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Article

A feasible classification method of wet masses to predict pellet formation of powdered herbal slices

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The aim of the current study was to explore the correlation between physical properties of wet masses and pellet quality by using powdered herbal slices as model drugs. Wet masses with 100 formulations were prepared by taking 20 kinds of powdered herbal slices as model drugs, microcrystalline cellulose as pelletization aid and five levels of added water as liquid binder. Physical properties of the wet masses such as hardness, adhesiveness, springiness, cohesiveness, chewiness, and resilience were measured by a texture analyzer. Meanwhile, the moisture retention capacities (MRC) of powdered herbal slices and wet masses were determined. Particles were classified after they were produced during spheronization. Principal component analysis, factor analysis and classification analysis were performed on the data. Wet masses could be classified into three groups by taking Ha as the first classification index and Ha/Sp as the second classification index. The correct rate of the classification was 91.00%. If Ha value of wet masses was greater than 15610 g, pellets of type ① would form, otherwise, pellets of type ② or type ③ would form based on Ha/Sp value. Then a classification plot of wet masses was developed to predict pellet formation of powdered herbal slices. Meanwhile, the probable mechanism of pellets formation during spheronisation was concluded in this study, which provided useful information to improve pellet quality.

Keywords: Extrusion-spheronization. Physical properties. Wet mass. Powdered herbal slices. Principal component analysis.

INTRODUCTION

Extrusion-spheronization, first suggested by by Reynolds (1970) and Conie (1970) is a multi-step mechanical process (Zolkefpeli, Wong, 2013) widely used in the pharmaceutical industry for manufacturing pellets (Lau *et al*., 2014). By a series of unit operations including dry blending, wet-massing, extrusion, spheronzation and drying (Krueger *et al*., 2013; Ghebre-Sellassie, Martin, 2003), pellets with a narrow size distribution and a low friability were prepared (Dukic-Ott *et al*., 2009). Nowadays, pellets, as a kind of multi-particulate oral solid dosage form with a main advantage of high drug loading have drawn much attention (Chamsai, Sriamornsak, 2013).

The mechanisms about extrusion-spheronization have been discussed continuously. In 1985, a mechanism about extrusion-spheronization was proposed that the extrudates underwent the stages of forming cylinders with equal lengths, cylinders with round edges, dumb-bell shaped particles and elliptical particles, finally resulting in spheres (Rowe, 1985). Baert *et al.* (1993) extended the mechanism by advancing a theory that the dumb-bell shaped particles would break into two spheres with cavities outside in the spheronization

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process (Vervaet *et al.*, 1995). A new mechanism was raised that the cyclindrical extrudates went through three stages of becoming cylinders with rounded edges and fractured fines, dumb-bell shaped particles with agglomerated fines and elliptical particles by deformation and agglomeration among particles (Liew *et al.*, 2007) and finally were spheronized into spheres (Koester *et al.*, 2012). Koester and Thommes (2010) and Bryan *et al.* (2015) summarized these mechanisms, respectively. Previous study of our team (Gao *et al.*, 2013) investigated the relationship between the physical properties of wet masses and the different shapes of the obtained particles after spheronization. The results showed that the wet masses need a suitable range of hardness (Ha) and chewiness (Ch), which will help them first break into short cylinders and then form the short cylinder into an intermediate shape with rounded edges, eventually forming spherical particles due to suitable elasticity (Sp), resilience (Re), cohesion (Co) and small adhesion (Ad).

Texture analysis (TA) is commonly used to investigate the mechanical response of solids and liquids in the food and cosmetic industry (Estellé *et al.*, 2006), such as the texture measurement of fruit (Giongo *et al.*, 2013) and meat products (Martinez *et al.*, 2004; Ávila *et al.*, 2014). Nowadays, it has been applied to the chemical (Nalesso *et al.*, 2015) and pharmaceutical industry (Mércia, Suzana caetano, 2007). By the wet mass analysis, the physical properties of wet masses (Gao *et al.*, 2013) can be characterized, such as Ha, Sp, Co, Ch, Ad and Re (Bourne, 1978; Singh *et al.*, 2013).

Traditional Chinese medicine (TCM) has been used in China for thousands of years to treat people with poor health (Bian *et al.*, 2012). TCM preparations commonly used are generally made of the extract of herbal slices to reduce the daily dose (Pretoro *et al.*, 2010). However, TCM preparations made directly from powdered herbal slices account for 27% in Chinese Pharmacopoeia 2015 edition (National Pharmacopoeia Committee, 2015). Some herbal slices are usually ruled to be directly made into preparations because they have better clinical effect than extracts (Li, 2009; Zou *et al.*, 2015). On one hand, some aromatic traditional Chinese drugs can avoid the volatilization of the active ingredients. One the other hand, some precious medicinal materials such as Sanqi (Notoginseng Radix Et Rhizoma) could reduce the loss of drugs and save the resources. The last but not the least, the main active ingredients are insoluble in water in many animal medical slices containing protein and protein hydrolytic products (Liu *et al.*, 2015). Therefore, it's quite necessary to study the process and the concept of pellet formation when using powdered herbal slices as model drugs. Our previous work (Gao *et al.*, 2013) gave much information on wet masses and pellet quality assessment in extrusion-spheronization process by taking microcrystalline cellulose as pelletization aid and lactose, hydroxypropyl methylcellulose grades, powdered herbal extracts as model drugs with different drug loadings. A structured protocol for the classification of wet mass was developed to predict the formation and quality of the pellets. However, it is still unclear whether the protocol can be applied to the process when using powdered herb as model drugs.

The aim of the current work was to explore the effect of the physical properties of wet mass on pellet formation and to develop a protocol to predict pellet quality by using powdered herbs as model drugs.

MATERIAL AND METHODS

Material

Microcrystalline cellulose (MCC, lot number F06010004) with a mean particle size of 50 μm used as the excipient, was obtained from Anhui Sunhe Pharmaceutical Excipients Co., Ltd, China. 20 kinds of Traditional Chinese herbal slices were purchased from Shanghai Cambridge Chinese Herbal Slices Co., Ltd, China. The herbal slices were as follows: Citri Reticulatae Pericarpium (Chen Pi, CRP, lot number 150314), Aurantii Fructus (Zhi Ke, AF, lot number 150112), Paeoniae Radix Alba (Bai Shao, PRA, lot number 150319), Chrysanthemi Flos (Ju Hua, CF, lot number 150225), Moutan Cortex (Mu Danpi, MC, lot number 150226), Chaenomelis Fructus (Mu Gua, CHF, lot number 141225), Astragali Radix (Huang Qi, AR, lot number 150321), Zingiberis Rhizoma (Gan Jiang, ZR, lot number 150321), Glycyrrhizae Radix Et Rhizoma (Gan Cao, GRER, lot number 150323), Dioscoreae Rhizoma (Shan Yao, DR, lot number 150320), Angelicae Sinensis Radix (Dang Gui, ASR, lot number 150314), Ligustri Lucidi Fructus (Nv Zhenzi, LLF, lot number 150104), Eriobotryae Folium (Pi Paye, FE, lot number 150312), Puerariae Lobatae Radix (Ge Gen, PLR, lot number 151005), Uncariae Ramulus Cum Uncis (Gou Teng, URCU, lot number 151008), Inulae Flos (Xuan Fuhua, IF, lot number 150928), Rehmanniae Radix (Di Huang, RR, lot number HP2015120603), Plantaginis Semen

(Che Qianzi, PS, lot number XD2015122201), Curcumae Rhizoma (E Zhu, CR, lot number 2015041302), Ophiopogonis Radix (Mai Dong, OR, lot number HP2015051601). CRP, AF, CHF and LLF are from the fruit of herbs, PRA, MC, AR, ASR, PLR, RR and OR from the root of herbs, CF and IF from the flower of herbs, ZR, DR, URCU and CR from the stem of herbs, EF from the leaf, PS from the seed and GRER from both root and stem. Ultrapure water which was used as the moistening liquid and liquid binder, was generated by Millipore Direct-Q3 system.

Dry milling

Powdered herbal slices were prepared by a DFT-250 electric milling machine (Shanghai, China). After repeated milling and sieving through an 80 mesh sieve, the powdered model drugs were obtained (Kumar, Burgess, 2014).

The size and size distribution of powdered herbal slices

The sizes of the powdered herbal slices were determined by a Mastersizer 2000 particle size analyzer (Malvern, Worcestershire, UK) fitted with a dry powder feeder and laser beam. The size distribution, defined as span, was calculated as follows:

$$Span = \frac{d_{90} - d_{10}}{d_{50}}$$

where d_{90}, d_{50} and d_{10} represented the corresponding 90th, 50th and 10th percentiles of the accumulative particle size distribution, respectively.

True density measurement of powdered herbal slices

An AccuPyc Pycnometer (AccuPyc II 1340 V1.05 Unit1 Serial No. 949) was employed for the true density measurement of powdered herbal slices with helium as analysis gas.

Extrusion-spheronization process

MCC, 20 kinds of model drugs and five levels of water were used in the study. 200 g of MCC-drug mixture powder loaded with 30% *w/w* drug was added into a container and was diluted by geometry for 5 min. Water was added by spraying onto the powder blends. The mixing and wetting processes were completed within 10 min. The amount of water added which was calculated as a percentage of the total mixture weight, was set at different levels to form different types of particle. Wet masses were extruded with a rotating speed of 60 r/min through a single axial screw extruder (E50, Chongqing Eagle Pharmaceutical Machinery Co, Ltd, Chongqing, China) fitted with a screen of 0.6 mm aperture diameter, 1 mm thickness and 15 aperture per inch, to produce extrudates.

100 g of extrudates were subsequently spheronized at 1200 r/min for 3 min using a spheronizer (S-250, Chongqing Eagle Pharmaceutical Machinery Co., Ltd., Chongqing, China) fitted with a friction plate of 250 mm diameter. Then the prepared particles were dried in an oven at 40 ºC for 3 h.

Texture measurement of wet masses

As there was little difference in the physical properties between wet masses and extrudates for the same formulation, the physical properties of the extrudates were measured by texture profile analysis (TPA). A texture analyzer TA-XT plus (Stable Micro System Ltd., UK) was used with an acrylic cylindrical cup of 55 mm in diameter as a sample container and an aluminum back extrusion probe A/B E connecting to a disk with a diameter of 45 mm. TPA was performed at room temperature and the parameters were set based on the study conducted by Ya Gao (Gao *et al.*, 2013). 30 g of extrudates in the sample container were axially compressed to 40% of the original height using a two-cycle compression test with 5 s allowed to elaspe between the two compression cycles (Zheng *et al.*, 2015). The trigger force was 1500 g, with a pre-test speed of 2 mm/s, test speed of 5 mm/s and post-test speed of 5 mm/s. Each sample was determined in three replicates by Exponent software (Exponent Stable Microsystem, version 6.1.7.0, Stable Microsystems Ltd., UK) and the results were averaged. The parameters Ha, Sp, Co, Ch, Ad and Re were acquired. Both extrusion-spheronization process and texture measurement of the same formulation were conducted on the same day in order to reduce error.

Categorization of pellets

Particles produced by extrusion and spheronization after drying in the oven were sieved using a 60 mesh sieve to separate the fine particle fraction. Then the

particles were divided into three categories according to the morphology of 50 randomly selected particles. The particles were divided into one type when the number was over 25. Type ①: clavate pellets, double sphere or dumb-bell shaped pellets; type ②: spherical pellets; type ③: oversized pellets (size > 0.2 mm).

The measurement of moisture retention capacity (MRC)

MRC is the ability of the materials to hold water when subjected to a certain force, which may finally influence the physical properties of wet masses (Tomer *et al*., 2001). Therefore, the MRC was conducted in this study for the water retention measurement of powdered herbal slices (Gao *et al*., 2013) and wet masses (Tomer, Newton, 1999).

MRC measurement of powdered herbal slices

MRC of powdered herbal slices (MRC_P) was measured using a 10.0 mL of centrifuge tube. 0.5 g of herbal slice powder sample was deposited into a 10.0 mL of centrifuge tube and 5 mL of ultrapure water was added to make powder uniformly suspended in water by vibrating the tube for 2 min. After keeping the suspension static for 10 min, the tube was vibrated for 2 min and centrifuged at 3000 r/min for 15 min. The supernatant liquid was then poured out. The MRC_P was measured by the following equation according to the percentage of residual water precipitated in the tube. The blank centrifuge tube was weighed as W_1 and centrifuge tube with precipitate was weighed as W_2.

$$MRC_P = \frac{W_2 - W_1}{0.5} \times 100\%$$

MRC of wet masses

MRC of wet masses (MRC_w) was measured using a 2.0 mL-centrifuge tube with an ultrafiltration centrifuge tube (Figure 1). Extrudates used to replace wet masses were cut into cylinders (5 mm in length and 1 mm in diameter). Then 0.3 g of the cylinders were put into the tube to be centrifuged at 5500 r/min for 30 min. Water contents of wet masses before and after centrifuge were W_{pre} and W_{post}, respectively. W_{water} was the added water content during the wet mass preparation process. The blank ultrafiltration centrifuge tube and the tube after centrifuge were weighed as W_1 and W_2, respectively.

$$MRC_w = \frac{W_{post}}{W_{pre}} \times 100\% = \frac{W_{pre} - (W_2 - W_1)}{W_{pre}} \times 100\%,$$

$$W_{pre} = \frac{0.3W_{water}}{100 + W_{water}}$$

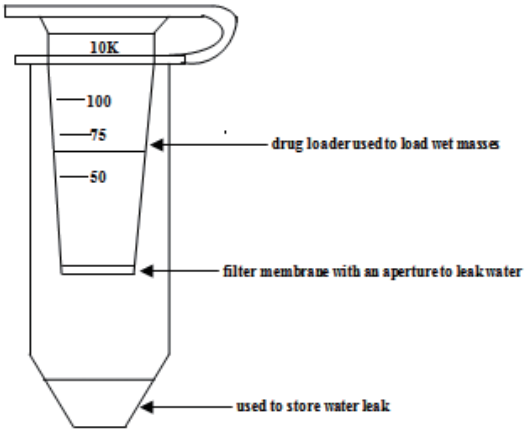

FIGURE 1 - The schematic diagram of ultrafiltration centrifuge tube.

Data analysis

The Uncrambler (V9.7, Camo Software, Oslo, Norway) was employed for the analysis of physical properties of wet mass and the particle types. The data could be simplified by producing a new set of principal components and retaining the minimum loss of information (Jolliffe, 2002).

The physical properties of wet masses and pellet types were classified through Waikato Environment for Knowledge Analysis (WEKA, V3.7.13, the University of Waikato Hamilton, New Zealand).

The physical properties of wet masses were correlated to those of the wet masses using Pearson's correlation analysis (SPSS Version 18.0 for Windows, SPSS Inc., IL, USA).

RESULTS AND DISCUSSION

The size distribution and true density results of 20 kinds of powdered herbal slices

The size distribution and true density results of 20 kinds of powdered herbal slices were shown in Table I, which indicated that after dry milling and through 80 mesh, the size, size distribution and true density of 20 kinds of powdered herbal slices were in the range of 70.27 ~ 80.54 μm, 2.14 ~ 2.87 and 1.50 ~ 1.55 g/cm^3, respectively, with no significant difference.

TABLE I – The size and size distribution, true density and MRC of powdered herbal slices (n=3, $\bar{x}$ ± s)

Powder herbal slices	d_{50} (μm)	Span	True density (g/cm^3)	MRC_p %
CPR	80.54 ± 0.00	2.38 ± 0.00	1.51 ± 0.00	427.06
AF	76.58 ± 0.00	2.14 ± 0.00	1.53 ± 0.00	442.18
PRA	72.05 ± 0.00	2.18 ± 0.00	1.53 ± 0.00	378.18
CF	71.72 ± 0.00	2.87 ± 0.00	1.54 ± 0.00	396.02
MC	70.27 ± 0.00	2.61± 0.00	1.52 ± 0.00	341.92
CHF	82.97 ± 0.00	2.58 ± 0.00	1.52 ± 0.00	346.66
AR	78.36 ± 0.00	2.54 ± 0.00	1.53 ± 0.00	262.36
ZR	75.07 ± 0.00	2.51 ± 0.00	1.53 ± 0.00	392.44
GRER	76.86 ± 0.00	2.47 ± 0.00	1.52 ± 0.00	356.48
DR	79.76 ± 0.00	2.57 ± 0.00	1.53 ± 0.00	327.24
ASR	75.76 ± 0.00	2.74 ± 0.00	1.55 ± 0.00	362.84
LLF	82.81 ± 0.00	2.63 ± 0.00	1.51 ± 0.00	327.52
EF	79.63 ± 0.00	2.42 ± 0.00	1.50 ± 0.00	575.18
PLR	83.16 ± 0.00	2.14 ± 0.00	1.52 ± 0.00	366.54
URCU	74.35 ± 0.00	2.73 ± 0.00	1.53 ± 0.00	388.32
IF	78.26 ± 0.00	2.39 ± 0.00	1.50 ± 0.00	389.21
RR	75.73 ± 0.00	2.18 ± 0.00	1.52 ± 0.00	350.32
PS	75.09 ± 0.00	2.37 ± 0.00	1.53 ± 0.00	300.09
CR	79.05 ± 0.00	2.17 ± 0.00	1.54 ± 0.00	288.84
OR	76.88 ± 0.00	2.44 ± 0.00	1.53 ± 0.00	352.46

The size and size distribution, true density and MRC of powdered herbal slices (n=3, $\bar{x}$ ± s)

Characterization of wet masses and pellets

The physical property data of the wet masses and the categories of pellets from 100 formulations were presented in Table II. The physical properties of different kinds of wet masses with five levels of water additon were quite different and the shapes of the obtained particles are also of different types. Compared with the physical properties of the wet masses which use lactose, hydroxypropyl methylcellulose grades, powdered herbal extracts as model drugs (Gao *et al.*, 2013), the Ha and Ch values in this work were significantly reduced. The possible reason was that there were many fibers in the wet masses when taking powdered herbal slices as model drugs and the longer fibers were not well compacted. So the wet masses were less dense, resulting in smaller values of Ha and Ch. It was also found that the Ad values were in a low level as they were less stick than the powdered herbal extract when wetted by water.

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x}$ ± s)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
1	CRP	80	15747 ± 557	-3.590 ± 0.209	0.595 ± 0.019	0.451 ± 0.010	4227 ± 358	0.129 ± 0.005	99.85	①
2	CRP	90	14608 ± 400	-6.473 ± 0.332	0.601 ± 0.038	0.450 ± 0.001	3947 ± 140	0.129 ± 0.003	96.97	①
3	CRP	100	13646 ± 258	-4.435 ± 0.207	0.652 ± 0.006	0.468 ± 0.005	4160 ± 80	0.134 ± 0.002	93.20	②
4	CRP	110	12456 ± 68	-10.181 ± 1.185	0.651 ± 0.022	0.378 ± 0.011	3070 ± 124	0.115 ± 0.001	92.62	②
5	CRP	120	11690 ± 360	-13.806 ± 1.390	0.678 ± 0.033	0.385 ± 0.009	3055 ± 213	0.122 ± 0.001	90.71	③
6	AF	80	18123 ± 715	-6.134 ± 0.540	0.596 ± 0.035	0.451 ± 0.005	4870 ± 225	0.127 ± 0.003	99.92	①
7	AF	90	16246 ± 207	-6.730 ± 0.727	0.595 ± 0.051	0.444 ± 0.005	4294 ± 330	0.125 ± 0.003	97.40	①
8	AF	100	14100 ± 278	-7.542 ± 0.826	0.588 ± 0.037	0.433 ± 0.010	3596 ± 358	0.121 ± 0.002	94.47	②
9	AF	110	12897 ± 329	-11.937 ± 0.076	0.637 ± 0.014	0.391 ± 0.007	3211 ± 101	0.116 ± 0.001	93.70	②
10	AF	120	12107 ± 88	-18.649 ± 2.238	0.660 ± 0.084	0.354 ± 0.006	2827 ± 312	0.111 ± 0.002	92.42	③
11	PRA	80	17442 ± 578	-6.193 ± 0.823	0.600 ± 0.044	0.451 ± 0.008	4715 ± 294	0.138 ± 0.006	98.42	①

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x} \pm s$)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
12	PRA	90	15793 ± 469	-3.011 ± 0.512	0.563 ± 0.027	0.462 ± 0.011	3891 ± 192	0.129 ± 0.006	94.02	①
13	PRA	100	14172 ± 545	-6.395 ± 0.291	0.570 ± 0.024	0.426 ± 0.006	3450 ± 320	0.135 ± 0.002	91.67	②
14	PRA	110	12736 ± 206	-11.376 ± 0.308	0.642 ± 0.035	0.367 ± 0.003	3006 ± 230	0.130 ± 0.001	91.34	②
15	PRA	120	12474 ± 347	-11.295 ± 0.750	0.662 ± 0.050	0.367 ± 0.004	3031 ± 260	0.137 ± 0.002	89.54	③
16	CF	80	17792 ± 273	-5.536 ± 0.780	0.579 ± 0.041	0.447 ± 0.002	4602 ± 410	0.122 ± 0.001	99.02	①
17	CF	90	16047 ± 442	-6.589 ± 0.451	0.571 ± 0.030	0.451 ± 0.003	4135 ± 188	0.122 ± 0.001	95.21	①
18	CF	100	14762 ± 322	-8.876 ± 0.245	0.553 ± 0.012	0.426 ± 0.012	3479 ± 167	0.119 ± 0.001	92.33	②
19	CF	110	13921 ± 581	-11.233 ± 0.903	0.558 ± 0.025	0.381 ± 0.025	2960 ± 150	0.117 ± 0.004	90.64	②
20	CF	120	13016 ± 419	-14.727 ± 0.493	0.748 ± 0.041	0.362 ± 0.041	3518 ± 29	0.115 ± 0.003	90.52	③
21	MC	80	17910 ± 387	-3.645 ± 0.175	0.549 ± 0.021	0.437 ± 0.004	4295 ± 119	0.119 ± 0.002	99.10	①
22	MC	90	15843 ± 64	-5.911 ± 0.783	0.536 ± 0.050	0.426 ± 0.007	3623 ± 409	0.120 ± 0.002	94.86	①
23	MC	100	14798 ± 216	-7.071 ± 0.705	0.587 ± 0.019	0.409 ± 0.010	3552 ± 26	0.118 ± 0.001	92.47	②
24	MC	110	14066 ± 289	-9.063 ± 0.421	0.552 ± 0.051	0.378 ± 0.015	2941 ± 357	0.119 ± 0.001	89.81	②
25	MC	120	13224 ± 318	-11.116 ± 1.472	0.594 ± 0.055	0.353 ± 0.001	2767 ± 198	0.116 ± 0.001	89.49	③
26	CHF	80	18004 ± 158	-5.514 ± 0.283	0.505 ± 0.014	0.440 ± 0.012	3995 ± 161	0.124 ± 0.002	98.57	①
27	CHF	90	16390 ± 374	-7.450 ± 0.190	0.516 ± 0.033	0.422 ± 0.014	3578 ± 399	0.124 ± 0.005	95.07	①

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x} \pm s$)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
28	CHF	100	15088 ± 377	-8.239 ± 0.444	0.561 ± 0.053	0.414 ± 0.021	3504 ± 382	0.120 ± 0.001	92.33	②
29	CHF	110	13376 ± 511	-10.343 ± 0.948	0.558 ± 0.028	0.351 ± 0.014	2614 ± 70	0.114 ± 0.002	91.47	②
30	CHF	120	12322 ± 194	-14.930 ± 1.576	0.672 ± 0.010	0.321 ± 0.009	2657 ± 37	0.112 ± 0.003	89.79	①
31	AR	70	17219 ± 94	-4.304 ± 0.217	0.547 ± 0.028	0.444 ± 0.008	4182 ± 165	0.119 ± 0.003	92.63	①
32	AR	80	15900 ± 525	-6.629 ± 0.246	0.518 ± 0.038	0.426 ± 0.006	3499 ± 86	0.120 ± 0.002	89.20	①
33	AR	90	14538 ± 242	-7.960 ± 1.189	0.513 ± 0.027	0.398 ± 0.008	2972 ± 178	0.121 ± 0.001	84.94	②
34	AR	100	13477 ± 173	-10.507 ± 0.917	0.546 ± 0.020	0.373 ± 0.009	2747 ± 77	0.119 ± 0.003	84.47	②
35	AR	110	12078 ± 185	-18.652 ± 0.798	0.686 ± 0.072	0.340 ± 0.006	2810 ± 257	0.112 ± 0.001	83.45	③
36	ZR	80	17270 ± 169	-3.337 ± 0.217	0.544 ± 0.025	0.439 ± 0.003	4129 ± 208	0.125 ± 0.003	98.27	①
37	ZR	90	16278 ± 427	-5.309 ± 0.380	0.579 ± 0.048	0.441 ± 0.012	4147 ± 235	0.126 ± 0.003	95.85	①
38	ZR	100	15017 ± 676	-4.618 ± 0.355	0.545 ± 0.037	0.423 ± 0.008	3458 ± 138	0.126 ± 0.003	92.40	②
39	ZR	110	13483 ± 361	-8.660 ± 0.912	0.544 ± 0.041	0.394 ± 0.008	2893 ± 341	0.127 ± 0.002	91.47	②
40	ZR	120	13340 ± 173	-11.211 ± 1.356	0.569 ± 0.019	0.400 ± 0.014	3034 ± 91	0.122 ± 0.002	91.08	③
41	GRER	70	19283 ± 1040	-3.207 ± 0.373	0.517 ± 0.060	0.426 ± 0.017	4235 ± 458	0.119 ± 0.007	98.95	①
42	GRER	80	19243 ± 2142	-3.371 ± 0.482	0.486 ± 0.015	0.418 ± 0.008	3915 ± 565	0.118 ± 0.007	94.82	①
43	GRER	90	15610 ± 380	-6.758 ± 0.270	0.500 ± 0.044	0.392 ± 0.007	3054 ± 239	0.109 ± 0.001	91.98	②

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x}$ ± s)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
44	GRER	100	13955 ± 454	-11.709 ± 1.100	0.543 ± 0.016	0.363 ± 0.012	2749 ± 121	0.102 ± 0.000	90.73	②
45	GRER	110	11943 ± 261	-16.075 ± 2.193	0.546 ± 0.038	0.341 ± 0.011	2221 ± 105	0.099 ± 0.003	89.62	②
46	DR	80	19305 ± 291	-3.309 ± 0.240	0.559 ± 0.026	0.436 ± 0.012	4706 ± 333	0.133 ± 0.002	98.57	①
47	DR	90	18390 ± 218	-6.388 ± 0.584	0.577 ± 0.016	0.427 ± 0.010	4525 ± 125	0.129 ± 0.003	94.65	①
48	DR	100	17164 ± 138	-5.093 ± 0.732	0.548 ± 0.040	0.399 ± 0.009	3759 ± 373	0.122 ± 0.002	92.80	②
49	DR	110	15188 ± 579	-12.513 ± 0.802	0.594 ± 0.027	0.363 ± 0.008	3271 ± 157	0.114 ± 0.004	89.94	②
50	DR	120	14148 ± 329	-10.528 ± 0.839	0.569 ± 0.026	0.360 ± 0.015	2903 ± 256	0.117 ± 0.002	89.73	③
51	ASR	60	19132 ± 723	-4.067 ± 0.510	0.536 ± 0.039	0.447 ± 0.004	4577 ± 182	0.127 ± 0.001	99.02	①
52	ASR	70	17816 ± 959	-4.470 ± 0.325	0.525 ± 0.006	0.441 ± 0.006	4126 ± 261	0.127 ± 0.003	95.95	①
53	ASR	80	15277 ± 230	-6.390 ± 0.461	0.536 ± 0.010	0.424 ± 0.002	3473 ± 53	0.121 ± 0.001	91.97	②
54	ASR	90	13338 ± 257	-12.850 ± 1.413	0.595 ± 0.045	0.372 ± 0.045	2949 ± 198	0.113 ± 0.001	91.41	②
55	ASR	100	11657 ± 286	-20.334 ± 1.825	0.687 ± 0.092	0.319 ± 0.010	2549 ± 234	0.105 ± 0.003	89.20	③
56	LLF	80	17659 ± 787	-3.523 ± 0.447	0.557 ± 0.047	0.445 ± 0.006	4371 ± 243	0.125 ± 0.001	98.72	①
57	LLF	90	16563 ± 372	-3.700 ± 0.463	0.568 ± 0.043	0.424 ± 0.007	3989 ± 289	0.122 ± 0.001	94.30	①
58	LLF	100	15458 ± 182	-3.673 ± 0.307	0.561 ± 0.027	0.419 ± 0.011	3634 ± 262	0.118 ± 0.003	93.93	②
59	LLF	110	14452 ± 475	-3.858 ± 0.147	0.604 ± 0.025	0.427±0.012	3721 ± 236	0.115 ± 0.004	90.90	②

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x} \pm s$)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
60	LLF	120	12120 ± 236	-8.966 ± 0.476	0.563 ± 0.023	0.346 ± 0.007	2359 ± 43	0.110 ± 0.003	89.30	③
61	EF	100	16373 ± 564	-6.545 ± 0.606	0.512 ± 0.020	0.409 ± 0.004	3428 ± 184	0.114 ± 0.001	99.93	①
62	EF	110	15756 ± 812	-9.106 ± 0.691	0.521 ± 0.043	0.362 ± 0.001	3562 ± 324	0.110 ± 0.001	99.24	①
63	EF	120	13207 ± 494	-13.149 ± 1.329	0.590 ± 0.017	0.331 ± 0.014	2581 ± 247	0.102 ± 0.003	97.00	②
64	EF	130	11962 ± 130	-17.643 ± 0.285	0.570 ± 0.043	0.295 ± 0.007	2013 ± 161	0.097 ± 0.002	95.75	②
65	EF	140	10928 ± 390	-35.541 ± 2.068	0.735 ± 0.036	0.263 ± 0.004	2111 ± 78	0.092 ± 0.002	95.20	③
66	PLR	80	18003 ± 538	-3.800 ± 0.125	0.534 ± 0.021	0.451 ± 0.008	4335 ± 99	0.113 ± 0.004	98.02	①
67	PLR	90	15900 ± 102	-6.010 ± 0.106	0.576 ± 0.037	0.433 ± 0.018	3966 ± 312	0.117 ± 0.001	95.65	①
68	PLR	100	14933 ± 339	-6.939 ± 0.214	0.605 ± 0.052	0.412 ± 0.011	3723 ± 341	0.117 ± 0.001	92.42	②
69	PLR	110	13747 ± 577	-9.014 ± 0.198	0.711 ± 0.044	0.390 ± 0.015	3812 ± 157	0.116 ± 0.005	90.01	②
70	PLR	120	12338 ± 376	-11.102 ± 0.354	0.782 ± 0.036	0.353 ± 0.015	3404 ± 310	0.102 ± 0.004	89.67	③
71	URCU	80	17988 ± 447	-5.013 ± 0.290	0.579 ± 0.052	0.463 ± 0.004	4824 ± 135	0.119 ± 0.001	99.10	①
72	URCU	90	15997 ± 547	-5.999 ± 0.239	0.618 ± 0.015	0.451 ± 0.008	4456 ± 221	0.122 ± 0.002	97.82	①
73	URCU	100	14082 ± 599	-7.121 ± 0.503	0.632 ± 0.039	0.443 ± 0.013	3942 ± 120	0.123 ± 0.005	95.02	②
74	URCU	110	13004 ± 169	-9.183 ± 0.342	0.659 ± 0.056	0.432 ± 0.009	3704 ± 283	0.117 ± 0.001	92.11	②
75	URCU	120	12000 ± 674	-12.335 ± 0.441	0.699 ± 0.034	0.387 ± 0.014	3246 ± 331	0.122 ± 0.002	89.14	③

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x} \pm s$)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
76	IF	80	18005 ± 552	-6.336 ± 0.398	0.569 ± 0.046	0.453 ± 0.022	4640 ± 296	0.116 ± 0.006	98.45	①
77	IF	90	16358 ± 275	-6.749 ± 0.265	0.597 ± 0.029	0.446 ±0.006	4360 ± 104	0.105 ± 0.003	94.01	①
78	IF	100	13986 ± 79	-7.522 ± 0.623	0.622 ± 0.055	0.431±0.015	3751 ± 78	0.121 ± 0.002	91.53	②
79	IF	110	12900 ± 520	-10.959 ± 0.497	0.636 ± 0.026	0.411 ±0.012	3371 ± 176	0.111 ± 0.005	91.01	②
80	IF	120	12056 ± 187	-17.690 ± 0.550	0.670 ± 0.071	0.382 ± 0.009	3088 ± 387	0.111 ± 0.007	89.87	③
81	RR	80	17902 ± 169	-6.177 ± 0.274	0.577 ± 0.079	0.452 ± 0.021	4672 ± 131	0.128 ± 0.001	96.15	①
82	RR	90	16002 ± 382	-6.002 ± 0.553	0.599 ± 0.050	0.449 ± 0.015	4305 ± 225	0.119 ± 0.008	93.56	①
83	RR	100	14223 ± 198	-8.775 ± 0.240	0.616 ± 0.033	0.436 ± 0.007	3824 ± 310	0.135 ± 0.001	91.51	①
84	RR	110	12788 ± 388	-11.118 ± 0.652	0.647 ± 0.016	0.400 ± 0.008	3309 ± 200	0.120 ± 0.002	89.45	②
85	RR	120	12447 ± 259	-11.949 ± 0.388	0.662 ± 0.040	0.361 ± 0.013	2975 ± 425	0.127 ± 0.004	88.23	③
86	PS	70	19227 ± 106	-3.001 ± 0.229	0.557 ± 0.032	0.426 ± 0.008	4558 ± 327	0.119 ± 0.002	95.33	①
87	PS	80	18047 ± 311	-3.442 ± 0.157	0.585 ± 0.028	0.417 ± 0.008	4395 ± 155	0.119 ± 0.003	92.41	①
88	PS	90	16009 ± 505	-7.669 ± 0.524	0.620 ± 0.039	0.389 ± 0.005	3857 ± 131	0.109 ± 0.002	89.58	①
89	PS	100	13988 ± 288	-11.669 ± 0.365	0.646 ± 0.036	0.384 ± 0.010	3469 ± 275	0.118 ± 0.004	88.41	②
90	PS	110	13024 ± 99	-15.074 ± 0.783	0.650 ± 0.051	0.370 ±0.013	3132 ± 152	0.109 ± 0.001	88.00	②
91	CRP	80	18476 ± 113	-6.131 ± 0.635	0.573 ± 0.027	0.461 ± 0.009	4874 ± 98	0.119 ± 0.003	94.55	①

(continuing)

TABLE II – The physical properties of wet masses and categories of pellets from 100 formulations (n=3, $\bar{x} \pm s$)

No.	Model Drug	Water(w/w,%)	Ha (g)	Ad (g·s)	Sp	Co	Ch	Re	MRCw(%)	Categories of particles
92	CRP	90	16550 ± 274	-7.113 ± 0.525	0.602 ± 0.062	0.450 ± 0.010	4484 ± 119	0.129 ± 0.003	92.57	①
93	CRP	100	14406 ±131	-7.347 ± 0.576	0.639 ± 0.010	0.447 ± 0.008	4112 ± 387	0.124 ± 0.005	91.01	②
94	CRP	110	12563 ± 512	-10.807 ± 0.632	0.659 ± 0.027	0.432 ± 0.006	3580 ± 417	0.114 ± 0.005	88.24	②
95	CRP	120	11681 ± 210	-13.669 ± 0.554	0.679 ± 0.029	0.357 ± 0.020	2834 ± 57	0.122 ± 0.003	86.54	②
96	OR	80	18231 ± 77	-6.335 ± 0.698	0.579 ± 0.029	0.451 ± 0.016	4764 ± 119	0.107 ± 0.002	96.54	①
97	OR	90	16236 ± 113	-6.744 ± 0.225	0.595 ± 0.047	0.442 ± 0.009	4274 ± 231	0.122 ± 0.002	92.13	①
98	OR	100	14000 ± 504	-7.453 ± 0.290	0.615 ± 0.044	0.429 ± 0.004	3695 ± 62	0.106 ± 0.002	91.54	②
99	OR	110	12970 ± 286	-12.094 ± 0.883	0.640 ± 0.035	0.403 ± 0.024	3344 ± 128	0.115 ± 0.002	89.81	②
100	OR	120	12017 ± 102	-16.565 ± 0.790	0.660 ± 0.052	0.366 ± 0.016	2905 ± 204	0.113 ± 0.001	88.76	③

According to Table III, significant correlations were found between MRC_w and the six physical properties of wet masses, except the correlation between Sp and Re. In addition, the correlations were all positive except the correlation between Sp and other physical properties. Meanwhile, the Ha, Ad, Sp, Co, Ch and Re values of 20 kinds of powdered herbal slices were plotted in Figure 2. The results revealed that the increase of added water ratio was accompanied by a significant decrease of the Ha, Ad, Co, Ch, Re values and a significant increase of the Sp value, apart from few data.

The physical property data of wet masses were averaged and standardized, and then a radar chart was plotted (Figure 3). The chart indicated that different types of pellets possessed different shapes because of different physical properties of wet masses. For example, wet masses for pellets of type ① had bigger Co, Ch, Ha, Re and smaller Sp values, but wet masses for pellets of type ③ had bigger Sp and smaller Ha, Ad, Ch, Co values. If good pellets were obtained, the wet masses should have medium values of physical properties.

MRC data of powdered herbal slices and wet masses were shown in Table I, Table II and Figure 4, respectively. For the 20 kinds of powdered herbal slices, MRC_p of AR and EF were in the lowest and highest location, respectively. MRC_w of wet masses from 20 kinds of powdered herbal slices decreased with increasing water ratio. Pearson's correlation analysis (Table III) showed that MRC_w was correlated with Ha, Ad, Sp, Co, Ch and Re of wet masses. Therefore, MRC_w data of wet masses were regarded as one of physical properties in the classification analysis of wet masses.

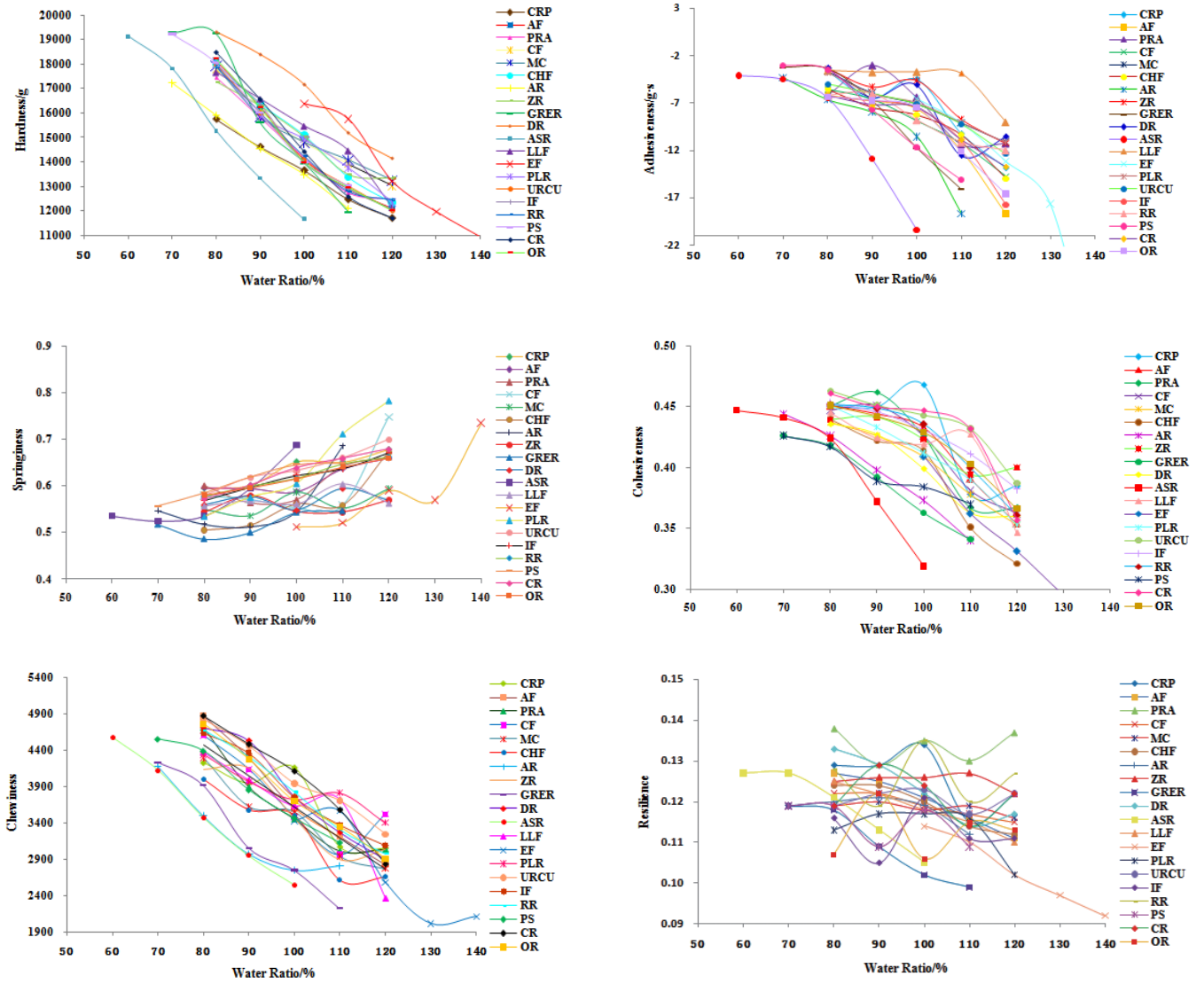

FIGURE 2 - The six physical properties plot of wet masses from 20 kinds of powdered herbal slices (A. Hardness; B. Adhesiveness; C. Springiness; D. Cohesiveness; E. Chewiness; F. Resilience).

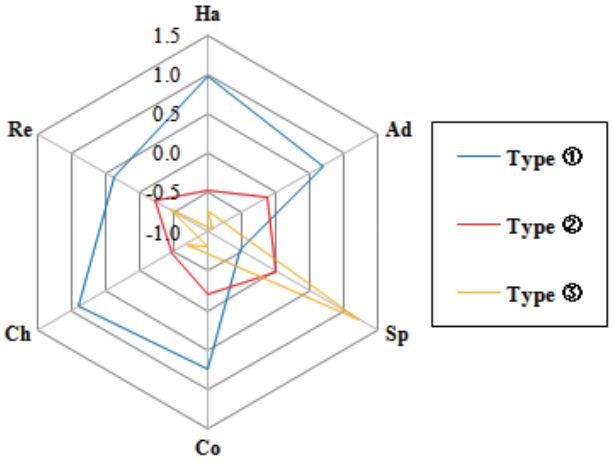

FIGURE 3 - Radar chart of the physical properties of wet masses for three types of particles.

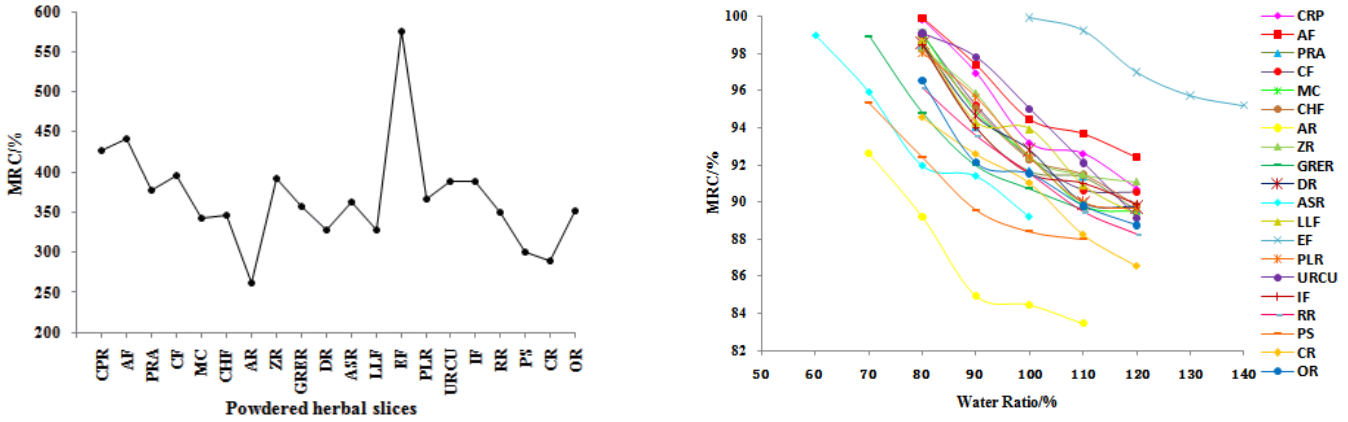

FIGURE 4 - MRC plots of powdered herbal slices (a) and wet masses (b) from 20 kinds of TCM.

TABLE III – Pearson's correlation analysis result among MRC_w and the six physical properties of wet masses

	Ha	Ad	Sp	Co	Ch	Re	MRC_w
Ha	1.000	0.768**	-0.637**	0.716**	0.844**	0.370**	0.693**
Ad	0.768**	1.000	-0.599**	0.830**	0.742**	0.563**	0.475**
Sp	-0.637**	-0.599**	1.000	-0.382**	-0.243*	-0.186	-0.413**
Co	0.716**	0.830**	-0.382**	1.000	0.884**	0.604**	0.517**
Ch	0.844**	0.742**	-0.243*	0.884**	1.000	0.496**	0.636**
Re	0.370**	0.563**	-0.186	0.604**	0.496**	1.000	0.211*
MRC	0.693**	0.475**	-0.413**	0.517**	0.636**	0.211*	1.000

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).

Classification of wet masses

The physical property data of wet masses in Table II were analyzed by using principal component analysis (PCA) in order to classify the wet masses. PCA scores plot (Figure 5A) showed that the first two principals could generally divide the 100 formulations into three parts, which explained 68% and 16% of the physical properties, respectively. Meanwhile, PCA result made by SPSS demonstrated the λ value corresponding to the first two principal components had taken up a cumulative percentage of 83.54% and the λ of the first PCs was 4.053 shown in Table IV. λ was the eigenvalues in PC analysis, representing the variance of PCA scores, and when λ value is more than 1, the corresponding PCs would be retained. Therefore, PC1 proves to be more important than PC2. Compared with Sp, Ha, Ad, Co, Ch and Re were in the opposite directions in the first principal component (Figure 5B). Ha and Sp might be the more valuable parameters if the results of PC1 and PC2 were taken into account simultaneously. Ten-fold cross-validation method was used for further classification

analysis with the averaged physical properties of wet masses as input variable and categories of particles as output variable. A J48 pruned tree of wet masses classification with 91% correctly classified formulations was obtained. According to the result, the wet masses could be classified into 3 groups by taking Ha as the first classification index, Ha/Sp as the second classification index, respectively. It seemed that other physical parameters didn't contribute to the classification of wet masses, including MRC. If Ha value of wet masses was more than 15610 g, it would form pellets of type ①. If Ha value was no more than 15610 g, it would form pellets of type ② or type ③ based on Ha/Sp value; type ① was produced when Ha/Sp value was over 18843, and type ③ was formed when Ha/Sp value was less than 18843. Therefore a very simple classification plot of wet masses was obtained which used to predict the types of particles under the drug loading of 30% (Figure 6A).

If Ha/Sp was taken subjectively as the first classification index and Ha as the second one, another simple classification plot of wet masses was gained (Figure 6B). And there were still 9 formulations incorrectly classified. Therefore, it could be concluded that Ha/Sp and Ha play an equally important role in the spheronization process. Other physical properties such as Ad, Ch, Co, Re and MRC had no contribution to the classification plot and could not enhance the classification accuracy.

Therefore, the functions of physical properties of wet mass could be concluded in spheronization process when the mechanisms of pellets formation (Figure 7) were argued. The cylindric wet masses would be cut by the shear plate and were not prone to produce deformation due to their higher hardness. Clavate, double sphere or dumb-bell shaped pellets were produced because of the difficulty in cutting of cylindric wet masses. So a smaller Ha value would benefit the cutting process. Particles are tumbled, collided, and rotated in the spheronization process, and are shaped by mechanical forces such as centrifugal force, friction force, elastic force and so on. With the decrease of Ha, particles become soft and easy to deform, and then they are combined together under the mechanical forces in the spheronization process. Another case was that particles became easily recovered with the increasing Sp, and then embedded in each other. Finally, oversized pellets were obtained. Therefore the wet masses require a proper range of Ha, which would help them to be initially broken up into short cylinders, and formed the short cylinder into an intermediate shape with round edges and finally, forming spherical pellets as a result of a suitable Sp.

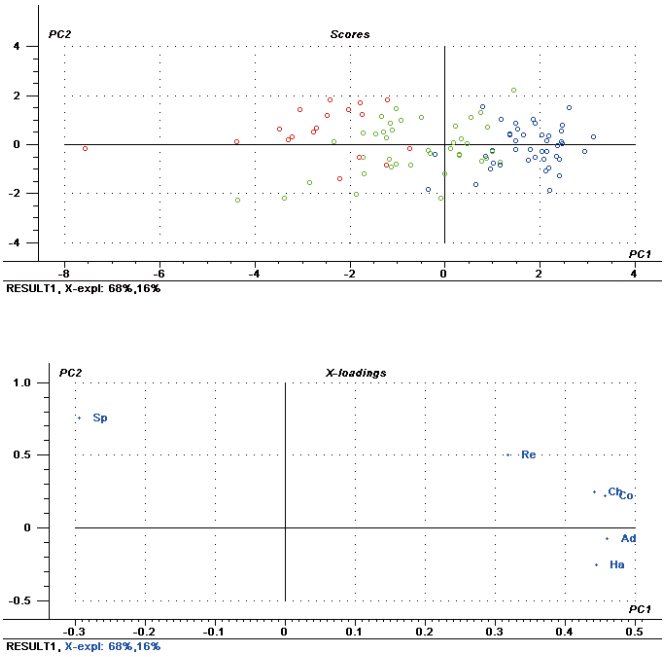

FIGURE 5 - (A) PCA score plot of the physical properties of wet masses for type ① (◯), type ② (◯) and type ③(◯). (B) PCA loading plot of the physical properties of wet masses.

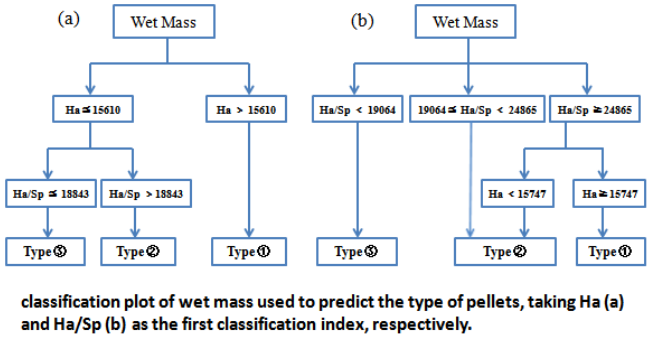

FIGURE 6 - classification plot of wet mass used to predict the type of pellets, taking Ha (a) and Ha/Sp (b) as the first classification index, respectively.

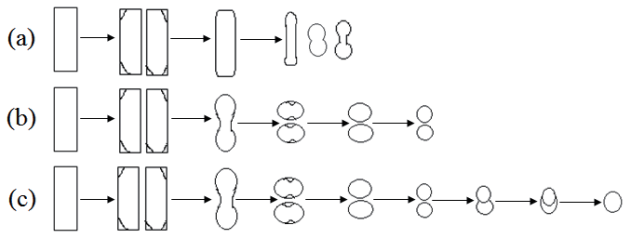

FIGURE 7 - The probable formation mechanisms of pellets in spheronization process(a) clavate, double sphere or dumb-bell shaped pellets; (b) spherical pellets;(c) oversized pellets.

TABLE IV – PCA result of the physical properties of wet masses

Component	Initial Eigenvalues			Extraction Sums of Squared Loadings		
	λ	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	4.053	67.548	67.548	4.053	67.548	67.548
2	0.960	15.995	83.542			
3	0.615	10.245	93.787			
4	0.236	3.942	97.729			
5	0.129	2.151	99.880			
6	0.007	0.120	100.000			

CONCLUSIONS

In this study, a classification plot of wet masses which was used to predict pellet types for powdered herbal slices with 30% drug loading is exhibited. Taking Ha as the first classification index, Ha/Sp as the second, the wet masses could be classified into three types. Therefore, the quality of the final product can be predicted in accordance with their physical properties. Meanwhile, the functions of physical properties of wet mass were concluded in spheronization process when the mechanisms of pellets formation were argued, which may provide useful information to improve pellet quality.

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CONFLICT OF INTEREST

The authors report no declarations of interest.

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