Unit 2

Routes of drug administration

Brainstorming

A. Which routes of drug administration do you know? Can you think of cases in which each one should be selected? Are you aware of how they affect the formulation of medicines?

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Brainstorming

A. Do you know what kind of medicinal formulations are administered orally? Can you think of any advantages or disadvantages in the choice of this route of administration?

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Oral route

Oral route

B. Do you know or can you guess if the following statements are true or false?

1. The action of a drug in a tablet begins minutes after its administration.
2. A tablet is more suitable for pediatric use than other formulations administered orally.
3. Other medication that the patient may have taken affects the solubility of the drug administered in tablet form.
4. Enteric coating of tablets reduces the possibility of inactivation of the drug by the acidity of the stomach.
5. Tablets disintegrate faster than capsules in the body.
6. Emulsion formulations may take the form of capsules.
7. Suspensions are unsuitable for patients suffering from tonsillitis.

You can check your answers by reading the text.

The absorption pattern of drugs varies considerably between individual drug substances as well as between the different administration routes. Dosage forms are designed to provide the drug in a suitable form for absorption from each selected route of administration. The following discussion considers briefly the routes of drug administration and whilst dosage forms are mentioned, this is intended only as an introduction since they will be dealt with in greater detail later in this book.

Oral route

The oral route is the most frequently used route for drug administration. Oral dosage forms are intended usually for systemic effects resulting from drug absorption through the various epithelia and mucosa of the gastrointestinal tract. A few drugs, however, are intend-

ed to dissolve in the mouth for rapid absorption or for local effect in the tract due to poor absorption by this route or low aqueous solubility. Compared with other routes, the oral route is the simplest, most convenient and safest means of drug administration. However, disadvantages include relatively slow onset of action, possibilities of irregular absorption and destruction of certain drugs by the enzymes and secretions of the gastrointestinal tract. For example, insulin-containing preparations are inactivated by the action of stomach fluids.

Table 1.2 *Variation in time of onset of action for different dosage forms*

Time of onset of action	Dosage forms
Seconds	i.v. injections
Minutes	i.m. and s.c. injections, buccal tablets, aerosols, gases
Minutes to hours	Short-term depot injections, solutions, suspensions, powders, granules, capsules, tablets, modified-release tablets
Several hours	Enteric-coated formulations
Days to weeks	Depot injections, implants
Varies	Topical preparations

Whilst drug absorption from the gastrointestinal tract follows the general principles described later in this book, several specific features should be emphasized. Changes in drug solubility can result from reactions with other materials present in the gastrointestinal tract, as for example the interference of absorption of tetracyclines through the formation of insoluble complexes with calcium, which can be available from foodstuffs or formulation additives. Gastric emptying time is an important factor for effective drug absorption from the intestine. Slow gastric emptying can be detrimental to drugs inactivated by the gastric juices and can delay absorption of drugs more effectively absorbed from the intestine. In addition, since environmental pH can influence the ionization and lipid solubility of drugs, the pH change occurring along

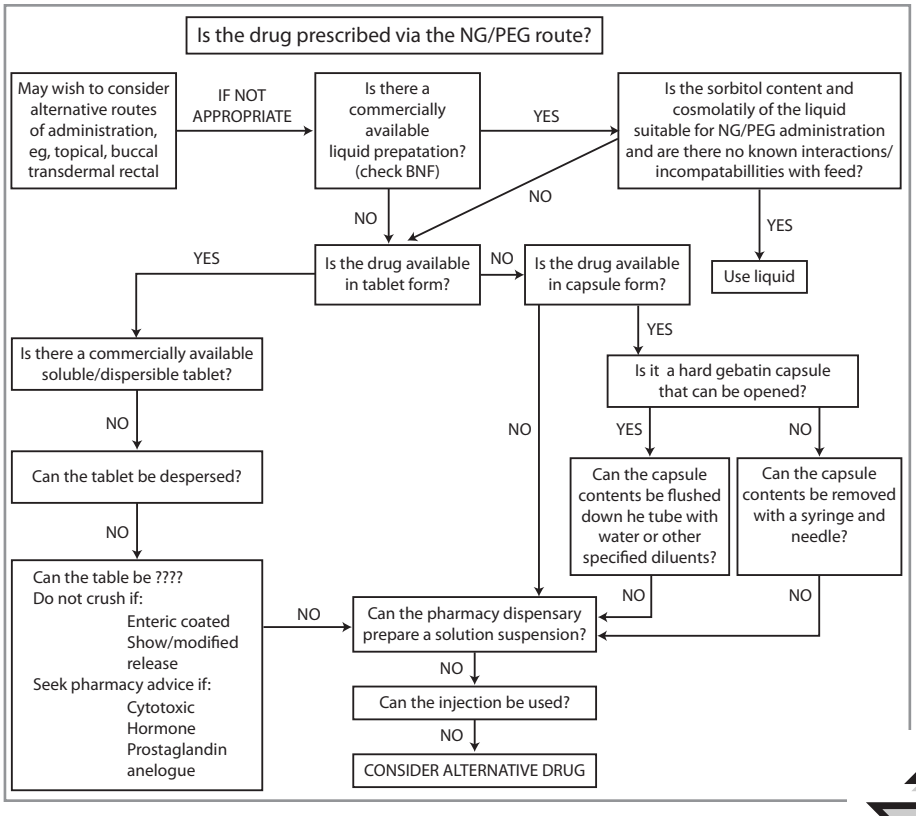
the gastrointestinal tract, from a pH of about 1 in the stomach to approximately 7 or 8 in the large intestine, is important to both degree and site of drug absorption. Since membranes are more permeable to unionized rather than ionized forms and since most drugs are weak acids or bases, it can be shown that weak acids, being largely unionized, are well absorbed from the stomach. In the small intestine (pH about 6.5), with its extremely large absorbing surface, both weak acids and weak bases are well absorbed.

The most popular oral dosage forms are tablets, capsules, suspensions, solutions and emulsions. Tablets are prepared by compaction and contain drugs and formulation additives which are included for specific functions, such as disintegrants which promote tablet break-up into granules and powder particles in the gastrointestinal tract, facilitating drug dissolution and absorption. Tablets are often coated, either to provide a protective barrier to environmental factors for drug stability purposes or to mask unpleasant drug taste, as well as to protect drugs from the acid conditions of the stomach (enteric coating). Increasing use is being made of modified-release tablet products such as fast dissolving systems and controlled, delayed or sustained-release formulations. Benefits of controlled-release tablet formulations, achieved for example by the use of polymeric-based tablet cores or coating membranes, include reduced frequency of drug-related side-effects and maintaining steady drug-plasma levels for extended periods, important when medications are delivered for chronic conditions or where constant levels are required to achieve optimal efficacy, as in treating angina and hypertension.

Capsules are solid dosage forms containing drug and, usually, appropriate filler(s), enclosed in a hard or soft shell composed of gelatin. As with tablets, uniformity of dose can be readily achieved and various sizes, shapes and colors of shell are commercially available. The gelatin shell readily ruptures and dissolves following oral administration and in most cases drugs are released from capsules faster than from tablets. Recently, renewed interest has been shown in filling semi-solid and microemulsion formulations into hard gelatin capsules to provide rapidly dispersing dosage forms for poorly soluble drugs.

Suspensions, which contain finely divided drugs suspended in a suitable vehicle, are a useful means of administering large amounts of drugs that would be inconvenient if taken in tablet or capsule form. They are also useful for patients who experience difficulty in swallowing tablets and capsules and for pediatric use. Whilst dissolution of drugs is required prior to absorption, fine particles with a large surface area are presented to dissolving fluids which facilitate drug dissolution in the gastrointestinal tract, absorption and thereby the onset of drug action. Not all oral suspensions, however, are formulated for systemic effects and several are designed for local effects in the gastrointestinal tract. On the other hand, solutions, including formulations such as syrups and linctuses, are absorbed more rapidly than solid dosage forms or suspensions since drug dissolution is not required.

Aulton, M., 2007: 7-8



Task C

Can you answer the following questions using the information in the extract you have read?

1. What are the disadvantages of the oral route of administration?

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2. What are the factors that affect drug absorption when this route is selected?

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3. What do tablets consist of?

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4. Why are tablets coated?

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5. In which cases can suspensions prove useful?

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Task D

Can you explain the meaning of the following words as these appear in the extract? *(the number of the paragraph they appear in is given in the brackets)*

(1) onset: . . . . . .

(2) detrimental: . . . . . .

(2) permeable: . . . . . .

(3) side-effects: . . . . . .

(3) optimal: . . . . . .

(4) readily: . . . . . .

(4) ruptures: . . . . . .

(5) vehicles: . . . . . .

Task E

Can you match the following words with the definitions given? *(the number of the paragraph they appear in is given in brackets)*

1. any of a group of organic compounds that are greasy to the touch, insoluble in water, and soluble in alcohol and ether; together with proteins and carbohydrates, they constitute the chief structural components of living cells: . . . . . .

2. lubricating membrane lining an internal surface or an organ, as the alimentary, respiratory, and genitourinary canals: . . . . . .

3. syrupy preparation containing medicaments exerting a local action on the mucous membrane of the throat: . . . . . .

4. (in a cell or gland) the act or process of separating, elaborating, and releasing a substance that fulfills some function within the organism or undergoes excretion: . . . . . .

5. gelatinous case enclosing a dose of medicine: . . . . . .

6. pertaining to, or affecting the stomach and intestines: . . . . . .

7. any attack of painful spasms characterized by sensations of choking or suffocating: . . . . . .

Rectal route

Brainstorming

A. What do you know about this route?

1. Do you know what drug formulations are administered by this route?

. . . . . .

. . . . . .

2. When would this route be selected?

. . . . . .

. . . . . .

3. What are the disadvantages of this route?

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If you cannot answer these questions, you can read the extract to get the information.

Rectal route

Drugs given rectally in solution, suppository or emulsion form are generally administered for local rather than systemic effects. Suppositories are solid forms intended for introduction into body cavities (usually rectal but also vaginal and urethral) where they melt, releasing the drug, and the choice of suppository base or drug carrier can greatly influence the degree and rate of drug release. This route of drug administration is also indicated for drugs inactivated by the gastrointestinal fluids when given orally or when the oral route is precluded, as for example when a patient is vomiting or unconscious. Drugs administered rectally enter the systemic circulation without passing through the liver, an advantage for drugs significantly inactivated by the liver following oral route absorption. Disadvantageously, the rectal route is inconvenient and drug absorption is often irregular and difficult to predict.

Aulton, M., 2007: 8

Task B

Can you find which words in the extract mean the following?

1. a hollow space within the body, an organ, a bone, etc.: . . . . . .
2. pertaining to the passage leading from the uterus to the vulva in certain female mammals: . . . . . .
3. pertaining to the membranous tube that extends from the urinary bladder to the exterior and that in the male conveys semen as well as urine: . . . . . .
4. excluded: . . . . . .

Parenteral route

Brainstorming

A. What do you know about this route of administration concerning the formulations used, the advantages and disadvantages of its use and the cases in which it is preferred?

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B. Would you assess these statements as true or false?

1. The amount of drug absorbed by the organism is more predictable when it is administered parenterally.

2. Depot preparations can be formulated by solution injections.

3. Local anesthetics make use of vasodilators.

You can check your guesses by referring to the extract.

Parenteral route

A drug administered parenterally is one injected via a hollow needle into the body at various sites and to varying depths. The three main parenteral routes are subcutaneous (s.c.), intramuscular (i.m.) and intravenous (i.v.). Other routes such as intracardiac and intrathecal are used less frequently. The parenteral route is preferred when rapid absorption is essential, as in emergency situations or when patients are unconscious or unable to accept oral medication, and in cases when drugs are destroyed, inactivated or poorly absorbed following oral administration. Absorption after parenteral drug delivery is rapid and, in general, blood levels attained are more predictable than those achieved by oral dosage forms.

Injectable preparations are usually sterile solutions or suspensions of drugs in water or other suitable physiologically acceptable vehicles. As referred to previously, drugs in solution are rapidly absorbed and thus injection suspensions are slower acting than solution injections. In addition, since body fluids are aqueous, by using suspended drugs in oily vehicles, a preparation exhibiting slower absorption characteristics can be formulated to give a depot preparation, providing a reservoir of drug which is slowly released into the systemic circulation. Such preparations are administered by intramuscular injection deep into skeletal muscles (e.g. several penicillin-containing injections). Alternatively, depot preparations can be achieved by subcutaneous implants or pellets, which are compacted or molded discs of drug placed in loose subcutaneous tissue under the outer layers of the skin. Such systems include solid microspheres (e.g. polylactide co-glycollic acid homo- and copolymers) containing proteins or peptides (e.g. human growth hormone and leuprolide). More generally, subcutaneous injections are aqueous solutions or suspensions which allow the drug to be placed in the immediate vicinity of blood capillaries. The drug then diffuses into the capillaries. Inclusion of vasoconstrictors or vasodilators in subcutaneous injections will clearly influence blood flow through the capillaries, thereby modifying the capacity for absorption. This principle is often used in the administration of local anesthetics with the vasoconstrictor adrenaline, which

delays drug absorption. Conversely, improved drug absorption can result when vasodilators are included. Intravenous administration involves injection of sterile aqueous solutions directly into a vein at an appropriate rate. Volumes delivered can range from a few milliliters, as in emergency treatment or for hypnotics, up to liter quantities, as in replacement fluid treatment or nutrient feeding.

Given the generally negative patient acceptance of this important 40
route of drug delivery, primarily associated with pain and inconvenience, recent developments have focused on 'needle-free' injection systems and devices which propel drug in aqueous solution or powder form at high velocity directly through the external layers of the skin.

Aulton, M., 2007: 8

Task C

If you wish to know more about this route of administration, consider reading the extract. Then you find answers to the questions that follow.

1. When would this route of administration be preferred?

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. . . . . .

2. What are the advantages of this route compared to the others?

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. . . . . .

3. How does the drug reach the blood circulation in the case of subcutaneous injection?

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4. What are the more recent developments in this route and what are they trying to achieve?

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Task D

Using the context, can you try to explain what these words mean as they appear in the text? *(the number of the paragraph appears in brackets)*

(1) via: . . . . . .

(1) attained: . . . . . .

(2) tissue: . . . . . .

(2) vicinity: . . . . . .

(2) conversely: . . . . . .

(3) velocity: . . . . . .

Task E

E. The text contains several terms associated with the fields of medicine and biology, both associated with pharmacy. Can you try to match the definitions on the left with the terms on the right?

1. dosage form of a drug that acts over a period of time by controlled-release processes or technology

2. drug that causes narrowing of the blood vessels

3. situated or lying under the skin

4. one of the system of branching vessels or tubes conveying blood from varying parts of the body to the heart (loosely, any blood vessel)

5. minute blood vessel between the termination of the arteries and the beginnings of the veins

6. introduced into or occurring in the space under the arachnoid membrane of the brain or spinal cord

7. agent or drug that produces sleep; sedative

8. capable of decaying through the action of living organisms

a. subcutaneous

b. intrathecal

c. susceptible

d. depot preparation

e. capillary

f. vasoconstrictor

g. vein

h. hypnotic

Task F

Two words that you have met in this text are *intravenous* and *intramuscular*. They both start with the prefix *intra,* meaning 'within', which is used in the formation of compound words. There are several others.

Some prefixes are given below. Can you think of what they mean and think of words that start with them?

intra-: 'within', ...

bio-: . . . . . .

trans-: . . . . . .

hydro-: . . . . . .

counter-: . . . . . .

cyto-: . . . . . .

naso-: . . . . . .

uni-: . . . . . .

Over to you

There are times when information contained in a text or book is not enough to help us comprehend something or new questions come up. In such cases we need to look for further sources that will help us gain better insight into what we are studying or researching. Ability to look for and locate various sources of information is one of the basic skills of university students, scientists, researchers.

The present extract contains the phrase 'sterile solutions' without giving any further information about them. Supposing you were interested in what these are, how would you go about finding more information on them? Can you try your methods and report back on them? Can you also share the information you may find?

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Topical route

Brainstorming

A. Do you know what formulations are applied topically?

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B. Can you tell if the following statements are true or false?

1. The topical route is effective for systemic drug delivery.

2. Formulations intended for application to the nose are viscous.

You can see if you were right by crosschecking your answers with the information in the extract.

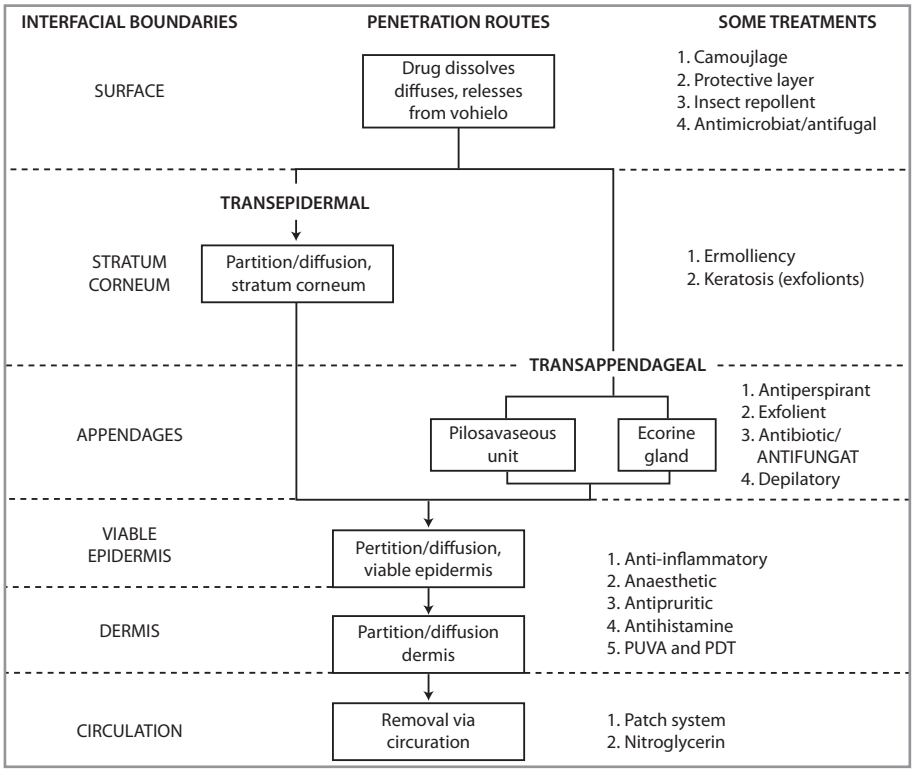
Topical route

Drugs are applied topically, that is to the skin, mainly for local action. Whilst this route can also be used for systemic drug delivery, percutaneous absorption is often poor and erratic, although several transdermal patches delivering drug for systemic distribution (e.g. glyceryl trinitrate patches for the prophylaxis and treatment of angina) are available. Drugs applied to the skin for local effect include antiseptics, antifungals, anti-inflammatory agents, as well as skin emollients for protective effects.

Pharmaceutical topical formulations – ointments, creams and pastes – are composed of drug in a suitable semi-solid base which is either hydrophobic or hydrophilic in character. The bases play an important role in determining the drug release character from the formulation. Ointments are hydrophobic, oleaginous-based dosage forms whereas creams are semi-solid emulsions. Pastes contain more solids than ointments and thus are stiffer in consistency. For topical application in liquid form other than solution, lotions, suspensions of solids in aqueous solution or emulsions are used. Recently, interest in transdermal electrotransport systems has grown. Here, a low electrical potential maintained across the skin can improve drug transport.

Application of drugs to other topical surfaces such as the eye, ear and nose is common and ointments, creams, suspensions and solutions are utilized. Ophthalmic preparations are required, amongst other features, to be sterile. Nasal dosage forms include solutions or suspensions delivered by drops or fine aerosol from a spray. Ear formulations in general are viscous to prolong contact with affected areas. 20

Aulton, M., 2007: 9



Having read the text, can you answer the following?

1. What formulations are applied topically?

. . . . . .

. . . . . .

Task C

2. Why is the base of a topical formulation important?

. . . . . .

. . . . . .

Task D

The words that follow appear in the extract. Can you guess what they mean?

(1) erratic: . . . . . .

(2) potential: . . . . . .

Task E

Conversely, can you find what terms the following definitions refer to?

1. medication used to reduce redness, swelling, pain, tenderness and disturbed function of an area of the body, that is caused esp. as a reaction of tissues to injurious agents: . . . . . .

2. having the power of softening or relaxing, as a medicinal substance; soothing, esp. to the skin: . . . . . .

3. administered, removed, or absorbed by way of the skin, as an injection, or transdermal drug: . . . . . .

4. having the nature or qualities of oil: . . . . . .

5. soft, unctuous preparation, often medicated, for application to the skin: . . . . . .

Respiratory route

Brainstorming

A. Do you know what kind of formulations would be administered by this route? What medical problems could they be used to treat?

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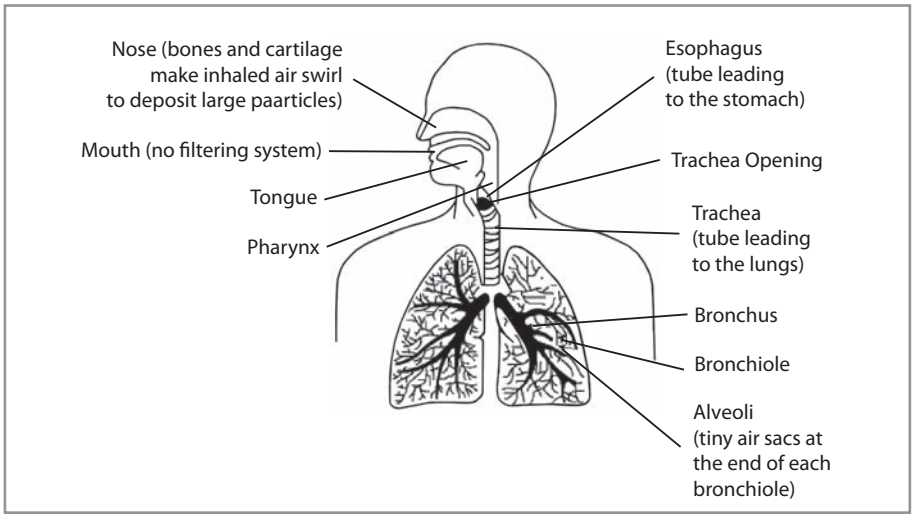
You can check your answers with the text.

Respiratory route

The lungs provide an excellent surface for absorption when the drug is delivered in gaseous, aerosol mist or ultrafine solid particle form. For drug particles presented as an aerosol or solid form, particle size largely determines the extent to which they penetrate the alveolar region, the zone of rapid absorption. Drug particles that are in the region 0.5 – 1 μm diameter reach the alveolar sacs. Particles smaller than this range are either exhaled or, if larger, deposited upon larger bronchial airways. This delivery route is particularly useful for the direct treatment of asthmatic problems, using both powder aerosols (e.g. sodium cromoglycate) and metered aerosols containing the drug in liquefied inert propellant (e.g. salbutamol sulphate aerosol). Importantly, this delivery route is being increasingly recognized as a useful means of administering the therapeutic agents emerging from biotechnology requiring systemic distribution and targeted delivery, such as peptides and proteins.

Aulton, M., 2007: 9



Task B

Do you know?

1. Why is the particle size of a drug important when it is presented as an aerosol form?

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2. Why is the presence of an inert propellant important in metered aerosols?

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Task C

Certain words of the extract are defined as follows. Can you find which they are?

1. cloudlike aggregation of minute globules of a substance: . . . . . .
2. pertaining to the air cells of the lungs, formed by the terminal dilation of tiny air passageways: . . . . . .
3. breathe out: . . . . . .
4. laid down by a natural process; precipitated: . . . . . .
5. pertaining to either of the two main branches of the trachea: . . .
. . . . . .
6. having no pharmacological action, as the excipient of a pill: . . . .
. . . . . .