

*Original Article*

## **Application of Taguchi Method to Investigate the Effects of Process Factors on the Production of Industrial Piroxicam Polymorphs and Optimization of Dissolution Rate of Powder**

Alen Shahbazian<sup>a,b</sup>, Asghar Davood<sup>a\*</sup> and Alireza Dabirsiaghi<sup>b</sup>

<sup>a</sup>*Department of Medicinal Chemistry, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran.* <sup>b</sup>*Department of Pharmaceutical Sciences, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran.*

### **Abstract**

Piroxicam has two different crystalline forms (known as needle and cubic forms), that they are different in physicochemical properties such as biological solubility. In the current research, using Taguchi experimental design approach the influences of five operating variables on formation of the piroxicam polymorph shapes in recrystallization were studied. The variables include type of solvent, cooling methods, type of mixture paddle, pH, and agitator speed. Statistical analysis of results revealed the significance order of factors affecting the product quality and quantity. At first using the Taguchi experimental method, the influence of process factors on the yield, particle size and dissolution rate of piroxicam powder was statistically investigated. The optimum conditions to achieve the best dissolution rate of piroxicam were determined experimentally. The results were analyzed using Qualitek4 software and it was revealed that the type of solvent and method of cooling respectively are the most important factors that affect the dissolution rate. It was also experimentally achieved that some factors such as type of agitator paddle, pH and agitation rate have no significant effects on dissolution rate.

**Keywords:** Piroxicam; Polymorph; Particle size; Recrystallization; Dissolution test.

### **Introduction**

Piroxicam is a non-selective prostaglandin G/H synthase (better known as cyclooxygenase or COX) inhibitor that acts on both prostaglandin G/H synthase 1 and 2 (COX-1 and -2). COX catalyzes the conversion of arachidonic acid to a number of prostaglandins involved in fever, pain, swelling, inflammation, and platelet aggregation. Piroxicam antagonizes COX by binding to the upper portion of the active site and preventing its substrate, arachidonic acid, from

entering the active site. The analgesic, antipyretic and anti-inflammatory effects of piroxicam occur as a result of decreased prostaglandin synthesis. Piroxicam also inhibits the migration of leukocytes into sites of inflammation and prevents the production of thromboxane A<sub>2</sub>, an aggregating agent, by platelets (1, 2, 5, 6 and 7).

Industrial powder of piroxicam is an amorphous white powder but piroxicam also has two different needle and cubic polymorphs crystalline shapes (1, 5 and 6). They are different in physicochemical properties such as biological solubility. Different solvents, different technological procedures (melting, rapid and slow cooling) and some other operating

\* Corresponding author:

E-mail: adavood@iaups.ac.ir

**Table 1.** Selected factors and their levels.

Description	unit	1	2	3
Type of agitator paddle(A)	-	turbine	propeller	butterfly
Type of cooling(B)	-	fast	slow	Cold water droplet
Type of solvent(C)	-	ethanol	Water/ethanol	pp.glycole/ethanol
Agitation Speed(D)	rpm	100	200	300
pH(E)	-	6	7	8

parameters such as pH, agitation speed and agitator paddle shape affect the particles shapes and formation of polymorphous piroxicam (1-3 and 17).

In the current study using Taguchi experimental design approach, the influences of some main physicochemical properties, possibilities of their formation and their avoidance were examined and then the dissolution rate of piroxicam powder was optimized.

## Experimental

### Experimental design

The conventional one-at-a-time approach to evaluate the influences of process parameters on

product quality or quantity requires numerous experimental runs (particularly when a lot of variables are to be investigated at different levels) to fully explore the entire parameter space. In this respect, the Taguchi experimental design method can reduce the number of experiments while retaining data collection quality. The quantified and comparative analysis of the factor effects is the second advantage of this approach (9, 10).

The first important step in design of experiment is the proper selection of factors and their levels. In this study, five operating factors include the type of solvent, type of cooling (rapid and slow cooling), type and shape of mixture paddle, pH, and agitator speed were considered

**Table 2.** Taguchi orthogonal array for experiments based on coded levels

Run no.	Operating variables				
	A	B	C	D	E
1	1	1	1	1	1
2	1	2	2	2	2
3	1	3	3	3	3
4	2	1	1	2	2
5	2	2	2	3	3
6	2	3	3	1	1
7	3	1	2	1	3
8	3	2	3	2	1
9	3	3	1	3	2
10	1	1	3	3	2
11	1	2	1	1	3
12	1	3	2	2	1
13	2	1	2	3	1
14	2	2	3	1	2
15	2	3	1	2	3
16	3	1	3	2	3
17	3	2	1	3	1
18	3	3	2	1	2

**Table 3.** The measured responses for each run.

Run no.	Measured parameters				
	Yield%	Particle size	Particle shapes	Melting point(°C)	Dissolution percent in first 30 minutes%
1	69	157	needle	201.0	109.6
2	92	96.6	cubic	204.5	31.0
3	89	145	needle	188.5	87.3
4	81	128	needle	201.5	100
5	96	117	cubic	205.0	27.5
6	85	130	cubic	203.6	38.1
7	86	96.6	needle/cubic	205.1	59.0
8	92	86.6	needle/cubic	205.3	88.3
9	86	80.1	needle	202.1	34.6
10	97	74.1	cubic	204.9	34.5
11	98	84	needle	202.9	45.9
12	87	152	cubic	205.5	19.3
13	86	175	cubic	204.7	31.6
14	89	66.4	cubic	204.5	29.8
15	87	68.5	needle/cubic	205.2	58.5
16	86	132	cubic	197.7	78.2
17	87	42.9	needle	203.7	37.2
18	84	74.1	cubic	203.9	27.1
Industrial sample		110	amorphous	203.0	43.9

in three levels (Table 1).

The factors and their levels have been chosen according to a literature review on previous publications as well as industrial recipes for production and optimization of piroxicam powder (1, 4-8). For design of experiments with five factors and three levels for each factor, a standard  $L_{18}$  orthogonal array was employed (Table 2).

Each row of the matrix represents one run at specified condition. In order to avoid the systematic bias, the sequence in which these runs were carried out was randomized. The statistical analysis of the results was carried out

using Qualitek-4 (Nutek Inc.) software (9, 10).

#### Materials

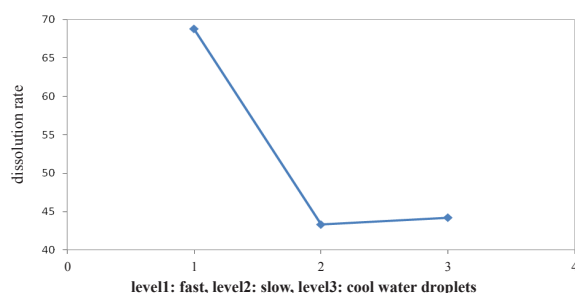
Piroxicam was kindly supplied by shahid Razakani pharmaceutical Company (Iran). The HPLC chromatography analysis showed a purity of 99.99% for this powder. Merck grades of 96% ethanol, propylene glycol and sodium hydroxide (all with purity over 99.99%), were used as solvent and pH regulator, respectively. Deionized water (with conductivity below  $0.5 \mu S/cm$  at  $25^\circ C$ ) was used throughout the work.

#### Recrystallization

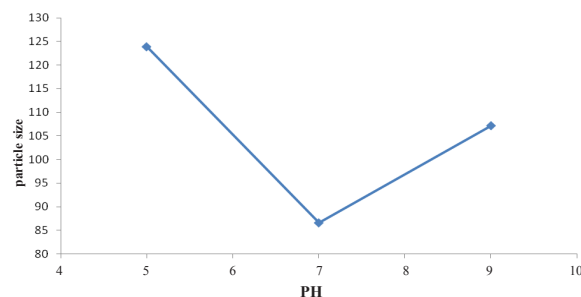
A 1.5 L stainless steel reactor was used

**Table 4.** Analysis of variance (ANOVA) for particle size.

Factor	DOF	Sums of squares	Variance	F-ratio	importance
Type of agitator paddle(A)	2	3829.5	1914.8	1.841	3
Type of cooling(B)	2	6090.9	3045.4	2.93	1
Type of solvent(C)	2	1895.4	947.7	0.911	4
Agitation Speed(D)	2	257.99	128.99	0.124	5
pH(E)	2	4204.0	2102.0	2.021	2



**Figure 1.** Influence of type of cooling on particle size.



**Figure 2.** Influence of pH on particle size.

for batch recrystallization of piroxicam. The mixture paddle is one of the important factors that selected three different types include (parallel, turbinal and plus shape), which connected to a digital agitation controller. The recrystallization reactor wall was equipped with two rectangular baffles. The mixing and recrystallization temperature was measured by a sensitive thermometer ( $\pm 0.1^\circ$  placed inside the reactor, and was controlled by a Ben marry set. At first step of recrystallization, the reactor was first charged with 0.5 liter of solvent according to the experimental design table (Table 2).

The system was warmed up to about  $60^\circ\text{C}$  and the initially amorphous powder (according to maximum solubility of piroxicam in current solvent and temperature for making saturated solution) was added and then pH regulator (NaOH, 0.01N) was added and pH was controlled with a digital pH meter set. After 10 minutes, the homogenous solution will be ready for recrystallization of piroxicam. The ben marry was exchanged with an ice bath or other cooling systems. When crystals were formed the precipitated crystals were separated and dried in  $35^\circ\text{C}$  drying oven (1, 2, 11-14).

### Characterizations

#### Yield determination

In this study the reaction yield was measured as one of the responses. Samples were taken at the end of recrystallization, dried for 24 h. in vacuum oven at  $35^\circ\text{C}$  and weighted. The following equation (Eq. 1) was used to calculate the reaction yield (g recrystallized piroxicam / g initially piroxicam):

$$\text{Yield} = \frac{m_2}{m_1} \times 100 \quad \text{equation (1)}$$

Where  $m_1$  and  $m_2$  are the amount (grams) of final dried recrystallized piroxicam and initial samples, respectively (1, 9).

#### Particle size and shape measurement

A  $1\text{ mg.mL}^{-1}$  suspension of piroxicam powder in distilled water at  $25^\circ\text{C}$  of each run sample was prepared and then put in ultrasonic bath to disperse the particles, finally particle size analysis were determined by Qudix-scatheroscope Particle size analyzer. This method was applied identically to all 18 samples to keep a similar condition for samples (1, 2 and 15-17).

**Table 5.** Analysis of variance (ANOVA) for dissolution rate.

Factor	DOF	Sums of squares	Variance	F-ratio	Percent
Type of agitator paddle(A)	2	184.01	92.003	0.12	5
Type of cooling(B)	2	2524.06	1262.03	1.653	2
Type of solvent(C)	2	3499.17	1749.6	2.292	1
Agitation Speed(D)	2	1250.83	625.5	0.819	3
pH(E)	2	853.3	426.7	0.558	4

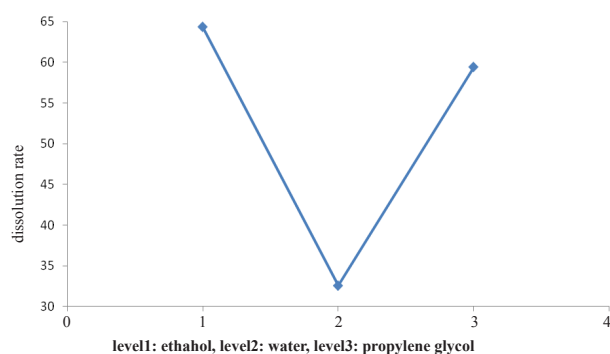


Figure 3. Influence of type of solvent on dissolution rate.

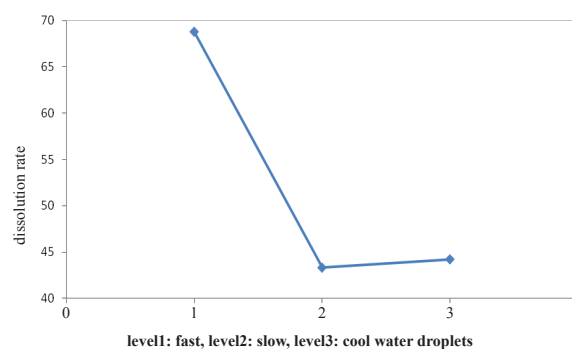


Figure 4. Influence of type of cooling on dissolution rate.

### Dissolution rate test

For determination of dissolution rate, 100 mg of the crystals was added to 250 mL of distilled water at 25 ° C in a dissolution testing device according to references (Dissolution Tester Erweka-DT800, Japan). Rotation speed was 100 rpm. At regular intervals (15 minutes; 0, 15, 30, 60), samples were taken, and the volume was replaced. Concentrations were determined using the UV-spectrophotometer at 350 nm (UV-160A spectrophotometer, Shimadzu, Japan) (1, 15-17).

## Results and Discussions

Eighteen experiments were carried out according to Table 2. The results of all measurements are summarized in Table 3.

In Taguchi method the results are statistically analyzed using analysis of variance (ANOVA) to determine the partial contribution of each operating factor on the response. The strategy of ANOVA calculation is to extract from the results that how much each factor is effective on response or responses of experiments (9, 10). This statistical table also distinguishes the significant factors. There are many statistical terms in ANOVA table, among them few are

more meaningful. The F-ratio is a criterion for distinguishing the important factors from those with less significance. It should be emphasized that the interpretation of ANOVA table is valid just in the range of levels considered for each factor. The main effects of factors are determined using average values of response at each level (9, 10).

### Effects of process parameters on particle size

Table 4 shows the analysis of variance for particle size. As it is observed, the predominant factor for controlling the particle size in recrystallization process is the type of cooling and pH is the second major effective factor. The type of mixture paddle and type of solvent show low effects on the particle size formation. It is implied from data in ANOVA table that the agitation speed has no significant influence on particle size. These statistical results have been confirmed by reported literatures (11-15, 17).

Figure 1 indicates the effect of type of cooling on particle size. It shows that slow cooling (level 2) results in formation of the smallest particle versus other levels and Figure 2 shows the second level (pH=7) is the best pH for formation of the smallest particles.

Table 6. Optimum conditions for dissolution rate.

Factor	Describe	Level
Type of agitator paddle(A)	turbine	1
Type of cooling(B)	fast	1
Type of solvent(C)	ethanol	1
Agitation Speed(D)	200	2
pH(E)	9	3

**Table 7.** properties of optimum powder.

Parameter	Result
Particle size( $\mu\text{m}$ )	138
Particle shape	needle
Dissolution rate%	127.6

#### *Effects of process parameters on dissolution rate*

Table 5 shows the ANOVA table (analysis of variance) of dissolution rate of piroxicam samples. As it is observed the predominant factors for controlling the dissolution rate in samples are the type of solvent and then type of cooling respectively. The pH and agitation speed during crystallization process have slight affects on the dissolution rate of sample powders and type of agitator paddle has no significant effect on the response.

Figure 3 indicates that the effect of type of solvent on dissolution rate. It shows that ethanol solvent causes to produce better particles versus other levels at dissolving rate. Figure 4 shows after type of solvent factor, the first level (fast cooling) is the best versus other levels for formation of faster dissolution rate particles.

Table 5 shows the optimum conditions for the best response (fast dissolution rate particles) that Qualitek4 software suggests of particle size data.

#### *Optimum conditions for producing fast dissolution rate particles*

Table 6 shows the software suggests optimum conditions for crystallization process

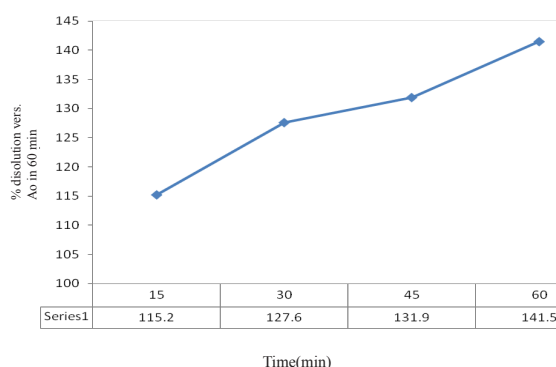
to produce the best powder by increased dissolution rate.

The optimum condition for attaining the best powder by increased dissolution rate is reported in Table 6. The best level of each factor for improvement of response is given in this table.

These conditions were tested again and the powder was extracted and purified by current last methods that used for other samples. The properties of prepared powder were reported in Table 7.

Dissolution rate of prepared powder was tested again and reported in Figure 5. Results reveal the prepared powder shows 27.6 % faster releasing more than industrial sample.

Based on these results it is revealed that an optimum particle size between 120-169  $\mu\text{m}$  and needle crystals are the best style for dissolution rate of piroxicam powder. The needle shape of particles is more important than particle size. Run 6, 13, 16 response shows particles with cubic shape and optimum size (120-160  $\mu\text{m}$ ) have no effective dissolution rate but particles with needle shape demonstrate better dissolution rate so it is confirmed the conditions for the best dissolution rate are an optimum particle size in range of 120-160  $\mu\text{m}$  and needle shape crystals.

**Figure 5.** Dissolution rate of optimum powder.



## Conclusions

Using Taguchi experimental design the influence of five operating variables on particle size and dissolution rate of industrial piroxicam powder in recrystallization process was statistically analyzed. The main conclusions are summarized below:

1) Type of cooling and pH of recrystallization process show maximum effects on the

Particle size with respect to the selected levels in this study.

2) Slow cooling and pH=7 result in producing small particles but acidic pH and fast cooling result in producing larger particles.

3) Type of solvent and type of cooling in recrystallization process demonstrate the maximum effects on dissolution rate of prepared particles.

4) Ethanol solvent and fast cooling result in producing the particles with best dissolution rate.

4) The optimized conditions to prepare the powder with the best dissolution rate are summarized below:

- ☐ type of solvent = ethanol
- ☐ type of cooling = fast
- ☐ agitation speed = 200
- ☐ pH=9
- ☐ type of mixture paddle: turbine

The optimum produced powder has 27.6% faster releasing versus industrial sample in first 30 minutes. Our obtained results reveal that an optimum particle size between 120-169  $\mu\text{m}$  and needle shape crystals are the best style for dissolution rate of piroxicam powder.

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