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VISCOSITY LOWERING OF DIFLUNISAL FATTY SUPPOSITORY BY HYDROGENATED LECITHINS

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Keywords

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ABSTRACTS

Diflunisal (DIF), salicylic acid derivative, is a non-steroidal anti-inflammatory drug (NSAID). Preparation of DIF suppositories which have a good bioavailability was attempted. Suppositories containing DIF (250 mg, oral dose) were made by the fusion method with Pharmasol B-115 (1050 mg). However, the DIF suppository melt revealed high viscosity, and the finding was considered to be not acceptable for manufacture. Accordingly, the in-

vestigation was designed to select an optimum additive which is effective to lower the viscosity of the suppository melt. The viscosity of the suppository melt was determined by utilizing rotating-cylinder viscometer and then Bingham viscosity and yield value were evaluated. As the results, some lecithins and magnesium stearate were found to be effective to lower the viscosity of DIF suppository melts. The rheologically optimum formulation contains Lecinol S-10 (4%) and this formulation was evaluated. In the evaluation, physical properties such as melting point, hardness, softening time, viscosity etc., were measured by common methods. Their properties were satisfactory and were practically stable at 5°C. DIF itself was also stable in suppository melts at 60°C.

INTRODUCTION

Diflunisal, 5-(2,4-difluorophenyl) salicylic acid is a non-steroidal anti-inflammatory drug (NSAID), and available commercially in the dosage form of tablets. Though it has been suggested that it is a relatively safe drug, like all other NSAIDs it produces gastrointestinal side effects. As with other NSAIDs, this limits its value in patients who are prone to gastric irritation, peptic ulcer, etc. Rectal therapy in such clinical situations could be of great value. In addition, suppository form has other advantages, such as easy administration to infant, easy control of drug release profile by selection of adequate additives/bases, etc. Some NSAIDs had been applied to suppositories successfully, and their clinical efficacies were reported (1-2). For salicylic acid derivatives such as DIF, fatty bases are reported to be superior to water soluble bases from a viewpoint of physicochemical interaction (3), tolerability (4), and rectal absorption (5), etc. Hence, the purpose of this study was to formulate DIF suppositories with Pharmasol B-115. Two concerns were, however, revealed from the conventional DIF suppositories prepared by use of Pharmasol B-115; 1)

viscosity of DIF suppository melts was too high, 2) bioavailability in dogs was not enough in comparison to that of oral dosing, this was in conformity with the findings reported by Moolenaar et al. (5). Accordingly, in this study an optimum additive which would be effective to overcome the aforementioned concerns, in particular for high viscosity concern was investigated in common additives involve the absorption enhancers and viscosity lowering agents; those are surfactants (6-8), medium chain length saturated fatty acids (9), their esters (10) their salts (13), phospholipids (6,8), bile acids (6) etc.

EXPERIMENTAL

Materials

Diflunisal (DIF) was supplied from Merck Sharp & Dohme Ltd. Pharmasol B-115 and Panacete 800 were purchased from Nippon Oils and Fats Co., Ltd., Tokyo. The sources of materials used as additives were as follows: Lecinols (grade; S-10, S-10M, S-10Ex, Y-10 and Y-10E), N-acyl-aminoacid (sarcosinate LH), polyglycerin fatty acid ester (sefsol 668), glyceryl-monocaprylate/tricaprylate/monooleate/dioleate, and non-ionic surfactants from Nikko Chemicals Co., Ltd., Tokyo; soybean lecithin from Iwai kagaku Co., Ltd., Tokyo; soybean lecithin SLP-white from True-lecithin Ind. Co., Ltd., Mie; egg lecithin from E. Merck, Dermastad; egg lecithin PL-30, PL-60 and PL-100H from Q.P. Co., Ltd., Tokyo; bile acids, glyceryl-trilaurate/triparmitate/tristearate/trioleate, and other esters from Tokyo Kasei Chemical Ind. Co., Ltd., Tokyo; amino acids from Junsei Chemical Co., Ltd., Tokyo; Stearic acid metal salts from Nakarai Chemicals Ltd., Kyoto; β-cyclodextrin from Sanraku-ocean Co., Ltd., Tokyo. The other materials were of highest grade available.

Preparation of Samples

Appropriate amount of additives and DIF were added to molten base, Pharmasol B-115, with stirring. The mixture was, then, res-

tirred vigorously using the Ultradisperser (Junke & Kunkel KG, WG). The resultant homogeneous mixture allowed to cool to 40°C and subjected for the viscosity tests. The resultant homogeneous mixture was also separately molded into suppository by cooling at 5°C in plastic containers for the physicochemical tests.

Measurement of Viscosity

Viscosity of suppository melt was measured by a B8H type rotary viscometer (Tokyo keiki Co., Ltd., Tokyo) equipped with HH-1 spindle at 40°C. Bingham viscosity and yield value were calculated approximately from the slope and intercept of the shear stress vs. shear rate plots.

Measurement of Hardness

Hardness of cylindrical suppository (8 mm h.) which was provided by cutting middle portion of suppository was measured in its diameter direction using Schleuniger-2E type tablet hardness tester.

Measurement of Melting Point

Melting point of suppository was measured according to the standard method (11).

Measurement of softening Time

The softening time was measured using a similar apparatus reported by Krowczynski(12). Glass tube (10 mm i.d.) in which 20 mm length suppository was inserted in the bottom was vertically set in water bath at 37°C, and falling time of 10 mm of the glass bar (8 mm e.d., 25 g) placed upon the suppository from start was measured.

Physicochemical Stability

Suppository hardness, melting point, softening time and viscosity were evaluated in accordance with the aforementioned test methods in change of time at 5°C. DIF content in change of time at 60°C was also evaluated.

Assay Method of DIF in Suppository

DIF concentration in suppository was determined by high-performance liquid chromatography (HPLC). Firstly, 20 ml of

methanolic solution containing p-chlorobenzoic acid (0.625 %) as an internal standard was added to the suppository sample weighed exactly, then the mixture was heated with stirring at 50°C until homogeneous solution is obtained. After shaking for 5 min. at 50°C, the solution was cooled in an ice bath. The precipitations formed were separated by centrifugation for 10 min. at 3000 rpm. Then, the supernatant was filtered through a 0.45 μm membrane filter. The solution (0.5 ml) was then diluted with methanol to 25 ml. The standard samples were also operated in a similar manner as above. Those diluted solution (10 μl) was applied to HPLC with the following conditions; Solvent delivery system, 1040A type (Hewlett Packard Co., USA), equipped with an UV detector (wavelength; 254nm), a monitor, a autosampler and a microcomputer was used. Separation was carried out at room temp. and flow rate of 1.8 ml/min, using μ-Bondapack ODS (4mm i.d. x 30 cm, Waters, USA) as a column and the mixture of water, methanol, acetonitrile and conc. acetic acid (45/40/17/6) as an eluent.

Homogeneity of DIF in Suppository

Uniformity of DIF concentration among suppositories and homogeneity of DIF concentration between upper and lower segments of suppository were evaluated.

RESULTS AND DISCUSSION

Viscosity Properties of DIF dispersed Pharmasol Base

Viscosity of suppository melt is considered as critical property not only for producibility but also for suppository extension, drug release and eventually for drug efficacy. In the cases of drugs which high dose is required such as DIF, high amount of drug should be dispersed in the base. As a results the suppository melt of such drugs is a concern because of the high viscosity which is usually observed in high concentration suspension (13). Accordingly, viscosity of DIF/base system was investigated. Rheogram generated from base alone showed

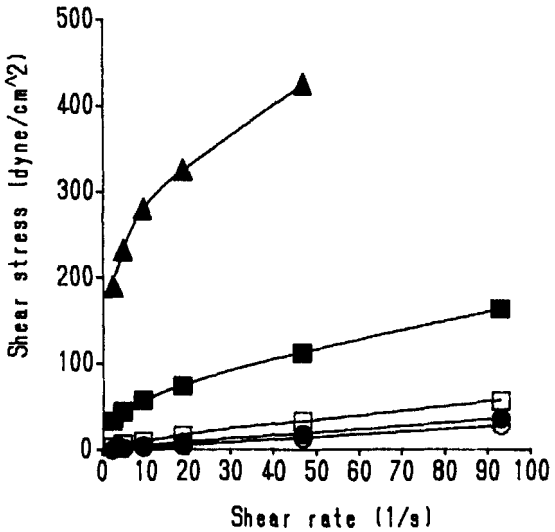

Fig. 1. Rheograms of Pharmasol B-115 (base) Melts containing 0% (○), 5% (●), 10% (□), 20% (■) and 30% (▲) of Diflunisal at 40°C

Newtonian behavior as shown in Fig. 1. After that, up to 10 % of DIF concentration, their rheograms showed resemble profile to that of base alone. When the DIF concentration was increased to 20 %, however, the rheogram showed Bingham behavior having yield value, with further increase of DIF concentration the rheogram appeared non-linearity (non-Bingham flow) having significant increase of Bingham viscosity (Fig. 2) and yield value (Fig. 3). Similar phenomenon was reported by T. Matsumoto et al.(14) on polymer suspension.

Screening of Additives Having Viscosity Lowering Effect

In due consideration of single therapeutic dose of DIF for adult (250 - 500 mg) and optimum suppository weight (1 - 2 g), DIF concentration in suppository base is considered to be around or exceed 20 %. However, a viscosity of the suppository melt in such a drug concentration range was too high as shown in Fig. 1. Accord-

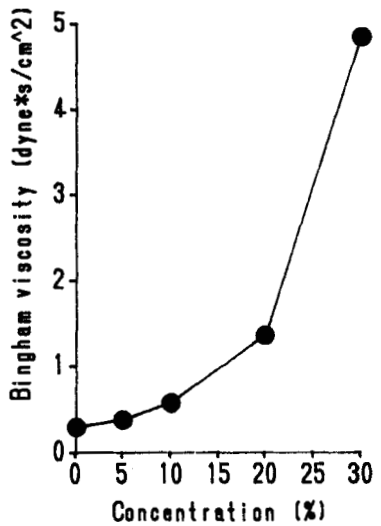

Fig. 2. Effect of Concentration of Diflunisal on Bingham Viscosity of Pharmasol B-115 Melt at 40°C

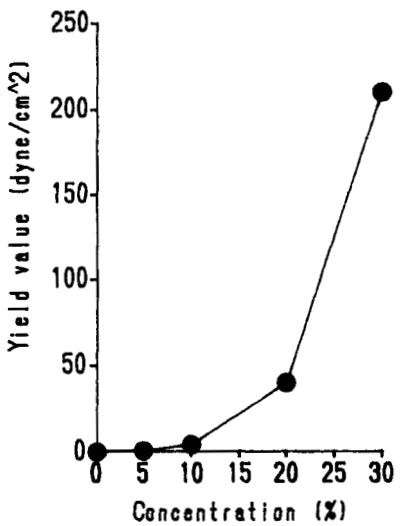

Fig. 3. Effect of Concentration of Diflunisal on Yield Value of Pharmasol B-115 Melt at 40°C

Table I. Effect of Additives on Bingham Viscosity and Yield Value of Diflunisal Suppository Melt at 40°C

Additive	Bingham viscosity (dyn*s/cm^2) concentration (%)			Yield value (dyn/cm^2) concentration (%)		
	0.8	4.0	8.0	0.8	4.0	8.0
None	(1.16)			(47.3)		
Surfactants (HLB)						
MGS-B (3.0)	1.31	1.68	--	51.4	107.1	--
SO-15 (3.7)	1.17	1.37	1.24	95.7	62.0	52.0
SO-15Ex (4.5)	1.04	1.11	1.26	42.2	38.9	46.8
MYS-4 (6.5)	1.15	1.28	1.13	44.0	45.3	48.3
MGS-BSE (8.0)	1.09	1.29	--	75.8	121.3	--
MGS-150 (10.0)	1.35	1.45	--	90.3	70.3	--
MYS-10 (11.0)	1.08	1.13	1.26	58.9	88.6	93.4
BL-4.2 (11.5)	1.23	1.10	1.19	49.2	47.2	47.0
BL-9Ex (14.5)	1.15	1.25	1.25	45.0	48.1	41.9
MYS-25 (15.0)	1.27	1.40	*1.27	93.4	75.8	*38.6
BL-25 (19.5)	1.22	1.38	*1.12	79.9	73.3	*19.8
SLS ---	--	--	3.06	--	--	192.8
Fatty acids						
Capric acid	--	--	0.94	--	--	60.3
Na caprate	--	--	high	--	--	high
Lauric acid	--	--	1.05	--	--	57.1
Na laurate	--	--	high	--	--	high
Myristic acid	--	--	1.12	--	--	60.9
Esters						
Ethyl caprirate	--	--	1.15	--	--	46.4
Ethyl laurate	--	--	1.01	--	--	48.5
Ethyl myristate	--	--	1.02	--	--	46.8
Diethyl sebacate	-	--	1.26	--	--	56.0
Diethyl adipate	--	--	0.78	--	--	48.3
Isopropyl myristate		--	1.07	--	--	47.6

Glycerides						
Panacete 800	--	--	1.07	--	--	45.1
monocaprylate	--	--	1.45	--	--	44.8
tricaprylate	--	--	1.20	--	--	44.9
trilaurate	--	--	1.27	--	--	44.1
tripalmitate	--	--	1.41	--	--	43.6
tristearate	--	--	2.92	--	--	24.8
monooleate	--	--	1.54	--	--	37.9
dioleate	--	--	1.29	--	--	30.5
trioleate	--	--	1.45	--	--	53.5
Lecithins						
soybean	0.95	0.84	0.84	14.2	4.0	2.6
egg	0.92	0.79	0.87	7.9	1.2	0.1
hydrogenated	0.91	1.02	1.34	6.25	1.0	2.5
Bile acids						
cholic acid	--	1.53	--	--	64.2	--
deoxycholic acid	--	1.81	--	--	87.4	--
Amino acids						
l-histidine	--	1.49	--	--	67.8	--
l-methionine	--	1.52	--	--	49.4	--
l-valine	--	1.28	--	--	86.1	--
l-lysine	--	1.40	--	--	39.5	--
l-hydroxyproline	-	1.31	--	--	71.8	--
N-acyl amino acids						
lauroylsulcosine	-	1.29	--	--	39.6	--
N-acetyl-l-cysteine		1.47	--	--	65.8	--
Others						
β-cyclodextrin	--	1.47	--	--	82.6	--
gelatin	--	1.79	--	--	50.5	--
Mg stearate	--	0.94	--	--	10.5	--
Sefsol 668	--	2.31	--	--	29.0	--
Saponin	--	1.49	--	--	59.5	--

*) separation of phase was observed.

Table II. Effect of Lecithins on Bingham Viscosity and Yield Value of Diflunisal Suppository Melt at 40°C

additive* (4 %w/w)	phospholipids content (%)	PC content (%)	Bingham** viscosity (dyn*s/cm^2)	Yield** value (dyn/cm^2)
none	-	-	1.16	47.3
soybean lecithins				
soybean lecithin	60<	NC	0.84	4.0
SLP white	95<	25-30	2.78	0.9
egg lecithins				
egg lecithin	60<	NC	0.79	1.2
PL-30	30<	25<	1.02	4.9
PL-60	60<	55-65	0.94	3.1
PL-100H	95<	70-80	0.92	1.5
hydrogenated lecithins				
Lecinol S-10	95<	25-30	1.02	1.0
Lecinol S-10M	95<	55-65	1.24	8.1
Lecinol S-10Ex	95<	95<	2.02	118.4
Lecinol Y-10	95<	20-25	1.04	13.6
Lecinol Y-10E	95<	80-90	1.48	21.1

PC; phosphatidylcholine, NC; not concentrated

*; all additives did not lower the viscosity of base alone.

**; each value represents the mean of 2-3 determinations.

ingly, an investigation in search of optimum additives which have viscosity lowering effect was conducted.

As the results, some lecithins and magnesium stearate were found to be effective to lower the viscosity of DIF suppository melt, whereas other additives investigated were no effect or rather

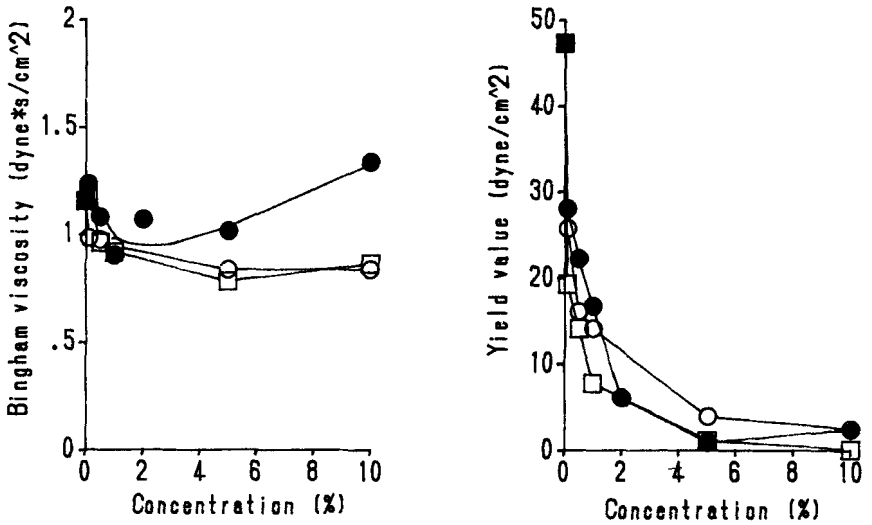

Fig. 4. Effects of Concentration of Lecinol S-10 (●), Soybean Lecithin (○) and Egg Lecithin (□) on Bingham Viscosity (left) and Yield Value (right) of Diflunisal/Base System at 40°C

badly effected and increased the viscosity, as shown in Table I. Further investigation was attempted on lecithins and stearic acid metal salts. In the cases of lecithins, all lecithins tested except for Lecinol S-10Ex significantly lowered the Bingham viscosity and/or yield value.

The degree of the viscosity lowering effect by soybean lecithins and hydrogenated lecithins depended on phosphatidylcholine (PC) content, while that by egg lecithins was independent of the phospholipids content and PC content, as shown in Table II. These findings indicate that the viscosity lowering effect of lecithins may be owing to not only PC itself but also cooperative action with other phospholipid and/or other admixture.

A relation of the additive concentration and viscosity lowering effect was investigated in three effective additives, soybean lecithin, egg lecithin and Lecinol S-10; up to 4 w/w % of additive concentration on the all additives conducted, a little decrease of

Bingham viscosities and significant decrease of yield values were observed as shown in Fig. 4.

With higher concentration of additives except Lecinol S-10, no significant change was observed on both of Bingham viscosity and yield value; Lecinol S-10 showed an increasing trend on Bingham viscosity as shown in Fig. 4.

The yield value of suspension is well observed in the systems forming the network structure of particles in solvent (15). It is also known that the destruction of the network structure or alternation of particle surface characteristics by adding the third component to suspension often results in lowering or disappearance of the yield value (16). Followings were observed in the DIF/base system: 1) The needles of DIF was microscopically observed to form the entangled structure in base melt. 2) Lecithins did not lower the viscosity of base alone. 3) Viscosity lowering effect of lecithin in DIF suppository melt was observed more remarkably on yield value decrease than Bingham viscosity decrease. These results obtained above suggested that the viscosity lowering effect may be due to an inhibitory action of lecithins to network structure formation of DIF crystalline in suppository melts .

Further attempt was expanded to use of magnesium stearate and its related compounds; the viscosity lowering effect was observed only on magnesium salt and other salts and lubricant used did not show the effect or rather badly effected as shown in TableIII. Magnesium stearate heighten the viscosity of base alone same as the other salts, but characteristically lowered the Bingham viscosity and yield value of DIF/base system. The reason is not obvious why only the magnesium stearate was effective in reducing the viscosity of DIF/base system. One thing which may be considered as the reason is the intrinsic property of the additive itself. However, it seems reasonable to say that such effect may appear on the basis of the combination of various factors. As a result, magnesium stearate may affect the formation of the network structure, likewise that of lecithins. However, additive effects to rheology

Table III. Effect of Salts of Stearic Acid and Talc on Bingham Viscosity and Yield Value of DIF Suppository Melt at 40°C

Additive*	Bingham viscosity (dyn*s/cm^2)			Yield value (dyn/cm^2)		
	% incorporated			% incorporated		
	0.8	4.0	8.0	0.8	4.0	8.0
None	(1.16)			(47.3)		
Sodium salt	--	high	--	--	high	--
Magnesium salt	1.05	0.94	1.31	21.0	10.5	13.8
Calcium salt	1.01	2.31	5.87	18.4	72.5	163.3
Aluminum salt, moon	1.62	1.65	2.17	58.8	38.8	36.0
Aluminum salt, di	1.30	1.49	2.07	39.9	36.2	45.0
Aluminum salt, tri	1.26	1.29	1.73	35.9	27.7	30.6
Talc (lubricant)	1.27	1.43	1.99	43.2	44.0	75.9

Each value represents the mean of 3 determinations.

*) All additives heighten the Bingham viscosity of base alone.

in suspension system have not been studied so much, and further detailed investigations to clarify the mechanism of our findings are needed.

In regard to drug absorption from suppositories, indomethacin calcium salt and magnesium salt were reported (17) to be superior to that of free acid. While, it has also been reported (18) that a presence of calcium ion prevented the effect of absorption enhancement of salicylic acid etc. DIF, like salicylic acid, contains hydroxyl and carboxyl group, then, its potential activity of absorption enhancement might be prevented when such ion should be incorporated. While with phospholipids, it has been reported that a phospholipid was effective to promote insulin absorption from rectum with the similar mechanism of adjuvant effect observed on

Table IV. Physical Properties of Diflunisal Suppository and Two Commercially Available Suppositories

Suppositories	m.p. (°C)	hardness (kg)	softening time (sec)	viscosity B.Vis. (dyn*S/cm^2)	viscosity Y.Value (dyn/cm^2)
Diflunisal*	35.5	6.5	412	1.02	1.0
Futraful**	35.8	6.4	426	1.21	4.8
Salazopyrin***	35.9	3.3	452	1.14	5.7

*; Diflunisal suppository containing 4% lecinol S-10
**; Futraful zupo N (Taiho pharm. Ind. Co.,Ltd.)
***; Salazopyrin suppository (Green cross Co.,Ltd.)

salicylic acid. As the results, phospholipids which probably have the both effects of viscosity lowering and absorption enhancement were considered to be the optimum additive for DIF suppositories. Among the various phospholipids, Lecinol S-10 is superior in its physical stability and was selected for the further studies.

Physical Properties of DIF Suppository incorporated Lecinol S-10

Through our studies it became clear that Lecinol S-10 was effective for the viscosity lowering of DIF suppository melt and the optimum concentration was 4 % w/w. In order to investigate its practicality, physical properties of DIF suppository incorporated 4 % w/w Lecinol S-10 were evaluated by comparing with well known suppositories in the market; no significant difference on physical properties required for suppository was observed among the suppositories subjected, as shown in Table IV.

Table V. Weight, Uniformity and Homogeneity of Diflunisal Suppository containing 4% Lecinol S-10

parameter	Diflunisal suppository mean ± S.D.	numbers
weight (mg)*	1299.3 ± 2.1	10
uniformity (mg/1.3g)	125.1 ± 0.2	10
homogeneity		
upper segment	100.3 ± 0.23	5
lower segment	100.2 ± 0.12	5
upper/lower ratio	1.001	

*; dispensed using Crepsi P type suppository dispenser

Table VI. Physicochemical Stability of Diflunisal Suppository containing 4% Lecinol S-10 at 5°C

Item	Time (week)					
	Initial	1	3	6	10	12
Physicochemical						
% remaining of DIF*	100	100.6	---	100.7	---	99.8
hardness (kg)	6.5	5.1	5.5	---	5.0	---
m.p. (°C)	35.5	35.4	35.3	---	35.3	---
softening time (s)	391	414	368	---	422	---
B. visco. (dyn*s/cm^2)	1.18	1.27	1.35	---	1.24	---
Y. value (dyn/cm^2)	4.7	6.6	6.5	---	11.5	---
Appearance						
collapse	N.O.	N.O.	N.O.	---	N.O.	---
cracking	N.O.	N.O.	N.O.	---	N.O.	---

N.O.; not observed. *; at 60°C, open

Homogeneity and uniformity were also conformed to the requirements, as shown in Table V. Further, physical and chemical stability were evaluated at 5°C and 60°C, respectively. No significant change on viscosity, melting point, softening time, hardness and appearance was observed for period for up to 10 weeks as shown in Table VI. DIF itself was also stable in suppository melt for up to 12 weeks. The stability data suggest the practical usefulness of our DIF suppository formulation.

CONCLUSIONS

A conventional DIF suppository which contains usual clinical dose of DIF in Pharmasol B-115 showed high yield value. Suitable additives to lower the viscosity were, accordingly, investigated. Lecithins containing phospholipids as main components, and magnesium stearate commonly used as a lubricant were found to be effective for viscosity lowering of DIF suppository melt. Among them, Lecinol S-10 (hydrogenated lecithin) could be evaluated as the most optimum one for DIF suppository.

Physical properties and physicochemical stability on DIF suppository in which 4% w/w of Lecinol S-10 incorporated were investigated. The results were all enough on homogeneity, uniformity and on stability profiles of viscosity, softening time, melting point, hardness and potency. DIF suppository incorporated Lecinol S-10 was also evaluated successfully for the practical use from a viewpoint of physicochemical properties. Adjuvant effects of phospholipids are well known on some drugs, and further investigation is planned on absorption enhancer effect of Lecinols in DIF suppository.

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