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Design and Evaluation of Sustained Release Suppositories of Nimesulide

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Nimesulide sustained release suppositories were formulated by 2^3 full factorial design using polymers such as agar, polyethylene glycol-6000 and sodium carboxymethylcellulose. The unconventional non-melting, non-disintegrating suppositories were prepared using fusion method and their *in vitro* release kinetics were studied. Physical characteristics such as dimensions, homogeneity, crushing strength and drug content uniformity were evaluated. Among the various formulations, formulation (N_3) with agar (6%), polyethylene glycol–6000 (4%) and sodium carboxymethylcellulose (1.5%) showed maximum drug release (93.69%) by concentration independent manner.

Nimesulide is a second generation non-steroidal anti-inflammatory agent, which is widely used in the long term therapy of rheumatoid arthritis, in alleviating pain and inflammation. Its biological half-life have been reported to be 3 to 4 h[1], necessitates multiple daily dosing for maintaining therapeutic effect throughout the day. Nimesulide suffers from drawbacks of gastro intestinal, dermatological and central effects[2-3]. As those conditions are chronic, nimesulide can be formulated as a rectal sustained release formulation in order to minimize its severe adversities over smooth gastro intestinal muscles.

The present work was aimed at preparing sustained release suppositories of nimesulide using unconventional, however reported to be useful[4], bases like agar, sodium carboxy methyl cellulose (SCMC) and polyethylene glycol-6000 (PEG-6000). In addition, if these bases used in formulation, will have flexibility in storage conditions unlike suppositories formulated with conventional bases that necessitate proper storage conditions. The unconventional non-melting suppositories were prepared using fusion method and were examined for physical characteristics and *in vitro* release kinetics.

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MATERIALS AND METHODS

Nimesulide was a generous gift provided by Micro Labs, Hosur. Polymers used are agar flakes-microbiological grade, sodium carboxymethylcellulose and polyethylene glycol-6000, which were purchased from S. D. Fine Chem., Boisar.

Preparation of sustained release suppositories:

Suppositories were prepared using fusion method (pour molding)[5] after dissolving the polymeric base materials such as agar, PEG-6000 and SCMC in the mixture of 0.9 ml water, 0.3 ml of glycerin and 0.2 ml of 0.01 M sodium hydroxide. Though sodium hydroxide was mainly incorporated to improve the solubility of agar, it also aided in solubilization of nimesulide, thereby giving uniform drug dispersion (verified by homogeneity) and drug content uniformity. Polymeric bases in addition to accurately weighed amount of drug each calculated to prepare six suppositories were dispersed in the aforementioned solvent system and heated by using a water bath at 70-80° for 3 min to yield homogenous solution of drug in molten base. The amount of drug loaded in each suppository was constant (100 mg). The compositions of all batches are shown in Table 1.

TABLE 1: COMPOSITION AND PHYSICO CHEMICAL EVALUATION OF FORMULATIONS

Formulation code	Composition in %			Physical dimensions		Homogenicity	Drug content uniformity in (mg)*	Weight uniformity in (gm)*	Crushing strength in (gm)*
	Agar	PEG-6000	SCMC	Width in cm	Length in cm				
N_1	4	2	1.5	0.90	2.13	+	99.71	0.99	40.00
N_2	6	2	1.5	0.93	2.16	+	99.65	1.02	42.33
N_3	4	4	1.5	1.00	2.23	+	99.49	0.99	43.33
N_4	6	4	1.5	0.96	2.13	+	99.36	0.98	44.00
N_5	4	2	3.0	0.93	2.20	+	99.97	1.02	46.00
N_6	6	2	3.0	1.10	2.13	+	99.11	1.03	51.33
N_7	4	4	3.0	0.96	2.10	+	99.34	1.04	54.00
N_8	6	4	3.0	1.10	2.20	+	99.65	1.08	57.33

N_1-N_8 represent various formulations prepared using agar, PEG-6000 and SCMC. +-good, *-the average of three determinations.

Evaluation of sustained release suppositories:

The width and length of the randomly selected suppositories (two suppositories from each batch) were measured for their physical dimensions (appearance). After that the same number of suppositories were selected and cut longitudinally and the surface was examined with the naked eye (subjective evaluation) for the homogeneity. Twenty suppositories were weighed individually and the average was determined. No suppository should deviate from the average weight by more then 5% except that 2 should not deviate by more than 10%[6]. The crushing strength was determined for measuring fragility or brittleness of suppositories, which assess whether the suppositories will be able to withstand the hazards of packing, transporting and normal handling or not[7]. Uniformity of drug content was confirmed by analyzing the drug content in each batch after dissolving the suppositories in pH 7.4 phosphate buffer containing 20% v/v of PEG-400 and the absorbance was measured at 420 nm by using colorimeter.

***In vitro* release studies[8]:**

In vitro release studies were carried out for 12 h using the USP XXI dissolution apparatus I. The dissolution medium was 250 ml of phosphate buffer (pH 7.4) containing 20% v/v of PEG-400. The suppository was placed in the metal basket, which was rotated at 50 rpm. Samples (0.5 ml) were withdrawn periodically for 12 h after 1h interval and diluted with 0.1 N sodium hydroxide and analyzed colorimetrically at 420 nm[9] for drug content.

Statistics:

The study was designed statistically by 2^3 full factorial design, the validity of the design and usefulness of polynomial equation for predicting release parameters may be tested by using extra design check point. The polynomial equation was constructed using $t_{90\%}$ values it characterizes the entire release profile in terms of amount of drug release. By calculating actual polymer concentration from transformed proportions of each variable, the extra design check point formulation was designed. Statistical calculation was also adopted to estimate the main and interactive influences of polymer concentration.

RESULTS AND DISCUSSION

All formulations were found to have homogeneous drug distribution with excellent drug content uniformity, weight uniformity and sufficient mechanical strength to withstand abrasive forces causing disintegration of drug loaded formulation. Values are shown in Table 1. Formulations were categorised as follows. Group I - all the polymer concentrations at low level, Group II - any one of three polymer concentration at high level, Group III - any two of three polymer concentrations at high level and Group IV - all three polymer concentrations at high level. Comparative analysis of formulations in different groups were made using *in vitro* kinetic parameters such as amount of drug release at first hour as it may characterize burst effect, $t_{90\%}$ value as it may reveal the changes in the drug release pattern at the end of

the dissolution period and drug release rate as it may evidence the rate of the drug release at specific time units.

Although 28% of the loaded drug was released in the group I formulation, only 89.1% of the drug was released at the end of 12 h. Except two formulations (N_2 and N_3) containing high proportion of agar, burst effect was observed in all formulations. This may be due to the addition of sodium hydroxide, which might have solubilized the drug in the matrix. Since the diffusivity of the solubilized molecule is higher than that of unsolubilized one, burst effect was evident in almost all formulations. In addition to the presence of solubilized drug molecules, which results in faster release of drug molecules, release of drug particles embedded in surface of the matrix might also be contributory to burst effect.

When any one of three polymer concentration was raised to higher level (agar 6%, PEG- 6000 4% and SCMC 3%), the changes in the release profile were significant and it mainly dependent on the polymer characteristics. When agar concentration was increased to 6% (N_2) not only the drug release through burst effect was reduced to the extent of 13.9% but also total amount of drug release was brought down to 67.2%. These effects are mainly due to the high molecular weight and intricate polymer structure of agar, which may raise the matrix density and diffusional resistance. Role of matrix resistance in determining incidence and extent of burst effect was further confirmed by formulation N_3 in which PEG-6000 pore forming agent, was kept at high concentration (4%). Free solubility of PEG-6000, might have disrupted the matrix integrity by forming pores and channels and the drug release maybe mediated through pore diffusion rather than matrix diffusion. Moreover, this phenomenon was observed in intact hydrophilic matrix. When concentration of SCMC was raised to high level (3%), it reduced the amount of drug release through burst effect as compared to PEG-6000, nevertheless comparable to agar. In all group II formulations significant impact due to polymer characteristics such as solubility, density and diffusivity was observed in every respect from determining extent of burst release to total amount of drug release at the end of 12 h. Despite the changes in the release rate of group II formulations, they revealed capability to release the drug in concentration dependent manner except when PEG-6000 was at high concentration in which unpredictable rates of matrix erosion might have shifted the mode of drug release.

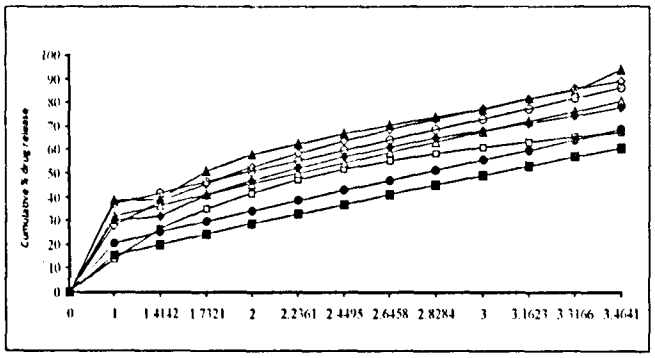

Fig. 1: Higuchi's plot of *In vitro* drug release profile of different batches of sustained release suppositories.

N_1(—◇—) N_2(—□—) N_3(—▲—) N_4(—△—) N_5(—♦—) N_6 (—●—) N_7 (—O—) N_8(—■—) represent various formulations of sustained release suppositories of nimesulide.

In order to study the interactive influence of variables over release profiles, group III formulations having any two of three at higher polymer concentrations were evaluated. Agar (6%) and SCMC (3%) continued to exhibit their negative impact over burst effect and release rate in these formulations was mainly due to above discussed reasons. The order of negative impact, based on total amount of drug release was agar and SCMC>agar and PEG-6000, albeit changes in release rate were unsubstantial. Therefore, interpretation using statistical methods was consulted before conclusive arrival of results. Calculation to find out main as well as interactive (two way and three way) effects revealed the nature and magnitude of impact with lucid numericals with sign and value respectively. In two factor interactions the permanent role of agar and SCMC were evident, maybe because of their higher concentration at different levels. Surprisingly, interactive influence of SCMC and PEG-6000 combination was more than that of agar and PEG-6000 combination. This could be due to competitive solubility of SCMC and PEG-6000 in dissolution media by which each reduces solubility of one another and resulted in maintenance of matrix integrity for long period. Where as, agar and PEG-6000 combination in which quickly dissolving PEG-6000 disrupted matrix integrity of agar that posses no threat to solubility of PEG-6000 because of its own limited solubility. Two way interaction between agar and SCMC and three way interaction between agar, PEG-6000 and SCMC were insignificant and no reasonable interpretation can be made from these values.

Since, the design was optimized statistically using 2^3 factorial designs, it is possible to authenticate the design by selecting extra design checkpoint based on polynomial

TABLE 2: *IN VITRO* RELEASE DATA OF SUSTAINED RELEASE SUPPOSITORIES OF NIMESULIDE

Formulation code	Zero order plot		Higuchi's plot	Drug released at the end of 12 h (mg)	$T_{90\%}$
	Regression	Slope	Regression		
N_1	0.99	5.32	0.99	89.12	11.49
N_2	0.95	4.44	0.99	67.23	15.75
N_3	0.99	4.80	0.98	93.69	11.43
N_4	0.99	4.45	0.99	80.60	14.06
N_5	0.99	4.43	0.98	77.72	14.07
N_6	0.99	4.35	0.98	68.45	16.90
N_7	0.99	4.45	0.98	86.17	12.80
N_8	0.99	4.10	0.99	60.78	19.04

N_1-N_8 represents various formulations of sustained release suppositories of nimesulide.
Theoretical Value of nimesulide 100 mg was loaded for each suppository.

equation, $Y=B_0+B_1(X_1)+B_2(X_2)+B_3(X_3)+B_{12}(X_1X_2)+B_{13}(X_1X_3)+B_{23}(X_2X_3)+B_{123}(X_1X_2X_3)$. Predicted to exhibit $t_{90\%}$ value of 12.1, the extra design checkpoint batch (agar 5.7%, PEG-6000 2.25%, SCMC 1.75%) was observed to have $t_{90\%}$ value of 12.2. The statistical insignificance of the difference between the predicted and observed response not only validates the design but also confirms usefulness of the polynomial equation in predicting the *in vitro* kinetic parameters. The values are shown in Table 2.

In order to elucidate mode and mechanism of drug release, the *in vitro* data was transformed and interpreted at graphical interface constructed using zero order and Higuchi's equation[10] respectively. Almost all formulations released the drug in idealistic sustained release concentration independent mode and mechanism of drug release was chiefly diffusion controlled which were evident from pearson correlation coefficient values.

In conclusion, formulation N_3 (containing 4% agar, 4% PEG-6000, 1.5% SCMC) was found to release the drug in concentration independent manner, to the extent of 93.69%. Hence it may improve the patient compliance.

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