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

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ABSTRACT

The aim of this study was to obtain prolonged action by preparing semi-solid matrices (SSM) into hard gelatin capsules using Oxprenolol as a model drug.

SSM formulations were prepared by using different lipophilic and hydrophilic pharmaceutical excipients, polyethylene glycols as channeling agent in the semi solid mass and Gelucires.The release kinetic of drug from these formulations was determined and compared with the commercial preparation in the form of polymeric matrix of this drug.

Among the generally used excipients, we have found that Gelucires were the most appropriate excipients for preparation of SSMs and drug release from these dosage forms can be improved by the method mentioned above depending on quantity and type of channeling agent which was used.

INTRODUCTION

One of the lectures given at the 1978 European Capsule Technology Symposium entitled "The Hard Capsule with the Soft Centre" outlined the technology of SSM prepared by filling flowable and semi solid drugs into hard gelatin capsules. This type of formulation has many advantages over conventional solid dosage forms (1-5).

* The preparation feasibilities of formulations, including liquid, semi solid drug and the pharmaceutical excipients, appear.
* The formulations are simple and the functional excipients such as lubricants, glidants, binders, disintegrants are not necessary.
* The manufacturing method is simplified by mixing and direct filling processes.
* It is the most simple way for producing the controlled drug release.

In addition, SSM technology has an another advantage for the formulator: One of the main problems that face the research and development scientist is the production of small quantities of a dosage form for trials; clinical, stability, assay, etc. For many formulations it is difficult to reproduce on the small scale a product that has the same properties as the final industrial product. The SSM technique is different in this respect because of the use of a volumetric pump to measure the dose. There is little difference between the product filled using a syringe and that filled on a full scale production machine provided that the same heating conditions have been used (2).

The existing difficulties for the production of the preparations in the form of SSM are; the filling process of flowable material into hard gelatin capsules and not being leakage between the cap and body of the capsule of this material by means of solidify immediately after the capsules are closed. For the

production of SSMs three method are used to prevent the problems (6, 7).

* Thermocap method
* Thixocap method
* Composed method

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

In the Thermocap method, the viscosity of system is changed by heating. In another words, the system becoming flowable at the certain temperature is filled into hard gelatin capsules by dosing At the room temperature the system, immediately becomes hard and forms non-flowable state.

MATERIALS and METHODS

Materials:

The two groups excipients were used in the preparation of formulations according to the thermocap method. The excipients used were Miglyol 812, Imwitor 742 (Dynamit Nobel), Precirol ATO-5 (Gattefossé), Cutina HR (Henkel KG), beeswax (Merkim), Glyceryl monostearate (Henkel KG), polyethylene glycol 4000 and 6000 (Hoechst AG) increasing drug release as a channeling agent in the first group. In the second group, nine different types of Gelucires (G) differentiated with melting points (first number) and hydrophilic-lipophilic balance(HLB)(second number)values such as G 42/12, G 44/14, G 46/07, G 48/09, G 50/13, G 53/10, G 54/02, G 62/05, G 64/02 (Gattefossé) were used. The active ingredient used in this study is Oxprenolol Hydrochloride (Ciba-Geigy).

Preparation of Capsules:

The excipients in each formulation shown in the Table 1 and 2 were weighed in the glass beaker and heated to 5 - 10^{o} C above the melting point on the water bath and drug was added to the molten

TABLE 1

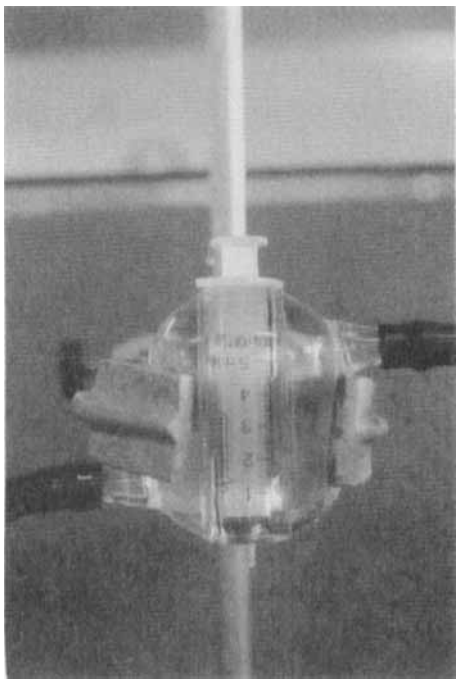
SSM formulations prepared with different lipophilic materials and PEGs (first group).

Formule	F2A	F2B	F2C	F2D	F2E	F2F	F2G	F2H
Material				%				
Oxprenolol HCl	15.4	26.6	26.6	26.6	26.6	26.6	26.6	26.6
Imwitor 742	63.4							
Miglyol 812		58.7	51.3			22.0	14.7	
Precirol ATO-5		14.7	14.7	14.7				
Cutina HR					14.7	14.7		
Beeswax							22.0	
Glycerylmonostearate								14.7
PEG-4000	21.2		7.4	58.7	58.7	36.7	36.7	
PEG-6000								58.7

TABLE 2

SSM formulations prepared with different Gelucires (second group).

Formule	F3A	F3B	F3C	F3D	F3E	F3F	F3G	F3H	F3I	F3J
Material					%					
Oxprenolol HCl	50	50	50	50	50	50	50	50	50	50
Gelucire 42/12	50									
Gelucire 44/14		50								
Gelucire 46/07			50							
Gelucire 48/09				50						
Gelucire 50/13					50					
Gelucire 53/10						50				
Gelucire 54/02							50			
Gelucire 62/05									50	45
Gelucire 64/02								50		
Aerosil 200										5



PHOTOGRAPH 1

The injector and glass water jacket used for volumetrically dosing.

vehicle with continuous stirring. Then, mixture was poured into a plastic injector and volumetrically filled into size 1 hard gelatin capsules (Elanco, Qualicaps, L36). The glass water jacket around this injector prevented the solidification of this mixture during the filling process and capsules were closed (Photograph 1).

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 for one hour and then, simulated intestinal fluid, pH 7.5 were used as dissolution mediums. The dissolution test 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.

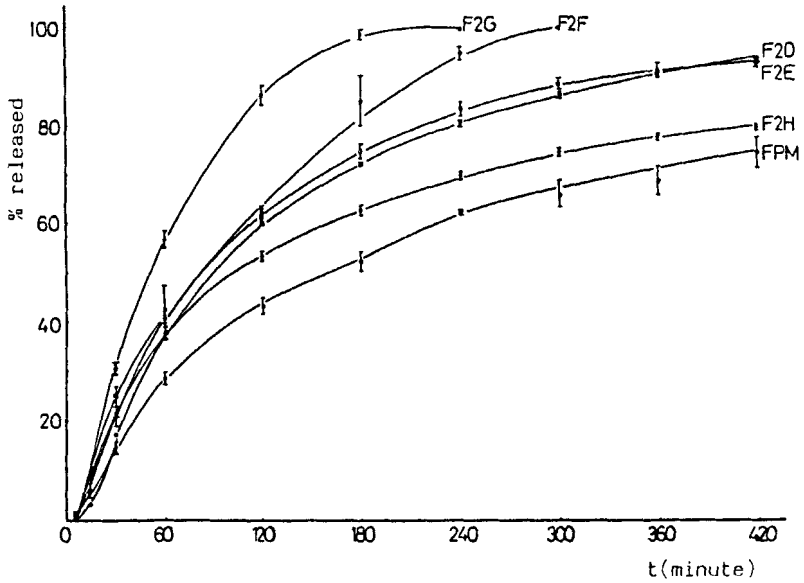


FIGURE 1

Release profiles of drug from first group SSM formulations.

Evaluation of Data Obtained from the Release Studies:

The data obtained from the dissolution tests were applied to six different kinetics such as zero order, first order, Hixson-Crowell, modified Hixson Crowell, $Q \rightarrow \sqrt{t}$, RRSBW distribution and the effect of different excipients on the release of the active substance was observed (8-14). 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

In the F2A formulation which is among the first group thermocap system formulations, all of the drug was released in one hour because of the disintegration of the mass in the capsule. The drug release from F2B and F2c formulations didn't occur due to

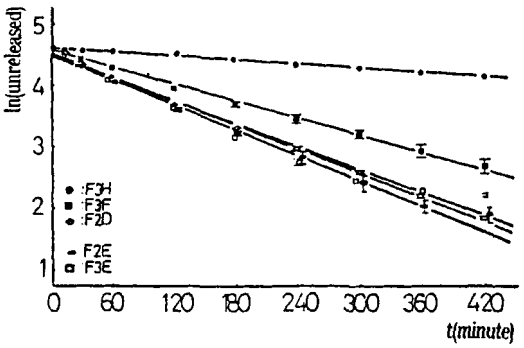


FIGURE 2

Drug release from SSM preparations according to the first order kinetic.

extremely hydrophobic contents. PEG-4000 was added to F2C for formation of porous channels in the mass, but it didn't produce the positive effect on the drug release, either (15).

In the F2D, Precirol ATO-5 (HLB 2) was added to PEG-4000 for ensuring the hydrophobicity, thus 94 % of drug was released in a period of seven hours (Figure 1). In the F2E, Cutina HR instead of precirol ATO-5 was used. As a result, 93 % of drug was released in seven hours F2D (Figure 1).

All of the drug was released in five hours from F2F and released in three hours from F2G. Cutina HR (m.p. 86-88^{o} C), beeswax (m.p. 62-66^{o} C) were used respectively for giving semi solid character to formulations together with PEG-4000, Miglyol 812 (Figure 1).

Among the first group thermocap formulations, F2H gave the best result. 80 % of drug was released at the end of seven hours from this formulation which was prepared with glyceryl monostearate (HLB 3.8) and PEG-6000 producing hydrophilicity (Figure 1).

According to the kinetic examinations, the slow release of drug from capsule contents followed Hixson Crowell's kinetic in the case of disintegrated mass in the dissolution medium. But, in the case of non-disintegrated mass, the slow release of drug followed

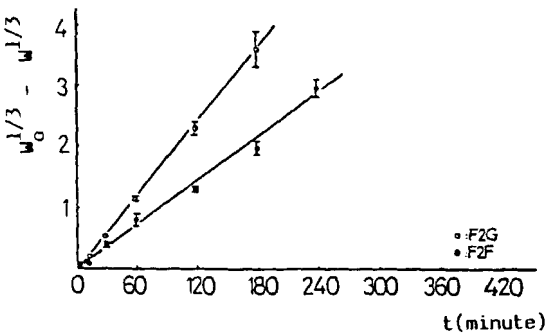


FIGURE 3

Drug release from SSM preparations according to the Hixson Crowell's kinetic.

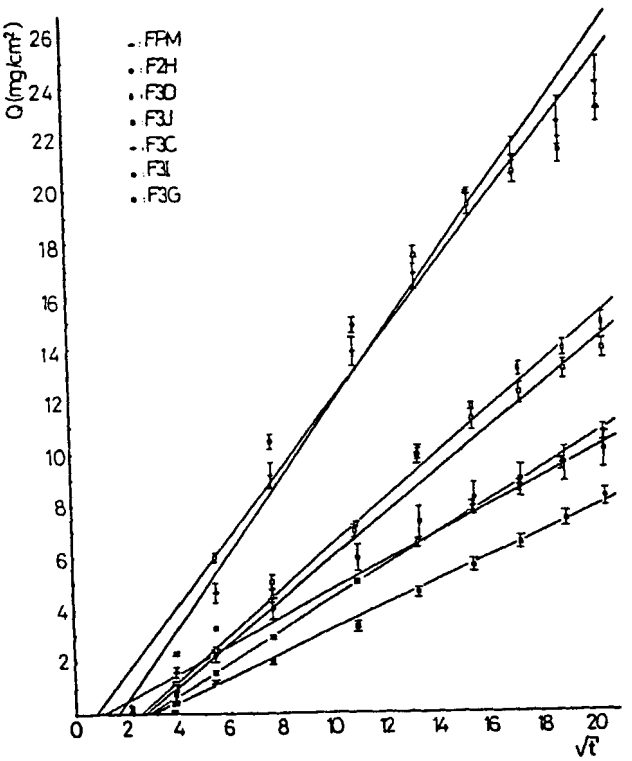


FIGURE 4

Drug release from SSM preparations according to the $Q \rightarrow \sqrt{t}$ kinetic.

TABLE 3

Determination coefficients of applied kinetics.

formule	Applied Kinetics					
	zero order	first order	Hixson Crowell	Modified Langen-bucher	$Q \rightarrow \sqrt{t}$	RRSBW
FPM	0.9081	0.9848	0.9650	0.9416	0.9869	0.9527
F2D	0.8750	0.9963	0.9681	0.8628	0.9665	0.8867
F2E	0.8585	0.9914	0.9579	0.8620	0.9619	0.8882
F2F	0.9541	0.9585	0.9883	0.9359	0.9873	0.9480
F2G	0.9280	0.9422	0.9991	0.9220	0.9637	0.9637
F2H	0.8543	0.9557	0.9246	0.8903	0.9600	0.9083
F3C	0.9581	0.9806	0.9741	0.8817	0.9982	0.8930
F3D	0.9446	0.9771	0.9656	0.9289	0.9956	0.9355
F3E	0.8535	0.9671	0.9300	0.9099	0.9558	0.9310
F3F	0.9198	0.9964	0.9794	0.8546	0.9890	0.8701
F3G	0.9801	0.9913	0.9885	0.9228	0.9952	0.9270
F3H	0.9970	0.9993	0.9993	0.9207	0.9741	0.9012
F3I	0.9042	0.9294	0.9166	0.8538	0.9834	0.9012
F3J	0.9107	0.9525	0.9378	0.8633	0.9883	0.8710

TABLE 4

Oxprenolol HCl/Gelucire formulations, melting points of Gelucires and the percent of cumulative amount of drug released at the end of seven hours.

Formule	Gelucire vehicle	Melting point range deg.C	Released % ± SE*
F3C	46/07	43 - 49	39.49 ± 0.3058
F2D	48/09	45 - 50	52.39 ± 1.160
F3E	50/13	47 - 51	90.57 ± 1.732×10^{-3}
F3F	53/10	51 - 55	85.39 ± 1.767
F3G	54/02	52 - 55	31.89 ± 1.225
F3I	62/05	60 - 65	35.13 ± 1.285
F3H	64/02	62 - 66	37.34 ± 1.060

* SE : Standart error.

first order kinetic, especially, $Q \rightarrow \sqrt{t}$ kinetic (Figure 2, 3, 4 and Table 3).

In nine different types of Gelucires formulations and one combined Gelucire formulation which were shown in Table 2, only two of them (F3A, F3B) were eliminated since the drug was completely released in one hour. This can be explained by the low melting points of G 42/12 and G 44/14, besides erosion, disintegration of G 42/12 and dissolution of G 44/14 in dissolution medium (15, 16).

The melting points of Gelucires used for other formulations and the percent of cumulative amount of drug released from these formulations at the end of seven hours were shown in Table 4 (Figure 5). In the second group thermocap formulations, it was observed that the percent of cumulative amount of drug released was a function of HLB values of Gelucires (3). This relationship between cumulative amount released and HLB value is exponential i.e. first order (figure 6).

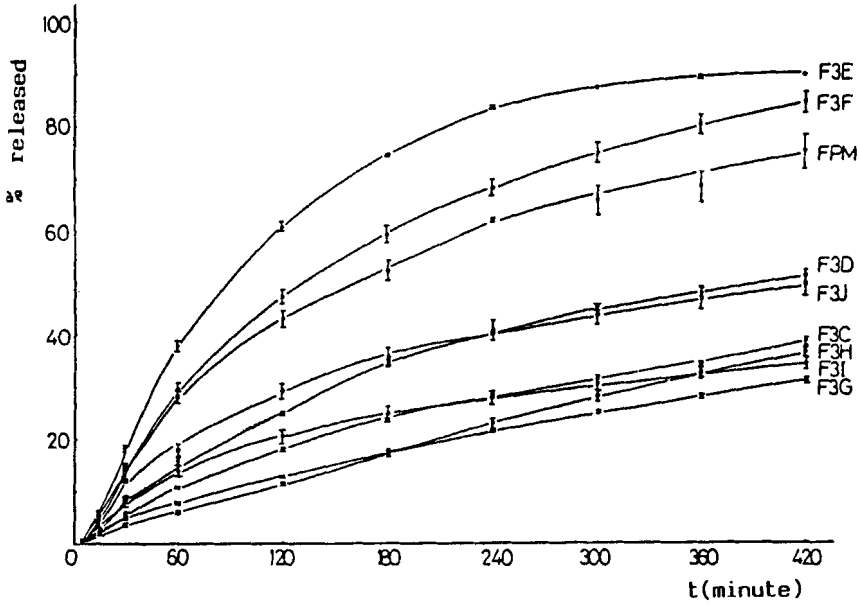


FIGURE 5

Release profiles of drug from second group SSM formulations.

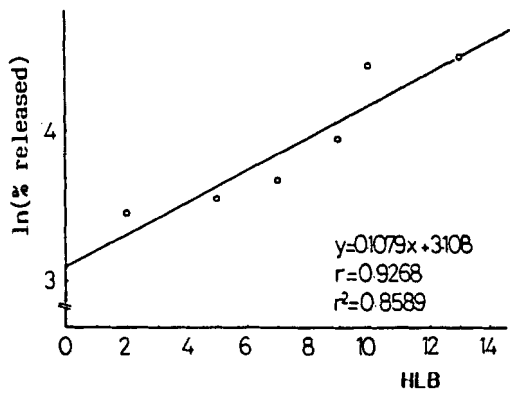


FIGURE 6

The relationship between drug release and Gelucire HLB value.

In the F3J, it was aimed to increase the drug release by adding hydrophilic Aerosil 200 into Gelucires which have low HLB values. In this way, the amount of drug released from F3J was increased about 20 % when it was compared with F3I (Figure 5).

All of the formulations prepared with Gelucires followed first order and $Q \rightarrow \sqrt{t}$ kinetics (Table 3, Figure 2, 4). This emphasizes that the most appropriate excipients for preparations of SSM should be chosen from Gelucires.

In conclusion, the results of this study showed that according to the purpose, for preparation of SSMs which produce slow release of drug, some conditions should be fixed. These are;

* The behavior of mass during the filling process i.e. convenience of flow property of mass.
* no leakage of content between cap and body of capsule,
* no disintegration of mass for slow release of drug,
* no dissolution of pharmaceutical excipients ensuring the slow drug release in the dissolution medium,
* the HLB values of the hydrophobic excipients should not be low, in the case of low HLB, hydrophilic excipients can be added, in this way, porous matrix structure produces,
* being suitable with especially $Q \rightarrow \sqrt{t}$ matrix kinetic of drug release kinetic,
* not being the interaction between drug-excipient-capsule wall (physically and chemically) such in all of the dosage forms.

FOOT NOTES

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