

PHARMACEUTICS AND FORMULATIONS 1B

PHAR5714

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UNIT OF STUDY COORDINATOR CONTACT DETAILS

Name of coordinator	A/Prof. Veysel Kayser
Telephone number (ext)	x13391
E-mail address	veysel.kayser@sydney.edu.au
Consultation times	By appointment: any mutually convenient time between 9.00 and 5.00, weekdays

UNIT OF STUDY DESCRIPTION

In this unit of study, as structured at the present and based on the Faculty of Pharmacy standard format, the intention is that students learn to evaluate the physicochemical principles, design, formulation, and manufacture of pharmaceutical dose forms. The formulation of liquid dose forms including parenteral, nasal, ophthalmic and aural products is discussed. Related topics such as diffusion and dissolution of drugs, drug solubilisation, surface and interfacial tension, surface active materials, micelle formation, pharmaceutical complexes and drug-packaging interactions are covered. Other topics covered in this unit include solid dose forms and particle science, rheology; dispersion dose forms including suspensions, colloidal dispersions, and emulsions; topical dose forms and semisolids; inhalation pharmaceutical aerosols; protein and peptide drugs and formulations; rectal products; novel drug delivery technologies. Aspects pertaining to the stability of dose forms are also presented in this unit.

PHARMACEUTICS AND FORMULATION: AIMS/GOALS

How this unit of study relates to previously studied units	Concepts studied in this unit of study will be further developed in "Integrated pharmaceuticals" and "Pharmacy Practice".
The key focus or purpose of this unit	This unit is designed to introduce students to the principles governing the formulation and manufacture of pharmaceutical dose forms, and assist them to develop skills in evaluating those dose forms.
How this unit of study prepares students for subsequent units	Concepts studied in this unit of study will be further developed in "Integrated pharmaceuticals" and "Pharmacy Practice".
How this unit helps students to develop generic or other skills	The learning activities in this unit of study encourage the development of generic skills such as effective communication of information, applying theory to practice, critical thinking, accessing and organizing knowledge, ethical behaviour and problem-solving skills.

LEARNING OUTCOMES FOR THIS UNIT OF STUDY

On successful completion of this unit of study, students should be able to:

1. Demonstrate an understanding of, and skills in critical evaluation of the principles involved in the formulation of medicines
2. Explain the design and formulation of drug delivery systems and apply these principles to patient care.

3. Apply safe laboratory practices and competently use standard laboratory equipment.
4. Critically examine scientific data in order to arrive at evidence base conclusions and apply the acquired knowledge in problem solving situations.
5. Relate theory to practice and effectively communicate this information in any area of pharmaceutical science.

LEARNING COMMITMENTS

Total number of practical hours	8
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ASSESSMENT

Practical assessment

Due date	Two 4 -hour sessions over 2 consecutive weeks: Please see list on Blackboard
Relative weighting	30 % (practical assessment must be passed to satisfy the requirements of the course)
Description of task	The practical exercise will be performed in small groups (See UoS for laboratory roster) during the scheduled practical sessions. The objective is to assess individuals' and groups' abilities to understand the underlying principles of the course through experimental investigation and critical analysis. Each practical will be marked according to the performance in the laboratory and the practical report submitted by the students. All practicals must be attended. A roll will be taken. Each group has to hand in their assignment, completed as a group assignment. The questions to be answered for the assignment can be found at the back of the laboratory manual. Assignment must be submitted in the assessment box located in the Pharmacy administration office one week after the second laboratory section by 4.00 pm. Example: if you are doing the first lab on Monday of week 1 and second lab on Monday of week 2, your group report is due Monday week 3 by 4.00 pm at the latest. Each report must have a compliance group coversheet filled and signed. Failing to do so will result in failing the assessment. Students will need to complete a peer assessment.
Grading criteria	Pass 50-64%; Credit 65-74%; Distinction 75-84%; High Distinction 85-100%

ACADEMIC HONESTY GUIDELINES SPECIFIC TO THIS UNIT OF STUDY

In Pharmaceutics and Formulation, you will be expected to have group discussions on the practicals as well as tutorial questions. Students should not copy the work of their colleagues or that of students from previous years. In addition, you are required to acknowledge the resources and reference materials used whenever applicable. Your course coordinator should be consulted if there is any doubt concerning what can be regarded as plagiarism.

FURTHER ACADEMIC HONESTY GUIDELINES SPECIFIC TO THIS UNIT OF STUDY

The University takes a serious attitude towards academic honesty. This section outlines practices which are acceptable and those which are unacceptable in Pharmaceutics and Formulation.

In Pharmaceutics and Formulation, collaboration between students is strongly encouraged as a valued educational practice, and as an essential life skill. Similarly, the ability to locate, analyse, synthesise and communicate information from original source materials is highly valued. The boundaries of legitimate activity in relation to these aspects of teaching and learning are that:

Students are encouraged to work within groups for the purposes of collecting, collating, analysing, interpreting, and synthesizing information relating to specified group activities. When a group report is specified, all students within the group are expected to provide input into the final product, although the group may decide how best to achieve this end.

When an individual report or assignment is specified, the individual student is expected to write the report or assignment in his or her own words. Students must NOT share drafts or final copies of individual reports/assignments with other students, and in particular must NOT provide copies in either electronic or printed form to any other student.

Reference materials and sources must be appropriately acknowledged. The website provides details of acceptable referencing systems. It is acceptable to quote short pieces of text directly, with appropriate referencing. It is NOT acceptable to include significant sections of unoriginal text, with or without acknowledgement. No distinction is made in this context between material sourced electronically and material in other formats such as print.

If you are uncertain about what is acceptable, please seek advice from the course coordinator before submitting your assignment or report. You are also requested to read the University policy on Academic Honesty and Plagiarism:

<http://www.library.usyd.edu.au/elearning/learn/plagiarism/>

<http://sydney.edu.au/policies/showdoc.aspx?recnum=PDO2012/254&RendNum=0>

PROGRAM OUTLINE

All labs are in room N355 Pharmaceutical technology laboratory. Refer to the Unit of Study for PHAR5714 on the USyd E-learning website for laboratory time allocation, notes and changes.

FACULTY OF PHARMACY LABORATORY SAFETY

Introduction

The study of pharmaceutical sciences is a fundamental part of any pharmacy curriculum. Since pharmaceutical science has developed largely as a result of experimentation, your study of pharmacy will be augmented by laboratory experiences that will be used to demonstrate, clarify and develop the principles discussed in lectures and tutorials. Your laboratory manual, along with discussions with your demonstrator, will help in your efforts to realise these objectives. However, the laboratory experience is what you make of it and you must take responsibility for your learning.

A laboratory environment differs considerably from the outside world, and it is necessary to make a few adjustments. Certain codes of conduct pertaining to your safety and that of others must be observed at all times: moreover, there are certain prescribed procedures for using glassware and other pieces of equipment.

Once you have read the following rules you will be asked to sign the attached form. This is to certify that you did, in fact read the rules and agree to adhere strictly to them at all times. Once you adopt the operating rules as a code to be followed at all times, you will be able to profit from and enjoy your lab experiences to a greater degree. You will be able to complete the experiments given in your lab manual in a relatively safe environment.

A proper respect for good housekeeping practices will prevent contamination of your laboratory glassware from hindering ion effects. This, and your correct use of glassware and other equipment, should ensure your success with the experiments you will execute through the course of the semester.

Safety rules

Work in the laboratory should be a safe experience. It will be safe; however, only if certain safety precautions are followed without exception. The safety rules that will form a large portion of your code of conduct in the laboratory are listed as follows:

1. In the first lab session locate safety equipment with the aid of your demonstrator or technical staff. Find the eye-wash, emergency shower, fire extinguisher, fire blanket and all exits that are to be used in an emergency. Your demonstrator and technical staff will describe the variety of safety equipment in your lab room.
2. Mobile Phones are to be switched off and not used in the laboratory.
3. Always use appropriate Personal Protective Equipment (PPE). Eye protection and lab coats are compulsory at all times in the laboratory. Prescription eyeglasses should be worn under the goggles if they are normally needed. Contact lenses are discouraged, because of their tendency to harbor various fumes, and increase the likelihood of eye injury. Please notify your demonstrator/technical staff that you are wearing contact lenses if you become aware of eye irritation.
4. Disposable gloves will be provided if necessary. Do not wear your lab coat or gloves outside the lab.
5. Wear clothes that cover your torso and legs. Clothing will often give a few extra seconds of protection that make the difference between a hole in the jeans and a nasty burn on your leg. Midriff T's, ripped up jeans, and mini's, although fashionable, are not acceptable.
6. Appropriate footwear needs to cover the whole of the top of the foot. Students will not be able to enter the lab wearing open toed shoes, thongs, sandals or high heels.
7. If any chemical comes in contact with your eye, the most effective first aid is the immediate flushing of the eye with copious amounts of water. Often, this will save the eye from additional injury and pain. There is an eye-wash in each lab room. Inform the demonstrator and send someone for help, continue flushing the eye for fifteen minutes (30 minutes for bases) or until trained medical help arrives and directs you to do otherwise.
8. Long hair in a lab is a hazard. Tie it back and keep it out of harm's way.
9. There is nothing wrong with not knowing how to do something. There is something very wrong with trying to do something you know nothing about. PLEASE, if you have any questions or aren't sure about something, ask the lab manager.
10. Do not eat, drink, chew gum, apply cosmetics, or put anything into your mouth while in the laboratory. Thousands of chemicals have been used in these lab rooms, and traces of them are on every table. Although invisible, these chemicals can still be potent. So to avoid inadvertently ingesting a harmful chemical, don't even put your pen in your mouth to hold it.
11. Do Not Hurry! There is plenty of time to complete each lab exercise. Adequate pre-laboratory preparation is essential; it can cut wasted steps and speed the final outcome. Read and outline your experimental procedure before starting each lab. This is guaranteed to get you finished in plenty of time.
12. Do not taste any chemical. Even those that might have pleasing odours often times have harmful effects if ingested.
13. Never smell a chemical directly. Use your hand to waft the odour to your nose. This dilutes the odour and can prevent accidental burning of the nasal passages, and prevent mucus membranes from some of the more potent vapours like ammonia.
14. Any and every cut, bruise, burn, scratch, and injury that occurs in the laboratory must be reported. Even if you feel it is minor, it still should be reported to your demonstrator or technical, who will determine if it should be further medical attention is required.
15. Never pipette a solution by mouth. Always use pipette filler.
16. Never open flammable liquids near an open flame. Pressurized vapours often escape, creating the potential for a flash fire. Keep all flammable liquids away from open flames.
17. Use extreme caution when heating any liquid in a closed or constricted container. For example, when heating a liquid in a test tube, always apply heat at the interface of the solution and the air. Heating below this point can cause bumping which is the rapid evaporation and evolution of steam below a liquid layer, which causes hot dangerous fluids to be ejected from the test tube. Also, be aware of where your tube is pointed, so if bumping does occur the projectile does not hit your face or your neighbour's face.
18. Never remove a chemical from the laboratory for any reason. This is grounds for expulsion and other severe disciplinary action.
19. Running, horseplay or any incident involving water bottles, will result in expulsion

from lab for the day and loss of all marks for that lab; a second incident will result in ejection from class.

20. If you are called upon to dilute or use concentrated reagent, please remember to add the reagent to water. NEVER ADD WATER TO A CONCENTRATED REAGENT!!! A reaction, and possible spraying of the concentrated reagent may occur. Ask if advice/help is needed.

21. Do not deviate from the planned experiment. Mixing uncalled for chemicals is costly, and dangerous. When discovered it will result in ejection from the class.

22. Never work in the lab alone. You must have the authorization of your demonstrator to start a lab.

23. Always handle glass tubing with care. Many times it has burrs and hairline cracks that can break if they are over-stressed.

24. Always hold containers below face level while stirring and observing its contents.

25. Be aware and wary of your neighbours' actions. Are they following the safety rules? A neighbour's silliness off may cause you injury, if you're not watching out for them.

26. Use a fume cupboard when required by the lab manual or directed by your demonstrator. Safe fume cupboard operation requires that the opening be at the yellow and black tape marks or lower. If the hood door is open higher than that point, chemicals can actually be drawn out and into your face. Check the opening level each time you use a fume cupboard.

27. Maintain aisles free from obstruction. Close lab drawers when not in use. Push chairs in toward the counter, and keep all unnecessary books, bags, and coats out of the aisles.

28. Wash your hands carefully after each lab, and whenever you come in contact with any substance. Hands contaminated with potentially harmful chemicals may harm your face, eyes, mouth, and mucus membranes without even being felt on your hands.

Housekeeping rules

Good housekeeping in the laboratory will provide a safe work site in which you may be assured that chemicals are not contaminated. Please obey the following rules:

1. Notify your demonstrator or a member of the technical staff so that broken glass may be cleaned up immediately. All glass and other sharp objects should be placed in the waste glass box located in each lab. NEVER throw glass in the waste bin!

2. Needles must be disposed of in the yellow sharps containers

3. Infectious material will be disposed of in the infectious materials bin.

4. Notify your demonstrator or a member of the technical staff of any chemical spill immediately! Do not attempt to clean it up yourself until it has been neutralised by trained personnel.

5. Never pour any chemical down the drain! Recovery containers are usually located in each hood. If none are available or are full, ask for one in the stockroom.

6. Don't insert a pipette, or dropper into a common stock bottle. This may contaminate the bottle. Instead, pour the amount needed into a beaker and then pipette or dropper from there.

7. Always read a bottle's label twice, to avoid a mix-up. The wrong chemical can lead to accidents or unexplainable results.

8. Often times reagent bottle tops become stuck. Notify your demonstrator or a member of the technical staff if this occurs.

9. Use special care when handling bottle stoppers. Treat them as if they were contaminated, being careful not to set them down, or they will pick up contaminants from the counter. Please ensure that you replace stoppers in the bottle as soon as you have finished with that bottle.

10. Take only the portion of chemical you need. You can always return for more. Never return the unused portion as it may be contaminated.

11. At the end of each lab period, be sure to put all unknown samples back where they came from, return all checked out items to technical staff.

Basic prep room procedures

1. Your student card is required before quartz cuvettes, weights or spatulas can be given out.

2. If you forget your eye protection you may borrow a pair of safety glasses, however you will need to give your student card to the technical staff. If you forget on more than one occasion then you will lose 10% of your marks for each experiment after the first occasion

NOTE:

You will not be allowed in the laboratory if you are not wearing appropriate Personal Protective Equipment (PPE). Eye protection and lab coats are compulsory at all times in the laboratory.

PRACTICAL BOOK (TABLETS: FORMULATION, PROCESSING AND EVALUATION)

The 2 practicals are printed on the following pages:

EXP 1: TABLET FORMULATION AND TESTING

EXP 2: TABLET FORMULATION AND TESTING

Important rules on practical component

1. The course consists of 2 practicals. As discussed in the course overview it is essential that you attend both these classes.
2. Students should attend the sessions allotted in the timetable. Failure to attend will result in a zero mark unless special consideration is given.
3. Practical should be read through ***prior*** to attendance, to enable completion of the experimental in the allotted time. No extensions will be given.
4. Practical classes will be conducted in groups; the data analysis and write up of each class must be done as a group.
5. Assignments should be submitted with compliance coversheets (failure to comply will result in a zero mark) in the assessment box located in the Pharmacy administration office one week after the second laboratory section by 4.00 pm.
6. Peer assessments for each member in the group are due by the same time and date.

Formulation, processing and evaluation - group assignment cover sheet

FACULTY OF PHARMACY

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Unit of study code (mandatory):	
Unit of study name:	
Course coordinator:	
Tutor's name:	
Assignment:	
Assignment topic:	
Date submitted:	

Declaration

Each student must confirm that your assignment meets the academic honesty requirements by signing below:

- I have read and understood the *University of Sydney Student Plagiarism: Coursework Policy and Procedure*.
- I understand that failure to comply with the *Student Plagiarism: Coursework Policy and Procedure* can lead to the University commencing proceedings against me for potential student misconduct under Chapter 8 of the *University of Sydney By-Law 1999* (as amended).
- This work is substantially my own, and, to the best of my knowledge, the work of the others in my group only. To the extent that any part of this work is not my own or the work of others in my group, I have indicated that it is not my own by acknowledging the source of that part or those parts of the work.
- I have not re-used previously submitted material in this assignment.
- I have not engaged someone else to complete this assignment.
- I have retained a duplicate hard copy of this assignment.

Student name	SID	Signature	Date

HANDING IN THIS ASSIGNMENT AS A GROUP IMPLIES THAT EACH MEMBER HAS CONTRIBUTED EQUALLY TO THE ASSIGNMENT. WE REALISE THAT WE MAY BE ASKED TO IDENTIFY THOSE PORTIONS OF THE WORK CONTRIBUTED BY EACH OF US AND REQUIRED TO DEMONSTRATE OUR INDIVIDUAL KNOWLEDGE OF THE RELEVANT MATERIAL BY ANSWERING ORAL QUESTIONS OR BY UNDERTAKING SUPPLEMENTARY WORK, EITHER WRITTEN OR IN THE LABORATORY, IN ORDER TO ARRIVE AT THE FINAL ASSESSMENT MARK. EXPERIMENT 1&2

Aim of this practical class

To gain familiarity with the equipment and techniques used in the manufacture of common solid oral dose forms and the principles behind manufacturing practices for pharmaceutical products which relate to quality assurance.

Specifically, to produce Ibuprofen tablets using both direct compression and wet granulation methods, and, to compare the quality of the products using British Pharmacopoeia standards.

Learning objectives from this practical

- Formulate a tablet by choosing appropriate amounts of excipients to produce tablets of acceptable quality.
- Prepare and compare tablets using the direct compression and wet granulation methods.
- Perform the necessary in-process tests during manufacture of the tablets.
- List the equipment required for the manufacture and testing of tablets, and understand their operation.
- Understand the reasons for tablet coatings and the methods used in their manufacture.
- Perform the relevant quality control tests on manufactured tablets.
- Reconcile the actual yield with the theoretical yield.
- Perform calculations for quality control.
- Document relevant data in an acceptable form.

Pre-laboratory exercises

You are **required** to read through the practical guidelines prior to coming to the practical/workshop session.

Background

Tablets are compressed powders and/or granules. This is the most common oral dose form used because the tablets are easy to administer and simple and cheap to mass-produce.

The advantages of tablets as an oral dose form are:

- Precise and accurate means of delivering both small and large dose drugs
- Physical and chemical stability
- Competitive unit production costs
- Convenience and palatability of administration
- Ability to modify release patterns if desired

When designing tablets, the following characteristics must be determined:

Select an appropriate size and shape

- Must be able to be swallowed (capsule shape is easier to swallow)

Select additives (non-toxic, stable, as few as possible and in the least concentration)

- To improve processing characteristics, such as flow, mixing, granulation, drying, compressibility, hardness and friability
- To improve ease of administration and acceptability
- To stabilize the drug chemically or physically
- To achieve desired release characteristics

Select an appropriate manufacturing method

When considering conventional immediate release tablets, after the tablets are made they must have uniform content, have ready disintegration of their structure and an easy dissolution of the drug. They must be stable to air, light, moisture and temperature and be robust in terms of physical manipulation. They must also be of the specified chemical purity and be 'clean'.

Size and Shape

Tablet size will depend on the dose of drug to be given the physical form of the drug and the amount of additives or excipients, plus the method of manufacture. As an example, if the form of Paracetamol,

which normally does not compress well, is changed to a free flowing easily compressible form, it is possible to compress 500mg of paracetamol with less than 100mg of excipients. Very tiny tablets also are difficult to compress and they are difficult for patients to handle. At the opposite end, tablets including up to 1 g of drug are on the market, but these are not very acceptable to patients or consumers and often must be compressed into a capsule shape to enable them to be swallowed.

Additives / excipients and fluidity

The type and amount of excipients will depend on the physical/ chemical properties of the active ingredient as well as the manufacturing process. The main concern of the tablet formulator is to have a form of the drug that is free flowing. Some materials such as crystalline aspirin or sugar are naturally free flowing. Most materials, however, require granulation to improve flow properties. If the flow properties are poor, this will lead to variation in fill of the tablet die and thus result in weight variation of tablets and therefore dose variation.

There are many physical characteristics that will affect flow properties of a material. These include:

- Mean particle size and particle size distribution
- Shape of the particles
- Surface texture and presence of adsorbed surface films
- Degree of consolidation

Flow can be improved by:

- Changing the particle shape (flake to sphere)
- Changing particle size (increase or decrease)
- Changing particle size distribution (depending on the shape of the particles 1 - 40µm will flow poorly, 40 - 100µm will flow better, while 100 - 1000µm is best.)
- Adding flow conditioners in very small amounts (Giant, anti-caking agents or lubricants / starch, silicates, talc or salts of stearates)

Testing of powder flow is usually performed by measuring the angle of repose or the dynamic flow. To manufacture tablets on modern rotary and single punch machines, uniform flow into tablet dies is required.

Flow rates of granular materials through an orifice, which is the same size as the die can be measured as weight per time and any hesitation of flow, noted.

Mixing

Mixing is the process by which two or more solid materials in particulate form are scattered in a system. Each particle varies in the size, shape and surface characteristics.

Mixing and segregation occur simultaneously

The types of mixes are:

- Perfect mix: each particle lies next to a particle of the other component.
- Random mix: the probability of sampling a particular type of particle is proportional to the number of such particles in the mix with the lowest possible standard deviation.
- Ordered mix: mechanical ordering, particulate adhesion and granulated or coated ordered mixtures.
- Total mixing is a balance or equilibrium between randomisation and ordering.

In a dry solids mixer, particles will change their relative positions only when subject to movement. Passing ingredients through a sieve, sifting, will give some mixing and aid in the dispersion of agglomerated particles.

Mixing can be achieved by tumbling using Y or V cone, cube or double cone, or turbula mixers.

Agitators depend on the motion of a paddle or blade to produce convective mixing for example a ribbon mixer or the Hobart mixer as used in the laboratory.

Tablet Methods

Three methods of manufacture have been used. Materials for direct compression must already be free flowing. The methods dry-granulation and wet-granulation are processing steps added to ensure a free-flowing powder. The methods will be described then; lists of possible excipients will be given.

Dry Granulation

This is the least favoured option. Dry granulation involves compacting the components of a tablet formulation by means of a heavy-duty tablet machine to form large compacts of “slugs” which are then broken down and sieved until they are free flowing granules.

Advantages	Disadvantages
No heat or liquid required. Equipment less sophisticated. Can be a much shorter process than wet granulation.	Tablets often have poorer appearance than those prepared by wet granulation. Dose variation may be a problem due to fractionation or segregation of drug and diluent. Increased lubricants can often retard release of drugs.

Wet Granulation

Advantages	Disadvantages
Drug is bound into granules so homogeneity is generally good. Appearance of tablet is usually good.	Large amount of time and expensive equipment required. Binding agent may adversely affect release of drug. Cannot be used for heat-labile drugs. Solvent used may affect stability of drug.

Direct compression

This is the preferred method for new chemical entities (NCEs). Drug is simply mixed with a free-flowing compressible vehicle such as granular dextrose, granular sucrose or spray-dried lactose; a lubricant is added and the mixture is compressed.

Advantages	Disadvantages
Lower capital cost for facilities and equipment Lower labour costs Easier to validate No heat or liquid required. No binding agent involved	Capacity of vehicles for fine cohesive drugs is often limited to 20% of total tablet weight or even less. Can only be used for drugs with doses of more than 200mg if the drug itself is free flowing and compressible, so raw materials specifications mixing, flow and compression properties are much tighter. As the drug is not bound into granules, segregation of drug and vehicle can occur in tablet machine hopper. The mixing step is critical.

Excipient list

Excipient Type	Comment	Examples
Diluent (filler)	To increase the amount in tablets or to give a proportion of tablet contents, which are easily compressible	Lactose Dicalcium Phosphate Microcrystalline cellulose Sugars: Sucrose Mannitol, sorbitol, dextrose,
Binders	To agglomerate particles for granulation	Acacia Alginic acid Carmellose sodium Ethyl/Methyl Cellulose Gelatine/Starch Polyvinyl-pyrrolidone
Glidant	To improve flow	Colloidal silica Talc Stearic acid
Lubricant	To overcome friction between powders and tablet Punches and Dies. May result in reduced dissolution rate of the drug because the lubricant may inhibit wetting of the tablet by the dissolution medium. Use in small quantities at the end of mixing	Magnesium Stearate Talc Stearic acid
Disintegrant	Form pathways in tablet matrix drawing water into structure. Swells, rupturing particle bonds in tablet	Starch Alginates PolyPlasdone XL
Wetting agent		Sodium Lauryl Sulphate

EXPERIMENTAL: MANUFACTURE OF 200 mg IBUPROFEN TABLETS

Ibuprofen, 2-(4isobutylphenyl)-propionic, acid is a widely used non-steroid anti-inflammatory agent. It is slightly soluble in water and has poor flow and compaction characteristic owing to its needle like crystalline structure. Ibuprofen is prescribed in high doses (200-800 mg), which normally precludes its direct-compression manufacture into suitable sized tablets.

Recently a number of pre-granulated formulations have appeared on the market containing from 65 to 90% Ibuprofen.

Ibuprofen tablets are required to be film coated to mask the intense bitterness. The tablets produced in this class will not be coated but enteric-coated commercial tablets will be used for part of the prac.

Experimentation

The formulation and the manufacture of Ibuprofen tablets will require two working groups, one group to prepare tablets by Direct Compression, the other to prepare tablets by Wet Granulation. Both groups, however, are to participate in all demonstrations and to be aware of and to present the methods, operations and results for both manufacturing procedures. Tablets from each method of manufacture will be compared with regard to weight variation, hardness, friability, content uniformity, and disintegration and dissolution characteristics.

DIRECT COMPRESSION

IBUPROFEN 200 mg TABLETS

THEORETICAL YIELD: 500 TABLETS

Components	Uses and comments	Amount per tablet	Amount Per 500 tablets	Amount actually weighed
Ibuprofen granules (contains 3% PVP*)		206 mg		
Lactose D.C. (direct compression)		220 mg		
Starch		24 mg		
Ac-di-sol*		6 mg		
Avicel 102		50 mg		
Magnesium stearate BP		6 mg		
Total weight				

* PVP (Polyvinylpyrrolidone)

* Ac-di-sol (Cross-linked sodium carboxymethyl cellulose)

Manufacturing directions

Calculate the quantities of each of the materials required to produce 500 tablets, weighing each of the materials individually in small plastic containers (use only granulated Ibuprofen and direct compression lactose).

Combine all of the materials (except the magnesium stearate) by passing each through a 1000 micron mesh sieve and transfer the contents to the mixing container.

Mix in the Turbula mixer for 12 minutes, stop the mixer, add the sieved magnesium stearate and continue mixing for a further 3 minutes. (The optimum mixing time of 15 minutes has been predetermined).

Flow rate

Determine the bulk flow rate (g/sec) of the granule mix. For the method, refer to the wet granulation section.

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Moisture content

Determine the moisture content of the granules using the Infra - Red Moisture Determination Balance. Tare the moisture balance and evenly distribute approximately 2g of the powder on the weighing pan. Close the lid and press start to activate the heater. When the weigh reading has stabilised, (an alarm will sound) record the percentage weight loss on drying (LOD).

LOD %	Dry weight %

Theoretical tablet weight

Calculate the required tablet weight and determine the percentage deviation allowed by the British Pharmacopoeia.

Weight (mg)	Upper weight limit	Lower weight limit

Tabletting

Transfer the granules to the hopper of the tablet machine.

The Direct Compression tablets are compressed using a 10.35mm concave punch and die set. Initially, adjustments are made to the lower punch setting and the tablets compressed manually until a tablet of satisfactory weight is produced. The pressure applied by the upper punch is increased progressively until tablets of the correct hardness are obtained.

The tablet machine is then operated and approximately 30 tablets produced, collecting the tablets in a 1000-micron mesh sieve. Dust the tablets with compressed air and again determine the weight and hardness of several tablets.

Friability

Accurately weigh 20 tablets and determine their friability (for method, see the appendix - Friability of uncoated tablets).

Initial weight (20 tablets)	
Final weight	
Weight loss%	

Disintegration in water

Use 6 tablets to perform the B.P. disintegration test for uncoated tablets (Appendix for details). Record the time taken for disintegration in minutes.

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Control charts

If the tablet weight, hardness, friability and disintegration are within the prescribed limits, tablet the batch, recording in the table below the mean and standard deviation of the weight (mg) of 5 consecutive tablets, these tablet groups being taken at one minute intervals. In addition, check the hardness (N) of one of the 5 tablets every minute. Tabulate your results below.

(If the weight of the tablets exceeds the B.P. limits during the production run, or the hardness of the tablets is excessive, notify the tablet machine operator promptly so that the tablet machine can be stopped and readjusted.)

Time (Mins)	0	1	2	3	4	5	6
Tablet 1 wt							
Tablet 2 wt							
Tablet 3 wt							
Tablet 4 wt							
Tablet 5 wt							
Mean wt							
Std Dev							
Hardness							

Construct a mean mass and standard deviation control chart based on the above results. (Read the section titled Quality Control Charts).

Weight uniformity

Calculate the weight uniformity of your tablets based on the above results (35 tablets).

Mean weight (mg)	St. dev. (mg)	Number of tablets outside theoretical weight limits

Hardness

Using the hardness results above and the results for an additional 3 tablets (10 in total), calculate the mean hardness for your tablets.

Mean hardness (N)	St. dev. (N)	Min hardness (N)	Max hardness (N)

Yield

Weigh the remaining batch of tablets and record the yield. Account for any deviation from the theoretical yield. This is called yield reconciliation.

Total weight of tablets	Total number of tablets

WET GRANULATION

IBUPROFEN 200mg TABLETS THEORETICAL YIELD: 1500 TABLETS

Components	Uses and comments	Amount per tablet	Amount per 1500 tablets	Amount actually weighed
Ibuprofen		200 mg		
Lactose B.P.		130 mg		
Starch B.P.		20 mg		
Avicel 101		50 mg		
PVP solution 20%		As required		
Weight after drying				
Ac-di-sol		1%		
Magnesium stearate		0.5%		
Total weight				

Manufacturing directions

Calculate the amounts of Ibuprofen, lactose, starch and avicel required to produce 1500 tablets, weighing each ingredient into a large plastic container.

Combine the **four** ingredients and mix in the planetary mixer for 10 minutes.

Prepare the granulation binder by measuring 150mls of the 20% PVP solution. Add the binder slowly, over approximately 5 minutes, adding additional water, if necessary, to bring the granulating mass to a suitable consistency.

Granulate, by passing the wet mass through a suitable screen on the Jackson – Crockatt Granulator using the shallow angled granulating head.

Dry the granules by heating in the fluid bed drier for 4 to 5 minutes at 60° C.

Detach the granulating screen from the granulator, clean the screen and place in the oven to dry. While the granules are drying, continue with the flow studies on the previously sieved and sized granules.

Granule flow studies

Granulation material of the Wet Granulation formula has been prepared and fractionated on a nest of sieves for 10 minutes, using sieve sizes suggested by the table below.

Determine the flow rate of each of the sieve fractions below through the number 10 (10mm) orifice of the flow tube. Plot the average size (micrometers) against flow rate (g/sec).

Sieve aperture (µm)	Size retained (µm)	Sieve cut average size (µm)	Flow rate (g/sec)
710	>710	>710	
500	710-500	605	
355	500-355	428	
250	355-250	303	
180	250-180	215	
125	180-125	153	
90	125-90	107	
<90	Fines		

Fine particles and flow rate

After the granules in the fluid bed drier have completely dried, reassemble the granulator using the dry sieving head (the sharper angled head) and sieve the dried granules.

Weigh 100g of the bulk material, sieve through a 125µm screen for 5min. and calculate the amount of fines (percentage weight of the sieved material). If the amount exceeds 20% it may be necessary to reduce the fines in the bulk material. Discard this 100 g of powder after you have finished (do not add it back to your mix).

If the amount of fines is satisfactory, proceed with bulk flow rate measurement for the powder mix. If not, consult the lab technician to reduce the amount of fines in the mixture and then measure the flow rate. If your flow rate is not sufficiently good for tableting, glidant may need to be added – consult the lab technician for this. If it is good, proceed with moisture content determination.

Determine the bulk flow rate (g/sec) of the granule mix.

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Glidant addition (if required)

Find the percentage of glidant that will significantly improve the flow rate of the granules.

- Determine the flow rate of the bulk material.
- Weigh 100g of the granule mix into a plastic bag and add 0.5g of the glidant (Select a suitable glidant with the assistance of the demonstrator). Mix the contents of the bag and determine the flow rate. If the flow rate is significantly improved, add a further 0.5% of glidant and repeat the flow rate measurement.
- Plot flow rate in g/sec versus percentage of glidant (To a maximum of 5% glidant) If the granule flow has been significantly improved, combine all granules, determine the weight and add additional glidant to affect optimum glidant percentage in the total mix.

Glidant %						
Flow rate (g/sec)						

Moisture content

Determine the moisture content of the granules (refer to the direct compression method).

LOD %	Dry weight %

Manufacturing continued

An external disintegrant (Ac-de-sol) and a lubricant (Magnesium Stearate) are also added at this stage. Note: If the glidant used has lubricating properties also, it may not be necessary to add any further lubricant to the system.

Weigh the amount of powder mix you have left and calculate 1% and 0.5% of this amount. Add 1% ac-de-sol to your mixture and mix in the Turbula mixer for 8 minutes. Then, add 0.5% magnesium stearate and mix for a further 3 minutes.

Theoretical tablet weight

Calculate the theoretical tablet weight and the percentage deviation allowed by the British Pharmacopoeia.

Weight (mg)	Upper weight limit	Lower weight limit

Tabletting

Transfer the granules to the hopper of the tablet machine.

The Wet Granulation tablets are compressed using a 10.32mm, concave punch and die set. Initially, adjustments are made to the lower punch setting and the tablets compressed manually until a tablet of satisfactory weight is produced. The pressure applied by the upper punch is increased progressively until tablets of the correct hardness are obtained.

The tablet machine is then operated and approximately 30 tablets produced, collecting the tablets in a 1000 μ -mesh sieve. Dust the tablets with compressed air and again determine the weight and hardness of several tablets.

Friability

Accurately weigh 20 tablets and determine their friability. (For method see the appendix: - Friability of uncoated tablets).

Initial weight (20 tablets)	
Final weight	
Weight loss%	

Disintegration in water

Use 6 tablets to perform the B.P. disintegration test for uncoated tablets (Appendix for details). Record the time taken for disintegration in minutes.

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Control charts

If the tablet weight, hardness, friability and disintegration are within the prescribed limits, tablet the batch, recording in the table below the mean and standard deviation of the weight (mg) of 5 consecutive tablets, these tablet groups being taken at two minute intervals. In addition, check the hardness (N) of one of the 5 tablets every two minutes. Tabulate your results below.

(If the weight of the tablets exceeds the B.P. limits during the production run, or the hardness of the tablets is excessive, notify the tablet machine operator promptly so that the tablet machine can be stopped and readjusted.)

Time (Mins)	0	2	4	6	8	10	12
Tablet 1 wt							
Tablet 2 wt							
Tablet 3 wt							
Tablet 4 wt							
Tablet 5 wt							
Mean wt							
Std Dev							
Hardness							

Construct a mean mass and standard deviation control chart based on the above results. (Read the section titled Quality Control Charts).

Weight uniformity

Calculate the weight uniformity of your tablets based on the above results (35 tablets).

Mean weight (mg)	St. dev. (mg)	Number of tablets outside theoretical weight limits

Hardness

Using the hardness results above and the results for an additional 3 tablets (10 in total), calculate the mean hardness for your tablets.

Mean hardness (N)	St. dev. (N)	Min hardness (N)	Max hardness (N)

Yield

Weigh the remaining batch of tablets and record the yield. Account for any deviation from the theoretical yield. This is called yield reconciliation.

Total weight of tablets	Total number of tablets

TABLET COATING

Coatings may be applied to tablets for several reasons, the more common include:

Protection - A coat may be applied to:

- Protect the drug formulation from atmospheric oxidation or hydrolysis on storage.
- Protect the drug from degradation in the stomach. (Enteric coating)

Masking - A coat may:

- Prevent the patient tasting a bitter drug.
- Improve the appearance of the tablet

Alteration of release pattern of drug - A coat may:

- Protect the stomach from gastric irritant material.
- Delay release until a certain region of the gastro - intestinal tract is reached.
- Facilitate sustained release.

Tablet coatings are divided into two methods

Sugar coating is mainly historical or for confectionary

Film coating

- Cellulose derivatives: used for protection and masking eg. ethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose.
- Acrylic acid derivatives: used for protection and masking eg. Eudragit 100
- Enteric coats: insoluble in the gastric fluid of the stomach (<5.5pH) eg. Cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate, Acrylic acid derivatives (Eudragit NE30D).
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The coating solutions or suspensions usually require the addition of a number of other

Materials. Among these are plasticisers, pigments and anti - adherents (eg. talc)

Aqueous coating is the preferred method of coating although lengthier and more difficult to do.

Specifications for coats

- Disintegration within limits.
- Dissolution within limits
- For Enteric coats disintegration in neutral pH but not in acid pH
- Appearance
- Thickness
- Lack of pits, cracking.

The British Pharmacopoeia monograph for Ibuprofen tablets specifies that the tablets are to be coated. HOWEVER, YOU WILL NOT BE COATING YOUR TABLETS IN THIS PRACTICAL. INSTEAD, YOU WILL USE COMMERCIAL, ENTERIC-COATED TABLETS FOR A DISINTEGRATION TEST TO SEE THE EFFECT OF THE ENTERIC COATING.

QUALITY CONTROL TESTS

On top of the friability, disintegration, weight uniformity and hardness (resistance to crushing) quality control tests you have done earlier, perform the uniformity of content and dissolution tests on your uncoated tablets. Also, perform the disintegration test for the commercial, enteric-coated tablets.

Uniformity of content – direct compression

Weigh 10 tablets individually using the analytical balance. Place each tablet in a 100ml beaker and add 25ml of 0.2M phosphate buffer. Using the ultra-sonic bath set the timer to ten minutes and sonicate the samples until the tablets have completely disintegrated (don't overload the ultrasonic bath – only 5 beakers at a time). Wash the contents of the beaker into 100ml volumetric flasks using the phosphate buffer solution and make up to volume. Attach a filter to a plastic syringe and filter 2 ml into a clean test tube. Accurately pipette 0.5ml from the test tube into another 100ml volumetric flask and dilute to 100ml with phosphate buffer. Using the UV spectrometer determine the absorbance of each of the ten samples at a wavelength of 243nm. Taking into account the dilution factors involved, calculate the ibuprofen content of each of the tablets. Record your results below.

Tablet	1	2	3	4	5	6	7	8	9	10
Weight (mg)										
Dilution factor										
Absorbance										
Conc. (mg)										

Bulk assay - wet granulation

Powder 20 tablets in a glass mortar. Accurately weigh into a 100ml beaker an amount of the powder equivalent to 200mg of ibuprofen (basically the theoretical weight of 1 tablet). Add 50ml of 0.2M phosphate buffer and sonicate the sample for 10min using the ultrasonic bath. Transfer the contents to a 100ml volumetric flask and make up to volume using the phosphate buffer solution. Attach a filter tip to a 10ml syringe and filter 2ml into a clean test tube. Accurately pipette 0.5ml into a 100ml volumetric flask and make up to volume using phosphate buffer. Using the UV spectrometer determine the absorbance of the sample at a wavelength of 243nm. Taking into account the dilution factor, calculate the average ibuprofen content of the tablets. Record your results below.

Weight of powder (mg)	
Dilution factor	
Absorbance	
Conc. (mg)	

Dissolution

There is currently no monograph in the British Pharmacopoeia for the dissolution of ibuprofen tablets. The TGA standard for tablets, pills and capsules specifies that ibuprofen is to be subjected to a dissolution test using the United States Pharmacopoeia method for determining dissolution.

The method employed is the rotating paddle method.

Fill each of the dissolution flasks with 900ml of the dissolution medium (0.2 M phosphate buffer, pH 7.2) using a one litre-measuring cylinder and allow the solution to reach 37°C. Lower the basket assembly until it stops (at a predefined height).

Set the rotation to 50 RPM.

Place only one tablet in each basket. Compare the dissolution rates of the direct compression and wet granulation tablets (three tablets from each group).

Withdraw 10 ml-filtered samples at four 15-minute intervals for one hour, transferring each sample to labelled test tubes. Accurately, pipette 2.5ml of each of the samples into 50ml volumetric flasks and make each to volume using the pH 7.2 phosphate buffer. Mix and determine the absorbances of the diluted samples in the UV spectrometer at a wavelength of 243nm.

The products comply with the B.P. requirements if 80% of the active ingredient has dissolved in one hour.

Absorbance Values

	Direct Compression				Wet Granulation			
Time (Min)	15	30	45	60	15	30	45	60
Tablet 1								
Tablet 2								
Tablet 3								

From the table above calculate the amount of ibuprofen dissolved at each time interval.

Concentration Values

	Direct Compression				Wet Granulation			
Time (Min)	15	30	45	60	15	30	45	60
Tablet 1								
Tablet 2								
Tablet 3								

Disintegration of commercial, enteric-coated tablets

Run the coated tablets in 0.1M HCl for 1 hour, check for signs of disintegration and record your results. Then, change the acid to phosphate buffer (0.2 M, pH 7.2) and run until disintegration occurs. Record the time it takes for the tablets to completely disintegrate.

Medium	Time (min) and result
0.1M HCl	
0.2M Phosphate buffer pH 7.2	

QUALITY CONTROL CHARTS

Quality control is achieved most efficiently, not by testing of finished products, but by building quality from the identification of variation, due to chance causes as compared to variation due to assignable causes. By identifying the assignable causes, the process can be improved to ensure adequate uniformity of the product.

Mean mass control chart

From previous experience using the tablet machine in your practical, based upon chance causes, tablets weighing between 630 and 650 mg exhibited a standard deviation of 4.5 mg and tablets weighing between 430 and 470 mg exhibited a standard deviation of 3.5 mg. Based upon the theoretical mass of your tablet, set up quality control limits for the chart monitoring the averages as follows:

Action limits	$= \bar{x} \pm 3.09 \frac{s.d.}{\sqrt{n}}$
Warning limits	$= \bar{x} \pm 1.96 \frac{s.d.}{\sqrt{n}}$

Where:

$\bar{x}$	The theoretical mean mass of tablet to be achieved
s.d.	The standard deviation of individual tablet weights
$\frac{s.d.}{\sqrt{n}}$	Standard error of the mean mass of n tablet
n	Number of tablet sampled consecutively at each inspection time, e.g. 5

Construct a control chart of mean tablet mass using the limits as calculated above. Plot the mean weight of 5 tablets every minute for the Direct Compression formula and every 2 minutes for the Wet Granulation Compression. Comment on the results as charted and the limits as set down.

Standard deviation control chart

Because the Mean mass control chart gives no indication of the variability about the mean, a Standard Deviation Control Chart is also employed.

Construct a control chart of the standard deviation perceived from each of the tablet samples. Use the Action and Warning limits as dictated below:

Action limits	$= s.d. \pm 3.09 \frac{s.d.}{\sqrt{2n}}$
Warning limits	$= s.d. \pm 1.96 \frac{s.d.}{\sqrt{2n}}$

Where:

$\frac{s.d.}{\sqrt{2n}}$	Standard error of the nominal standard deviation
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DISCUSSION AND REPORT

- (1) List the purpose of each of the ingredients used in your tablet formulation.
- (2) Briefly describe how the physical properties of materials used to produce tablets influence flow ability. Construct a chart of the flow studies and comment on your flow rate results.
- (3) To determine the optimum mixing time, samples of the powder must be taken and assayed. What factors are important in the sampling procedure?
- (4) Ibuprofen has a melting point of 75°C . Comment on the impact of the melting point on tablet production and quality.
- (5) Comment on the wet granulation bulk assay results and the direct compression content uniformity results. Discuss your results with respect to the standards.
- (6) Discuss the effects of moisture levels in the powders on the mixing of powders. What would be the optimum moisture content? Discuss your moisture content results with respect to the standards.
- (7) What are the reasons for coating Ibuprofen tablets?
- (8) What is the significance of the friability test? Discuss your results with respect to the standards.
- (9) What is the significance of the hardness test? Comment on the hardness of your tablets.
- (10) Comment on the mean mass control chart and standard deviation control charts and the importance of such monitoring. Construct graphs based on your results.
- (11) What is the significance of weight uniformity? What factors contribute to weight variation in the tablets and how could you rectify? Discuss your results with respect to the standards.
- (12) Discuss the fundamental difference between disintegration and dissolution and the significance of these two processes. Comment on all the disintegration and dissolution results, both with respect to the standards.
- (13) Comment on your yield values and their deviation from the theoretical values and discuss the importance of the yield value.

APPENDIX

EXTRACTS FROM THE BRITISH PHARMACOPOEIA

Resistance to crushing of tablets

This test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing.

Apparatus

The apparatus consists of two jaws facing each other, one of the jaws moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of 1 Newton.

Method

Place the tablet between the jaws, taking into account, where applicable, the shape, the break mark and the inscription; for each measurement orient the tablet in the same way with respect to the direction of application of the force. Carry out the measurement on 10 tablets, taking care that all fragments of the tablets have been removed before each determination.

Expression of the Results

Express the results as the mean, minimum and maximum values of the forces measured all expressed in Newtons. Indicate the type of apparatus and, where applicable, the orientation of the tablets.

Friability of uncoated tablets

This test is intended to determine, under defined conditions, the friability of uncoated tablets, and the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition.

Method

For tablets weighing up to 0.65g each, take a sample of twenty tablets, for tablets weighing more than 0.65g each, take ten tablets. Place the tablets on a sieve no.1000 and remove any loose dust with the aid of air pressure or a soft brush. Accurately weigh the tablet sample and place the tablets in the drum. Rotate the drum 100 times and remove the tablets. Remove any loose dust from the tablets as before. If no tablets are cracked, split or broken, weigh the tablets to the nearest milligram.

If the results are doubtful or if the mass loss is greater than 1%, repeat the test twice and determine the mean of the three tests. A maximum loss of 1% of the mass of the tablets tested is considered to be acceptable for most products.

Expression of the Results

The friability is expressed as the loss of mass and it is calculated as a percentage of the initial mass. Indicate the number of tablets used.

Uniformity of weight (mass)

Weigh individually twenty units taken at random and determine the average weight. Not more than two of the individual weights should deviate from the average weight by more than the percentage deviation shown in the table below.

Tablets (uncoated and film coated)

Average weight	Allowed percentage deviation
80mg or less	± 10
More than 80mg and less than 250mg	± 7.5
More than 250mg	± 5

Uniformity of content

The test for uniformity of content is based on the assay of the individual contents of active ingredients of a number of single dose units to determine whether the individual contents are within limits set with reference to the average content of the sample

Method

Using a suitable analytical method, determine the individual contents of active ingredient of ten dosage units taken at random.

Test

The preparation complies with the test if each individual content is between 85% and 115% of the average content. The preparation fails to comply with the test if more than one individual content is outside these limits or if one individual content is outside the limits of 75% to 125% of the average contents. If one individual content is outside the limits of 85% to 115% but within the limits of 75% to 125%, determine the individual contents of another twenty dosage units taken at random. The preparation complies with the test if not more than one of the individual contents of the thirty units is outside 85% to 115% of the average contents and none is outside the limits of 75% to 125% of the average content.

Disintegration test for uncoated tablets

The apparatus used is as described in the British Pharmacopoeia 2000; appendix X11A

Test

Use water as the liquid. Add a disc to each tube. Operate the apparatus for 15min, unless otherwise justified and authorised, and examine the state of the tablets. If the tablets fail to comply because of adherence to the disks, repeat the test on a further six tablets omitting the disks. The tablets comply with the test if all six have disintegrated.

Disintegration test for enteric-coated tablets

The apparatus used is as described under disintegration test for tablets and capsules, British Pharmacopoeia 2000, appendix X11A.

Method

Introduce one tablet into each tube, suspend the assembly in the beaker containing 0.1M *hydrochloric acid* and operate without the discs for 120 minutes, unless otherwise stated in the individual monograph. Remove the assembly from the liquid. No tablet shows signs of cracks that would allow the escape of the contents or disintegration, apart from fragments of coating. Replace the liquid in the beaker with *mixed phosphate buffer pH 6.8*, add a disc to each tube and operate the apparatus for a further 60 minutes or until disintegration occurs. Remove the assembly from the liquid. The tablets pass the test if all six have disintegrated.