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In vitro release studies on topical gel formulations of nimesulide

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Nimesulide (NM) is a nonsteroidal anti-inflammatory drug (NSAID) which has generally been administered orally and rectally [1]. Recently, Sengupta et al. [2] demonstrated that topical administration of NM may be a safe and effective alternative to oral and rectal routes. Topical administration of NSAIDs offers the advantage of locally enhance drug delivery to affected tissues. Therefore, in the case of regional inflammatory disorders such as muscle pain and osteoarthritis, the topical application of NSAIDs has been preferred [3]. The vehicle composition for topical formulations can influence the release of drug by changing the *stratum corneum* permeability or by increasing the thermodynamic activity of the drug [4]. To achieve optimal percutaneous penetration, it is necessary to determine the release characteristics of the drug in relation to the physicochemical properties of the vehicle [5, 6].

In this study, the influence of some penetration enhancers alone and/or in various combinations was investigated on *in vitro* release of NM from gel preparations based on Carbopol® 934 (Table 1). Physicochemical properties of the gel formulations were also determined. The solubility studies showed that incorporation of penetration enhancers caused a significant increase in drug solubility (F1–8) with the exception for F9–11 (Table 2). The latter could be attributed to the presence of oleic acid reducing solubility of NM (pK_a 6.5) [7]. It is significantly evident that penetration enhancers added to the formulations F1–11 decreased viscosity when compared with the control (FC) (Table 2).

The release characteristics of gels through a standard cellophane membrane (Visking Tubing, 18/32 UK) were evaluated using Franz-type diffusion cells. As shown in Table 2, the selected penetration enhancers influence the release rate of NM to some extent. F1–5 and F8 showed a significant increase in drug release rate when compared with FC. On the other hand, F6 and F7, F9–11 showed insignificant increase in this respect.

F1, F3 and F8 gave higher drug release rate than the others (F2, F4 and F5). The enhancement factors obtained for formulations F1, F3 and F8 are 2.3, 2.3 and 2.2, respectively. Effect of penetration enhancers can be attributed to the increase of NM solubility in the vehicle and/or decrease of the formulation viscosity. Several authors have also described the relationship in this respect for some other drugs as clonazepam and naproxen [8, 9].

F9–11 exhibited the lowest drug release rates. This could be explained by the fact that the weakly-acidic character of NM leads to a decrease of solubility in formulations containing oleic acid (F9–11) (Table 2). Formulations F6 and F7 also gave insignificant increase in drug release rate compared to FC (Table 2). These results could be attributed to an increase in viscosity.

Based on the data obtained in this study, the release rate of NM from gel formulations seems to be related mainly to the solubility of the drug in the vehicle and the formulation viscosity.

Table 1: Composition (w/w%) of nimesulide gel formulations

Formula Code	NM	C934	ETOH	ISOH	TC	PG	T80	OA	DW
FC	1.0	0.5	–	–	–	–	–	–	98.5
F1	1.0	0.5	–	30.0	–	20.0	–	–	48.5
F2	1.0	0.5	30.0	–	–	20.0	–	–	48.5
F3	1.0	0.5	–	–	40.0	–	–	–	58.5
F4	1.0	0.5	–	40.0	–	–	–	–	58.5
F5	1.0	0.5	40.0	–	–	–	–	–	58.5
F6	1.0	0.5	–	–	–	20.0	2.0	–	76.5
F7	1.0	0.5	–	–	–	20.0	3.0	–	75.5
F8	1.0	0.5	–	–	–	20.0	5.0	–	73.5
F9	1.0	0.5	–	–	30	–	–	2.0	66.5
F10	1.0	0.5	–	–	30	–	–	3.0	65.5
F11	1.0	0.5	–	–	30	–	–	5.0	63.5

NM: Nimesulide, C934: Carbopol 934, ETOH: Ethanol, ISOH: Isopropyl alcohol, TC: Transcutol, PG: Propylene glycol, T80: Tween 80, OA: Oleic acid, DW: Distilled water

Experimental

1. Materials

NM was supplied by Pfizer, Turkey. Transcutol® was a gift from Gattefossé, France. Carbopol® 934 was supplied by Goodrich Co., USA. Oleic acid, Tween® 80 and propylene glycol were purchased from Merck, Germany. All other chemicals were of analytical grade.

Table 2: Solubility, viscosity and release rate parameters of nimesulide gels

Parameter	Formula code											
	FC	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Solubility[a]	7.83	282.54	253.93	253.64	409.09	271.17	191.56	252.08	370.05	30.65	26.02	23.85
SD	± 0.58	± 2.67	± 3.73	± 1.96	± 3.35	± 3.04	± 1.51	± 3.18	± 2.46	± 0.60	± 0.72	± 0.87
Viscosity (cP)	17080	4660	5060	5320	4640	5560	9440	8920	7480	6840	6070	5240
Release rate k_o[b]	10.93	25.62	17.64	25.03	20.26	19.33	11.60	12.32	24.50	10.08	15.45	15.32
r^2 [c]	0.993	0.996	0.985	0.989	0.998	0.987	0.871	0.855	0.981	0.985	0.997	0.991
EF[d]	1.00	2.34	1.61	2.29	1.85	1.77	1.06	1.13	2.24	0.92	1.41	1.40

[a] solubility of drug in the gel vehicle (mcg/ml), values are means ± SD, n = 4
[b] release rate of drug ($mcg/cm_2 \cdot h$)
[c] determination coefficient
[d] enhancement factor

2. Preparation of the gels

The composition of NM gel formulations (F1–11) and the control (FC) is given in Table 1. Carbopol® 934 was dispersed in distilled water and left overnight, and then, triethanolamine was added to provide gelation. NM was separately incorporated with penetration enhancer(s) mentioned in Table 1. Subsequently, the latter was added to carbomer dispersion. The control formulation (FC) omitting enhancer was also prepared using the same process. Final pH of all the formulations was adjusted to 6.0 ± 0.1.

3. Solubility studies

The solubility of NM in each vehicle used for formulations was determined by suspending an excess amount of drug in 15 ml of aqueous solution of penetration enhancer(s). These mixtures were shaken continuously in a water-bath (25 ± 0.5 °C) for 24 h. Samples were filtered through a membrane filter and assayed spectrophotometrically at 393 nm for NM content.

4. Viscosity determinations

Viscosity measurements (Brookfield DV-II model viscometer) were performed for each gel formulation using a RV-7 spindle rotated at 100 rpm (25 ± 1.0 °C).

5. In vitro release studies

Cellophane membrane was presoaked in distilled water for 24 h (1 g) spread over cellophane membrane was mounted on Franz-type diffusion cells with a receptor compartment volume of 33.2 ml and an effective diffusion area of 3.14 cm^2. The receptor fluid was selected as phosphate buffer (pH 7.4) containing 25% (v/v) ethanol to maintain sink conditions. During the experiments, the receptor phase was kept at 37 ± 0.5 °C and continuously stirred at 600 rpm. At certain time intervals, 1 ml samples were withdrawn from the receiver compartment and replaced with an equal volume of fresh receptor fluid. The amount of the NM released through the cellophane membrane was analyzed spectrophotometrically at 393 nm. The results were the mean of five experiments. The release rate of NM from formulations was calculated from the slope of the curve where drug released per unit area was plotted versus time. The effectiveness of penetration enhancers (enhancement factor) was determined as the ratio of drug release rate to that of control (FC).

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Study of local anaesthetics, part 161: Influence of additives upon the release of a potential drug of a group of esters of phenylcarbamic acids from a hydroxyethyl cellulose hydrogel

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The paper is concerned with the influence of additives on the release of a derivative of phenylcarbamic acid from a hydrogel. The substance XIX Z [1], a potential local anaesthetic agent which is 129 times more efficient than the standard cocaine used in surface anaesthesia and 66 times more efficient than procaine used in infiltration anaesthesia has been studied.

The influence of the ointment base on the release of XIX Z was studied in a previous work [2], whereby hydroxyethyl cellulose (HEC) hydrogel was selected as the most suitable base. Since hydrogels inevitably contain humectants, emollients and preservatives, we studied the effects of these additives on the release of XIX Z with the objective to select such optimum composition that would ensure the fastest release of the substance.

The influence of humectants (propylene glycol (PG), glycerol (GL), sorbitol (SO)) on the release is shown in Table 1. The release is influenced by the type of humectant and its concentration. From the viewpoint of humectant effects highest rates of release of XIX Z were observed in the presence of sorbitol > glycerol > propylene glycol.

Since largest amounts of XIX Z were released in the presence of 5% SO > 15% GL = 5% PG, these concentra-

Table 1: Influence of the humectants on the release of XIX Z from hydrogels

Humectant	Liberated amount (%) after		k_H (h^{-1})	i_k	η_Q (Pa · s) (D = 220.5 s^{-1})
	0.25 h	3 h			
	17.94	71.09	0.419	0.994	1.230
PG 5%	17.66	72.43	0.414	0.991	1.264
10%	12.80	62.55	0.346	0.980	1.310
15%	12.32	66.77	0.362	0.975	1.369
20%	9.27	57.32	0.301	0.964	1.460
GL 5%	15.32	68.09	0.393	0.990	1.274
10%	13.91	69.15	0.389	0.986	1.320
15%	16.82	72.43	0.416	0.991	1.416
20%	14.24	67.70	0.376	0.985	1.463
SO 5%	21.48	76.56	0.460	0.995	1.110
10%	20.52	73.48	0.439	0.996	1.192
15%	18.37	68.71	0.404	0.996	1.241
20%	17.85	69.34	0.405	0.997	1.358

k_H: liberation rate constant
i_k: correlation index
η_Q: structural viscosity
PG: propylene glycol, GL: glycerol, SO: sorbitol