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Research Article

DEVELOPMENT OF PIROXICAM ORALLY DISINTEGRATING TABLETS BY FREEZE DRYING METHOD

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ABSTRACT

Objective: the aim of this research was to optimize piroxicam orally disintegrating tablets (ODT) formulation by freeze drying method.

Method: optimization was done by a 2^2 factorial design to observe the effect of gelatin as binder with levels of 1% and 2%, and ECG 505 as disintegrant with levels of 2.5% and 7.5%. The filler used was mannitol which also serves as sweetener. The mixture was suspended, filled into blisters and freeze dried. The physical characteristics of the resulting tablets were evaluated including hardness, friability, disintegration time and dissolution. Internal microstructures of the tablets were analyzed by Scanning Electron Microscope (SEM).

Results: Increasing level of gelatin from 1% to 2% increased the tablet hardness, lowered the tablet friability and increased the tablet disintegration time. Increasing levels of gelatin from 1% to 2% showed a greater influence than of ECG 505 on the tablet disintegration time, while increasing levels of ECG 505 from 2.5% to 7.5% showed a greater influence on the amount of piroxicam dissolved than of gelatin.

Conclusion: evaluation of tablets physical quality showed that within the "feasible area" of the design space, the tablets met the specifications of hardness, disintegration time and % piroxicam dissolved but did not meet the friability specification. The SEM photomicrographs showed that the tablets have a porous structure.

Keywords: Optimization, Orally disintegrating tablets, Piroxicam, Freeze drying, Physical quality of tablets.

INTRODUCTION

Peroral drug delivery route is the most commonly used and convenient to use by patients because it is the most natural, not harmful, easy to use and safe in terms of drug delivery. In certain people, the use of conventional tablets can give trouble, such as the elderly (geriatric) who are experiencing difficulties in using conventional dosage forms (solutions, suspensions, tablets, and capsules) because of hand tremors and dysphagia; and children (pediatric) who have problems in swallowing drugs because of muscular and nervous system has not fully developed. Also in patients who have trouble using conventional tablets, such as in mentally ill patients, patients who are paralyzed, patients who are unable to swallow and patients who have to avoid much water, as well as in people who experience nausea [1,2]. To overcome these problems, in recent years Orally Disintegrating Tablets (ODT) was developed as a pharmaceutical solid form which disintegrates and dissolves in the mouth within less than 60 seconds without the use of water [3,4]. ODT is also called fast dissolving tablets, mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapid melts, porous tablets, and quick dissolving tablets [5].

Piroxicam is a non steroidal anti inflammatory drug (NSAID) with analgesic effect commonly used in the treatment of acute and chronic rheumatoid arthritis and osteoarthritis [6]. Most of these diseases are experienced by the elderly, so piroxicam is suitable to be made as Orally Disintegrating Tablets which are easily consumed [7]. There are several methods of making Orally Disintegrating Tablets (ODT), among which direct compression, wet granulation, molding, spray drying, freeze drying and sublimation. In this research, optimization of piroxicam ODT formulation was done using freeze drying method. The advantage of freeze drying method is that this method yield more porous tablets having a rapid disintegration time, and have a good taste in the mouth due to rapid tablet disintegration. With this innovative dosage forms, it is expected that the patient compliance in using medication will be increased so that the goal of therapy can be achieved. Furthermore freeze drying process is carried on at a very low temperature so as to avoid any stability problems of the active pharmaceutical ingredient [8].

MATERIAL AND METHODS

Materials

Piroxicam (SIM, Italy), manitol (Cargill, USA), gelatin (was obtained from PT Mega Setya Agung, Indonesia), E.C.G-505 (Nichirin Co. was obtained as a gift sample from PT Lawsim Zecha, Jakarta)

Methods

Formulation design

This experiment is a 2^2 factorial design of experiment. Formulation of piroxicam ODT were made to contain 20 mg of piroxicam/tablet with different levels of binder and disintegrant as can be seen in Table 1.

Table 1: Formulation design of piroxicam Orally Disintegrating Tablet

Materials	F1	F2	F3	F4
Piroxicam	20 mg	20 mg	20 mg	20 mg
Mannitol	415 mg	415 mg	415mg	415 mg
Gelatin	1%	1%	2%	2%
ECG-50	2.5%	7.5%	2.5%	7.5%

Preparation of the tablets

Piroxicam, ECG-50 and mannitol were homogeneously mixed then a warm solution of gelatin was added and blended vigorously to form a stable suspension. The suspension was filled into blister (diameter 13 mm) using an injection syringe. Furthermore, blisters containing the suspensions were frozen at -40 °C for 3 hours and then put in a freeze dryer (VirTis, USA) with the following conditions: drying temperature: -55 ° C, pressure: 18 mTorr and drying time: 48 hours.

Evaluation of tablets

Hardness

Tablet hardness evaluation was carried out by means of Erweka TBH 220 Hardness Tester (Germany). Hardness test were performed on 5 tablets and its tensile strength were calculated.

Friability Test

Tablet friability evaluation was carried out by means of Erweka TAP 31 914 Friability Tester (Germany). Ten tablets were weighed and rotated at 25 rpm for 4 minutes. Weight loss was calculated in percentage.

Disintegration time

Examination of tablet disintegration time was carried out by Erweka ZT 501 Disintegration Tester (Germany) with 900 ml of distilled water (temperature of 37° ± 2°C) as medium.

Dissolution test

Determination of piroxicam ODT dissolution were performed using a type 2 dissolution test apparatus (Erweka DT-706, Germany), stirring speed of 50 ± 2 rpm and 900 ml of artificial gastric fluid without pepsin pH 1.2 (37° ± 0.5°C) was used as medium. Samples (5 ml) were taken at time intervals of 5, 10, 15, 20, 30 and 40 minutes with an injection syringe equipped with a Millipore filter paper (pore size 0.45 µm). At every sampling time, the dissolution media was replaced with an appropriate volume. The concentration of dissolved piroxicam was determined by UV spectrophotometer at maximum wavelength of ± 334 nm. Correction was done to calculate the concentration of dissolved piroxicam according to the dilution of the sample taken [9].

Scanning Electron Microscope (SEM)

The cross section of the ODT structure was observed by Scanning Electron Microscope (JEOL, JSM-840A, Japan), with a magnification of 200 times.

RESULT AND DISCUSSION

Observations of physical quality and the dissolution of the tablet can be seen in Table 2 and Table 3, while the dissolution profile is shown in Figure 1.

Table 2: Results of the the ODT physical quality evaluation

Physical Quality	F1	F2	F3	F4
Hardness (kP)	1.26 ± 0.12	2.19 ± 0.16	2.31 ± 0.34	3.49 ± 0.34
Tensile strength	0.015±0.002	0.025 ± 0.003	0.025±0.006	0.035±0.006
Friability (%)	25.57 ± 1.31	18.12 ± 0.57	15.78 ± 1.24	3.79 ± 0.66
Disintegration time (sec)	13.33 ± 1.15	18.33 ± 0.58	26.33 ± 2.31	22.0 ± 1.73

Table 3: Piroxicam dissolved (%) in simulated gastric fluid without pepsin pH 1.2

Times	% piroxicam dissolved			
(min)	F1	F2	F3	F4
0	0	0	0	0
5	92.44 ± 6.13	84.87 ± 3.04	80.58 ± 4.85	59.27 ± 10.79
10	96.70 ± 1.72	94.10 ± 3.57	95.88 ± 1.57	83.39 ± 4.76
15	97.29 ± 1.08	95.03 ± 1.39	97.61 ± 1.02	92.51 ± 2.91
20	99.78 ± 1.12	97.99 ± 1.78	98.89 ± 1.29	97.55 ± 0.28
30	99.68 ± 0.72	100.50 ± 0.78	100.03 ± 0.21	100.63 ± 0.20
40	100.49 ± 2.68	101.75 ± 3.19	101.32 ± 1.31	101.81 ± 0.25

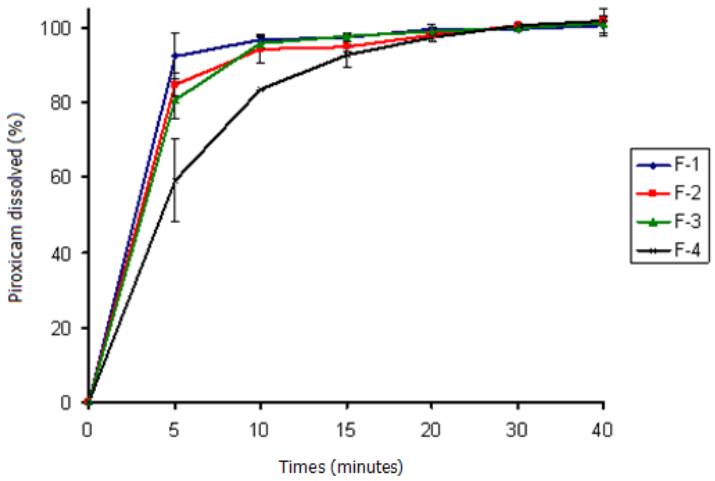

Fig. 1: Dissolution profile of piroxicam ODT in simulated gastric fluid without pepsin pH 1.2.

Contour plots of hardness, friability, disintegration time and dissolution of the tablets are shown in Figure 2. The main effect plots of gelatin and ECG 505 on tablet hardness, friability, disintegration time and amount of piroxicam dissolved (%) are shown in Figure 3.

Increasing level of gelatin from 1% to 2% increased the tablet hardness, lowered the tablet friability and increased the tablet disintegration time. Increasing the level of gelatin as binder will increase the bond's strength between the particles in the tablets. Increasing levels of gelatin from 1% to 2% showed a bigger impact than of ECG 505 on the tablet disintegration time, while increasing levels of ECG 505 from 2.5% to 7.5% showed a greater influence on the amount of piroxicam dissolved than of gelatin. Based on the "design space" obtained (Figure 4), it can be seen that the use of gelatin 1% and 2% as binder and ECG 505 2.5% and 7.5% as

disintegrant produced ODT that meet the specifications of hardness between 1kP to 3 kP, disintegration time between 30 seconds to 60 seconds and amount of piroxicam dissolved between 95% to 105%, but did not meet the specifications of the tablet friability (< 1%). The porous tablet formed by freeze drying process causes the tablets to be very fragile.

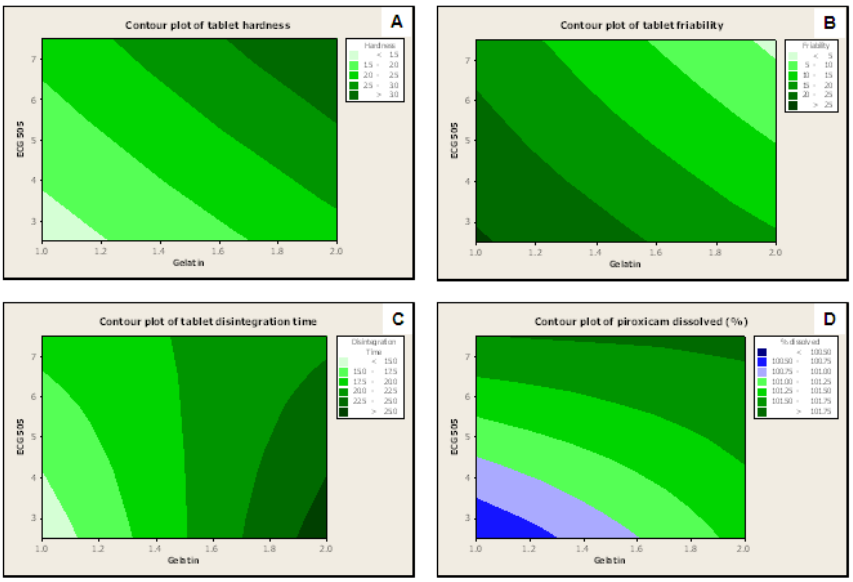

Fig. 2: Contour plots for (A) tablet hardness, (B) friability, (C) disintegration time and (D) amount of piroxicam dissolved (%).

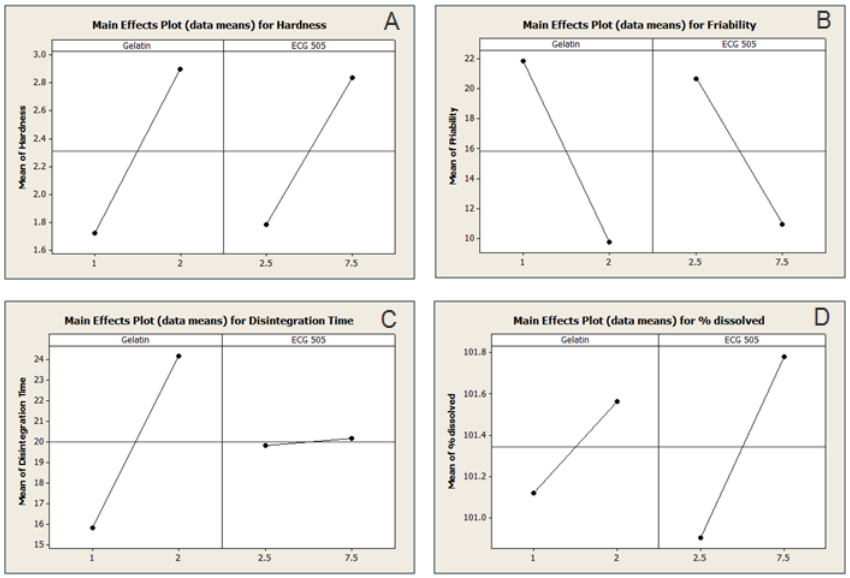

Fig. 3: Main effects plot of gelatin and ECG 505 for (A) hardness, (B) friability,C) disintegration time and (D) amount of piroxicam dissolved (%)

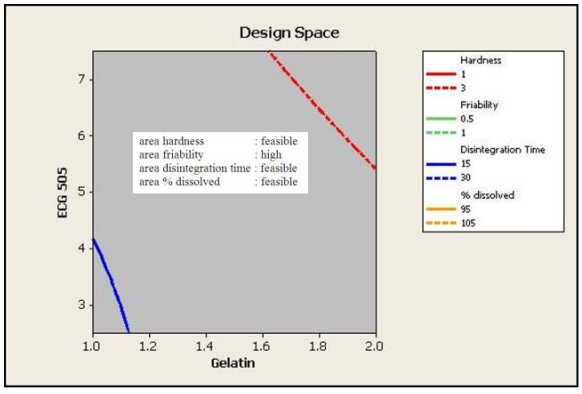

Fig. 4: Design space of hardness, friability, disintegration time and amount of piroxicam dissolved (%).

Freeze drying process produced tablets with high porosity because there is a sublimation of water that has been frozen and form cavities in tablet [10]. This porous structure accelerates the penetration of water into the tablet and makes the tablet disintegration time quicker [11]. Scanning Electron Microscope (SEM) was conducted to view the structure of the ODT and the result showed that increasing levels of gelatin and ECG 505 formed finer crystal and smaller tablet porosity (Figure 5). Porous structure formed on the tablet causes the penetration of saliva into the tablet through the cavities becomes faster so the tablet will have a rapid disintegration time [12].

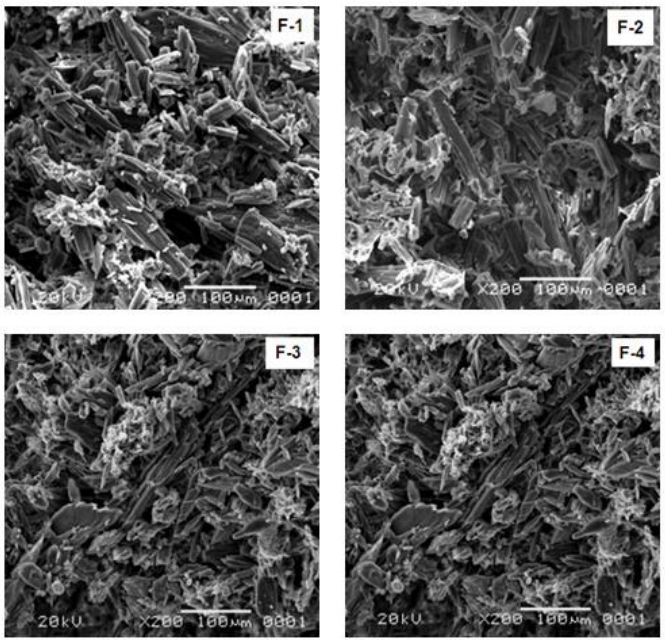

Fig. 5: SEM photomicrograph of piroxicam ODT (magnification 200 x).

Theoretically, increasing levels of ECG 505 would decrease the porosity of the ODT due to ECG 505 also serves as a binder [13]. In the manufacture of suspension, there is a possibility that ECG 505 is partly dissolved, and during the of freeze drying process, this dissolved ECG 505 formed a solid bridge that will inhibit the formation of porous structure so the smaller the tablet porosity.

CONCLUSION

From this experiment it could be concluded that the use of gelatin with levels of 1% and 2% and ECG 505 with levels of 2.5% and 7.5% within the "feasible area" of the design space produced tablets that meet the specifications of hardness, disintegration time and amount (%) of piroxicam dissolved but did not meet the friability specification. The SEM photomicrographs showed that the tablets have a porous structure.

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REFERENCES

1. Chang, R.K. Xiaodi, Guo, Burnside, B.A., Couch, R.A.,: Fast – Dissolving Tablet. Pharmaceutical Technology, 2000; 24 (6): 52-58
2. Sandeep D. J., Rahul N.K., Chetan M. J., Bharat W. T., Vijay R. P., Formulation And Evaluation Of Fast Dissolving Oral Film Of Levocetirizine Dihydrochlorid, International Journal of Pharmaceutical Sciences, 2012; 4 (1): 337-441
3. Arshad A.K., Sarfaraz M.D, Doddayya. H, Design And Evaluation Of Aceclofenac Fast Dissolving Tablets Prepared By Crystallo-Co-Agglomeration Technique, International Journal of Pharmaceutical Sciences , 2011; 3(4): 116-123.
4. Pfister, W.R. and Ghosh, T. K., Orally Disintegrating Tablets, Product, Technologies, and Development Issues, *www.pharmatech.com*. 2005.
5. Bhowmik, D., B, Chiranjib., Krishnakanth., Pankaj., and Chandira, R.M., Fast Dissolving Tablet: An Overview, Journal of Chemical and Pharmaceutical Research, 2009; 1 (1): 163-177
6. Wathoni N, Jessie S.P.,Sasanti T.D., Effect of Iontophoresis and Penetration Enhancers On The In Vitro Diffusion Of A Piroxicam Gel, International Journal of Pharmaceutical Sciences, 2012; 4(2): 215-218
7. Modasiya M.K., Lala I.I., Prajapati B.G., Patel V.M. , Shah, D.A., Design and Characterization of Fast Disintegrating Tablets of Piroxicam, International Journal of PharmTech Research, 2009; 1(2): 353-357.
8. Shaikh, S., Khirsagar, R.V., Quazi, A., Fast Disintegrating Tablets: An Overview of Formulation and Technology. International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2, p.9-14.
9. Wurster, D. E., V. D. Taylor., Dissolution Kinetics on Certain Form of Prednisolon, Journal of Pharmaceutical Sciences, 1965; 54: 670 – 676.
10. Gupta, A., Mishra, A.K., Gupta, V., Bansal, P., Singh, R., and Singh A.K., Recent Trends of Fast Dissolving Tablet- An Overview of Formulation Technology, International Journal of Pharmaceutical and Biological Archives , 2010; 1(1): 1-10.
11. Hickey, A. J. and Ganderton, D., Pharmaceutical Process Engineering, Marcell Dekker, Inc., New York, 2001; p.102-105.
12. Kundu, S., Sahoo P. K., Recent Trends In The Development of Orally Disintegrating Tablet Technology, Pharma Times, 2008; 40 (4): 11-14.
13. Rowe, R. C., Sheskey, P. J., and Quinn M. E., Handbook of Pharmaceutical Excipients, 6th. Ed., London : The Pharmaceutical Press, 2009; p. 17-118, 278-281, 424-428.