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THE PREPARATION OF PROLONGED ACTION FORMULATIONS IN THE FORM OF SEMI SOLID MATRIX INTO HARD GELATIN CAPSULES OF OXPRENOLOL II. THIXOCAP METHOD

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ABSTRACT

In this study, it was aimed to obtain prolonged release preparations in the form of semi solid matrices (SSM) of Oxprenolol as a model drug into mixtures possessing thixotropic property by filling in the hard gelatin capsules.

The results of this study showed that the formulation, prepared with liquid paraffin and Cutina HR, gave kinetic values close to that of the polymeric matrix preparation of Oxprenolol HCl used for comparison. However, in the thixotropic formulations, prepared with Isopropyl Myristate and Isopropyl Palmitate by adding Arerosil 200, the drug release was slow, therefore the release in expected period of time and level can be ensured by adding different proportions of hydrophilic substances forming channels in the mass without damaging thixotropic structure.

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INTRODUCTION

The gelatin capsule has been an established dosage form for almost 150 years. In current commercial pharmaceutical usage, gelatin capsules fall into two categories;

* The hard gelatin capsules
* The soft gelatin capsules

The hard gelatin capsules consist of two pieces as cap and body, and these hard gelatin capsules are used to contain substances being drug and drug mixtures in the solid form (powder, granules, micro-capsules, pellets etc.). However, soft gelatin capsules include plasticizers such as glycerin, gom arabic, sorbitol, sucrose, polyols and consist of only one piece and they are used to contain drug and drug mixtures in the liquid and semi solid form (oil, emulsion, suspension, ointment, solution, paste, etc.). But, some of essential disadvantages exist at the production of soft gelatin capsules containing flowable and semi solid substances (1-4).

* A specialized group is necessary for formulations and filling processes of drug, according to the specific technological method and know-how.
* They require significantly more gelatin for encapsulation of a given dose of drug than hard gelatin capsules.
* The outer diameters of soft gelatin capsules exhibit more deviations than hard gelatin capsules.

Therefore, the possibility of filling the flowable and semi solid substances into hard gelatin capsules, has also investigated.

The aim of this study is to obtain prolonged action preparations in the form of SSM. The preparations were prepared according to the thixocap method in the hard gelatin capsules using Oxprenolol HCl.

In the thixocap method, the drug is added to thixotropic mixtures and this dispersion, kept flowable state by mixing, is filled into hard gelatin capsules. After that process, the system produces stable and resistant SSM form against leakage by gelation. Particularly, at the preparation of thixocap formulations the

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measuring of viscosity is important because of the following factors (5, 6).

* Convenience of flow property of mass during the filling process into capsules.
* Dosage homogeneity.
* The reproducing ability of the product as a final industrial product related with the process validation.

Due to these factors, the excipient mixtures are prepared by adding thickening agents such as Aerosil, beeswax, stearic acid, cetyl alcohol, polyethylene glycols (PEG) with high molecular weights (> 4000) to liquids such as vegetable oils, mixed esters in liquid form, PEG 400, 600 and the rheological properties of these are examined and then, suitable mixtures are selected (7, 8).

MATERIALS and METHODS

Materials:

In the preparation of formulations according to the thixocap method, the excipients used were arachis oil (Birpa), liquid paraffin (Birpa), isopropyl myristate and isopropyl palmitate(Türk Henkel), beeswax (Merkim), Aerosil hydrophob (Wecker-Chemie GmbH), Aerosil 200 (Degussa), Cutina HR (Henkel KG), PEGs (Merk, Hoechst) and Oxprenolol HCL (Ciba-Geigy) as a model drug was used.

Preparation of Capsules:

The excipients in each formulation shown in the Table 1 were weighed in the glass beaker and heated on the water bath (model: Brookfield Colora). The prepared mixtures were at room temperature for 24 hours and then, measured with normale spindles by using Brookfield LVTD viscometer. During this process, scale values (F/A) of each mixtures were read at the eight different rates of viscometer by keeping ten seconds at each rate and the rheograms were drawn with these values (Figure 1-5).

After the rheograms were examined, the drug was added to mixtures possessing thixotropic property with continuous stirring.

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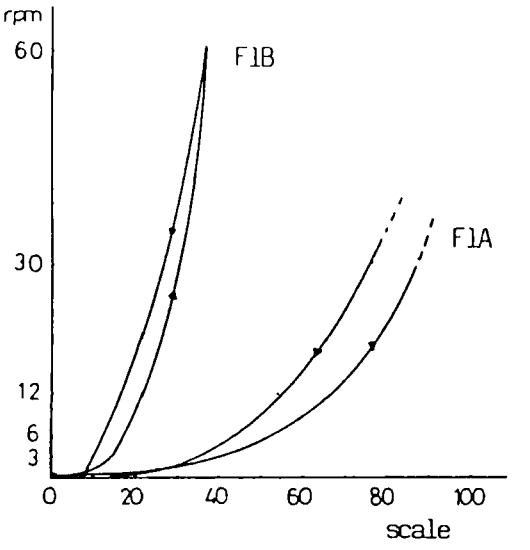

FIGURE 1

The rheograms of F1A and F1B formulations(Spindle number:4).

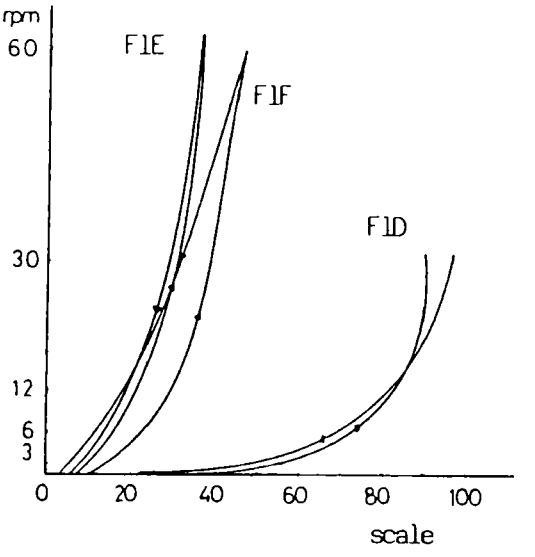

FIGURE 2

The rheograms of F1D, F1E and F1F formulations(Spindle number:4).

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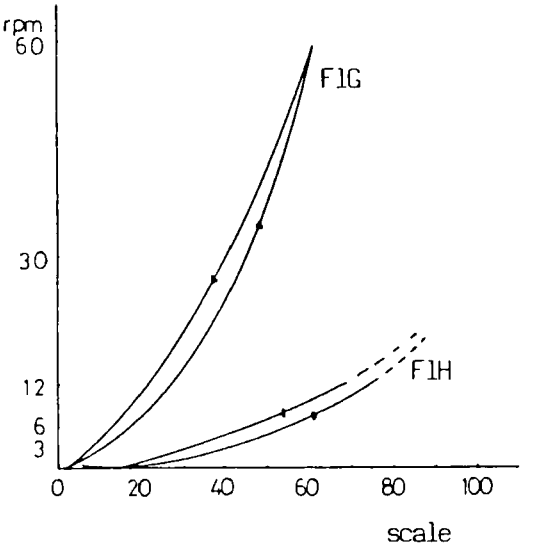

FIGURE 3

The rheograms of F1G and F1H formulations(Spindle number:4).

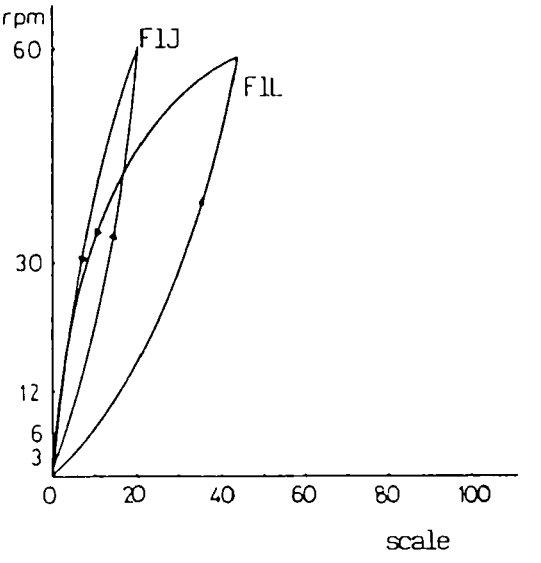

FIGURE 4

The rheograms of F1J and F1L formulations(Spindle number:3).

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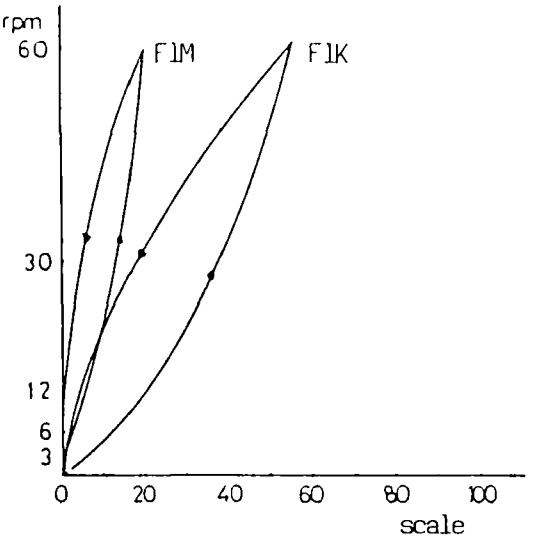

FIGURE 5

The rheograms of F1K(Spindle number:3) and F1M(Spindle number:4) formulations.

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Then, these formulations were volumetrically filled into size 1 hard gelatin capsules (Elanco, Qualicaps, L 36) by using a plastic injector and capsules were closed.

In-vitro Release Studies:

Drug release from the capsules was assessed using flow through cell (Column method, model: Desaga). Simulated gastric fluid, pH 1.2 were used for one hour and then, simulated intestinal fluid, pH 7.5, were used as dissolution mediums. The dissolution tests were continued for seven hours. Samples were analyzed by UV-Spectroscopy (model:Pye-unicam Sp 8-100 Spectrophotometer) at the maximum wavelength of 271 nm for Oxprenolol HCL.

Evaluation of Data Obtained From the Release Studies

The data obtained from the dissolution tests were applied to five different kinetics such as zero order, first order, Hixson-

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TABLE 1

SSM formulations which were prepared according to the thixocap method.

Formule	F1A	F1B	F1D	F1E	F1F	F1G	F1H	F1I	F1J	F1K	F1L	F1M
Material						%						
Oxprenolol HCl	50	50	50	50	50	50	50	50	50	50	50	50
Arachis oil	45	47										
Liquid paraffin			46.5	47	46.5							
PEG 400						47.5	46	46				
Isopropyl myristate									45		45	
Isopropyl palmitate										45		45
Beeswax	5	3										
Aerosil hydrophob			2	1.5			1.5	1.5	5	5		
Cutina HR			1.5	1.5	1.5							
PEG 6000						2.5	2.5					
PEG 10000								2.5				
Aerosil 200					2						5	5

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Crowell's , $Q \rightarrow \sqrt{t}$, RRSBW distribution and effect of different excipients on the release of the active substance was observed. The release kinetics of drug from these SSM preparations were compared with the commercial preparation (formulation code:FPM) in the form of polymeric matrix of this drug. In this study, the formulations which released the total drug in one hour were cancelled.

RESULTS and DISCUSSION

When the rheograms shown in Figure 1-5 were examined, it was seen that all of the mixtures were plastic or pseudoplastic systems possessing thixotropic character. In these systems, viscosity decrease as increasing rate of viscometer, the system becomes flowable (9,10). In contrary case, the thixotropic structure set up again and the system becomes resistant against flowing. Among the thixotropic mixtures, the mixtures which have high viscosity and turn to normal state at the short time (rate of recovery) are valuable in regard to filling into capsules and not being leakaged. When we examined this situation from rheograms we saw that the plastic viscosity of some mixtures was high (F1A, F1D, F1F, F1G, F1H). On the other hand, down curves of excipient mixtures of F1A, F1K, F1L formulations were not close to up-curves. This indicates us that rates of recovery in these mixtures are less than others. Although, thixotropy coefficient of systems was not calculated from rheograms as numerical parameter, the rheograms gave the quantitative knowledge to us (The scale values of excipient mixture of F1I formulation didn't read because of high viscosity and therefore the rheogram of this was not drawn).

In the F1A and F1B formulations, 3 % of drug was only released at the end of one hour due to extremely hydrophobic contents. Therefore, plot of dissolution rate (Figure 6) doesn't include these results.

The agents responsible for flowing property were liquid paraffin, Aerosil and Cutina HR in the F1D, F1E and F1F formulations. But, Aerosil hydrophob used in the F1D, F1E didn't ensure porosity required for release of drug. Therefore, Aerosil 200 which has

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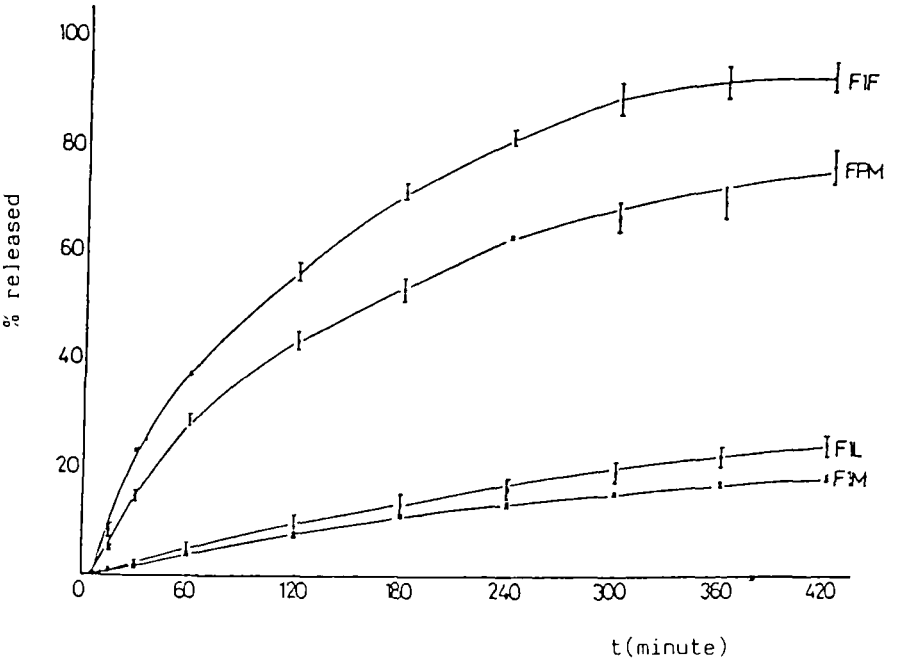

FIGURE 6
Release profiles of drug from thixocap formulations.

numerous hydroxyl groups was used in the F1F. Consequently, this formulation gave identical drug release profile to that of FPM used for comparison (Figure 6).

F1G, F1H, F1I formulations were prepared with PEGs possessing hydrophilic character and high (n) values. In the F1H and F1I, Aerosil hydrophob was used for ensuring the hydrophobicity. But, the drug release finished at one hour in all of three formulations.

Among the formulations prepared with isopropyl myristate and isopropyl palmitate, in the F1J and F1K, Aerosil hydrophob was used. But, Aerosil 200 was used in the F1L and F1M. It is observed that the drug release from F1L and F1M increased when the formulations were compared with each other for effect of hydrophilicity-hydrophobicity (Figure 6). But, the drug release from F1J and F1K didn't occur.

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TABLE 2

Determination coefficients of applied kinetics.

Applied Kinetics	Formules			
	FPM	F1F	F1L	F1M
Zero order	0.9081	0.8864	0.9910	0.9753
First order	0.9848	0.9947	0.9959	0.9830
Hixson Crowell	0.9650	0.9727	0.9944	0.9787
$Q \rightarrow \sqrt{t}$	0.9869	0.9759	0.9768	0.9335
RRSBW	0.9527	0.9221	0.9378	0.9335

The formulations (F1F, F1L, F1M) ensuring prolonged release, were examined for adaptation to different kinetics, too. Because these thixocap formulations are new dosage forms, relatively and it has not studied too much yet on these preparations. According to the kinetic examinations, it was observed that there is adaptation to all of kinetics, but the most r^2 values were obtained in first order kinetic (Table 2).

In conclusion;

* An important factor on the drug release from thixocap formulations is, hydrophobicity of content and the drug release from these systems can be controlled by using hydrophilic excipients ensuring porosity and forming channels in the mass without damaging thixotropic structure.
* Thixocap method applied by using rheological property without heating can be the reason of preference for filling heat sensible drugs into hard gelatin capsules.

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FOOT NOTES

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