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RESEARCH PAPER

A Research on Aspirin Sustained-Release Formulation

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ABSTRACT

Formulation design is a time-consuming work. Much effort has been made to simplify it by using experimental design or statistical analysis. In this work, polynomial regression and response surface methodology was used to characterize the relationship between tablet dissolution and HPMC content, and/or viscosity. The results revealed that through the combination of HPMC viscosity and content in formulation, an ideal dissolution profile could be produced. Pharmacokinetic research showed that a good linear correlation existed between absorption in vivo and dissolution in vitro. Dissolution could be used in quality controlling of aspirin sustained-release dosage forms.

INTRODUCTION

Research in formulation design has been flourishing since the appearance of pharmaceutical industrialization. But to achieve the best formulation under conditions of competing objectives and interactive effects by way of trial and error is time consuming, unreliable, costly, and often unsuccessful. With the development in mathematics and computer science, complicated data processing could be performed on high speed computers. It is now possible to minimize this time-consuming work through experiment design or statistic analysis technique by computer. Response surface methodology is a typical example of this kind. In this study, response surface methodology was used to characterize the relationship between tablet dissolution and hydroxypropylmethylcellulose (HPMC) content and/or viscosity, as a result, several optimal formulations were established basing on in vitro dissolution, and the correlation between in vitro and in vivo was also evaluated.

MATERIALS

Aspirin (Shandong Xinhua Pharmaceuticals, P. R. China); Hydroxypropylmethylcellulose (Metolose 90SH

4000SR, 15000SR and, 100000SR) (Shinetsu Chemical, Japan), and Cornstarch (Shenyang beer Ltd., P. R. China) were used in this work.

METHODS

Experimental Design

Base on the preliminary experiments, several formulations were designed. The values of HPMC content (x_1) ranging from 5 to 15% per tablet, and values of viscosity (x_2) being 4830, 15300, and 105000cps were used as independent variables. Dependent variables were the percentages of drug released at time 1, 2, 4, 8, or 12 hr. The data obtained were undergone polynomial regression analysis. Contour plots and response surface plots were structured according to these equations.

Tablet Preparation

Mixed powders (60g batches) of aspirin, HPMC, and cornstarch were granulated with 90% ethanol as a moist solution using a lab high shear mixer. After drying to moisture less than 3%, the granulations were mixed with 0.5% magnesium stearate, and compressed at a constant compression force of 100MN/m^2 using a single station tableting machine. Each tablet contained 650mg aspirin.

In Vitro Dissolution Studies

A dissolution test was performed using a dissolution tester. The China Pharmacopoeia paddle method was used at a rotation speed of 100rpm, and 900ml distilled water, maintained at 37°C, was used as dissolution medium. At a certain interval of time, 5ml aliquots were withdrawn and replaced by an equivalent volume of fresh medium, and the dilution was corrected when calculating the amount of drug released into the medium. Drug concentration was measured using a spectrophotometer at 256nm.

In Vivo Bioavailability Research

Tablets were administered to three dogs (two females and one male), weighing 10–15 kg. The dogs were fasted for 12 hr before the administration of tablets. Blood samples were taken at zero time and at fixed time intervals from the back leg vein. The aspirin level was monitored by using a Shimadzu 9A HPLC system. All pharmacokinetic parameters were extracted by using a 3P87 program.

RESULTS AND DISCUSSION

Formulation Design In Vitro

A successful hydrogel matrix formulation should contain polymers and diluents as little as possible, but release drug at constant (zero order or near zero order) rate as far as possible. Based on the preliminary research, 15 formulations of hydrogel matrix tablet were designed and experiment results underwent statistical analysis to give out polynomial equations between independent variables and dependent variables. In Table 1, the compositions of various formulation and dissolution results are listed.

The data analysis gives the following polynomial equations:

$$p_1 = -1.788x_1 - 1.413x_2 + 0.108x_1x_2 + 31.91 \quad (1)$$
$$N = 15 \quad R^2 = 0.6382 \quad F(3,11) = 11.650$$

$$p_2 = -6.370x_1 + 0.182x_1^2 - 0.181x_2^2 + 0.141x_1x_2 + 63.39 \quad (2)$$
$$N = 15 \quad R^2 = 0.8397 \quad F(4,10) = 24.798$$

$$p_3 = -11.974x_1 + 0.352x_1^2 - 0.329x_2^2 + 0.262x_1x_2 + 112.59 \quad (3)$$
$$N = 15 \quad R^2\ 0.9279 \quad F(4,10) = 58.177$$

$$p_4 = -14.184x_1 + 0.379x_1^2 - 0.406x_2^2 + 0.289x_1x_2 + 151.69 \quad (4)$$
$$N = 15 \quad R^2 = 0.9609 \quad F(4,10) = 109.383$$

$$p_5 = -6.052x_1 - 3.358x_2 + 0.167x_1x_2 + 127.53 \quad (5)$$
$$N = 15 \quad R^2 = 0.9391 \quad F(3,11) = 87.368$$

where N is the number of experiments, R^2, the correlation coefficient, F, the value of F-test. All of the individual terms in the above models were very significant according to student t-test (p-values < 0.05). The values of the coefficients of the independent variables (x_1 and x_2) relate to their effects on the dependent variables (p_1 to p_5). The coefficient of the combination term x_1x_2 are measures of contribution of the interaction between the independent variables x_1 and x_2. The positive and negative signs indicate synergistic and antagonistic effects respectively.

The negative signs for coefficients for x_1 and x_2 in all the five equations showed that both HPMC content, and HPMC viscosity, contribute negatively to the amount of drug released. The positive coefficients of interaction terms suggest a synergistic interaction be-

Table 1

The Levels of Independent Variables and the Dissolution Results

Lot #	Independent Variables		Dependent Variables				
	x_1	x_2	P_1 1	P_2 2	P_3 4	P_4 8	P_5 12 h
A	5	0.48	30.05	43.43	69.49	95.76	100.00
B	8	0.48	15.21	23.48	37.84	61.39	71.05
C	10	0.48	12.12	18.90	29.95	50.00	68.11
D	12	0.48	10.25	15.57	20.56	42.00	54.80
E	15	0.48	8.17	11.37	16.04	25.04	33.80
F	5	1.53	20.80	33.83	60.57	91.65	97.38
G	8	1.53	10.43	21.23	37.77	59.48	72.88
H	10	1.53	12.51	18.43	29.29	47.34	58.66
I	12	1.53	10.71	15.71	25.37	43.11	56.21
J	15	1.53	6.02	9.94	16.84	29.13	40.62
K	5	10.50	13.12	20.39	34.35	56.96	73.06
L	8	10.50	14.01	19.05	30.31	47.61	60.19
M	10	10.50	10.66	13.57	20.18	32.57	44.02
N	12	10.50	8.01	11.41	17.01	26.92	36.41
O	15	10.50	7.45	10.32	15.28	24.71	32.28

*Note: X_2 = HPMC viscosity/10^4.

tween the viscosity and content of HPMC. But compared with the coefficients of x_1 and x_2, the coefficient for interaction term is quite small, indicating a less important factor to affect the drug release.

The contour plots illustrate the relationships on two dimensional surface. The same line in the plot represents the same percent release at different x_1 and x_2 combination. They are extremely useful when investigating the effects of independent variables on dependent variables. The response surfaces enable us to visually check the effects of independent variables on dependent variables in three dimensions. The curvature in the response surfaces represents the contributions of x_1^2 and x_2^2.

Figure 1A shows at low HPMC content region the initial drug release (in 1 hr) decreases rapidly as the HPMC viscosity increases, whereas at high HPMC content region, initial drug release is invariable or increases slightly as HPMC viscosity increases.

Figure 1B, 1C, and 1D indicate that drug release at 2, 4, and 8 hr decreases with the increase of HPMC content, but shows a curvature relationship vs. HPMC viscosity. This curve may be due to the insufficient data of x_2 for regression analysis. Figure 1E indicates that as the HPMC content or HPMC viscosity increases, the drug release percentage decreases.

Another important use of contour plot is to estimate the independent variables according to the desired dependent variable values. USP proposes that dissolution windows be established at 25, 50, and 100% of the dosage interval (1). A dissolution window at 1 hr should be included to detect possible "burst effects" of dose dumping. A constrained condition is therefore established according to USP standard as shown in Table 2.

Superimpose contour plots (Fig. 1A–E), and find the region on which dissolution conforms the requirement of dissolution window, as shown in Figure 2. The x_1 and x_2 in the shaded regions are the desired independent variables (i.e., actual viscosity and HPMC content). Formulation B and D is seen in this region.

Analysis of the Plasma Level Profiles

In order to research the correlation between in vitro and in vivo, six of these 15 formulations and a conventional tablet (FR) were subjected to bioavailability study in dogs. Plasma levels and pharmacokinetic parameters are presented in Figure 3 and Table 3, respectively.

All these six formulations showed lower C_{max} and longer MRT than the available tablet, and as the HPMC content or viscosity increased, C_{max} decreased and MRT increased gradually. All these six formulations seemed satisfactory in prolonging effecting time and lowering side effects which may arise from high C_{max}. Though we know that it is effective when aspirin plasma is about

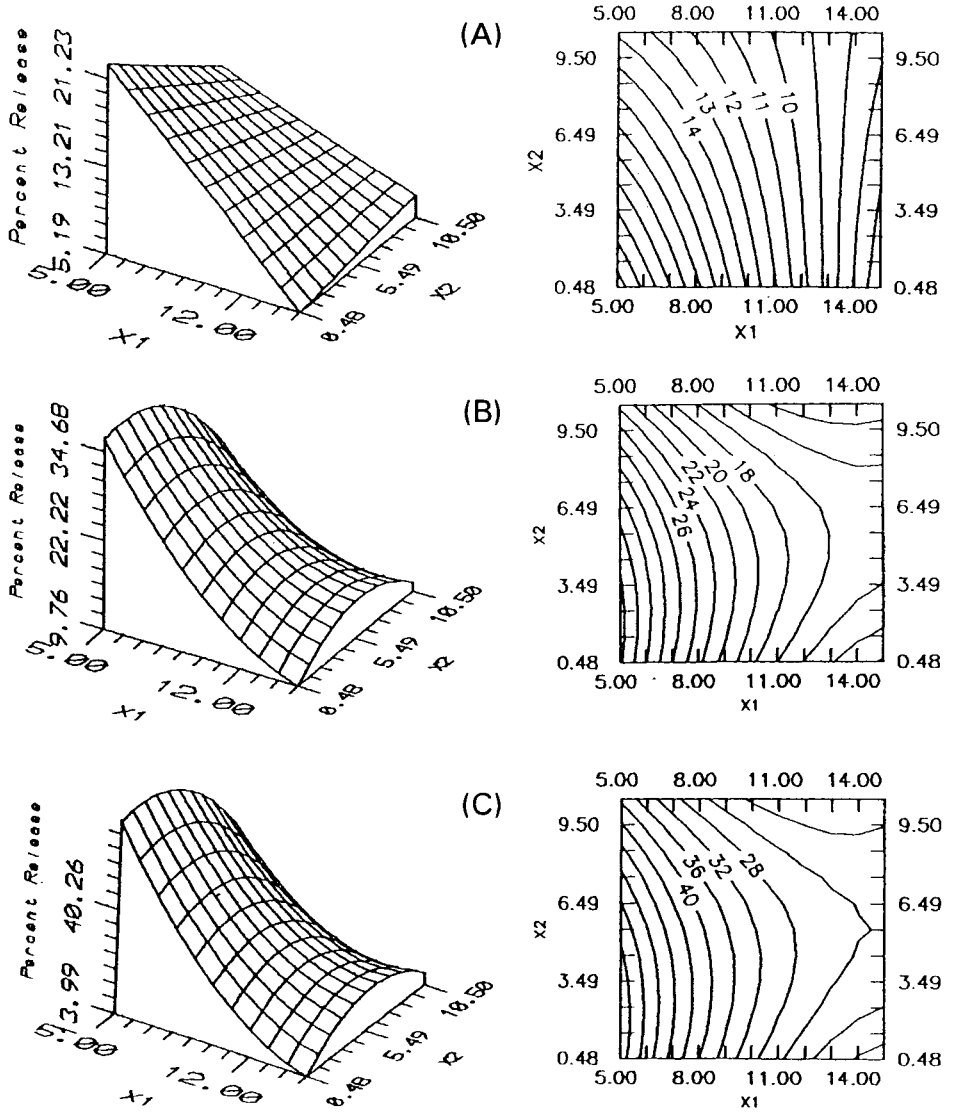

Figure 1. The contour plots and response surfaces of percent release of aspirin from sustained release matrix tablets. A, in 1 hr; B, in 2 hr; C, in 4 hr; D, in 8 hr; E, in 12 hr.

Table 2

The Expected Dissolution Window

Time (hr)	1	2	4	8	12
Dissolution window(%)	5–20	10–30	25–55	50–85	>75

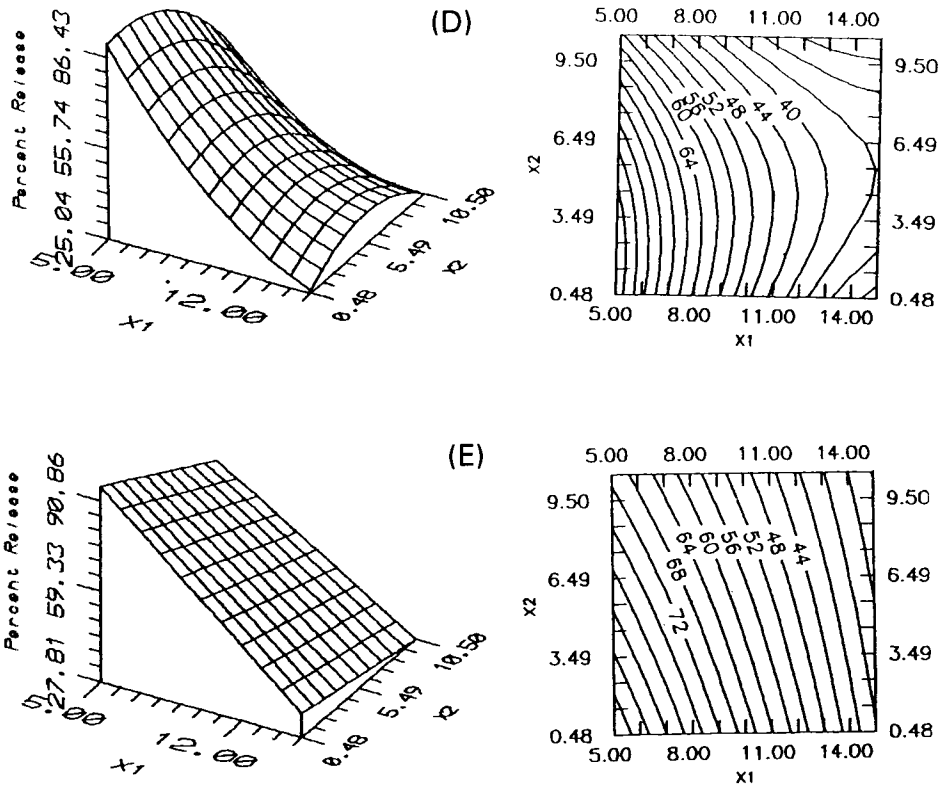

Figure 1. Continued

200–300 μg/ml (2), we can not discern which formulation is the best one because of the lack of reports on effecting plasma concentration in dog. Therefore, it is necessary to conduct further evaluation on human volunteers.

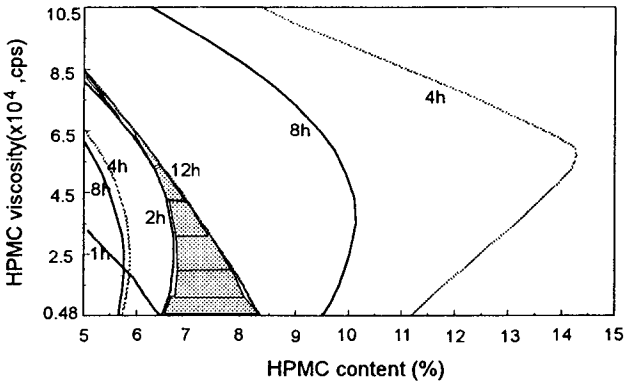

Figure 2. Superimposed plot for the constrained optimal formulations of aspirin matrix tablets.

Evaluation on the Correlation Between In Vitro and In Vivo

It has been recognized with certainty that the knowledge of dissolution behavior, and of the factors affecting its performance is of paramount importance in the design, evaluation, control and therapeutic efficacy of solid dosage forms. But the use of dissolution in these fields must base on the solid foundation of the correlation between in vitro and in vivo.

The dissolution profiles and the absorption profiles based on Wagner-Nelson equation for these six formulations are shown in Figure 4. Excellent correlations were obtained when the amount absorbed at time t in vivo was correlated with the amount dissolved in the respective time period in vitro. The correlation equations are presented in the graphs respectively. Where F is the absorption fraction in vivo and f is the dissolution fraction in vitro. All the correlation coefficients are more than 0.98. The positive intercept on the abscissa is in-

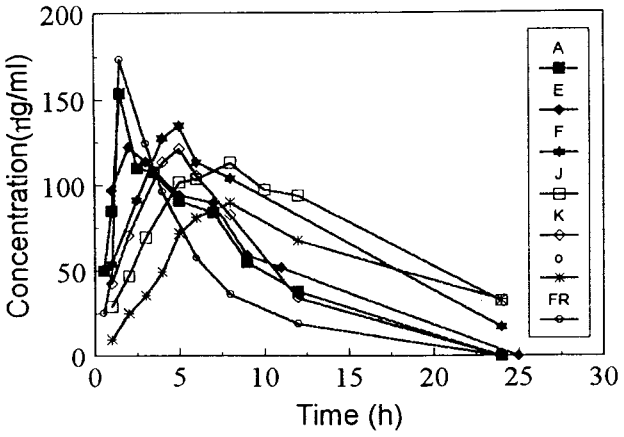

Figure 3. Aspirin plasma concentration after oral administration.

dicative of the lag time before the drug dissolves and appears in the systemic circulation. The slope of the regression equation is a relative value of absorption rate in vivo vs. dissolution rate in vitro. Unit slope is expected as it reflects the synchronization of these two process. The slopes of formulation A and F are smaller than unit, indicating that the absorption rate of aspirin in vivo is slower than the dissolution rate in vitro. The slope of formulation J, K, and O are larger than 1, indicating that the absorption of aspirin in vivo is faster than dissolution in vitro. The biggest slope for formulation E is perhaps caused by the chew of tablets by dog or other experimental error. In conclusion, dissolution test using 900ml distilled water and USP paddle method II at 100rpm can imitate the absorption of aspirin in vivo for formulation A, F, and K because the slopes of the regression equation are near to unit.

Table 3

Pharmacokinetic Parameters (n = 3)

Form No.	HPMC Visco.	HPMC (%)	$T_{1/2}$	T_{max}	C_{max}	AUC	MRT
A	4000	5	2.11	2.78	126.94	965.33	6.41
E	4000	15	2.48	2.94	124.22	1006.42	5.75
F	15000	5	5.33	4.55	120.36	1634.54	10.76
J	15000	15	7.93	7.31	103.50	2159.11	15.33
K	105000	5	2.66	4.19	113.91	1135.65	6.85
P	105000	15	11.20	8.23	77.65	1950.48	19.50
FR	—	—	1.39	2.22	144.23	709.74	5.44

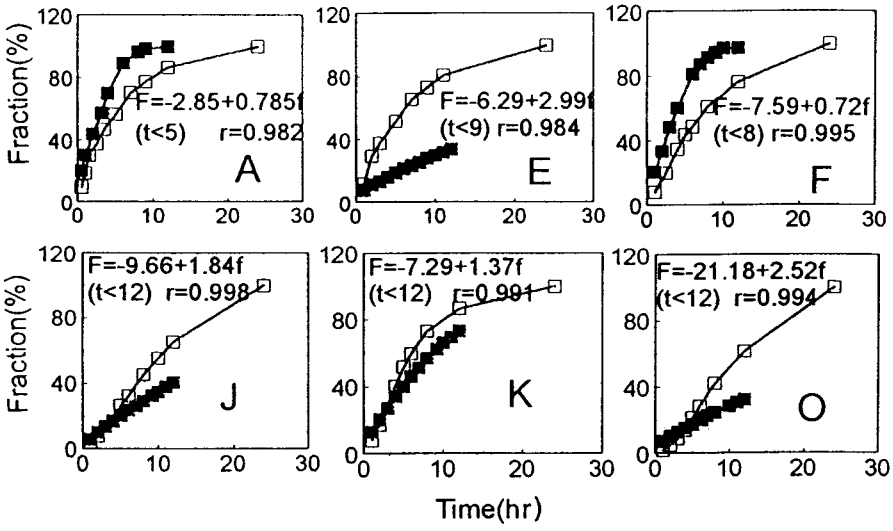

Figure 4. Fractions of aspirin released in vitro and absorbed in vivo. (■) in-vitro; (□) in-vivo.

CONCLUSIONS

Using aspirin as model, sustained release formulations were designed. Response surface methodology was used to find the optimal formulation. The results proved that through the combination of HPMC viscosity and content in formulations, an ideal dissolution profile could be produced.

Pharmacokinetic research showed that a good linear correlation exists between in vivo and in vitro, Dissolution could be used in quality controlling of aspirin sustained-release dosage forms.

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