嘉南藥理科技大學教師專題研究計畫成果報告

計畫名稱：固體藥品攜帶系統及應用

計畫編號：CNPH005

執行期間：88 年 9 月 1 日至 89 年 6 月 30 日

計畫類別：個別型

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摘要

In this project, a drug carrier system using kollidon CL to entrap the drug nifedipine was studied. The six months storage study indicates it is stable to heat and low moisture environment. The carrier system can increase the dissolution of the entrapped drug. This carrier system can be used in a powder, or capsule dosage form.

關鍵字：carrier system, entrapment, stability

前言

Recently, many delivery systems have being developed to fit the various need of therapy with less side effects and more target-oriented. Not only drug itself but drug carrier becomes very important. Drug carrier can affect the absorption, disposition, and bioavailability of drug.

In the category of colloidal carrier delivery system, liposomes and nanoparticles are mentioned most. Each has its advantages and pitfalls. Liposomes are biocompatible but with problems like stability and scale-up of manufacturing. Nanoparticles are more stable but less biocompatible.

In this project nifedipine was chosen as model drug as its dose is small and easy to incoporate into carrier. The loading efficiency should not be a problem. Besides, nifedipine has very low solubility and is prepared in soft capsule dosage form and osmotic pressure system. In Taiwan, many manufacturers prepare nifidipine in solid dosage form and suffer the low dissolution problem.

We are considering a carrier system which make the preparation of of nifidipine easy, not like soft capsule or osmotic pressure system. In the beginning, lipid system was considered. However, due to the technical difficulty it was changed to polymer system. In order to increase the dissolution of nifedipine, several polymers with hydrophilic and disintegrating properties were chosen.

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Materials

Nifidipine, crospovidone (Kollidon CL) , sodium starch glycolate (Primojel), sodium croscarmelose (Ac-Di-Sol), dichloromethane are all USP grade.

Method of drug loading

The loading of nifidipine into polymer was by dissolving nifidipine in a suitable solvent

(dichloromethane), and add into the polymer, mix well, and evaporate the organic solvent completely.

Loading efficiency

For one part of nifedipine, ten parts of polymer was used.

Stability study

Drug inside the Kollidon Cl was put in a constant temperature and humidity environment. Since the nifedipine is degraded by light, all experiment was conducted in a dark environment.

Content uniformity study

(1) The nifedipine inside the kollidon CL carrier will be mixed well and then shaken in a demixing pattern, samples will be taken and assayed. (2) The nifedipine and Kollidon CL, lactose, or starch will be mixed well , then shaken in an exactly demixing condition, samples will be taken and assayed. The content uniformity of (1) and (2) will be compared.

Results and discussion

Kollidon CL as a drug carrier

In the past(1) , we already knew that there is interaction between nifedipine and Kollidon CL. However, the nature of interaction has been mysterious to us. After the DSC, X-ray, and SEM studies, it seems to us that the interaction is the entrapment of nifedipine inside the Kollidon CL. For the polymer Ac-Di-Sol and Primojel, DSC shows t nifedipine is not entrapped inside the polymer. Increasing the polymer content to about 20 to 1 does not help to entrap the nifedipine. Probably, the structure of polymer may be responsible and the amount is less important for the entrapment.

Application of this system as drug carrier system

Since Kollidon CL is hydrophilic and with disintegrating property. The application considered was its dissolution-enhancing efficiency. It was found that the dissolution rate of nifedipine entraped inside this carrier was greatly enhanced compared with nifedipine alone. The increase was due to the molecules inside the cross-linking PVP, which inhibit the crystallization and its growth of nifedipine, and in an amorphous state as shown by SEM and DSC.

Stability of the carrier system

Unless the stability of this carrier system is good enough, otherwise there is no practical

use of this drug carrier system. In the past we found that under 75% RH 50 ℃, the dissolutionof nifedipine in the carrier system dropped about 25 % to 40 % after three months storage The decrease of dissolution was due to the transition of amorphous form to crystalline form. Another stability study with less humidity at 30 %RH and 60 ℃ was conducted for six months. It was found that the stability was very good with only minor degradation. We think that the moisture is the factor responsible tfor the transition of amorphous state into crystalline state.

Application in the ordered mixing

The content uniformity of very low dose ingredient has been a great concern in the pharmaceutical manufacturing. It is known that ordered mixing (2) may help to decrease the demixing tendency. When the active ingredient is entrapped inside the Kollidon Cl polymer, it is possible that carrier system may reduce the demixing.

The validation of analytical method was met with greeat difficulty. This part of study remains to be continued..

Reference

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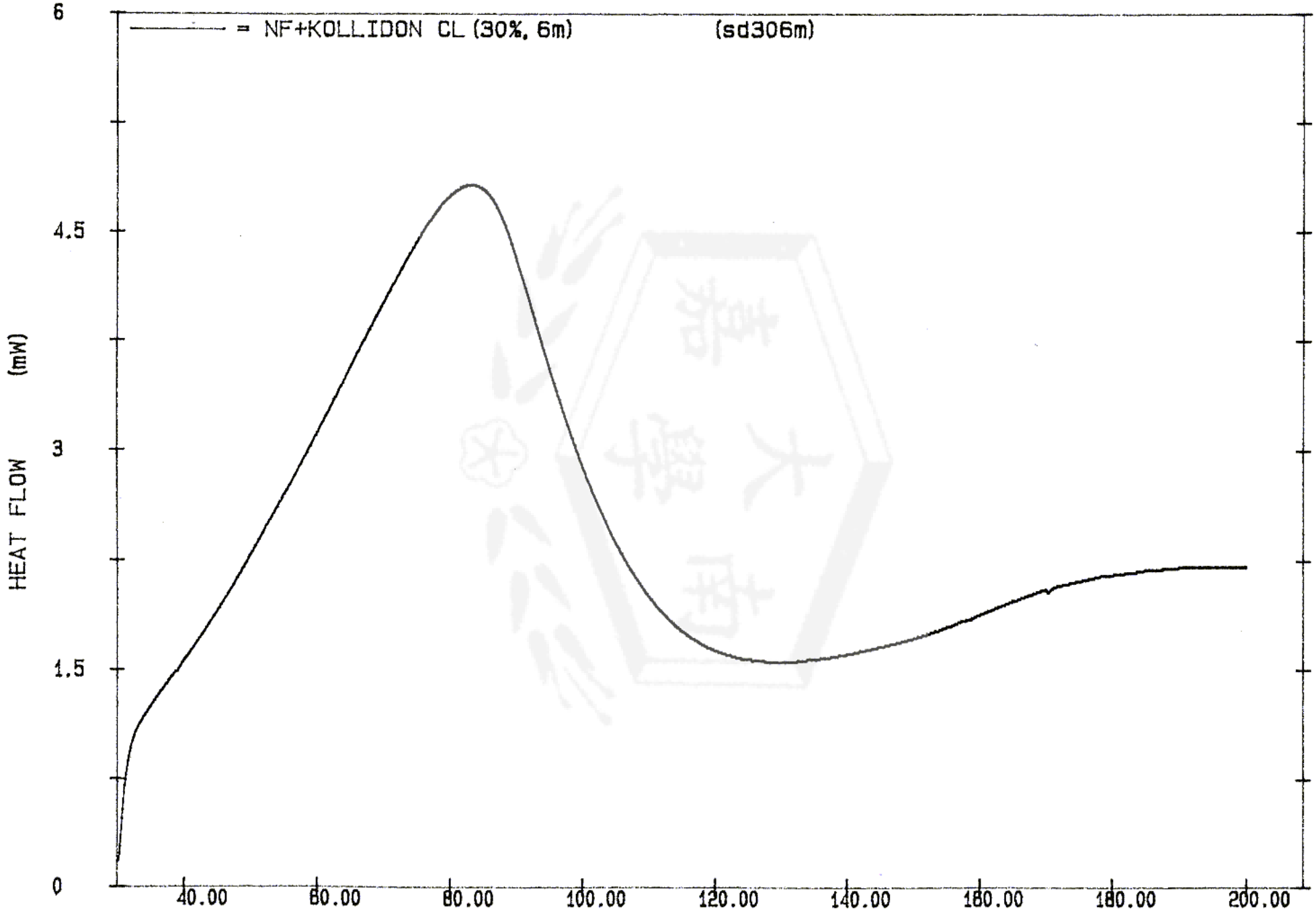
= NF+KOLLIDON CL (30%, 6m)
(sd306m)
HEAT FLOW (mW)
6
4.5
3
1.5
0
40.00
60.00
80.00
100.00
120.00
140.00
160.00
180.00
200.00

儲存條件：	60 C	30 % RH				
儲存時間：	Six month					
Calibration Curve						
No.	ug/ml	Nifedipine	Caffeine	NF/CA		
1	1	32452	97746	0.332		
2	2	66442	98986	0.671		
3	4	135728	98482	1.378		
4	8	269704	98736	2.732		
5	10	335580	95628	3.509		
6	20	672917	98850	6.807		
Constant		9.231916E-03				
X Coefficient		0.341650782				
R sequared		0.999684616				
No.	Nifedipine	Caffeine	NF/CA	Conc.	%	
1-5	281919	98078	2.874	8.386	75.5	
1-10	304188	95497	3.185	9.296	83.7	
1-15	321202	94974	3.382	9.872	88.8	
1-20	323589	96833	3.342	9.754	87.8	
1-30	325914	100948	3.229	9.423	84.8	
1-40	319366	101109	3.159	9.218	83.0	
1-50	285353	102623	2.781	8.112	73.0	
1-60	296685	88193	3.364	9.819	88.4	
2-5	285822	97168	2.942	8.583	77.2	
2-10	313748	98773	3.176	9.270	83.4	
2-15	300278	94936	3.163	9.231	83.1	
2-20	330568	97676	3.384	9.879	88.9	
2-30	331572	101801	3.257	9.506	85.6	
2-40	339121	97749	3.469	10.128	91.1	
2-50	330123	110852	2.978	8.690	78.2	
2-60	305280	177317	1.722	5.012	45.1	
3-5	291723	96724	3.016	8.801	79.2	
3-10	316646	97258	3.256	9.502	85.5	
3-15	329161	96002	3.429	10.009	90.1	
3-20	334114	100203	3.334	9.733	87.6	

3-30	335970	101400	3.313	9.671	87.0	
3-40	342718	101100	3.390	9.895	89.1	
3-50	332394	91980	3.614	10.550	95.0	
3-60	325822	88595	3.678	10.737	96.6	
4-5	288022	97193	2.963	8.647	77.8	
4-10	306709	101808	3.013	8.791	79.1	
4-15	321760	96906	3.320	9.691	87.2	
4-20	325031	104617	3.107	9.067	81.6	
4-30	329310	99075	3.324	9.702	87.3	
4-40	328561	97436	3.372	9.843	88.6	
4-50	315695	95054	3.321	9.694	87.2	
4-60	324724	96767	3.356	9.795	88.2	
	皆有少量分解物產生					