Automation of the Manufacturing Process of Cold Remedy Granules by a Tumbling Fluidized Bed Applying the Fuzzy Control Method

Satoru WATANO,*[,a] Toru FUKUSHIMA,[a] Kei MIYANAMI,[a] Takayuki MURAKAMI,[b] and Toshiharu SATO[b]

Department of Chemical Engineering, University of Osaka Prefecture,[a] 1–1 Gakuen-cho, Sakai, Osaka 593, Japan and Quality Control Department, Taiho Pharmaceutical Co., Ltd.,[b] 224–2, Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771–01, Japan. Received December 20, 1993; accepted February 4, 1994

The automated manufacturing process of cold remedy granules using a tumbling fluidized bed will be described. Powdered materials, containing salicylamide and acetaminophen as the main components and having been used for the extrusion process previously, were granulated by a tumbling fluidized bed. Effects of the operational variables on the properties of granules were investigated, which led to the conclusion that the exact control of bed height and moisture content was indispensable for continuously producing desired granules. The fuzzy control method based on a linguistic algorithm of if-then rules was applied to the bed height control, and programmed control of the moisture content was used for the continuous operation from mixing, granulation to drying. By means of the system developed, a series of operations could be conducted automatically. Properties of the granules thus obtained were evaluated, and a comparison of the granules by this process to those by the extrusion process used previously was conducted. It was concluded that by means of the control system developed, desired granules which had sharp particle size distribution, high yield, *i.e.*, almost 100% of granules, large apparent density and remarkably good flowability were easily produced.

Keywords automation; granulation; fuzzy control; tumbling fluidized bed; cold remedy granule

Process validation, defined by the FDA as establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes, has become a serious problem in a pharmaceutical industry. In order to clarity the inspection of the validation or to make these standard easily adaptable to the Good Manufacturing Practices (GMP), an automated manufacturing process is indispensable. Although a few examples of Factory Automation (FA) have already been reported, there remain many problems to be solved regarding the measurement and control of powder handling processes. Especially, dynamic characteristics of the powder handling process are difficult to understand due to the incompleteness of the measuring techniques and to unpredictable changes in properties. Therefore, it is difficult to establish a model-based control system because of these difficulties.

Fuzzy control, proposed by Zadeh,[1)] is a method for realizing a process control by means of describing the experience or knowledge of skilled operators as if-then rules; thus, it is thought to be the most suitable for the control of powder handling processes.

In this paper, the establishment of an automated manufacturing process of cold remedy granules containing salicylamide and acetaminophen as the main components using a tumbling fluidized bed, which had been previously conducted by extrusion and related several unit operations without a control, was described. The system, consisting the fuzzy control of bed height and programmed control

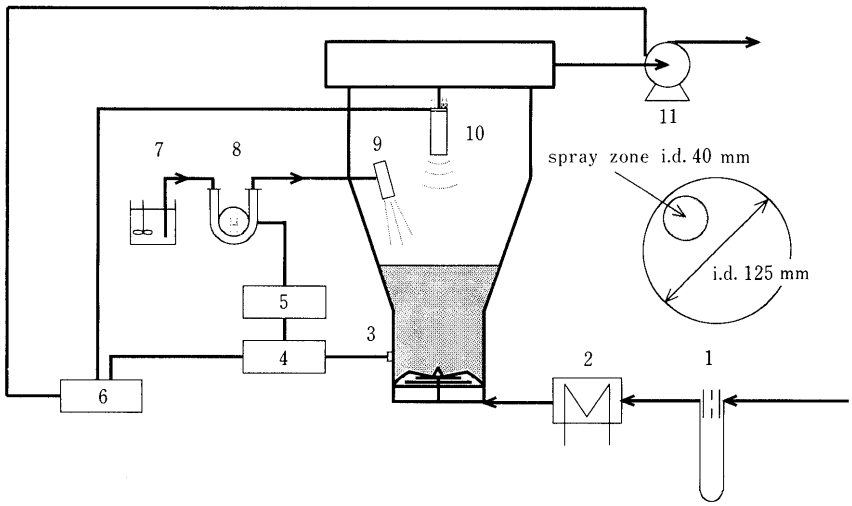

Fig. 1. Experimental Set Up

1, orifice; 2, heater; 3, optical fiber; 4, IR moisture sensor; 5, PID controller; 6, fuzzy controller; 7, binder liquid; 8, pump; 9, spray nozzle; 10, ultrasonic sensor; 11, blower.

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of the moisture content, was designed and developed for continuous automated operation. Physical proprieties of the granules obtained were also investigated to evaluate the system.

Experimental

Equipment Figure 1 is a schematic diagram of the experimental apparatus employed. A tumbling fluidized bed granulator[2,3] (NQ-LABO, Fuji Paudal) was used for a wet granulation. Details of the equipment and the measurement system of the operational variables were the same as previously reported.[4,5]

Bed height was measured by an ultrasonic displacement sensor located 320 mm above the bottom. Its body was a cylinder made of stainless steel with a diameter of i.d. 30 mm and a length of 83.5 mm. At the top of the sensor, an oscillator was equipped for the purpose of preventing powder adhesion, and a small amount of compressed air was blown to brush the sensor. A thermistor for the measurement of the air temperature was equipped to correct the ultrasonic propagation velocity. The detection range of the sensor was between 60 and 300 mm, which was translated to an analog signal from 4 to 20 mA. The sampling interval of the sensor was selected to be 50 ms (20 Hz), considering the moving speed of the powder bed.

Moisture content of the granules during the granulation was continuously measured by an IR moisture sensor[4] (Wet-Eye, Fuji Paudal). The mixing, granulation and drying processes were automatically operated using a moisture programmed control.

Materials Table I gives the list of powder samples used. A purified water was used as a binder liquid, which was sprayed by a binary nozzle located 100 mm above the bed, inclined to form a spray zone (i.d. 40 mm) near the wall.

Particle Size Distribution A row-tap shaker was used. The shaking time was selected to be 3 min and the charged weight was 10 g.

Friability Friability of the granules was evaluated by the weight percent of fraction over 60 mesh after rotation in a friabilater at 25 rpm for 20 min.

Dissolution and Disintegration Dissolution and disintegration tests were performed in accordance with the JP XII method.[6] Purified water was used for the medium.

Specific Surface Area Specific surface area of the granules was calculated by means of a BET method using liquid nitrogen as an adsorbate. A Nikkiso Model 4200 was used as an analyzer.

Angle of Repose, Apparent Density Powder tester (Hosokawa Micrometritics Laboratory) was used.

TABLE I. Powder Materials

Materials	Weight (g)
Salicylamide	107
Acetaminophen	59
Anhydrous caffeine	12
Chlorpheniramine maleate	1
Excipient	117
Hydroxipropylcellulose	4
(Total)	300

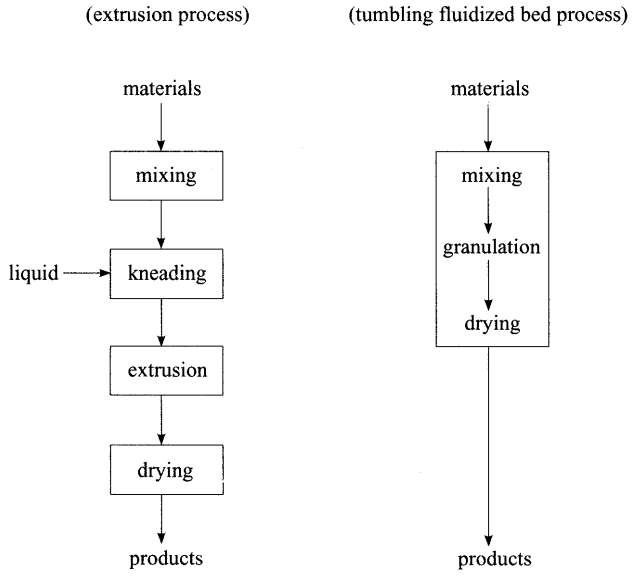

Fig. 2. Comparison of Granulation Process

Results and Discussion

Tumbling Fluidized Bed Process Comparison between the tumbling fluidized bed process applied in this study and an extrusion process which was previously used to produce cold remedy granules is illustrated in Fig. 2. Since the extrusion process consists of several unit operations such as mixing, kneading, extrusion and drying, there is a large possibility for contamination, and many disadvantageous points were found, so that the process efficiency is not very good and the process automation is difficult to establish. By contrast, since the tumbling fluidized bed process can undergo mixing, granulation and drying operations in one vessel, automation of the process is easy and contamination is prevented. Therefore, we tried to establish the automated production process of cold remedy granules by the tumbling fluidized bed using the

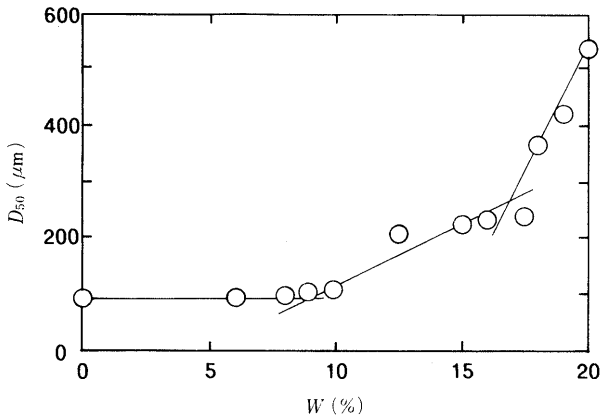

Fig. 3. Plots of Geometric Median Particle Size D_{50} as a Function of Operational Moisture Content W

Inlet air temperature, 60 °C; agitator rotational speed, 300 rpm.

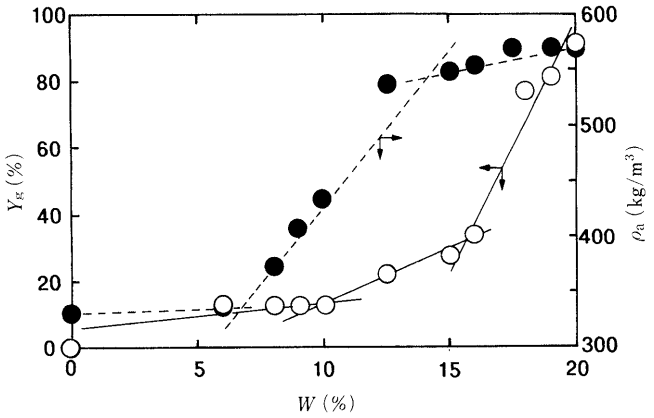

Fig. 4. Plots of Yield of Granules Y_g and Apparent Density ρ_a as a Function of Operational Moisture Content W

Inlet air temperature, 60 °C; agitator rotational speed, 300 rpm.

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same formula as adopted in the extrusion process.

Optimum Operational Conditions for Producing Granules First of all, optimum operational conditions for producing the desired granules were investigated. Accordingly, granulation was conducted at various levels of operational moisture content; thereafter, the effects of moisture content on geometric median particle size, yield of granules and apparent density were examined.

The results are shown in Figs. 3 and 4. From Fig. 3, geometric median particle size, D_{50} had a linear correlation with operational moisture content, W. Granule growth was observed above 7 or 8% of the moisture content, and above $W=16\%$, remarkable granule growth was found. As previously reported,[4] powder samples were porous and water absorbing power was strong, any binder liquid added to the particle was perfectly permeated and liquid bridges could not be formulated on the surface of the granule particles. When the powder samples were dampened to more than 7 or 8% of the moisture content, liquid bridges were partly formulated and slight granule growth was found. With a moisture content greater than 16%, the surface was saturated with water, and rapid granule growth was found.

From Fig. 4, yield of granules, Y_g (fraction over 42 mesh) and apparent density, ρ_a also increased with an increase in moisture content. It was, therefore, concluded that granulation must be conducted at greater than 19% moisture content to produce desired granules of sufficient particle size and distribution for oral dosage granules.

Effects of Operational Variables on Bed Height In the previous chapter, we suggested that the moisture content must be kept at greater than 19% to produce desired granules of sufficient particle size distribution. In addition, to densify the particles and to make them spherical, effective tumbling motion was needed; hence, it was necessary to maintain a bed height as low as possible. In this case, however, problems such as blocking and channeling were often observed. It was because the particles were densified and adhesion power increased remarkably, particles were no longer fluidized unless a large amount of air was supplied.

In the low moisture content range, however, adhesion of particles on bag filters or to the walls of the column were found, and a lot of fine powder accompanied by fluidized air passed through the bag filters in the initial stage of the granulation because of the finely powdered materials. In this case, air must not be increased unless the powders were dampened to some extent.

In order to clear up these problems, bed height must be controlled to the most suitable value for granule growth; concretely, the bed height must be regulated as small as possible to avoid adhesion at the initial stage, and it should

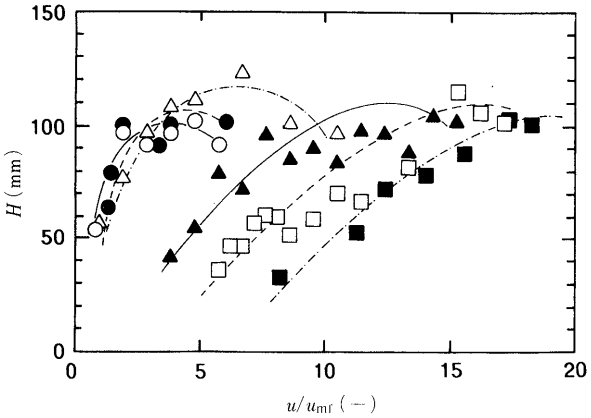

Fig. 5. Effect of u/u_{mf} on Bed Height H at Various Levels of Operational Moisture Content

○, $W=5.0\%$; ●, $W=7.5\%$; △, $W=10.0\%$; ▲, $W=12.5\%$; □, $W=15\%$; ■, $W=17.5\%$; u_{mf}, 0.071 m/s.

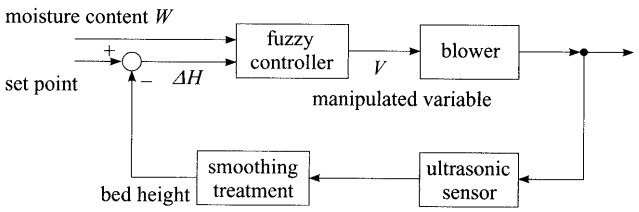

Fig. 6. Schematic Diagram of Fuzzy Control System Applied

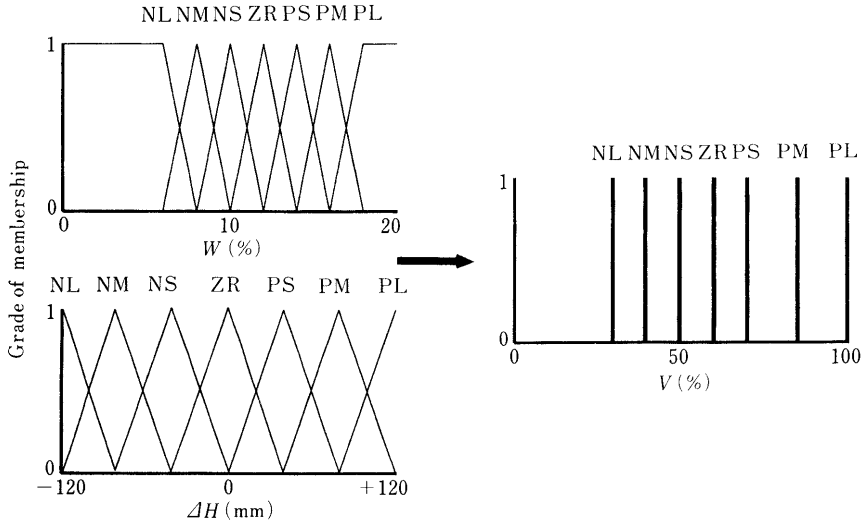

Fig. 7. Membership Functions of Antecedent and Consequent Clause

NL, negative large; NM, negative medium; NS, negative small; ZR, zero; PS, positive small; PM, positive medium; PL, positive large.

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be kept at a favorable fluidization constant at the final stage to prevent blocking and channeling.

Figure 5 illustrates the effects of inlet air velocity (u/u_{mf}) on bed height, H at various levels of moisture content. Here, u_{mf}, defined as a minimum fluidization air velocity at a dry condition, was estimated to be 0.071 m/s, and u/u_{mf} indicated a dimensionless air velocity.

From Fig. 5, it was found that the relation between bed height and u/u_{mf} was closely connected with granule growth; in other words, air velocity needed for fluidization was small in the initial ungranulated stage, whereas it increased remarkably with the progress of granulation.

In the low moisture content stage, since the powder samples were not so densified and adhesion power not so large, small fluidization air was sufficient. Here, we found that the bed height took a maximum value; the bed height no longer increased in spite of an increase in air velocity in maintaining the moisture content. This was because the adhesion of particles on the wall of the column or bag filter became remarkably large, thus the bed height measured decrease in spite of intense fluidization.

As the granulation progressed, the powder samples were sufficiently densified and adhesion power became large; air needed for fluidization increased remarkably.

At the final stage of granulation, near the $W=18\%$, the air velocity required for the fluidization was about 17 or 18 times as large as that of the initial u_{mf}. It was concluded that bed height was remarkably influenced by granule growth, hence the moisture content must be taken into consideration when we control the bed height during granulation.

Application of Fuzzy Inference on Bed Height Control It was obvious from the experimental investigations that the effects of operational variables on the bed height were so complicated that dynamic characteristics of the bed height were difficult to understand. Hence, the establishment of a model-based control system was also impossible. Therefore, we here attempted to apply fuzzy inference to the bed height control. In addition, if the experience and intuition of skilled operators can be applied to the bed height control, a good response and stability will be expected.

Figure 6 shows the developed fuzzy control system of bed height. Operational moisture content, W, and bed height, ΔH, which was the difference between the set point value and measured value of bed height, were adopted as input variables. Manipulated variable, V, which was a result of fuzzy inference, was fed to the blower to control bed height. Fuzzy inference was conducted by means of a min–max composition method[7-9] using triangular-shaped membership functions for the antecedent clause and real number set for the consequent clause (Fig. 7). Here, NL—PL are the levels of input variables: NL (negative large), NM (negative medium), NS (negative small), ZR (zero), PS (positive small), PM (positive medium) and PL (positive large).

Figure 8 illustrates the production rules applied. They were constructed on the basis of the following experience by skilled operators:

1) If moisture content is within the range of NL (low moisture content), minimum air is supplied at any bed height to prevent the adhesion of fine powders.

2) If moisture content is small (NM and NS), air velocity must be restrained slightly.

3) If moisture content is remarkably high, a large

		W						
		NL	NM	NS	ZR	PS	PM	PL
ΔH	NL	NL	NS	ZR	PS	PS	PM	PL
	NM	NL	NS	NS	ZR	PS	PS	PM
	NS	NL	NM	NS	ZR	ZR	PS	PM
	ZR	NL	NM	NM	NS	ZR	ZR	PM
	PS	NL	NL	NM	NS	NS	ZR	PS
	PM	NL	NL	NM	NM	NS	NS	PS
	PL	NL	NL	NL	NM	NM	NS	ZR

If W=NL and ΔH=NL then V=NL
If W=NM and ΔH=NL then V=NS
If W=NL and ΔH=NL then V=NL
⋮
If W=PM and ΔH=NL then V=PM
If W=PL and ΔH=NL then V=PL
If W=PL and ΔH=PL then V=ZR

Fig. 8. Production Rules for Fuzzy Inference

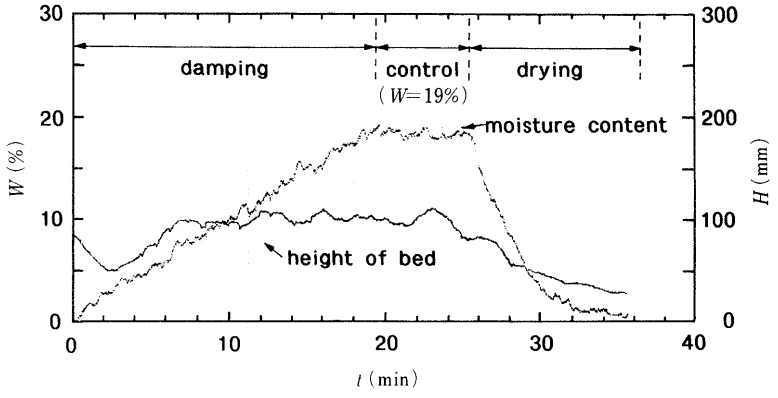

Fig. 9. Results of Bed Height Control by Fuzzy Inference

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amount of air is supplied to prevent the blocking. Rules 1) and 2) were contrived to prevent adhesion, while 3) is for avoiding blocking.

The output of V, which was needed for controlling the bed height, was determined by defuzzification using the center-of-gravity method.[7-9]

Figure 9 demonstrates the results of the fuzzy inference of bed height and temporal changes in moisture content. The bed height was regulated to a small value in the initial stage of granulation ($0\% \leqq W \leqq 6\%$) and was kept constant after that. No adhesion or blocking was observed throughout the granulation. Good response and stability was obtained, and control of the bed height was favorably conducted using fuzzy inference. The moisture content was also favorably controlled and was kept a 19% for 6 min without overshooting.

As a result of the bed height control, spherical with well-compacted granules, which had been impossible by conventional fluidized bed techniques, were easily and automatically produced.

Evaluation of the Granules Obtained Table II lists the physical properties of the granules obtained by the tumbling fluidized bed system and the previous extrusion system. Sharp particle size distribution and a high yield of granules were obtained in the tumbling fluidized bed system because of the exact moisture control at a high moisture content. Well-compacted granules with extremely good flowability were also obtained due to the tumbling and compacting by the agitator rotation. Uniformity of each content and disintegration time were also satisfactory. Although slight inferiority was found with the friability of the granules, it was too trifling to be considered a problem.

Table II. Properties of the Granules Obtained

Properties		Granulation process: Tumbling fluidized bed	Granulation process: Extrusion
Yield of granules		98.9%	98.8%
Geometric mean particle size		675 μm	521 μm
Geometric standard deviation		1.29	1.33
Apparent density		573 kg/m^3	546 kg/m^3
Friability		93.2%	97.4%
Angle of repose		25.7 deg.	33.3 deg.
Disintegration time		0.5—0.7 min	0.4—0.7 min
Specific surface area		340.1 m^2/kg	536.4 m^2/kg
Uniformity of content	Salicylamide	100.7%	100.2%
	Acetaminophen	100.8%	100.1%
	Chlorpheniramine maleate	101.4%	100.7%
	Anhydrous caffeine	99.0%	99.9%

Figure 10 demonstrates the dissolution properties of the main ingredients. With all ingredients, the dissolution rate of the ingredient from the granules by the tumbling fluidized bed process was slightly slower than that of the extrusion process. Since the specific surface area of granules by the tumbling fluidized bed process was remarkably smaller than that of the extrusion process, the liquid-solid contact area became small. In addition, the granules were so compacted by the tumbling motion that

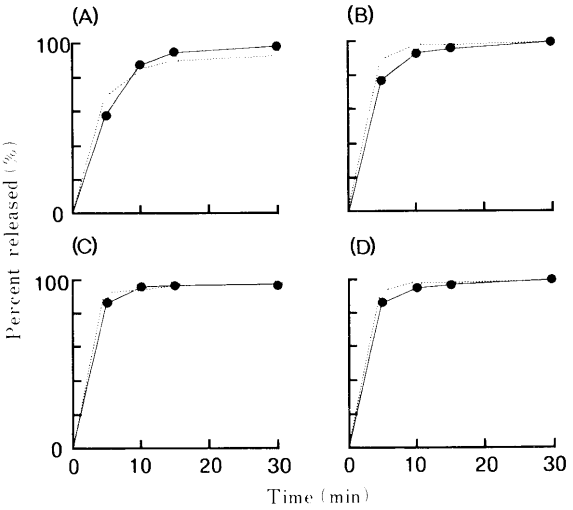

Fig. 10. Dissolution Rate of the Main Ingredients

(A) salicylamide, (B) acetaminophen, (C) chlorpheniramine maleate, (D) anhydrous caffeine.

●, tumbling fluidized bed process; ○, extrusion process.

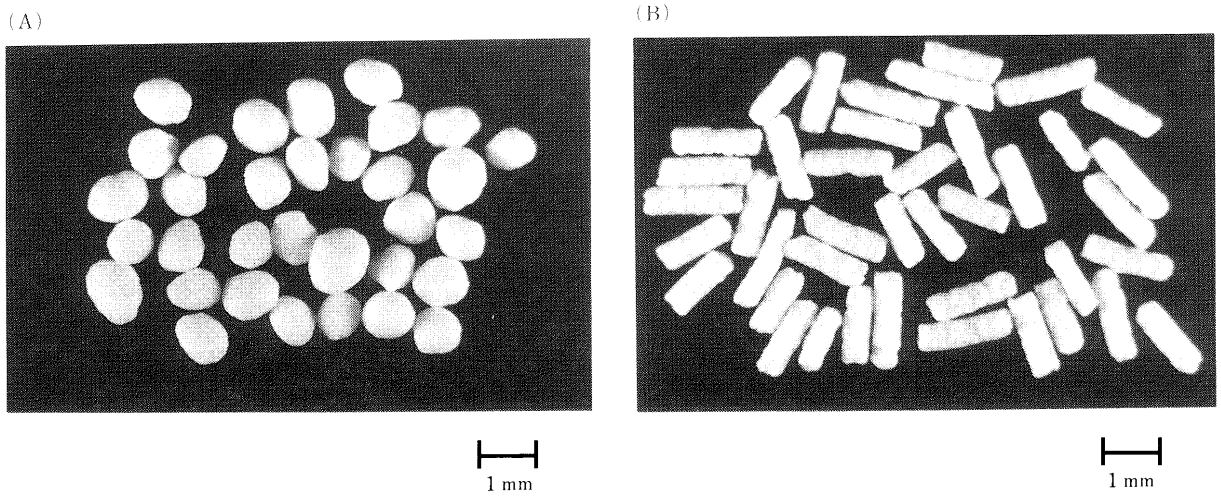

Fig. 11. Shape of Granules Obtained

(A) Tumbling fluidized bed process, (B) extrusion process.

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the granules were difficult to disintegrate. It was suggested that these factors resulted in the decrease of the dissolution rate; however, this inferior dissolution rate was too trifling for an oral dosage form to be a problem.

Figure 11 shows the shape of granules produced by each process. As is clear from Fig.11, granules made by the tumbling fluidized bed process were spherical in shape and smooth in surface, whereas the granules by the extrusion process were cylindrical with a rough surface. Due to the increase in spherical shape, flowability increased, hence it contributed to the increase in efficiency of transportation.

Conclusions

By means of the fuzzy control of bed height and the programmed control of moisture content, an automated manufacturing process of cold remedy granules was established using a tumbling fluidized bed process. Properties of the granules obtained were evaluated, and the availability was investigated. These were the conclusions:

1) An automated manufacturing process of cold remedy granules containing salicylamide and acetaminophen as the main components was established using a tumbling fluidized bed with control over the bed height and moisture content.

2) Since the bed height was remarkably affected by moisture content and its dynamic characteristics were difficult to understand, fuzzy inference based on a linguistic algorithm of if-then rules was applied to the bed height control. Good response and stability was obtained and problems such as adhesion of particles and blocking were fully prevented throughout the operation.

3) Sharp particle size distribution, high yield of granules, large apparent density and remarkably good flowability were obtained using the tumbling fluidized bed process. Unfortunately, granules made by this process indicated slightly smaller friability and a little longer dissolution rate of the main ingredient than those by the previous extrusion process. This inferiority, however, was too trifling to be considered a problem if the drug is applied as an oral dosage.

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