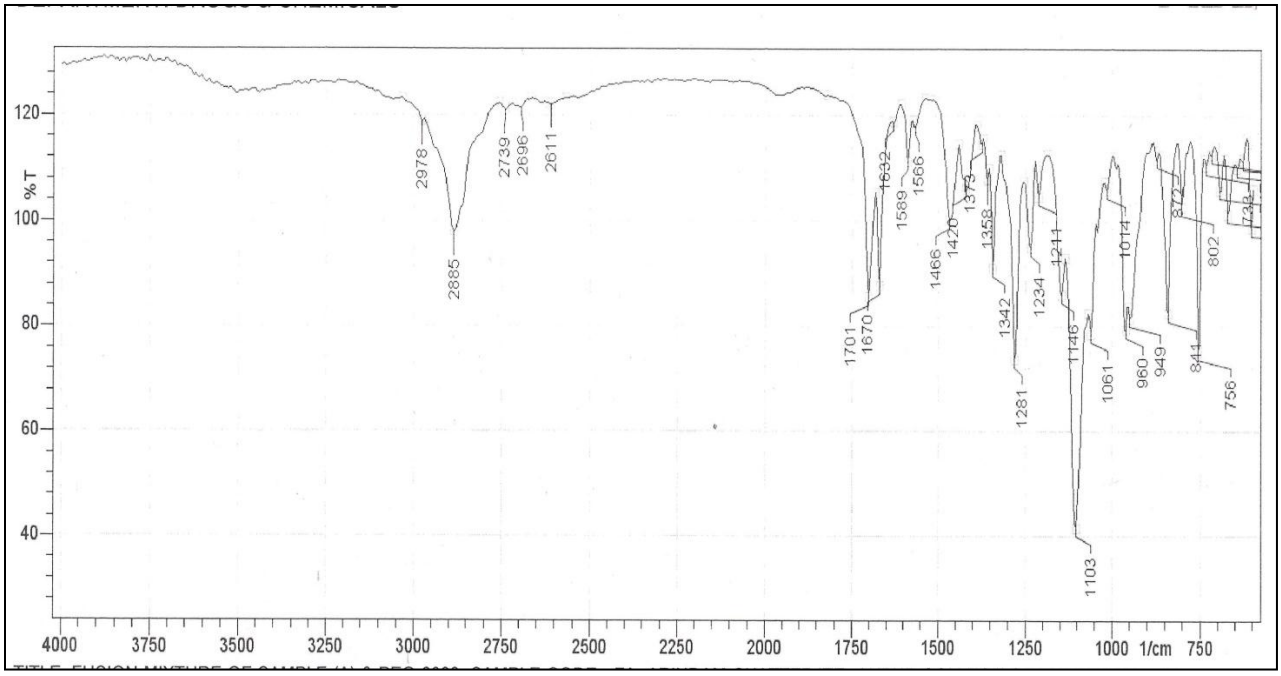

Figure 3: FT-IR Spectra of fusion mixture of PEG 4000 and Zaltoprofen

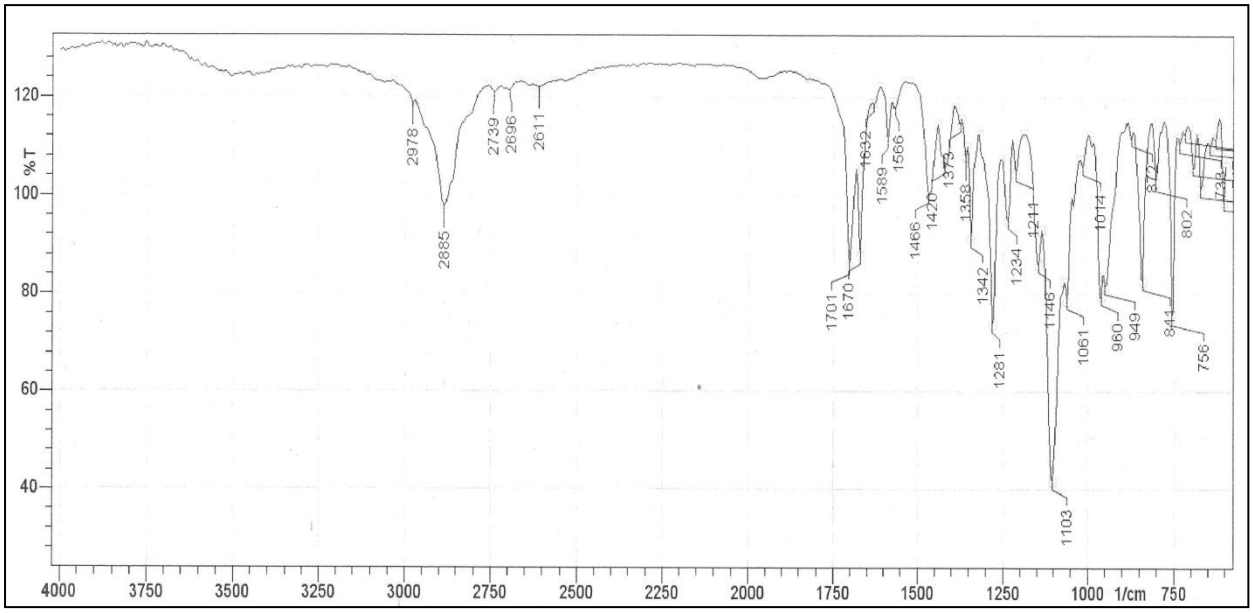

Figure 4: FT-IR Spectra of fusion mixture of PEG 6000 and Zaltoprofen

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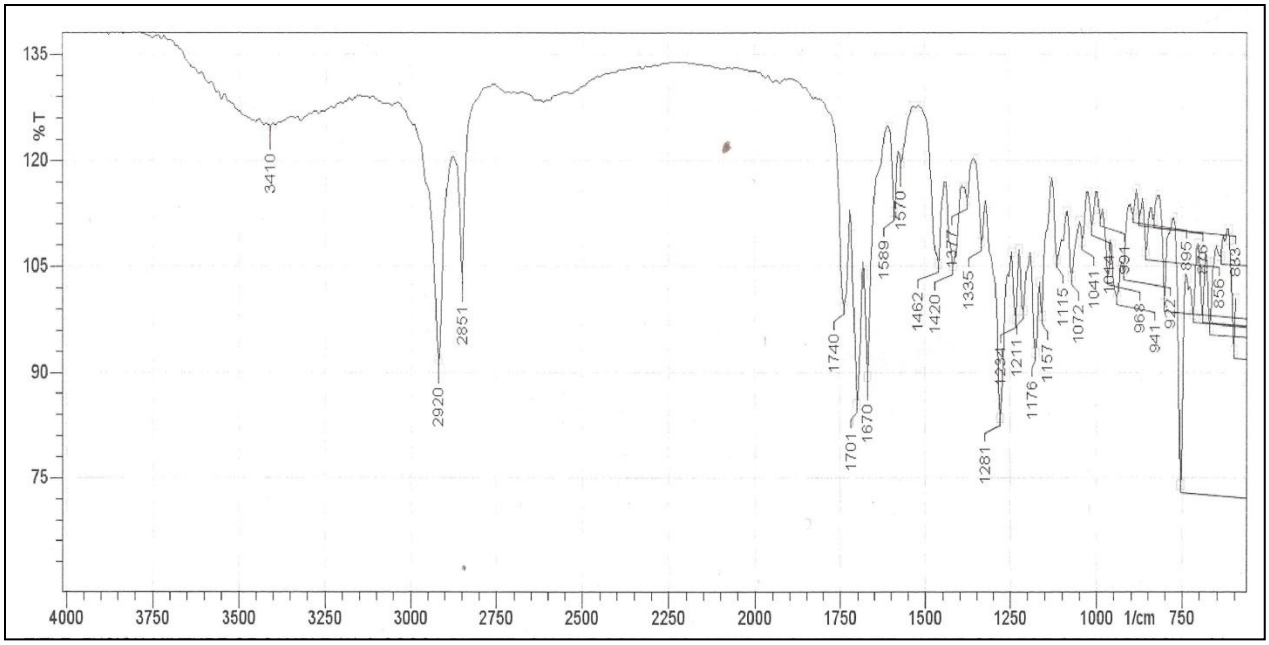

Figure 5: FT-IR Spectra of fusion mixture of Cocoa butter and Zaltoprofen

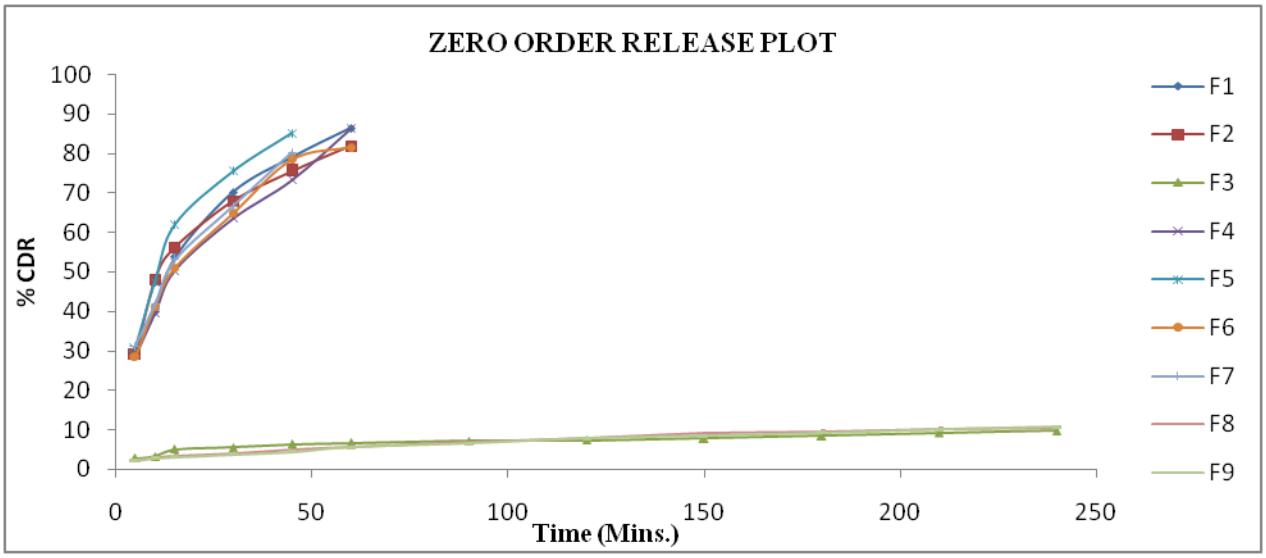

Figure 6: Zero order release plot of Formulation F1-F9.

Evaluation of prepared suppositories

Suppositories of Zaltoprofen were prepared by fusion method employing different bases such as PEG 4000, PEG 6000 and cocoa butter. The prepared suppositories were characterized for visual parameters (fissuring, pitting, fat blooming , exudation, migration of active ingredient, length, width, breaking strength, uniformity of weight and friability, melting time liquefaction time, content uniformity and i*n-vitro* release.

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Physicochemical Evaluation

All the formulations were found to have homogenous drug distribution with content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasives forces which causes disintegration of prepared suppositories. The width and length of randomly selected suppositories was found to vary from 0.806 cm to 0.890 mm and 1.811 to 1.87 cm for different formulation with good homogeneity and the effect of addition of other exicpients were negligible. The weight of the suppositories varied from 0.740 to 0.900 mg for different formulations of different bases. Each individual suppository did not vary more than 5% from the average weight. The breaking strength varied from 296 gm to 550 gm and friability ranged from 0.23 to 0.75% which was sufficient enough to prove their ability to withstand normal wear and tear during processing. Disintegration time was determined using disintegration test apparatus and time ranged from 7 min to 15 min. Addition of plasticizers reduce the disintegration time to a smaller extent. The D.T. was well within the limits specified by British Pharmacopoeia. Liquefaction time was observed in the range of 37 secs to 2mins 30 secs. Drug content was found to homogenous in all the formulations and well within the pharmacopoeial limits. It ranged from 76 to 84 mg. On evaluation of physical parameters it was seen that additives does not have a major effect on the physical properties of suppositories. Physical properties are governed by the type of base. The physicochemical evaluation results have been summarized in Table 2.

Table 2: Physicochemical Evaluation of Formulation F1-F9

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight(gm)	0.890 ±0.005	0.900 ±0.022	0.721 ±0.0.17	0.913 ±0.004	0.91 ±0.005	0.874 ±0.006	0.903 ±0.026	0.722 ±0.005	0.723 ±0.006
Length (cm)	1.818 ±0.016	1.811 ±0.047	1.818 ±0.024	1.863 ±0.019	1.861 ±0.021	1.856 ±0.018	1.873 ±0.025	1.855 ±0.024	1.86 ±0.021
Width (cm)	0.896 ±0.001	0.888 ±0.004	0.890 ±0.003	0.807 ±0.002	0.876 ±0.002	0.879 ±0.008	0.890 ±0.003	0.883 ±0.008	0.876 ±0.002
Breaking strength (gm)	485.66 ± 2.73	545 ±9.79	389.5 ±4.46	474.50 ±3.27	445.83 ±3.76	550.67 ±3.33	545.00 ±9.80	386.00 ±3.41	372.50 ±5.24
Liquefaction time (min)	2:65 ± 0:172	3:42 ±0:02	2:06 ±0:02	2:21 ±0:02	1:55 ±0:01	2:53 ±0:008	2:36 ±0:017	1:55 ±0:01	1:53 ±0:02
Melting time (min)	41:14 ±0:036	55:20 ±0:036	31:33 ±0:085	37:29 ±0:04	35:35 ±0:11	47:18 ±0:11	46:18 ±0:06	26:38 ±0:13	26:30 ±0:12
Disintegration time (min)	14:29 ±0:047	16:23 ±0:08	8:34 ±0:08	14:34 ±0:03	13:38 ±0:09	15:49 ±0:48	14:48 ±0.02	09:33 ±0.08	09:41 ±0.11
Drug content (mg)	81.18 ±0.091	82.27 ±0.091	79.48 ±0.139	83.48 ±0.139	81.18 ±0.091	78.60 ±0.139	79.75 ±0.139	79.18 ±0.091	79.45 ±0.091

In-vitro Dissolution Study

For adequate characterization of drug release rate from suppositories requires the determination of its appropriate release kinetics model (table 3).

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Table 3: In-vitro release data for Formulations F1-F9

Time (mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	29.855	29.107	2.782	28.760	30.795	28.446	31.228	2.117	2.255
10	39.840	47.982	3.297	39.520	47.400	41.112	41.774	2.858	2.792
15	53.759	56.228	5.049	50.378	61.993	50.974	53.037	3.387	3.006
30	70.199	67.851	5.564	63.486	75.579	64.886	66.552	4.022	3.758
45	79.176	75.500	6.389	73.269	85.139	78.382	80.272	4.869	4.402
60	86.337	81.858	6.698	86.279	-	81.496	-	5.610	5.583
90	-	-	7.110	-	-	-	-	6.774	6.442
120	-	-	7.316	-	-	-	-	7.727	7.731
150	-	-	7.728	-	-	-	-	8.997	8.375
180	-	-	8.347	-	-	-	-	9.526	9.234
210	-	-	9.171	-	-	-	-	10.161	9.986
240	-	-	9.686	-	-	-	-	10.479	10.737

Data obtained from dissolution studies were fitted to Zero-order, First-order, Higuchi and Korsmeyer Peppas' model to determine the kinetics of drug release. Percentage cumulative drug release from suppositories of Cocoa butter PEG 6000 and PEG 4000 were found to be 9.6, 81.85 and 86.33 % respectively Table. It was found that PEG 4000 bases release maximum Zaltoprofen from suppositories followed by PEG 6000 and cocoa butter. Factor which influences the rate of drug release from the base is the water absorbing capacity of base which facilitates the penetration of dissolution medium into the base with subsequent wetting and desorption of the drug. PEG bases are hydrophilic; hence they dissolve completely releasing the drug into the dissolution medium. PEG 4000 has maximum release among the PEG bases studied in this investigation as the molecular weight of PEG's increases their hydrophilicity decreases so, PEG 6000 has a lower cumulative percent drug release. From this study it is also seen that PEG bases are not suitable for designing sustained release suppositories of Zaltoprofen. *In vitro* release Cocoa butter suppositories were studied over 4hrs and it was seen that negligible amount of drug was released before the drug release was stopped. It may due to the higher lipophilicity of drug, can be deduced from partition coefficient, which hinders the release of Zaltoprofen in the dissolution media.

Effect of plasticizer

Role of plasticizer was studied on different bases. Two concentrations 10% and 30% of PEG 400 were used for the study. PEG 400 was easily miscible in PEG bases and cocoa butter. Therefore, the study was undertaken only on PEG and cocoa butter suppositories. It was seen that on using PEG 400 at 10% concentration does not reduce the dissolution time but decreases the percent cumulative drug release. Whereas at 30% concentration the PEG 400 reduces the dissolution time by 15 minutes in both PEG 4000 and PEG 6000 based suppositories. This may be due to higher hydrophilic nature of the PEG 400. Cocoa butter suppositories did not show any such difference, neither the release rate was changed nor the dissolution time was reduced.

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CONCLUSION

An attempt was made to formulate the suppositories of Zaltoprofen using different bases and plasticizer. For the investigation made, it could be concluded the PEG 4000 and plasticizer PEG 400 offer the better release of the drug and have good physical property. Thus, it could be concluded that Zaltoprofen suppositories can be prepared using PEG 4000 and PEG 6000. Further, *in-vivo* evaluation is necessary to predict the drug release and plasma level of the drug through this delivery system.

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REFERENCES

[1] Coben LJ, Lieberman HA. Suppositories, in: The theory and practice of industrial pharmacy, Lachman L, Lieberman HA(Eds.), CBS Publishers and Distributors, New Delhi, 2009, pp 586-587.
[2] Varshney HM, Chatterjee A. Asian J Pharma Clin Res 2012; 5(4).
[3] Ministry of health, Labour and welfare, Goverment of Japan. The Japanese pharmacopeia, 15th Edition, 2006, pp 1242-1243, 1517, 1654.
[4] Li L, Ma P, Cao Y, Tao L, Tao Y. J Biomed Res 2011; 25: 56-62.
[5] Silverstein RM, Webster FX, Kiemle DJ. Spectrometric identification of organic compounds, John Wiley & sons, Inc. New Jersey, 2005, pp 78-80.
[6] Skoog DA, Holler JE, Crouch SR. Principles of instrumental analysis, Thomson Higher education, Belmont, 2007, pp 900-903.
[7] Gold M et.al. Suppository Development and Production, in: Lieberman HA, Pharmaceutical Dosage forms: Disperse system, Vol. 2, Informa Healthcare, New York, 2008, pp. 447-496.
[8] Kokate A, Marasanapelle VP, Jasti BR, Li X. Physiological and biochemical barriers to drug delivery, in: Jasti BR, Xiaoling L. Design of controlled release drug delivery systems, McGraw Hill , New York, 2006, pp. 67.
[9] Nivatvongs S, Gordon PH. Surgical Anatomy, in: Nivatvongs S, and Gordon PH (Eds.), Principles and Practice of Surgery for the Colon, Rectum and Anus, Informa healthcare, New York, 2007, pp 4-22;
[10] Varshney HM, Tanwar YS. J Pharmacy Res 2010; 3(3): 561-565.
[11] Varshney HM, Tanwar YS. Int J Pharma Clin Res 2010; 1(1): 31-34.
[12] Varshney HM, Tanwar YS. Acta Pharmaceutica Sciencia 2010; 52: 129-136.
[13] Sah ML, Saini TR. Indian J Pharma Sci 2008; 70(4): 498-501.
[14] Loyd VAllen Jr. Ed. Quality control of suppositories, in: Suppositories, Pharmaceutical Press, London, 2008, pp. 141-142.
[15] Abass, H et.al. Int J Pharmacy Pharma Sci 2012; 4(1): 344-353.
[16] Patravale V et.al. AAPS Pharm Sci Tech 2010; 11(3): 1179-1184.
[17] Swiader K, et.al. Annales of Marie curie University Lublin 2011; 24(2): 159-167.

[18] Swamy PV et.al. Int J Pharmac Sci Nanotech 2009; 2(3): 654-660.
[19] Tarimci N, Ermis D. Int J Pharm 1995; 113: 65-71.