Journal of Chronotherapy and Drug Delivery

ORIGINAL RESEARCH PAPER

Microwave Drying of Tablet Granules: A Preliminary Study Towards Green Pharmacy

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Key words
Granule drying, Paracetamol, Microwave, Green pharmacy, Green chemistry

Abstract
In the concept of Green Pharmacy, all the pharmaceutical unit operations involving heat are carried out using microwave heating technique, an important non-conventional method. In India, microwave technique has not been explored for pharmaceutical applications. Hence, the present project was undertaken to standardize the drying process for pharmaceutical granulations by microwave technique. Eight batches of granules were prepared adapting microwave drying and compared with conventionally dried granules. The granules were prepared by wet granulation method followed by microwave drying at different intensities in a domestic microwave oven for different time intervals. The prepared granules were evaluated for moisture content, fines, bulk density, compressibility and flow properties. From the results, it was concluded that there was no difference between microwave dried and conventionally dried granules, except their moisture content. The granules were compressed into tablets after mixing with glidant and lubricant. The tablets were evaluated for weight variation, hardness, friability, drug content, disintegration and dissolution. The tablets prepared using microwave dried granules had properties similar to conventional tablets. The tablets prepared using granules dried at 650 to 850 W intensity had ideal properties comparable to the conventional tablets. From the study, it was concluded that by using microwave, drying time of granules is reduced by at least 10 times than the conventional method, which can save time and energy without affecting the quality of the tablets.

J Chronother Drug Deliv | Vol 7| Issue 3| 2016: 83-90

INTRODUCTION

With the increasing awareness of environmental pollution and related hazards, it has become a challenge for scientists to design newer or alternative ways for carrying out chemical reactions and pharmaceutical unit operations. The chemical manufacturing and isolation processes should be developed so that they do not cause permanent damage to the eco-system. This is an emerging field called green chemistry. According to an US award program, green chemistry is a process that encompasses all aspects and types of chemical processes including synthesis, catalysis, analysis, monitoring, separations and reaction conditions that reduces adverse impacts on human health and the environment relative to the current state of art.[1-4]

Very similar to Green Chemistry, a new concept called 'Green Pharmacy' is emerging, in developed countries, in which all the pharmaceutical unit operations involving heat are carried out using microwave. This concept has applications including sterilization of pharmaceutical preparations and auxiliary materials, thermo therapy, rapid dissolution of compounds, drying of granulations for tabletting, radio pharmaceutical compounding, drying of medicinal plants, preparation of essential oils from medicinal plants, inactivation of enzymes in food products, hydrolysis of proteins and peptides, activation of chromatographic adsorbents, fast detection of spots after vaporization of reagent, etc.[5]

In the past few years, microwave heating has been found to be a convenient source of energy not only in kitchen but also in chemical laboratories. Many of the above basic principles of green chemistry are best suited for microwave-induced reactions in chemistry laboratories. It is one of the simple, safe, fast, clean, eco-friendly and efficient synthesis. The method is found to be economic by saving of energy, fuel and electricity. A very short response time and better yields of the products are the main advantages of microwave heating.

Traditional pharmaceutics laboratories use heating using steam, hot air and electric mantles. A substantial amount of savings in time and electricity can be achieved by applying microwave techniques in routine experiments involving heating, at undergraduate and post-graduate levels. It is found to be a fast, safe and economic and acceptable technique at the university and college laboratories. Synthesis of drugs, intermediates, chemicals, activation of chromatographic adsorbents, determination of loss on drying, drying of glass wares, sterilization of glass wares and axillaries, drying of granules for the preparation of tablets, enzyme inactivation of food products, hydrolysis of proteins and peptides, saponification of oils, etc., are a few examples of use of microwave in laboratories.[5]

Major limitations of classical Pharmaceutics experiments are longer time, higher cost, longer reaction time and environmental pollution due to the use of large of quantities of solvents/reagents. Since the heating process is very short in microwave procedure, which saves fuel / electricity, and chemicals helps to reduce environment pollution.

Microwave induced heating and reaction rate enhancement techniques are just a decade old, but they have emerged as important non-conventional methods of reaction activation and pharmaceutical heating. However, in India, even though microwave technique has been evaluated for chemical reactions, it has not been explored for pharmaceutical applications. Hence, the present project was undertaken to standardize the drying process for pharmaceutical granulations by microwave technique.

EXPERIMENTAL

Materials

Paracetamol was obtained as gift sample from Sipali Chemicals, Chennai. Polyvinyl pyrrolidone (PVP) K-30 was obtained as gift sample from Sigma Chemicals, St. Louis. Starch-1500 was purchased from Colorcon, Goa. Avicel PH-101 (MCC) was obtained from Signet, Mumbai, Aerosil (Colloidal silicon dioxide) was obtained from Degussa, Mumbai. Magnesium stearate, was obtained from SD Fine Chem, Mumbai. All other chemicals and reagents used were of AR grade and were purchased from SD Fine Chem, Mumbai.

Formulation of Paracetamol Granules

In the present study, granules were prepared using paracetamol was used as model drug, PVP K-30 as binder, Starch-1500 as disintegrant, Avicel PH-101 as filler, Aerosil as glidant and Magnesium stearate was used as lubricant. The granules were prepared according to the formula given in Table 1.

Table 1. Formula used for the preparation of paracetamol tablets

Ingredients	Quantity per tablet (mg)
Paracetamol	250
PVP K-30 (binder)	40
Starch-1500 (disintegrant)	40
Avicel PH-101 (diluent)	64
Aerosil (glidant)	2
Magnesium stearate	4

Preparation of Granulating Medium

For the preparation of granulating medium, the binder was dissolved in distilled water and heated lightly on a hot plate with stirring. Water was added to make up the weight loss due to evaporation.

Conventional Granulation Procedure

Wet granulation technique was used for the preparation of granules.[6] The required quantities of drug and other excipients were weighed and passed through British Standard Sieve no. 60, to get uniform particle size. The powders were then mixed to get a uniform blend. The granulating medium was added to the powder blend and mixed well until a smooth dough was obtained. The wet granules were passed through sieve no. 10 and dried at 60°C for 30 min in a tray dryer. The dried granules were passed through sieve no. 16/22 and the granules which passed through sieve no. 16 but retained on sieve no. 22 were selected. The granules obtained through sieve no. 22 were considered as fines. Using conventional procedure, only one batch of granules was prepared.

Microwave Granulation Procedure

The required quantities of drug and other excipients were weighed and passed through British Standard Sieve no. 60, to get uniform particle size. The powders were then mixed to get a uniform blend. The granulating medium was added to the powder blend and mixed well until a smooth dough was obtained. The wet granules were passed through sieve no. 10 and dried at different intensities of microwave such as 90, 160, 350, 500, 650, 750, 850 and 900 W for different time intervals. After every 15 sec, the granules were observed for dryness and if not dried, the drying process was continued until the granules were completely dried. A total of eight batches of granules were prepared corresponding to different intensities used for drying. After complete drying, the dried granules were passed through sieve no. 16/22 and the granules which passed through sieve no. 16 but retained on sieve no. 22 were selected. The granules obtained through sieve no. 22 were considered as fines.

Evaluation of Granules

The granules prepared using both conventional and microwave procedure were evaluated for moisture content using IR balance, percentage of fines, bulk density, compressibility and flow properties using angle of repose.[7,8]

a. Moisture Content

The moisture content of the granules was determined immediately after drying using an infrared moisture balance. Accurately weighed granules (3 g) were placed into the pan of the IR balance and the IR was switched on until the weight reached a constant level. The final weight was noted. The weight loss, which represents moisture content, was calculated.

b. Percentage of Fines

The granules were passed through the British Standard Sieve no. 16/22. The material retained on sieve no. 22 and the fines obtained through sieve no. 22 were collected separately and weighed. From this, percentage of fines was calculated.

c. Bulk Density

A given quantity of the sample was transferred to a measuring cylinder and was tapped mechanically, using a tapping device (Electrolab, Mumbai, India) till a constant volume is obtained, which is referred as bulk volume (V_b). The bulk density of the sample was calculated.
Bulk density = Mass of powder / bulk volume of powder

d. Compressibility

The compressibility index of the granules was determined by using loose and tapped bulk densities of the granules, according to the equation given below:
Carr's Consolidation Index = [(TBD-LBD) x 100]/TBD

e. Flow Properties

A funnel was fixed at a particular height 'h' cm on a burette stand. A graph paper was placed below the funnel on the table. The sample whose angle of repose is to be determined was poured into the funnel by closing the bottom of the funnel. The bottom was opened and sample was allowed to fall onto the paper. The height (h) of the formed pile was measured and the circumference of the pile was drawn with the pencil on the graph sheet. The radius of the pile was noted as 'r' cm and the angle of repose was calculated as follows.
$\tan \theta = h/r$ or $\theta = \tan^{-1}(h/r)$
Where, h = height of pile, r = radius of pile, and θ = angle of repose

Preparation of Tablets

The granules were mixed with glidant and lubricant and compressed using a ten-station rotary tablet machine (Rimek, Ahmedabad) with 10 mm standard concave punches. The batch size was 50 tablets. After compression, the tablets were stored for 72 h with silica gel to allow elastic recovery and hardening. A total of nine batches of tablets were prepared, one batch corresponding to conventional granulation procedure and eight batches corresponding to microwave drying at different intensities.

Evaluation of Tablets

The prepared tablets were evaluated for weight variation, hardness, friability, drug content, disintegration time and *in vitro* dissolution profiles.

a. Weight Variation

The weight of ten tablets from each batch was determined using a digital balance and average weight and standard deviation were calculated.

b. Hardness

The hardness of a tablet is indication of its strength.[6] It is tested by measuring the force required to break the tablet across the diameter. The force is measured in kg/cm^2 and the hardness of about 4 kg/cm^2 is considered to be satisfactory for uncoated tablets.[7] Monsanto hardness tester (Cadmach, Ahmedabad, India) was used for this purpose. The hardness of three tablets was measured and the average hardness was calculated.

c. Friability

Friability is the loss of weight of tablet, due to removal of fine particles from their surfaces.[6] Friability test is carried out to assess the ability of the tablet to withstand abrasion in packing, handling and transport. Roche friabilator (Electrolab, Mumbai, India) was used for finding out the friability of the tablet. Ten tablets were weighed accurately and placed in friabilator. After 100 revolutions, the tablets were taken out from

the apparatus, de-dusted and weighed. The loss in weight indicates the friability of the tablets. Percent friability was determined by using the formula below:
Percent Friability = $[(w_1-w_2)\ 100] / w_1$
Where w_1 is the initial weight of tablets and w_2 is the final weight of tablets, after the test.

d. Drug Content

For the determination of drug content, the assay procedure described in Indian Pharmacopoeia was used.[9] Twenty prepared tablets from each batch were taken and each tablet was weighed accurately and powdered. A quantity of powder equivalent to 0.5 g of paracetamol was extracted with 60 ml of chloroform for 15 min and filtered. The drug content was determined after suitable dilution by measuring the absorbance at 257 nm, in a UV-visible spectrophotometer (Shimadzu 160-A, Japan).

e. Disintegration Time

The disintegration test is performed to determine the time required for complete disintegration of the tablet into small particles of size less than 10 mesh. It was determined using a disintegration test apparatus (Electrolab, Mumbai, India) at 37 ± 0.5 °C. The tablets were considered to have disintegrated when all the particles had passed through the wire mesh.

f. In vitro Dissolution

Dissolution studies were carried out using USP (XXIII) dissolution apparatus (Electrolab, Mumbai, India) following paddle method. Freshly prepared buffer of pH 5.8 (900 ml) was placed in the dissolution flask and allowed to attain a temperature of 37 ± 1°C. The tablet was placed at the bottom of the dissolution flask. The paddle was rotated at 50 rpm for 30 min. One ml of the sample was withdrawn at different time intervals of 5, 10, 15, 20, 25 and 30 min. After each withdrawal, the medium was replaced by equal amount of fresh buffer. The samples were diluted to 10 ml with dissolution medium and used for measurement of absorbance 257 nm, in a UV-visible spectrophotometer.

RESULTS AND DISCUSSION

Preparation and Evaluation of Granules by Conventional and Microwave Methods

One batch of granules corresponding to conventional wet granulation and eight batches corresponding to different microwave intensities of drying were prepared and evaluated for moisture content using IR balance, percentage of fines, bulk density, compressibility and flow properties using angle of repose. The results of the evaluation of granules are shown in Table 2.

Table 2. Properties of paracetamol granules prepared using conventional and microwave methods

Property	B1 90 W	B2 160 W	B3 350 W	B4 500 W	B5 650 W	B6 750 W	B7 850 W	B8 900 W	B9 CG
Drying time (min)*	9.00 ± 0.11	7.50 ± 0.12	5.50 ± 0.05	3.75 ± 0.20	3.25 ± 0.50	2.75 ± 0.50	2.15 ± 0.25	2.00 ± 0.25	30.00 ± 0.55
Moisture content (%)	10.14	9.17	3.56	1.81	1.55	1.56	1.54	2.35	5.25
Amount of fines (%)	3.52	2.81	2.32	2.29	2.28	2.66	3.82	3.37	3.88
Bulk density (g/cc)*	0.77 ± 0.01	0.82 ± 0.02	1.04 ± 0.06	0.77 ± 0.02	0.77 ± 0.01	0.77 ± 0.00	0.77 ± 0.00	0.77 ± 0.00	0.77 ± 0.00
Compressibility (%)*	14.15 ± 0.13	14.27 ± 0.04	9.86 ± 0.26	14.20 ± 0.05	14.22 ± 0.03	14.19 ± 0.01	14.20 ± 0.04	14.19 ± 0.02	14.19 ± 0.04
Repose angle (deg)*	29.15 ± 0.35	29.65 ± 0.02	32.11 ± 0.79	30.03 ± 0.07	28.88 ± 0.07	30.11 ± 0.02	30.08 ± 0.07	30.05 ± 0.07	29.84 ± 0.38

* The values are represented as Mean ± SD; n=3; CG- conventional granulation

The granule drying time was found to be very less in case of microwave drying. The conventional drying method took 30 min for complete drying of granules, whereas, the microwave method took a maximum of 9 min at lowest intensity (90 W). At the highest intensity (900 W), just 2 min time was sufficient to dry the granules completely.

The effect of microwave drying on different physical properties of granules was studied. The granules prepared by conventional method retained 5.25% of moisture, whereas, batches B3 to B8, prepared by microwave drying had moisture content less than 5%. The batches B1 and B2 which were dried at 90 and 160 W intensity of microwave, had 10.14 and 9.17% of moisture, respectively. This might be due to the use of very low intensities. The fines were found to be in the range of 2.28 to 3.82% in case of microwave dried granules. There was no significant difference in the amount of fines between microwave drying and conventional drying. Similarly, bulk density and compressibility also did not change when the granules were dried by microwave. The flow property of different batches of granules also did not change significantly. All the granules exhibited good flow. Finally, from the results of granules evaluation, it could be concluded that there was no difference between microwave dried and conventionally dried granules, except their moisture content.

Preparation and Evaluation of Tablets

The results of evaluation of physicochemical properties of tablets prepared using microwave dried and conventionally dried granules are shown in Table 3. The tablets were evaluated for weight variation, hardness, friability, drug content, disintegration and *in vitro* dissolution. The average weight and weight variation were within the IP specified limits for uncoated tablets[25]. The hardness of different batches of tablets was within the range of 3-5 kg/cm^2, which was again within specified limits. Only B8, which was prepared by granules dried at 900 W, had lowest hardness. This might be due to the reason that the granules had minimum moisture content, which might not be sufficient for producing sufficient hardness. There was no significant difference between conventional and microwave tablets. The conventional tablets had slightly higher friability than the microwave tablets. But, the results were within limits. There was no significant difference in the drug content of the conventional and microwave tablets, which indicated that the microwave heating of granules did not cause any thermal damage to the drug. The tablets prepared with granules dried at low intensities of microwave took 25 min for complete disintegration. This might be due to higher moisture content remaining in the granules. But, the tablets prepared with granules dried at higher intensities of microwaves exhibited disintegration time of 15 min. This might be again due to lower moisture retained in the granules, which makes them hygroscopic and exhibit reduced disintegration times.

Table 3. Properties of paracetamol tablets prepared using conventional and microwave dried granules

Property	B1	B2	B3	B4	B5	B6	B7	B8	B9
	90 W	**160 W**	**350 W**	**500 W**	**650 W**	**750 W**	**850 W**	**900 W**	**CG**
Average weight (mg)	410.00 ± 0.25	405.50 ± 0.22	398.50 ± 0.35	399.75 ± 0.25	400.25 ± 0.50	415.74 ± 0.05	413.29 ± 0.55	411.55 ± 0.52	405.00 ± 0.05
Hardness (kg/cm^2)	5.50 ± 0.50	5.45 ± 0.25	4.50 ± 0.25	4.25 ± 0.00	4.20 ± 0.50	4.20 ± 0.50	4.00 ± 0.25	3.20 ± 0.50	4.25 ± 0.50
Friability (%)	0.09	0.01	0.15	0.02	0.04	0.06	0.07	0.10	1.08
Drug content per tablet (mg)	249.07 ± 0.01	251.82 ± 0.02	249.04 ± 0.06	248.77 ± 0.02	249.25 ± 0.01	248.75 ± 0.05	249.97 ± 0.04	249.17 ± 0.25	250.55 ± 0.05
Disintegration time (min)	25	25	20	20	15	15	15	10	15

The values are represented as Mean ± SD; n=3; CG- conventional granulation

The results of *in vitro* dissolution studies of different batches of tablets pare shown in Figure 1. From the results, it was found that the tablets prepared by conventional granulation and those prepared by microwave granulation at intensities of 850 and 900 W exhibited good release profiles. They released 92-98% of drug in 60 min. The tablets prepared with granules dried at 90 and 160 W exhibited lowest dissolution rates. This might be due to the higher moisture content present in the granules. The other batches exhibited moderate dissolution profiles with 89-90% release in 60 min time. From the results, it can be concluded that the batches which were dried at the intensities of 650 to 850 W were ideal batches, and the results were comparable with that of conventional tablets. Hence, these two intensities can be used for drying of granules in regular pharmaceutics practical classes.

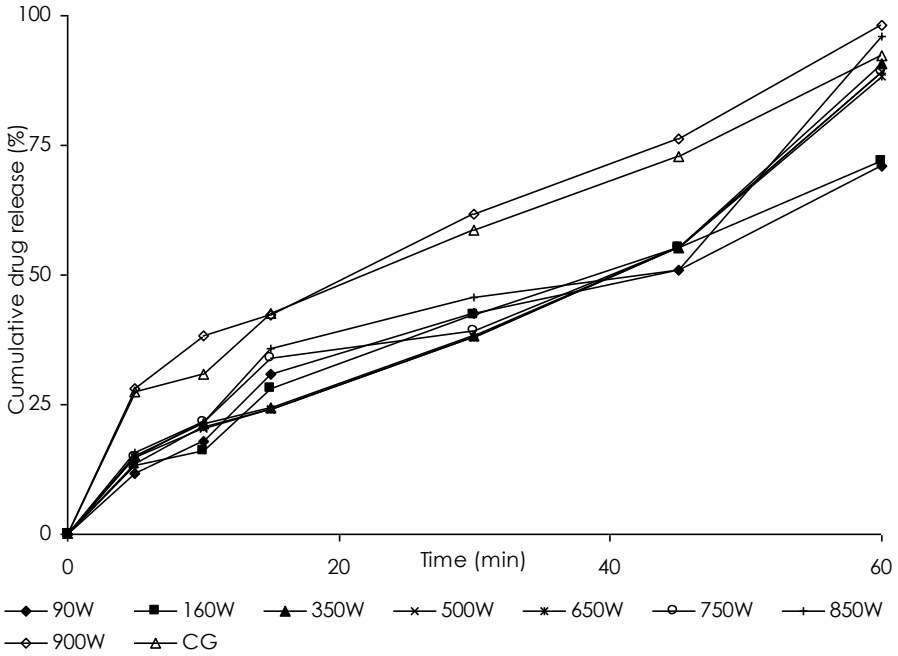

Figure 1. *In vitro* dissolution profiles of different batches of tablets prepared by microwave and conventional methods

CONCLUSION

In conclusion, it can be stated that tablet granulation can be dried successfully using a domestic microwave oven. By adopting microwave drying technique, tablet granules can be prepared in less duration of time, at least 10 times less than the conventional drying procedure. This technique can be used in regular practical classes involving drying of granules. This can save time, energy and cut down the cost of conducting practical classes. Also, use of such technique can reduce environmental pollution.

DECLARATION OF INTEREST

It is hereby declared that this paper does not have any conflict of interest.

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Received: August 5, 2016; Revised: September 3, 2016; Accepted: September 12, 2016