藥物食品檢驗局調查研究年報9:445－451,1991
Ann. Rept. NLFD Taiwan R.O.C. 9:445－451,1991

Study of Factors Affecting the Dissolution of Piroxicam Capsule

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(Received June 15, 1990)

ABSTRACT

The result of *in-vitro* dissolution test of several experimental piroxicam capsule formulation is presented. It is shown that excipients have certain degree of effect on the dissolution of piroxicam capsule. The dissolution rate can be reduced, when the capsule contains magnesium stearate more than 5%; this may be due to the lamination and subsequent adhesion to the dry agglomerate. The mixing time of magnesium stearate didn't exhibit significantly effect on the test. It was also found that 0.75% and 1.56% of sodium lauryl sulfate can increase the dissolution of piroxicam capsule which contains magnesium stearate. Heigher concentration of sodium lauryl sulfate (3.12%) can decrease the dissolution. However sodium lauryl sulfate is not recommended for the oral formulations and looking for the edible nonionic surfactant would be expected.

Key words : Dissolution, Piroxicam capsule, Excipients.

INTRODUCTION

An investigation of the quality of piroxicam capsule obtained from the market was made[1] in this laboratory in 1988. The results indicated that 36% of products had a low dissolution rate. An analysis of the excipients of these products indicated the presence of lactose, potato starch and magnesium stearate. Samyn and Jung[2] mentioned that magnesium stearate may interact with the gelatin of the capsule shell, thus lowering the disintegration and dissolution of the capsule; Chown and Chi[3,4] found that magnesium stearate may interact with ketorolac trimethamine, crospovidone, prednisolone. Many other reports[5-8] also called the attention to the amount of magnesium stearate in a formulation, and the blending time of the mixture which contains magnesium stearate. Thus the drug-excipient, the excipient-excipient interaction , the blending time, and the amount of magnesium stearate in the formulation may be assumed to

原載於中華藥學雜誌. 第四十二卷. 第六期. p.493－499.

play the important role in affecting the disintegration and dissolution of piroxicam capsule.

The purpose of this study is to find out the factors which affect the dissolution of piroxicam capsules.

EXPERIMENTAL

I. Materials

1. Standards
   (1) Piroxicam, U.S.P. Reference standard
   (2) Prednisone, U.S.P. Reference standard
   (3) Dissolution calibrator using 50 mg prednisone tablets, U.S.P.
2. Reagents
   Methanol, Ethanol, Hydrochloric acid, Sodium chloride.
3. Chemicals
   (1) Piroxicam, C.F.M. Co. Farmaceutical Milanese S.P.A., Milano..
   (2) Lactose, National Cooperaticeve Zuivelverkoop centrale.
   (3) Potato starch, Zetmeelbedrijven de Bijenkorf. B.V.
   (4) Magnesium stearate, E. Merck
   (5) Sodium lauryl sulfate
   (6) Capsule, No. 1, colorless

II. Apparatus

1. UV-Vis spectrophotometer, Hitachi 150-20
2. Dissolution Apparatus, Hanson QC72RB multiple spindle dissolution tester

III. Effect of the Amount of the Magnesium Stearate on the Dissolution

1. Preparation of piroxicam powders containing different amount of magnesium stearate
   Each ingredient was passed through standard sieve No. 80. The necessary amount of each ingredient was weighed according to the formulations shown in Table 1, and mixed in a bottle on a laboratory rotator at 35 rpm for 5 minutes.

Table 1. Piroxicam Powder Formulation Containing Different Amount of Magneisum Stearate

Formulation Number	1	2	3	4	5
Percentage of Magnesium stearate	0.5	1.0	2.0	4.0	5.0
Piroxicam, Gm	10.0	10.0	10.0	10.0	10.0
Potato starch, Gm	50.0	50.0	50.0	50.0	50.0
Magnesium stearate, Gm	1.6	3.2	6.4	12.8	16.0
Lactose, Gm, added to	320.0	320.0	320.0	320.0	320.0

2. Determination of the homogeneous degree of mixed powder

(1) Sampling

Ten samples were taken from different positions and analyzed by the follwoing procedure.

(2) Preparing the sample solution

A portion of sample equivalent to 2 mg of piroxicam was weighed accurately, transferred to a 200 ml brown volumetric flask, and 150 ml of 0.01N methanolic hydrochloric acid was added and shaked for 30 minutes, then made volume with same solvent, mixed and filtered.

The absorbance of the filtrate was measured by the following procedure.

(3) Preparing the standard solution (10 μg/ml)

2.5 mg of the piroxicam reference standard was accurately weighed and transferred to a 250 ml volumetric flask. An amount of 0.01N methanolic hydrochloric acid was added to volume and mixed.

(4) Determination of the concentration of piroxicam in sample solution.

The absorbance of sample solution and standard solution was measured at 242 nm, and the concentration of piroxicam in sample solution and the sample was calculated.

(5) Homogenous degree of sample powder

The Coefficient of Variance of piroxicam content in ten samples was found to be 3.78-6.00%after calculation of the above determinations.

3. Filling the capsules

The capsules were filled with the mixed powder, and wieghed accurately in order to have 320 mg of mixed powder in each capsule.

4. Dissolution test

The dissolution rate was determined by the basket method at 40 rpm using six capsules and following U.S.P. XXI, simulated gastric fluid was used as the dissolution medium.

IV. Effect of Blending Time on the Dissolution

Four powders of Formulation 1 were prepared by following the III. 1 procedure, except that the blending times are 5, 10, 20, and 30 minutes, respectively. Then the capsules were filled to run the dissolution test as before.

V. Effect of Particle Size on the Dissolution

A powder of Formulation 1 was prepared by following the III. 1 procedure, except that each ingredient was passed through a standard No. 40 sieve. The capsules were filled to run the dissolution test as before.

VI. Effect of Surfactant on the Dissolution

Each ingredient was passed through standard No. 80 sieve, then the necessary amount of each ingredient was weighed according to the formulation in Table 2. The ingredients of each formulation in a bottle were rotated on a laboratory rotator at 50 rpm for 5 minutes. The homogeneous degree of mixed powder was determined and the powder was filled in capsules to run

Table 2. Piroxicam Powder Formulation Containing the Different Amount of Sodium Lauryl Sulfate

Formulation Number	6	7	8	9
Percentage of Sodium lauryl sulfate	0	0.78	1.56	3.13
Piroxicam, Gm	10.0	10.0	10.0	10.0
Magnesium stearate, Gm.	1.6	1.6	1.6	1.6
Potato starch, Gm	50.0	47.5	45.0	40.0
Sodium lauryl sulfate, Gm	0	2.5	5.0	10.0
Lactose, Gm, added to	320.0	320.0	320.0	320.0

Table 3. Dissolution Data (%) of Piroxicam Capsule under Various Amount of Magnesium Stearate

Formulation No.	1	2	3	4	5
Concentration of Magnesium stearate	0.5	1.0	2.0	4.0	5.0
Capsule No. 1	92.7	82.7	70.1	56.1	36.1
Capsule No. 2	93.0	81.0	73.3	54.8	33.8
Capsule No. 3	93.3	83.4	68.2	52.8	35.1
Capsule No. 4	98.8	79.1	66.3	58.2	35.6
Capsule No. 5	97.1	94.6	74.5	57.6	37.2
Capsule No. 6	96.3	83.9	71.8	54.1	34.7
Mean ± S. D. (n=6)	95.2±2.5	82.5±2.1	70.7±3.1	55.6±2.1	35.8±1.8

$p<0.005$

the dissolution test as before.

RESULTS AND DISCUSSION

The dissolution data of piroxicam capsule containing different amounts of magnesium stearate were shown in Table 3. Analysis of variance on the effect of magnesium stearate indicated a significant effect on the dissolution ($p<0.001$). Tukey's test indicated that the dissolution rate decreased as the percentage of magensium stearate increased, and a linear relation was found between the dissolution rate and the percentage of magnesium stearate. The regression equation is $Y=97.4-11.8X$, where Y is the percentage of amount dissolved, X is the corresponding percentage of magnesium stearate; the regression coefficient being 0.984.

The dissolution data of piroxicam capsule made from different blending time were shown in Table 4. Analysis of variance indicated lack of significance and five minutes blending was enough to obtain a homogenous mixture.

Table 4. Dissolution Data (%) of Piroxicam Capsule Formulation 1 (Made from the different blending time)

Blending Time	5 min	10 min	20 min	30 min
Capsule No. 1	79.9	73.4	79.0	77.8
Capsule No. 2	75.3	73.1	74.7	78.0
Capsule No. 3	92.1	78.5	73.0	73.5
Capsule No. 4	75.6	80.1	85.1	81.4
Capsule No. 5	77.7	84.2	80.2	81.4
Capsule No. 6	77.0	82.5	81.6	82.8
Mean ± S. D. (n=6)	79.6±6.3	78.6±4.6	78.9±4.5	79.2±3.4

Table 5. Dissolution Data (%) of Piroxicam Capsule Formulation 1 (Made from different particle size)

Partile Size	40 mesh (420 μ)	80 mesh (177 μ)
Capsule No. 1	78.0	90.2
Capsule No. 2	70.2	87.7
Capsule No. 3	75.2	87.2
Capsule No. 4	77.9	88.9
Capsule No. 5	76.9	84.1
Capsule No. 6	71.6	92.3
Mean±S. D.	75.1±3.5	88.4±2.8

$p<0.005$

The dissolution data of piroxicam capsule made from different particle size of piroxicam were shown in Table 5, indicating that finer particles gave a faster dissolution as expected. Analysis of variance indicated that the effect of particle size was significant, the different particle size showing different rate of dissolution significantly ($p<0.001$).

From the above data, one may know that if the blending time is 5 minutes, and the particle size is 80 mesh, magnesium stearate may decrease the dissolution rate of piroxicam. Besides the factor that magnesium stearate may interact with the gelatin of the capsule, one of the other possible reasons is that magnesium stearate is hydrophobic in nature, it probably forms a physical insoluble film on the surface of piroxicam particle, thus decreasing the effective surface area of piroxicam particles on exposure to the dissolution medium and in turn decreases the dissolution rate. If this is correct, adding of a certain amount of surfactant should overcome this problem. Based on this assumption, sodium lauryl sulfate was selected to add into the Formulation 7, 8, and 9, while Formulation 6 containing no surfactant was served as a control. The dissolution data of these formulations were shown in Table 6. Analysis of variance indicated that the effect is significant ($p<0.01$). Tukey's test also showed that a different amount of

Table 6. Dissolution Date (%) of Piroxicam Capsule Containing the Different Amount of Sodium Laury Sulfate

Formulation Number	6	7	8	9
Percentage of Sodium lauryl sulfate	0	0.78	1.56	3.12
Capsule No. 1	73.6	111.5	93.3	13.7
Capsule No. 2	74.3	119.5	101.0	15.6
Capsule No. 3	75.3	118.7	102.6	16.8
Capsule No. 4	80.0	108.0	96.7	14.9
Capsule No. 5	71.9	112.3	100.9	15.1
Capsule No. 6	70.9	103.1	100.2	14.4
Mean±S. D.	74.3±3.2	112.2±6.3	100.3±21.	15.1±1.1

* $p<0.005$

sodium lauryl sulfate resulted in significant different dissolution ($p<0.01$). To compare the results, one can find that 0.78% and 1.56% of sodium lauryl sulfate contained in the formulation may significantly increase the dissolution, and 3.12% of sodium lauryl sulfate may decrease the dissolution. It is also observed that the solution of piroxicam capsule containing 3.12% sodium lauryl sulfate produced a milk-like turbidity. According to Read and Fredell[9], if the pH of the solution is below under 2.5, sodium lauryl sulfate may be hydrolyzed and forms the lauryl alcohol and sodium sulfate. Thus, in the simulated gastric fluid where the pH is 1.2, the milk-like turbidity is probably the result of hydrolysis of sodium lauryl sulfate. The dissolution of the piroxicam capsule containing 0.78% sodium lauryl sulfate was higher than 100%, this is hard to explain. Thus, further studies on the interaction between sodium lauryl sulfate and piroxicam, and on other surfactants are needed.

CONCLUSION

Magnesium stearate may significantly retard the dissolution of piroxicam capsule in simulated gastric fluid. A linear relationship was found between the dissolution and the amount of magnesium stearate contained in the capusle, the slope of this line being negative.

0.78% and 1.56% of sodium lauryl sulfate can increase the dissolution of piroxicam capsule which contains magnesium stearate. One of the possible resons is that sodium lauryl sulfate may break the physical hydrophobic film of magnesium stearate on the piroxicam particle. Higher concentration of sodium lauryl sulfate (3.12%) can decrease the dissolution probably due to the hydrolysis of sodium lauryl sulfate below pH 2.5. The dissolution of piroxicam capsule which contains 0.78% of sodium lauryl sulfate is over 100%. Thus, the detail mechanism still needs more study. Since sodium lauryl sulfate can inhibit the activity of pepsin, it is not recommended for the oral formulations and looking for the edible nonionic surfactants would be expected.

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中 文 摘 要

賦形劑對膠囊溶離度之影響

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本報告係以數種自行調配之 piroxicam 膠囊處方作體外溶離度試驗，以探討硬脂酸鎂之添加量及其混合時間，及添加不同量之硫酸月桂酯鈉對膠囊溶離度之影響。

經實驗結果顯示，添加硬脂酸鎂對 piroxicam 膠囊有顯著之影響，硬脂酸鎂添加量達 5%以上時，藥物粉末會形成黏滯性糰塊，導致溶離度降低；界面活性劑硫酸月桂酯鈉能減少以上糰塊之形成，因而消除硬脂酸鎂對 piroxicam 膠囊溶離度所造成之不利影響，並增加 piroxicam 之溶離度；但若添加達 3.12%時，則因形成難溶之複合物，反致溶離度降低。又當 piroxicam 粉粒變細時，表面積增加，溶解度也跟著增加，在本實驗中亦經證實。因此，賦形劑對膠囊溶離度確有很大之影響，審慎評估和適切選擇將有助於溶離度之提升，以增加療效。