INSTITUTE OF CHEMICAL TECHNOLOGY PRAGUE
Faculty of Chemical Technology
Department of Organic Technology

Specialized Laboratory for Drug production
(N111049)

Instructions

Solid dosage forms testing: Disintegration test and tablet friability and hardness

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Study program: *Drug synthesis and production*

Study field: *Drug production*

Location: *S25b*

Introduction

A highly economical method of tablet production, in which active pharmaceutical ingredients (APIs) and excipients are processed without granulation, is a direct compression (direct tableting). During this method, it is not necessary to produce granulates, which requires the use of several manufacturing steps, each of which has to be validated. Moreover it is a method without the use of a solvent. Hence, it is not necessary to dry the mixture and there is no need to worry about the devaluation of API due to humidity or elevated temperatures. Also the processing time and costs are cut. Very important characteristic of the tablets prepared by direct compression is the disintegration of tablets into primary particles and not into granulated aggregates, which enables higher rate of API release.

A direct compression is used particularly for the APIs with high efficiency. In this case, API is present in a strong minority in the dosage form, hence, the flowability and compressibility depend especially on the properties of excipients in the mixture. Therefore, the selection of the proper excipient or the combination of excipients is the base of every pre-formulation study.

Hence, the selection of the proper excipient based on the basic pharmaceutical tests will be the subject of this work.

Tasks

1. Familiarize yourselves with the chapters Solid dosage forms mass uniformity, Tablet friability, Disintegration test and Tablet hardness in the USP.
2. Prepare 14 tablets of 0,4g meeting the requirement on the mass uniformity of the solid dosage forms from 3 formulations of different composition. Discuss the differences in compressibility of the individual formulations.
3. Choose 5 tablets from each formulation and perform the friability test. Discuss the differences in friability between the tablets prepared from the different formulations.
4. Choose 3 tablets from each formulation and perform the disintegration test. Discuss the differences in the disintegration of the tablets prepared from the different formulations regarding the solubility of the excipient.
5. Choose 5 tablets from each formulation and perform the tablet breaking force test. Discuss the differences in the hardness between the tablets prepared from the different formulations.
6. Discuss the properties of the excipients and identify the most suitable formulation based on the performed experiments above. Explain your selection.

Instruments and procedures

Preparation of the pharmaceutical formulations

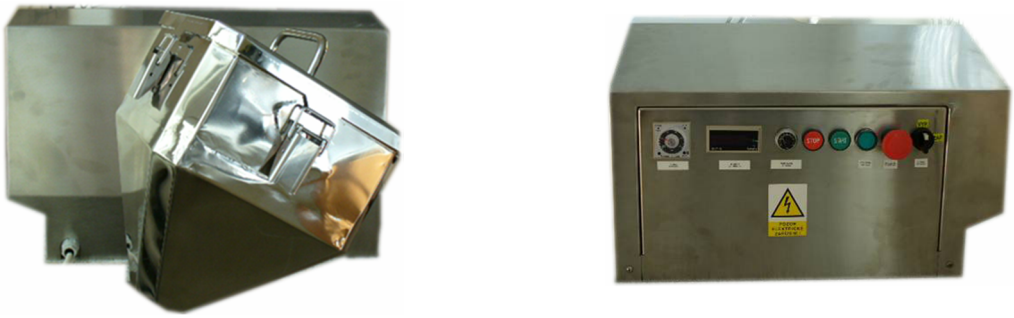
Prepare pharmaceutical formulations of different composition by homogenization the substances below. Calculate the amount of the individual components necessary for preparing 14-16 tablets. Put the components one by one into the plastic pot. Note the sample weight of the components.

Formulation A:
[1]Paracetamol: Avicel®: Magnesium stearate (1: 10 : 0,11)

Formulation B:
Paracetamol: Lactose: Magnesium stearate (1: 10 : 0,11)

Formulation C:
Paracetamol: Lactose: Avicel®: Magnesium stearate (1: 7,5: 2,5: 0,11)

After putting all the components into the pot pre-mix the mixture with a spoon, then close the pot carefully and put it into the vessel of 8 dm^3 of the laboratory blender Hotic (Fig. 1).



Obr. 1: Laboratory blender Hotic; front and rear view

After putting all three pots into the vessel, close it with the lid and fix the lid on each side using four holders.

Homogenization

1. Turn on the blender using the main switch on its rear side on the right (Fig. 1)
2. Push the button “PŘÍPRAVA ROTACE“. It should light up.
3. Set the rotation speed using a knob to 25 rpm (corresponds to a position 9 on the knob)
4. Turning the wheel “ DOBA ROTACE” set the blending period to 20 minutes (beware, it does not correspond to the value 0,2)
5. Begin the homogenization by pressing “START”

[1] Note: Paracetamol is not usually processed with direct compression, as the inclusion of excipients into the dosage form, which would enable the direct compression, would lead to the preparation of tablets with unsuitable size. In this work, paracetamol is used as a model substance simulating the API with good solubility.

6. Wait for the rotation speed being steady and adjust the rotation speed to 25 rpm according to the values on the display.
7. The rotation of the vessel should stop after 20 minutes. Also it is possible to stop the rotation anytime by pressing “STOP” button.

Direct compression

Perform the tableting using the hydraulic press Specac and the accessories for tablet preparation. (Fig. 2)

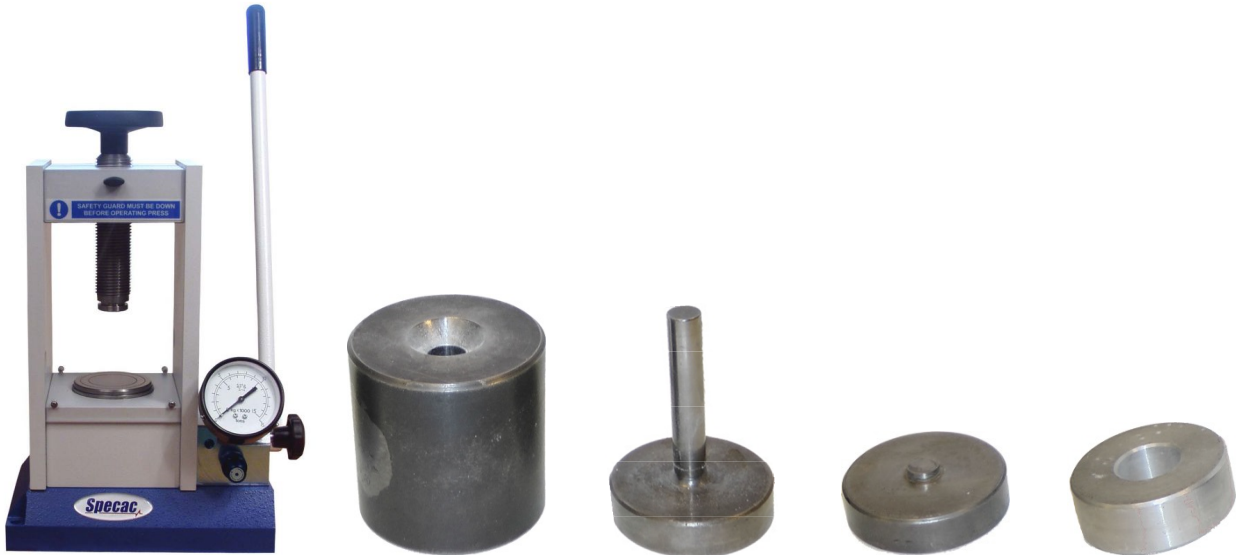


Fig. 2:Hydraulic press Specac and the accessories for tablet preparation

1. Weight the necessary amount of the formulation.
2. Close the die with the lower punch and put in the tableting formulation. By careful shaking the die put the rests of the formulation, which were captured on the die surface, inside the die.
3. Put the upper punch into the die, take the die with lower punch from the bottom part and opening the glass with upwards movement put the die in the middle of the hydraulic press.
4. Push the lead screw to the upper punch by lead screw handle movement.
5. Close the pressure release handle (on the right side of the press) by moving it in the direction “CLOSE”.
6. Perform the pressing by pumping the pump handle. Observe the force indicator movement and evaluate the compressibility of the mixtures based on the rate of the force decrease and the number of the pumping movements needed. Discuss the differences between the formulations.
7. When the indicator reaches the force of 10 000N end the pressing.

8. Open the the pressure release handle (on the right side of the press) by moving it in the direction “OPEN”.
9. Take the die from the press, put away the lower punch and dislodge the tablet by pushing the upper punch. If the dislodging is not possible, put in the middle of the press the aluminum wheel and put the die on the top of it. Then push the upper punch by lead screw movement.
10. Weight the tablets and for each formulation discuss if it meets the requirement on the tablet mass uniformity. For this purpose, calculate the average weight of the tablets and the relative deviation of the tablets form this average.

Tablet friability

1. Take 5 tablets from each formulation, get them rid of the dust using the compressed air, weight them a put in a friability tester. (Fig. 3)
2. Turn on the apparatus by pressing the knob “mains” a set the rotation speed to 25 rpm.
3. Start the rotation of the device by pressing “start/stop” button.
4. End the rotation after 4 minutes by re-pressing “start/stop” button.
5. Take out the tablets, get them rid of the dust and weight them.
6. Calculate the relative weight loss of the tablets and discuss the compliance to the requirement for the tablet friability test.
7. Discuss the differences between the formulations.

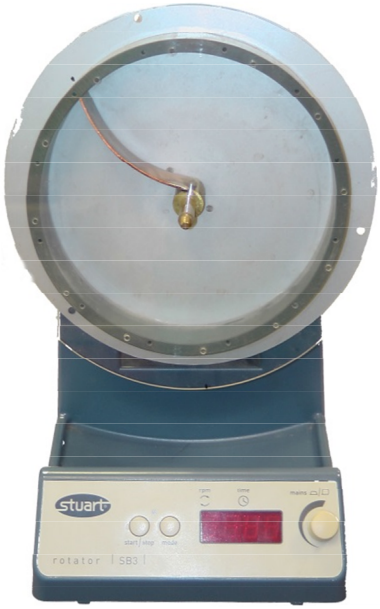


Fig. 3: Friability tester

Tablet disintegration

1. Take 3 tablets from each formulation for the disintegration test.
2. Into the beaker of 1000 ml put water of 37 ± 2°C. Fix the basket to the disintegration tester and place the beaker with water. Adjust the water level to achieve the bottom of basket being 15-20 mm below the water level at the top dead center movement of the basket.
3. Set the motor rotation speed to the minimal value (30 rpm).
4. Insert the tablet, turn on the motor and begin to measure the disintegration time.
5. Observe visually the course of the test.
6. The end of the test is the time when there is no residue of the tablet left in the basket.
7. If the tablet is not fully disintegrated within 15 minutes consider it as uncompliant, but continue the measurement until 25 minutes. If the tablet is still not disintegrated, perform the accelerated disintegration test using the motor speed 60 rpm with the remaining two tablets.
8. If the tablet disintegrates within 15 minutes, repeat the measurement three times. Use the average from the measurement as a result. Also indicate the standard deviation of the monitored variable.

Tablet hardness

1. Take 5 tablets from each formulation for the tablet hardness test, which will be performed on the TMZ-3U Electronic *Micro Sensor* device (fig. 4).
2. Turn on the device using the power switch on the front side of the device on the right.
3. At first, set the mode of the measurement for measuring the force: press „↓MENU“, enter the code „07“ , choose „0“ for the force measurement and confirm „ ↵ “ (ENTER).

4. Set the range of the measurement: : press „↓MENU“, enter the code „04“ , choose „2“ for the range until 750N and confirm „ ↵ “ (ENTER).

5. Now you can start the measurement. At first, measure the dimensions (diameter, thickness) of the tablet using the caliper. You will use these data for the subsequent calculation of the tablet tensile strength. Then insert the tablet in the middle of the instrument jaws, so that the tablet will be deformed in the perpendicular direction to the direction in which it was compressed (fig. 4 right). Press „↓MENU“, enter the code „01“ , and confirm „ ↵ “ (ENTER). This will crush the tablet and the display will show the value of force. Note this value.

6. After the end of the piston upwards movement remove the tablet and clean the instrument jaws.

7. Measure all 5 tablets. Express the results in the average, minimal and maximal value of the measured force in the Newton units.

8. Because of the influence of the tablet size on the force needed for the tablet crush, it is usual to calculate the tensile strength of the tablets. Calculate the value of the tensile strength according to eq. 1 and determine the relative standard deviation of the measurement.

$$T_S = \frac{2F}{\pi d v} \qquad (1)$$

Where *F* is a breaking force, *d* is the tablet diameter and *v* is its thickness.

9. Discuss the differences between the formulations.

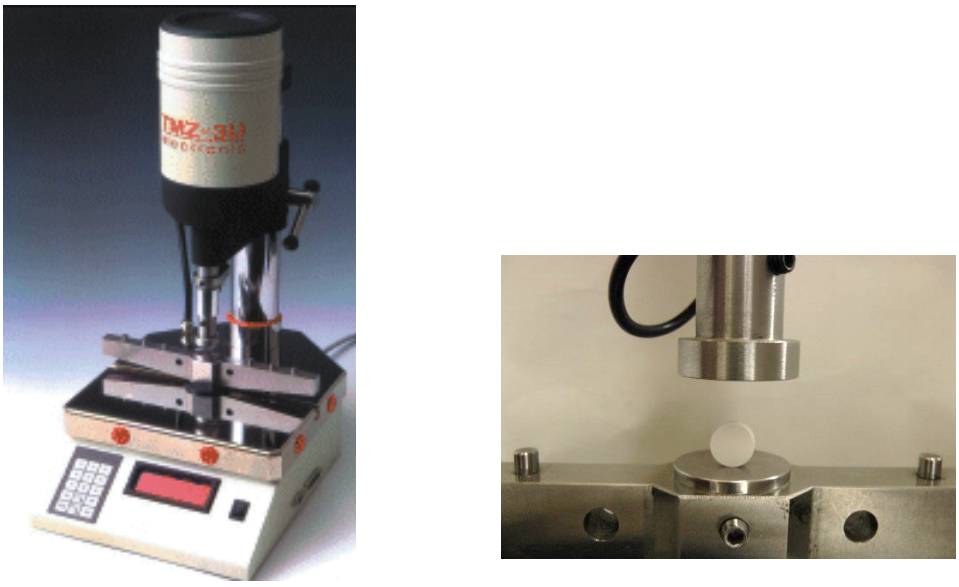


Fig. 4: The apparatus for the tablet hardness measurement MicroSensor (left). Correct position of the tablet between the instrument jaws (right).

Protocol requirements

→ Header, briefly stated the aims of the work, procedures of the work
→ Sample weights of the individual compounds in the tableting formulations
→ Weight of each tablet a the discussion of the dosage form mass uniformity
→ All measured variables of the performed tests and the discussion of the differences between the formulations
→ Visual evaluation of all tests performed
→ The choice of the suitable excipient based on the performed tests and visual evaluation
→ The proposal to improve the pharmaceutical formulation / extension of the preformulation study
→ Adjust the graphical form of the protocol according to the manual for the protocol of specialized laboratory preparation

References

1. J. S. Swarbrick, *Encyclopedia of Pharmaceutical Technology, Third Edition - 6 Volume Set*, Taylor & Francis, 2006.