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FORMULATION AND EVALUATION OF MEFENAMIC ACID SUPPOSITORIES

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Abstract

Mefenamic acid, 2-(2, 3-dimethylphenyl) amino benzoic acid a potent non-steroidal anti-inflammatory agent (NSAIDS), used to treat pain, including menstrual pain. It also decreases inflammation and uterine contractions. Like other NSAIDs, mefenamic acid causes irritation, vomiting, nausea, anorexia, hematemesis (vomiting blood), haematuria (blood in urine) and diarrhea when given orally. Consequently, an alternate route of administration to avoid or minimize the above side effects is preferred in the form of suppositories. Mefenamic acid suppositories were prepared by using oleaginous bases (oil soluble) and aqueous bases (water soluble). All the prepared suppositories were evaluated for various physical parameters like weight variation, drug content, hardness and melting point. The suppositories prepared with water soluble bases were within permissible range of all physical parameters. In-vitro release study was performed by USP type I apparatus using phosphate buffer pH 7.4 as dissolution media. The dissolution data obtained were fitted to zero order, first order, Higuchi, and korsmeyer's plot to understand the order and mechanism of drug release from the suppositories. In vitro drug released from water soluble bases (PEG) were found to be greater than that from oil soluble bases.

Keywords: Suppositories; Mefenamic acid; Cocoa butter; PEG 4000; PEG 6000; Glycero-gelatin

Introduction

A suppository is a drug delivery system that is inserted into the rectum (rectal suppository), vagina (vaginal suppository) or urethra (urethral suppository), where it dissolves or melts and is absorbed into the blood stream. They are used to deliver both systemically and locally acting medications. [1]

Rectal drug delivery has a number of advantages such as reduced hepatic first pass elimination of high clearance drugs, avoidance of gastric irritation associated with certain drugs in case of nausea, vomiting and when the patient is unconscious. Rectal route of administration is specifically useful for infants and children who have difficulty in swallowing oral medicine. Drug administered in suppository form can produce not only local effect but also systemic therapeutic action. Suppositories can be prepared by using lipophilic bases or by hydrophilic bases. These suppositories melt or dissolve in body fluids and release the drug. [2]

Mefenamic acid, 2-(2, 3-dimethylphenyl) aminobenzoic acid a potent non-steroidal anti-inflammatory agent (NSAIDS), [3] used to treat pain, including menstrual pain. Like other NSAIDs, mefenamic acid causes irritation, vomiting, nausea, anorexia, hematemesis, haematuria and diarrhea when given orally.

It is typically prescribed for oral administration. Mefenamic acid is marketed in the USA as Ponstel and is commonly known in UK as Ponstan.

Mefenamic acid decreases inflammation (swelling) and uterine contractions by a still-unknown mechanism. However it is thought to be related to the inhibition of prostaglandin synthesis. There is also evidence that supports the use of mefenamic acid for premenstrual migraine headache prophylaxis, with treatment starting 2 days prior to the onset of flow or 1 day prior to the expected onset of the headache and continuing for the duration of menstruation.

Since hepatic metabolism plays a significant role in mefenamic acid elimination, patients with known liver deficiency may be prescribed lower doses. Kidney deficiency may also cause accumulation of the drug and its metabolites in the excretory system. Therefore patients suffering from renal conditions should not be prescribed mefenamic acid.

Mefenamic acid is a competitive inhibitor of COX-1 and COX-2, which are responsible for the first committed step in prostaglandin biosynthesis. Decreasing the activity of these enzymes thus reduces the production of prostaglandins, which are implicated in inflammation and pain processes. [4]

Materials and Methods

Mefenamic acid was procured from Pfizer Ltd., Mumbai. Other ingredients are Polyethylene glycol 4000, Polyethylene glycol 6000 (Loba cheme, India); Gelatin (Loba cheme, India); Glycerin (Merck Ltd., India); Cocoa butter (National chemicals, India); Disodium hydrogen phosphate (SDFCL, India) and sodium dihydrogen phosphate (Merck Ltd., India). All other chemicals used were of analytical grade.

Preparation of Mefenamic acid suppositories [2]

Suppositories weighing 1-2 gm each , containing 100 mg of mefenamic acid was prepared using water soluble bases namely Polyethylene glycol base 4000 [F2] and 6000 [F3]; Glycero-gelatin base [F4] and oil soluble bases namely cocoa butter [F1] by hot process or fusion method or molding from melt technique using stainless steel moulds. The prepared suppositories were wrapped in aluminum foil, kept in refrigerator and were used in the investigation.

Evaluation

The prepared suppositories were evaluated for official and unofficial parameters via weight variation, content uniformity, hardness, melting point and dissolution test.

Weight variation

All the suppositories (made by the respective bases), were weighed and average weight was calculated. Then all the suppositories were individually weighed and the variation from the average was calculated.

Content uniformity

Mefenamic acid, practically insoluble in water, is soluble in equal mixture of phosphate buffer pH 7.4 and methanol. Three randomly selected suppositories were taken in 1000 ml standard flask containing 100 ml mixture of phosphate buffer pH 7.4 and methanol (50:50).The flask was shaken for desired period of time to dissolve the drug from suppositories. Absorbance of the resulting solutions after appropriate dilutions was measured on Shimadzu 1700, India UV spectrophotometer at 279 nm against the blank prepared using respective suppositories without drug.

Hardness (fracture point)

Hardness of the prepared suppositories was tested using Erweka hardness tester (Lab Hops, India). The weight required for suppository to collapse was taken as measure of hardness of the suppository. Hardness test or fracture point test was carried to determine the tensile strength of the suppositories to access whether they will be able to withstand the hazards of packing and transporting.

Melting point

The ascending melting point method was used to determine the melting point of each type of suppositories. Capillary tubes, 10 cm in length, sealed at one end, were filled with the formulation to about 1cm height, then was dipped in gradually heated electro-thermal thermometer.

Dissolution Test

Dissolution test was carried out in USP rotating basket dissolution apparatus (Scientific, India) using 900ml of phosphate buffer of pH 7.4. Rotation speed was controlled at 50 rpm while temperature was maintained at 37±0.5°c.

Five milliliter aliquots of the dissolution fluid were withdrawn at specified interval from the reservoir and each time replaced with equal volume of fresh dissolution medium. Withdrawn samples were suitably diluted and analyzed using Shimadzu 1700, India at 279 nm. Linear relation was obtained by plotting the absorption against the concentration of mefenamic acid in phosphate buffer pH 7.4 at different time intervals with equation Y=0.05845X+0.001(r=0.99998).

Analysis of dissolution data

The analysis of the mechanism of drug release from pharmaceutical dosage form is an important but complicated problem. The dissolution data obtained was fitted to zero order, first order, Higuchi, and korsmeyer's plot to understand the order and mechanism of drug release from the suppositories.

Zero order release kinetics

It defines a linear relationship between the fraction of drug released versus time.

$$Q = k_o t$$

where, Q is the fraction of drug released at time t and k_o is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

First order release kinetics

Wagner assuming that the exposed surface area of a dosage form decreased exponentially with time during dissolution process, suggested that drug release from most slow release formulation could be described adequately by apparent first order kinetics. The equation used to describe first order kinetics is

$$\ln (1-Q) = -k_1 t$$

where, Q is the fraction of drug released at time, (t) and k_1 is the first order release rate constant. Thus, a plot of the logarithm of the fraction of drug remained against time will be linear if the release obeys first order release kinetics.

Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) on the square root of time.

$$Q = k_2 t½$$

where, k_2 is the release rate constant. A plot of the fraction of drug released against square root of time will be linear, if the release obeys Higuchi equation.

Erosion equation

This equation defines the drug release based on erosion alone.

$$Q = 1-(1-k_3 t)^3$$

where, Q is the fraction of drug released at time t, k_3 is the release rate constant. Thus, a plot between $[1-(1-Q)^{1/3}]$ against time will be linear if the release obeys erosion equation.

Results and discussion

All the suppositories were evaluated for weight variation and found to be in limit (upper limit 5%). The percentage drug content of all the suppositories formulations were found to be between 90.20% $\pm$ 0.60 – 101.15% $\pm$ 1.33.The effect of hardness of suppositories prepared from different bases shown in table 1. It is clear that the hardness values of the tested suppositories range from (2.2 $\pm$ 0.1 to 3 $\pm$ 0.1 kg) with exception of glycerol-gelatin (<2.2 kg).

Melting range are shown in table 1, from these results, the suppository bases can be arranged with respect to melting point according to the following order, cocoa butter(31ºc) < glycerol-gelatin (32ºc) < PEG 6000(35ºc) < PEG 4000(36ºc).

Table 1: Evaluation of drug suppositories for various parameters

S. No.	Suppository bases	Hardness (kg)	Melting range (ºc)
01	Cocoa butter	2.3	30- 35
02	PEG 4000	2.8	35-45
03	PEG 6000	2.6	33-43
04	Glycero-gelatin	<2.2	31-37

In case of cocoa butter, the lowest amount of drug release was observed after 60 min as it has low melting point as compared to other bases. So, the release for cocoa butter was observed upto 3 hours and ⁄release was found to be 82.5%. Thus, in this case, a sustained release formulation was obtained.

The release of mefenamic acid from water soluble bases was found higher than that from oil soluble bases. The incorporation of water in PEG base enhanced the drug release.

To confirm the mechanism of drug release, the data were fitted to different equations. In Korsmeyer's equation, the exponent values (n) of all the formulation except F3 were found to be more than 1. This n value however, indicates super case-II transport mechanism while F3 followed Anomalous transport i.e. Non Fickian diffusion.

Table 2: In-vitro release of drug from different suppository base

S. No.	Time (Min)	Cumulative % release			
		Cocoa butter	PEG 4000	PEG 6000	Glycero-gelatin
01	15	4.25±0.11	12.32±0.38	25.14±0.36	4.87±0.15
02	30	7.61±0.67	42.66±0.42	82.27±0.22	14.56±0.60
03	45	17.24±0.33	85.18±0.81	95.74±0.57	41.69±26
04	60	27.50±0.19	97.61±0.87	96.09±0.73	50.42±0.94

Table 3: Kinetic treatment of dissolution data- Equation of line

Formulation	Zero Order	First Order	Higuchi	Korsmeyer
F1	0.4533x-2.278	-0.0022x+2.0129	3.1999x-3.9141	1.3575x-1.0185
F2	1.7812x-5.972	-0.0258x+2.2382	12.968x-14.273	1.5534x-0.7033
F3	1.7519x+7.292	-0.0271x+2.081	13.905x-6.3502	0.9961x+0.3047
F4	0.9177x-5.224	-0.0055x+2.0386	6.4848x-8.5652	1.7756x-1.4076

Table 4: Kinetic treatment of dissolution data-Correlation Coefficient (r^2) values

Formulation	Zero Order	First Order	Higuchi	Korsmeyer
F1	0.9458	0.9319	0.7683	0.9601
F2	0.9642	0.8734	0.8329	0.9763
F3	0.8751	0.9324	0.8985	0.854
F4	0.9346	0.9163	0.7605	0.9795

Figure 1: Comparative zero order release from different formulations

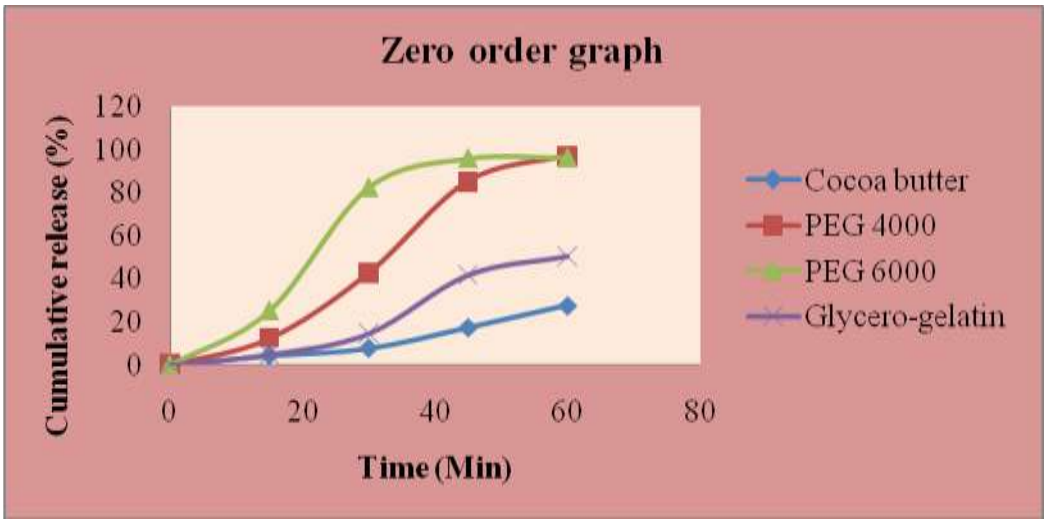


Figure 2: Comparative first order release from different formulations

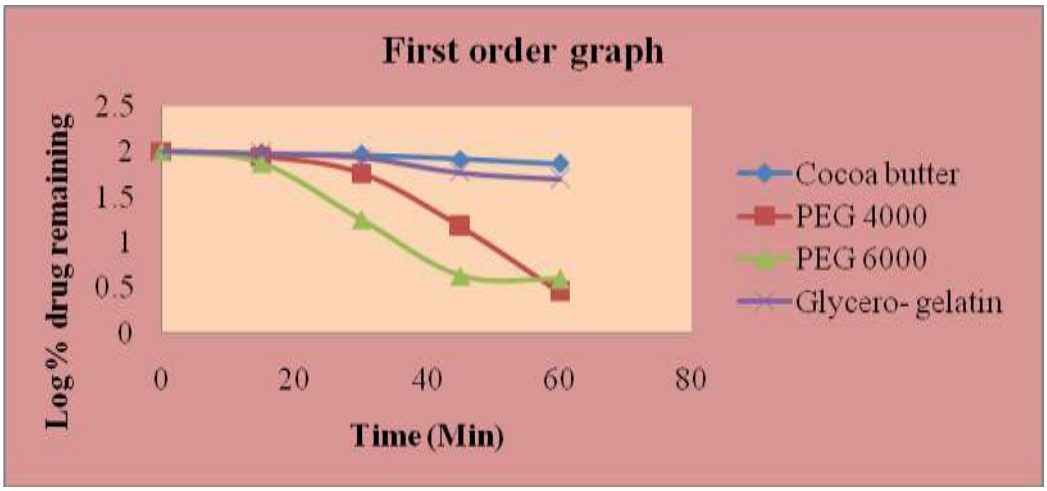


Figure 3: Comparative Higuchi order release from different formulations

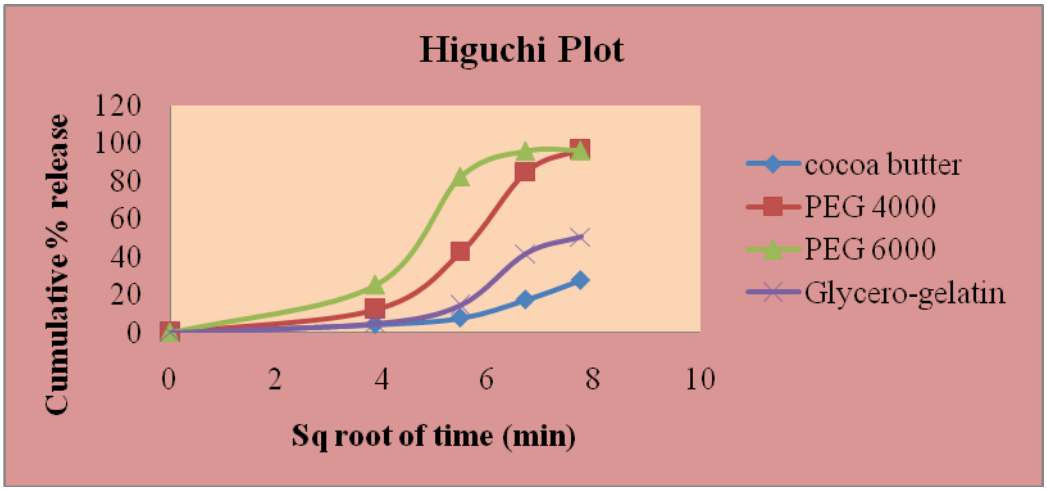
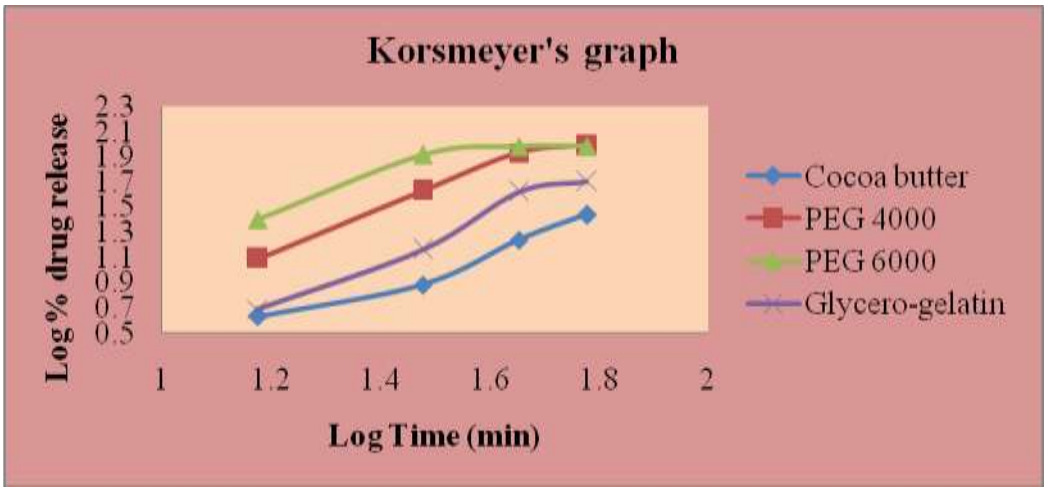


Figure 4: Comparative Korsmeyer's order release from different formulations



Conclusion

It is concluded that suppositories made up from water soluble bases gives faster drug release as compare to oil soluble bases. The use of cocoa butter as suppository base gives more sustained effect as compare to other bases. The results indicate that the suppository could potentially be viewed as a best delivery system.

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Conflict of Interest

None

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