Development and evaluation of immediate release diclofenac sodium suppositories

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Abstract: The objective of present study was to develop and evaluate polyethylene glycol (PEG) based diclofenac sodium suppositories. This study used water soluble PEG bases (1000, 4000 and 6000) in different combinations to formulate suppositories, which were further subjected for their physicochemical properties evaluation such as weight variation, average melting point, content uniformity and disintegration. Dissolution test was used to perform the *in vitro* release rate studies of the suppositories. The suppository (P3) containing PEG-6000 (50%) and PEG-4000 (50%) exhibited rapid *in vitro* release rate of diclofenac sodium. Moreover, homogeneous distribution of diclofenac sodium is found in all six formulations. The *in vitro* release patterns of diclofenac sodium from the marketed Voltral suppository (100mg) and formulated suppositories were also compared and found in standard limits.

Keywords:Water soluble bases, polyethylene glycol, suppositories, diclofenac sodium, *in vitro* release study.

INTRODUCTION

In recent times, incredible advancement has been made in the pharmaceutical field concerning drug design and formulation. The development which was previously inconceivable such as the rectal route of drug administration has evolved as beneficial in the cases where other routes are not sufficient for drug delivery (Aulton & Taylor, 2017; Brunton LL, 2001; Pugunes & Ugandar, 2013). On the other hand, several studies have shown the use of rectal route questionable and did not consider it appropriate (Samy, Hassan, Tous, & Rhodes, 2000; Shekokar, Borkar, Patil, & Jagatap, 2012; Tung, 2009). However, since ancient periods, medical practitioners used suppositories for treating proctologic disorders (Gupta, 2007; Pugunes & Ugandar, 2013). Suppositories are made by dissolving or dispersing one or more active substances in water or lipid soluble base and their combined form. These water-soluble bases melt at body temperature, and are dispersible (Berkó, 2002; British Pharmacopoeia, 2012; Dhanaraju, Kumaran, Baskaran, & Moorthy, 1998; Sinko, 2011). Compared to cocoa butter suppositories, mixture of polyethylene glycol suppositories withstands changes due to temperature variation and hence, exhibits more thermo-stability (D'souza & Shegokar, 2016; Noordin & Chung, 2009; Pugunes & Ugandar, 2013). According to Pugunes and Ugandar (2013), the mixture of polyethylene glycols is a better option in making suppositories for efficient and effective drug delivery. The same procedure is also suggested by Noordin and Chung (2009) and Zaghloul, Lila, Abd-Allah and Nada (2017).

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Diclofenac sodium is an active substance with antiinflammatory, antipyretic and analgesic effects. It belongs to cyclooxygenase inhibitors, and is substantially more potent than other therapeutic agents in same class of drugs; including naproxen and indomethacin (Brunton LL, 2001). In the United States, diclofenac sodium is approved for treating ankylosingspondolysis, osteoarthritis and rheumatoid arthritis due to its long term symptomatic relieving effects (Abdullah & Jawad, 2015). The attempts were made in current research to develop and evaluate conventional and immediate release diclofenac sodium suppositories using different combinations of polyethylene glycols (PEGs) including PEG-6000, PEG-4000 and PEG-1000.

MATERIALS AND METHOD

Materials

Diclofenac sodium, polyethylene glycols (PEG-1000, PEG-4000 and PEG-6000), citric acid and disodium hydrogen orthophosphate were purchased from Merck. Digital electronic balance (Sartorius AG Germany E CP 224 S, 144 11 166), UV spectrophotometer (Shimadzu Serial number A11454500172), Gallenkamptermostirrer 95-CAT melting point apparatus (serial number BKL-210, APP NO 880210), ERWEKA disintegration tester with 500ml Basket rack assembly (serial number 117719083a), and dissolution apparatus (ERWEKA DT 57424 HZ 50 D6072) with paddle (USP II) were used.

Method

Six formulations of 10 x 10=100 suppositories were developed; with different combinations of polyethylene

Table 1: Formulation codes and composition of the suppositories

Code	Drug (mg)	Suppository PEG Base Combination (q.s.)
P 1	50 mg	75% PEG-1000 + 25% PEG-4000
P 2	50 mg	50% PEG-1000 + 50% PEG-4000
P 3	50 mg	50% PEG-4000 + 50% PEG-6000
P 4	50 mg	75% PEG-1000 + 25% PEG-6000
P 5	50 mg	50% PEG-1000 + 50% PEG-6000
P 6	50 mg	25% PEG-1000 + 75% PEG-4000

Table 2: Physical characteristics of each formulated suppository

Code	Fissuring	Pitting	Fat blooming	Exudation	Homogeneity
P 1	No	No	No	No	No
P 2	No	No	No	No	No
P 3	No	No	No	No	No
P 4	No	No	No	No	No
P 5	No	No	No	No	No
P6	No	No	No	No	No

glycols bases including PEG-1000, PEG-4000 and PEG 6000; each by fusion method; using aluminum and brass suppository moulds with eight cavities. Bases were melted in the desired amounts to integrate 50mg diclofenac sodium and prepare suppository of 2.4 grams each by weigh. Using the same fusion method, 100 blank suppositories; 10 of each respective base combination; were also formed. The details of all formulations are tabulated in table 1.

In order to determine release rate and quality of formulated suppositories, following different tests were performed.

Visual characterization - The suppositories were randomly selected for visual characterization from each combination of PEGs. Homogeneity, exudation, fat blooming, pitting and fissuring were observed in the suppositories tested (Sahoo, Sudhakar, Ramana & Satyanarayana, 2017). All the formulations were examined with naked eye. These were cut longitudinally to check the surfaces.

Weight variation - Official method for weight variation from British Pharmacopoeia was utilized, and tested 20 suppositories from each base combination. The average weight of suppositories was calculated (Pugunes & Ugandar, 2013; Yong *et al*., 2009), with the limit that no any suppository differs from the average weight beyond ±7.5% to 10%, and not more than 2 suppositories be different by more than ±5% from the average weight (Setnikar & Pietra, 1969; Yong *et al*., 2009).

Content uniformity - 10 suppositories were taken randomly from each formulation, and at 37°C in water bath were individually melted. Then, in volumetric flask, separately melted suppositories were dissolved in citrophosphate buffer (100ml) having pH 7.2 (British Pharmacopoeia, 2012). Blank solution was formed by diluting blank suppositories with citro-phosphate buffer (pH 7.2). All the samples were filtered, and absorbance was measured at λ-max 276 nm.

Melting point - Melting point apparatus was used to determine the melting points of suppositories. When suppositories started melting, temperature was noted as melting point.

Disintegration test - The disintegration test was performed via randomly selecting three suppositories from each formulation and placing them in the disintegration apparatus, with persistent stirring rate at 37°C (Pugunes & Ugandar, 2013; Yong *et al*., 2009).

In vitro dissolution study - *In vitro* dissolution studies of suppositories were conducted in dissolution apparatus (USP II paddle). 500ml citro-phosphate buffer (pH 7.2) was used as dissolution medium with 100 rpm operated stirring time at constant temperature of 37°C. At specified intervals, 5ml of sample was withdrawn and replaced by 5ml fresh dissolution medium. The samples were filtered using ashless filter paper 203, diluted appropriately and analyzed at 276 nm (Hammouda, Kasim, & Nada, 1993; Pugunes & Ugandar, 2013; Varshney & Tanwar, 2009). The same procedure was performed for the marketed suppository Voltral 100 mg in order to compare its release rate with the formulated suppositories.

Standard calibration curve of diclofenac sodium - Concentration of 0.5mg/ml was prepared by dissolving

50.2mg of diclofenac sodium in 100ml of citro-phosphate buffer solution (pH 7.4). Following this; 2ml, 4ml, 6ml, 8ml, 10ml and 12ml of this solution were obtained and diluted to 100ml separately. 2ml aliquot, from each dilution, was then taken out for diluting to 20ml with citro-phosphate buffer solution (pH 7.2) and preparing the concentrations of 0.001, 0.002, 0.003, 0.004, 0.005, and 0.006 mg/ml. UV spectrophotometric analysis of these concentrations was performed at 276 nm wavelength (Gaud & Gupta, 2006; Jannin, Lemagnen, Gueroult, Larrouture, & Tuleu, 2014; Remington, 2006). Fig. 1 shows the recorded absorbance at the different prepared concentrations.

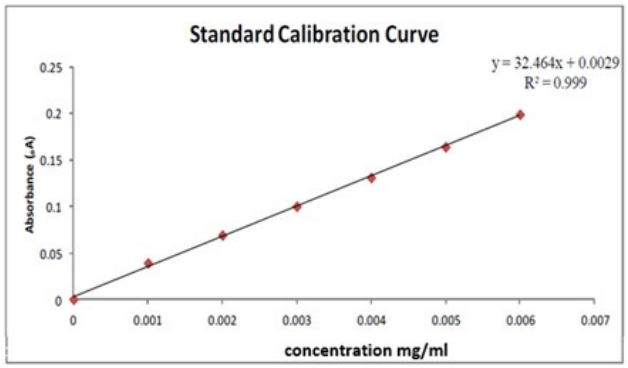

Fig. 1:Standard calibration curve of diclofenac sodium.

RESULTS

The physical evaluation of prepared diclofenac sodium suppositories exhibited no exudation, homogeneity, fat blooming, pitting and fissuring.

In vitro dissolution test, mechanical strength, melting point, disintegration, content uniformity and weight variation studies were conducted for further evaluation of these suppositories. The results of different evaluation parameters are shown below.

DISCUSSION

In view of the problems associated with oral administration of drugs; such as gastric irritation, nausea and vomiting; where parenteral administration is not recommended, an attempt was made to prepare diclofenac sodium suppositories with different ratios of polyethylene glycol bases 1000, 4000 and 6000 using fusion method. The physical evaluation results were found satisfactory for all the six formulated suppositories. This study confirmed the research work of diclofenac sodium suppositories development in different types of bases by Pugunes and Ugandar (2013), and reported matching results of physical characterization tests. The weight variation test results for all the suppositories were found to be within the acceptable range of <5%, indicating the good calibrations of mould. The content uniformity of the active pharmaceutical ingredient in formulations were noted to be 91.08%±0.603, 91.01%±0.6278, 91.25%± 0.659, 91.09%±0.362%, 91.39%±0.54 and 91.31%± 0.434 for P1, P2, P3, P4, P5 and P6, respectively. The content uniformity result met the range proposed by US Pharmacopoeia that drug content should lie within 85% to 115% with ≤6.0% relative standard deviation (RSD) of the labelled claim dose (50mg) per suppository (USP35/NF30, 2012). The melting points of all the formulated suppositories were found to be same i.e. 37°C, as reported by Pugunes and Ugandar (2013) for formulated suppositories using PEG bases. The disintegration test showed that suppositories of polyethylene glycol bases softened and disintegrated at 22.24 minutes ±0.1153, 23.56 minutes ±0.0802, 23.86 minutes ±0.0681, 22.75 minutes ± 0.0700, 24.52 minutes ±0.1212 and 23.86 minutes ±0.0850 for P1, P2, P3, P4, P5 and P6 respectively.

The release rates of the drug from prepared suppositories were dependent on the dissolving nature of bases employed. The *in vitro* release profiles of diclofenac sodium from different bases are shown in fig. 2.

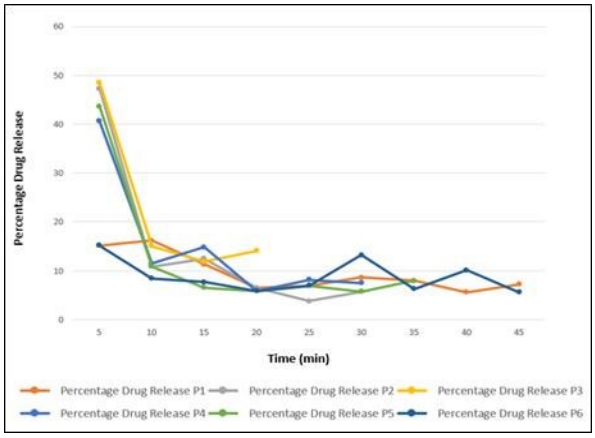

Fig 2:Comparative percentage drug release (CPDR) profile (P1, P2, P3, P4, P5, and P6).

All the formulated suppositories showed the rapid release pattern, as about 80% of diclofenac sodium was released within an hour from each combination of base. According to Zidan, Emam, Shehata, and Fakhr-eldin (2015); the higher release of active substance from PEG base combinations is due to the hydrophilicity, solubilizing effect and osmotic action of PEG 1000, PEG 4000 and PEG 6000. The result also exhibited substantial difference in release of diclofenac sodium from PEG base combinations compared to suppositories formulated using single PEG base (PEG 4000 or PEG 6000) by Pugunes and Ugandar (2013). Moreover, the significant result was observed in case of P3 (50% PEG 6000 + 50% PEG 4000), where 89.62% of drug was released at 20 minutes. The combination of PEG bases in P3, compared to other PEG base combinations in present study, approved the great influence of high molecular weight PEG base combinations on the release of active substance from

Table 3: Physico-chemical characteristics of formulations

Code	Weight Variation (g) (n= 20)	Drug Content % (n=10)	Average Melting Point °C	Disintegration Time (min)(n=3)
P 1	2.4870 ± 0.0833	90.08 ± 0.603	37.0°C	22.24 ± 0.1153
P 2	2.4160 ± 0.0196	91.01 ± 0.6278	37.0°C	23.56 ± 0.0802
P 3	2.4098 ± 0.0206	91.25 ± 0.659	37.0°C	23.86 ± 0.0681
P 4	2.433 ± 0.0309	91.09 ± 0.362	37.0°C	22.75 ± 0.0700
P 5	2.41151 ± 0.0113	91.39 ± 0.541	37.0°C	24.52 ± 0.1212
P 6	2.43833 ± 0.0209	91.31 ± 0.434	37.0°C	23.86 ± 0.0850

Table 4: Comparative percentage drug release (CPDR) profile (P1, P2, P3, P4, P5, and P6) and marketed suppository Voltral

X	Y						
	Comparative Percentage Drug Release (CPRD)						
Time (min)	P1	P2	P3	P4	P5	P6	Voltral
5	15.16	47.31	48.52	40.64	43.67	15.16	28.754
10	16.22	10.85	15.06	11.45	10.85	8.42	3.625
15	11.31	12.49	11.9	14.87	6.55	7.73	5.64
20	6.48	6.48	14.13	5.89	5.89	5.89	6.318
25	6.99	3.79		8.15	6.99	6.99	7.852
30	8.65	5.76		7.5	5.77	13.26	9.21
35	7.99				7.98	6.28	6.411
40	5.65					10.16	7.889
45	7.26					5.59	12.122

formulation. The solubility and release of drug from suppository increases using high molecular weight PEG bases (Bolourchian, Mahboobian, & Dadashzadeh, 2013). In addition, the *in vitro* comparative percentage drug release pattern of diclofenac sodium from the formulated suppositories P1, P2, P3, P4, P5, P6 and marketed Voltral suppository was found to be in the range of 15.16% to 7.26%, 47.31% to 5.76%, 48.52% to 14.13%, 40.64% to 7.5%, 43.67% to 7.98%, 15.16% to 5.59%, and 28.754% to 12.122% after 5 minutes and 45 minutes respectively (table 4 and fig. 3). Quantitatively release of drug was graded in the order P3>P4>P2>P5>marketed Voltral suppository>P1>P6.

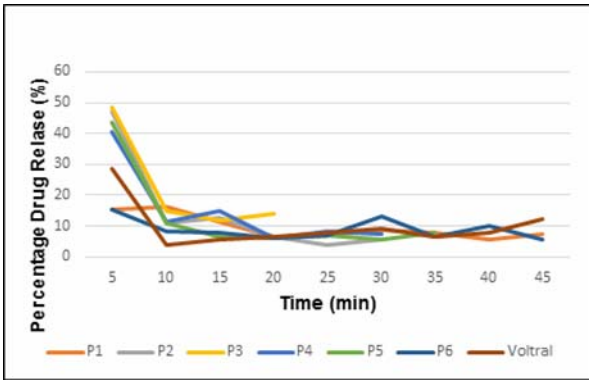

Fig 3:Comparative percentage drug release (CPDR) profile (P1, P2, P3, P4, P5, P6 and Voltral).

Diclofenac sodium is hydrophilic in nature. It is moderately or sparingly soluble in water (British Pharmacopoeia, 2012). Besides the hydrophilic nature of bases, the formulated suppositories exhibited faster release amongst different combinations in present study. The drug release from developed formulations in the present work has revealed a suitability of such preparations for therapeutic purpose, keeping in view the dissolution and disintegration in citro-phosphate buffer media. P3 can be considered as the immediate release formulation of suppository and the 50% PEG 6000 and 50% PEG 4000 can be consumed as a suitable base combination for developing rapid release diclofenac sodium suppositories.

CONCLUSION

On the basis of present work, particularly the results obtained from *in vitro* release rate studies, it can be concluded that PEG 6000 and 4000 can be utilized as a base for rapid release suppositories of Diclofenac sodium. The ratio P3 (50% PEG-4000 + 50% PEG-6000) is found good compared to other ratios of different diclofenac sodium suppositories. Therefore, it is recommended to perform further research respecting kinetic studies of the drug release for the highlighted (P3) combination of bases in future.

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