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Pharmaceutical Dosage Forms and New Drug Delivery Systems

The following are short descriptions of pharmaceutical dosage forms and preparations that may be dispensed in the hospital pharmacy or on the retail counter.

Aerosols

The term aerosol has a specific meaning denoting a fine dispersion of liquid or solid particles in a gas where the particle size is less than 50 μm in diameter, as in the case of mist or smoke.

Aerosols may be defined as the pressurised dosage form of medicament in which the liquid or solid drug or drugs are dissolved or suspended in gas. The gas used for this purpose is known as propellant. The aerosols are packed in a suitable container known as aerosol container, when pressure is applied to the aerosol system, the contents are expelled out through the opening of the valve in the form of mist, a coarse, wet or dry spray, a stream or as a foam. The aerosols used in the treatment of respiratory conditions, are atomised in devices known as atomisers or nebulisers. The type of atomiser used depends upon the viscosity of the spray solution, the more viscous the solution, the more powerful the atomiser needed.

Now a days pharmaceutical aerosols are frequently used both orally and topically to dispense a large number of drugs

including local analgesics, antiseptics, fungicidal agents, antibiotics and anti-inflamatory agents etc. A number of veterinary and pet products have also been put into aerosol dosage forms. A variety of non-pharmaceutical preparations such as personal deodorant sprays, cosmetic hair sprays, perfume sprays, shaving lathers, tooth paste and various house hold products such as spray starch, waxes, polishes, cleansers and lubricants are available as aerosols.

The potent drugs used for the relief of asthma are dissolved or suspended in a suitable solvent or propellant and are enclosed in a container which is fitted with a metering device that delivers a measured dose. Drugs administered in this way give rapid response and quick onset of action as compared with drugs administered orally. But the frequent use of such inhalations or sprays are not without risk and adverse reactions. Therefore it is advisable to warn the patient to strictly follow the directions given by the doctor and frequent use of such preparations should be avoided.

Aerosol containers provide a number of advantages over the more traditional methods of presentation of drugs that they are compact, convenient to carry and easy to apply evenly without touching the painful surfaces. A measured amount of drug and uniform doses are administered by metered valves. The product remains free from contamination and sterility of the preparation is maintained as no micro-organisms can enter the pack when the valve is opened. They also provide good protection from oxidation and light to those drugs which are destroyed by air and light. Hydrolysis of drugs is prevented since the propellants contain no water. Because the filling and sealing of pressurised aerosols require special machinery and techniques therefore these preparations are costlier than traditional dosage forms.

Applications

Applications are liquid or viscous preparations intended for application to the skin. Usually, they are suspensions or emulsions. Most of the official preparations contain parasiticides and are intended for only a limited number of applications.

They should be dispensed in coloured fluted bottles in order to distinguish them from preparations meant for internal use. The container should be labelled "for external use only" Examples of applications are calamine application compound, B.P.C., dicophane application, B.P.C.

Aromatic Waters

Aromatic waters are also known as medicated waters. They are dilute, usually saturated, aqueous solutions of volatile oils or volatile substances. Some of them have a mild therapeutic action but mainly they are used as flavouring agents in preparations meant for internal administration of drugs. Aromatic waters may be prepared either by diluting the concentrated waters or by shaking the volatile substances with water. Aromatic waters include anise water, camphor water, chloroform water, cinnamon water and peppermint water.

Cachets

Cachets consists of a dry powder enclosed in a shell, usually prepared from a mixture of rice flour and water by moulding into a suitable shape and drying. They are quite useful for administering the drugs with unpleasant taste and a large dose can be enclosed in a cachet than in a tablet or capsule.

There are two kinds of cachets; 'wet seal' cachets which are sealed by moistening the edges with water, and 'dry seal' cachets.

Before administration, a cachet should be immersed in water for a few seconds, then placed on the tongue and swallowed with a draught of water. Cachets should be stored and supplied in well closed air tight containers. Examples are sodium aminosalicylate cachets, sodium aminosalicylate and isoniazid cachets.

Capsules

Capsules are the solid unit dosage form of medicament in which the drug or drugs are enclosed in a practically tasteless, hard or soft soluble container or shell made up of a suitable

form of gelatin. Hard capsules are used for filling the solid substances. Hard gelatin capsules are available in a number of sizes which varies from 000 to 5, the former being the largest and latter the smallest. They are made up of two cylindrical halves, one slightly larger in diameter but shorter in length known as cap and the other slightly shorter in diameter but longer in length know as base. the medicament is filled in longer narrower half, then the cap is fitted over the open end by moistening edges of the lower half of the capsule.

Soft capsules are flexible in nature. They may be spherical, ovoid, cylindrical or tubes. The spherical capsules are also known as 'Pearls'. Soft gelatin capsules are used for enclosing the solids, liquids and semi-liquids.

Enteric coated capsules are the capsules which are treated or coated in such a way that the capsule does not disintegrate in the acidic medium of the stomach but disintegrate in the alkaline medium of the small intestine. Enteric coated capsules have been largely replaced by enteric coated tablets.

Capsules are increasing their popularity day by day. Hard capsule comes second to tablets in importance as solid unit dosage forms. Some of the capsules are administered through rectum and vagina and are convenient mode of administration of drugs than suppositories. For oral administration the capsule is placed on the tongue and swallowed with a drink of water.

Collodions

Collodions are the liquid preparations meant for external application to the skin. They are convenient applications for small cuts and abrasions and are also used when a prolonged contact between the skin and the medicament is required. The vehicle used is volatile and evaporates on application to skin, leaving a flexible, protective film covering at the site of application. They are applied with a brush or rod.

Flexible collodion contains pyroxillon, castor oil and alcohol in solvent ether. Alcohol and solvent ether are used as vehicle, pyroxillon as film producing agent and castor oil gives flexibility.

Creams

Creams are viscous semisolid emulsions intended for application to the skin. Creams differ from ointments that they have lighter body than ointments. Moreover due to the presence of water soluble bases they can be easily removed from skin and clothings. Creams may be of oil in water (aqueous creams) or water in oil (oily creams) type. The aqueous creams have a tendency to bacterial and mold growth, therefore a preservative must be added in their formulation. Examples are cetomacrogol cream, cetrimide cream, chlorhexidine cream, hydrocortisone cream etc.

Draughts (Haustus)

A draught is a liquid oral preparation taken as a single dose. If several doses are prescribed, each dose is dispensed in separate container. Ipecacuanha Emetic Draught, Paediatric; is an exception where several doses are prescribed in a multiple-dose container. Examples are : male fern extract draught and paraldehyde draught.

Dusting Powders

Dusting powders are meant for external application to the skin. They are usually mixtures of two or more than two ingredients in fine powder e.g. starch, kaolin, talc, zinc oxide etc. They must be homogeneous and in a very fine state of subdivision to enhance effectiveness and minimise local irritation, for this purpose they may be passed through sieve no 120. Dusting powders are applied to the skin for antiseptic, antipruritic, astringent, antiperspirant, absorbent, protective and lubricant purposes.

Dusting powders are dispensed in sifter-top containers or pressure aerosols. They may also be supplied in wide mouth containers and applied with powder puff, a soft brush or a sterile gauge pad but care must be taken to avoid mechanical irritation to the skin surface. Dusting powders should not be applied to open wounds or to raw surfaces. Examples are : dicophane dusting powder, zinc and salicylic acid dusting powder; zinc, starch and talc dusting powder.

Dentifrices

Dentifrices are substances or preparations which are generally used with the help of tooth brush for cleaning the surfaces of the teeth. They are available in the form of fine powders and pastes.

Ear Drops

Ear drops are the liquid preparations in which the drug or drugs are dissolved or suspended in a suitable vehicle like water, dilute alcohol, glycerin or propylene glycol and are intended for instillation into the ear with a dropper. They are generally used for cleansing the ear, drying weeping surfaces, softening the wax and for treating the mild infections.

Ear drops are dispensed in coloured, fluted bottles attached with a dropper or in suitable plastic containers. The containers should be labelled "for external use only". Examples are : hydrogen peroxide ear drops, phenol ear drops etc.

Elixirs

Elixirs are clear, pleasantly flavoured, sweetened hydroalcoholic liquid preparations for oral administration. The main ingredients of elixirs are ethanol and water but glycerin, sorbitol, propylene glycol; flavouring agents, sugar and preservatives may be incorporated to the preparation. The elixirs may be medicated or non-medicated. The medicated elixirs usually contain very potent drugs such as antibiotics, antihistaminics and sedatives. The non-medicated elixirs are used as flavours and vehicles. Examples are : chlorpheniramine elixir, diphenhydramine elixir, ephedrine elixir, paracetamol elixir, paediatric; piperazine citrate elixir etc.

Emulsions

Emulsions are the biphasic liquid dosage form of medicament in which two immiscible liquids (generally one of which is water and the other is some lipid or oil) are made miscible by the addition of a third substance known as emulgent

or emulsifying agent. Emulsions are comparatively pleasant to take than to take an oil as such.

Emulsions are of two types (a) oil in water type (O/W) (b) water in oil type (W/O). The former is generally for oral administration whereas the latter is generallv for application to the skin.

Emulsions should be supplied in wide mouthed containers labelled with "shake the bottle before use" label. Examples of emulsion are : castor oil emulsion, liquid paraffin emulsion, liquid paraffin and phenolphthalein emulsion etc.

Enemas

Enemas are aqueous or oily solutions or suspensions intended for introduction into the rectum for their purgative, sedative, anthelmintic, anti-inflammatory or nutritive effects. They may also be used for X-ray examination of the lower bowel. Among the commonly used drugs in solution form which act as cleansing enemas include isotonic solution of sodium chloride, sodium bicarbonate 2%, sodium phosphate, magnesium sulphate, soap and a combination of these substances. The other drugs in the form of enemas include olive oil, arachis oil, chloralhydrate, paraldehyde, turpentine, alum, tannic acid, barium sulphate etc.

Usually solutions in volume of 500 ml to 1000 ml, depending on the age and condition of the patient is introduced as enema. However the commercially available concentrated enemas are introduced in small volumes of 100 to 200 ml. Large volume enemas should be warmed to body temperature before administration. Examples are : paraldehyde enema, soap enema etc.

Eye Drops

Eye drops are sterile aqueous or oily solutions or suspensions for instillation into the eye. They are usually applied into the space between the eye ball and eyelids or on to the corneal surface. The main requirement of eye drops is that they should be sterile, usually isotonic, buffered and free from foreign particles to avoid irritation to the eye. They usually contain

substances having antiseptic, anaesthetic, anti-inflammatory, mydriatic or miotic properties or substances used for diagnostic purposes.

Eye drops should be dispensed in glass or suitable plastic containers with a screw cap fitted with a rubber teat and glass dropper for easy application of the drops or the containers may be fitted with a narrow nozzle from which the drops can be directly instilled into the eye. Examples are : atropine eye drops, chloramphenicol eye drops, cocaine eye drops, hydrocortisone eye drops, hyoscine eye drops, pilocarpine eye drops, sulphacetamide eye drops etc.

Eye lotions

Eye lotions or eye washes are sterile aqueous solutions used for irrigating the eye. They are usually applied with a clean eye bath or sterile fabric dressing and a large volume of solution is allowed to flow quickly over the eye.

Eye lotions are usually supplied in concentrated form and are required to be diluted with an equal volume of warm water immediately before use. They should be freshly prepared and should not be stored for more than 2-3 days as they may be contaminated with micro-organisms on prolonged storage. Eye lotions should be isotonic and free from foreign particles to avoid irritation to the eye. The drugs used for preparing eye solutions include sodium chloride, sodium bicarbonate, boric acid, borax and zinc sulphate.

Eye lotions should be dispensed in coloured fluted bottles. The container should be labelled "for external use only". Examples are : sodium bicarbonate eye lotion and sodium chloride eye lotion.

Gargles

Gargles are aqueous solutions used for the prevention or treatment of throat infections. Usually they are concentrated solutions and should be diluted with warm water before use. In using the gargles they are brought into intimate contact with the mucous membrane of the throat and are allowed to remain there for a few moments after which they are thrown

out of the mouth. Some of the analgesic preparations like aspirin gargles may be swallowed afterwards.

Gargles should be dispensed in white fluted bottles.

Gels

Generally gels are the aqueous colloidal suspensions of the hydrated forms of insoluble inorganic drugs. Examples are aluminium hydroxide gel, aluminium phosphate gel, milk of magnesia etc. They are generally used as antacid.

Glycerins

They are also known as glycerites. Glycerins are the viscous preparations in which the drug is dissolved in glycerin with or without heating. They are generally used as antiseptic or anti-inflammatory preparations. Examples are ichthammol glycerin, phenol glycerin, tannic acid glycerin etc.

Granules

Granules are the solid dosage form of medicament in which the powdered drug or drugs are mixed with sweetening, flavouring and colouring agents. A suitable granulating agent is added to moisten the powder and mixed thoroughly. The wet mass is passed through a suitable sieve and granules dried at a temperature of 60°C. They are supplied in glass containers and the patient is asked to add sufficient freshly boiled and cooled water to constitute a liquid preparation.

Effervescent Granules

These are specially prepared solid dosage form of medicament, meant for internal use. They usually contain citric acid, tartaric acid, sodium bicarbonate and medicament, a sweetening agent such as saccharin or sucrose may be incorporated.

When these granules are added to water, the acids react with sodium bicarbonate to librate carbon dioxide and the preparation is taken while effervescing or immediately afterwards. These preparations act as antacid.

Implants

Implants are sterile small tablets meant for insertion under the skin by giving a small cut into the skin which is stitched afterwards. They are used to provide slow and continuous release of the drug for a long time ranging from 3 to 6 months or even more. These tablets are more commonly used in animals than human beings. Generally steroidal hormones like testosterone, stilbesterol etc. are formulated as implants.

Infusions

Infusions are liquid preparations which are either prepared by infusion process or by diluting 1 part of concentrated infusion with 9 parts of water. Infusions should be freshly prepared and must be used within 12 hours of their preparation. Examples are concentrated compound gentian infusion and concentrated senega infusion.

Inhalations

Inhalations are the liquid preparations containing volatile ingredients. They are used to relieve nasal congestion and inflammation of the respiratory tract. They may be placed on a pad or added to hot water and vapours inhaled for five to ten minutes. Examples are benzoin inhalation, menthol and eucalyptus inhalation.

Injections

Injections are the sterile liquid preparations containing one or more medicaments dissolved or suspended in a suitable vehicle and are meant for introduction into the body tissues by means of an injection under or through one or more layers of the skin or mucous membrane. Examples are ampicillin injection, dextrose intravenous infusion, gentamycin injection etc.

Insufflations

These are the finely divided powders meant for introduction into the body cavities such as ears, nose, tooth sockets and

vagina with the help of an apparatus known as insufflator, to which it would be difficult to apply the powder directly.

Irrigations

These are the solutions containing medicaments used to treat infections of the bladder, vagina and nose. These are introduced into the cavities by means a soft rubber tube known as catheter. They are generally used as antiseptic, anti-inflammatory or cleansing solutions.

Jellies

Jellies are transparent or translucent non-greasy semisolid preparations meant for external application to the skin or mucous membrane. They are used for medication or lubrication purposes. Some of them are also used as contraceptive jellies. Examples are proflavin jelly, ichthammol jelly etc.

Linctuses

Linctuses are sweet, viscous liquid preparations usually containing medicinal substances which have demulcent, sedative or expectorant properties. They are used for the treatment of cough. Linctuses are swallowed slowly in small doses without addition of water. Examples are codeine linctus, noscapine linctus etc.

Liniments

Liniments are liquid or semiliquid preparations meant for external application to the skin. Liniments are applied by rubbing or friction but should not be applied to the broken skin. They should be dispensed in coloured fluted bottles in order to distinguish from preparations meant for external use. The bottle should be labelled "for external use only" and "shake the bottle before use". Examples are soap liniment, white liniment etc.

Lotions

Lotions are liquid suspensions or dispersions meant for external application to the skin without friction. They usually

contain alcohol and glycerin because alcohol hastens drying and produces cooling sensation whereas glycerin keeps the skin moist for a sufficient long time.

Lotions should be dispensed in a coloured fluted bottle with "for external use only" and "shake the bottle before use" label. Examples are calamine lotion and salicylic acid lotion.

Lozenges

Lozenges are the solid dosage form of medicament which are meant for slow dissolution in the mouth. Along with medicament they contain a sweetening agent, flavouring agent and a strong binding agent. They may be prepared either by moulding or by compression. Examples are compound bismuth lozenges, liquorice lozenges etc.

Mixtures

Mixtures are liquid dosage form of medicament in which drug or drugs are dissolved or suspended in a suitable aqueous vehicle, they may be sweetened and flavoured. They are freshly prepared and consumed within a few days. Mixtures are meant for oral administration and generally several doses are contained in a bottle, when only one dose is there it is known as haustus or draught.

For indiffusible solids a suitable suspending agent will have to be incorporated to make the substance diffusible, so as to measure the dose easily. The containers of such mixtures should be labelled "shake the bottle before use". Examples are aluminium hydroxide mixture, kaolin mixture, magnesium sulphate mixture etc.

Mouthwashes

Mouthwashes are usually aqueous solutions in concentrated form with a pleasant taste and flavour used for rinsing, deodorant, refreshing or antiseptic action. Medicated mouthwashes may contain astringents, antibacterial agents, protein precipitants or other agents. They are generally used after dilution with warm water, on the mucous membrane of

the mouth. Examples are compound sodium chloride mouthwash and zinc sulphate and zinc chloride mouthwash.

Nasal drops

Nasal drops are usually aqueous solutions intended for instillation into the nostrils by means of a dropper. They are commonly used for their antiseptic, local analgesic or vasoconstrictor properties. Examples are ephedrine nasal drops.

Ointments

Ointments are the soft semisolid preparations meant for external application to the skin or mucous membrane. They usually contain a medicament dissolved, suspended or emulsified in the base. Ointments are used for their emollient and protective action to the skin. Examples are compound benzoic acid ointment, calamine ointment, cetrimide emulsifying ointment etc.

Ophthalmic Ointments

Ophthalmic ointments are meant for application to the eye. They should be sterile and free from irritation. They should be packed in sterile containers which should keep the preparation sterile until whole of it is used up. Examples are atropine eye ointment, chloromycetin eye ointment.

Paints

Paints are the liquid preparations meant for external application to the skin or mucous membrane. They generally have a volatile solvent which evaporates quickly to leave a dry film of the medicament. Throat paints are viscous preparations which are applied to the throat. They contain high contents of glycerin due to which the preparations remain sticking to the site of application and prolong the action of the medicament. Examples are coal tar paint, compound iodine paint.

Pastes

Pastes are semisolid preparations meant for external application to the skin. They differ from ointments in that they generally contain a large amount of finely powdered solids such as starch, zinc oxide, calcium carbonate etc. They provide a protective coating over the areas to which they are applied. They may be applied directly to the affected part or by spreading on a suitable backing material which is then applied to the affected area. Examples are magnesium sulphate paste, zinc and coal tar paste.

Pessaries

Pessaries are the solid unit dosage form of medicament meant for introduction into the vagina. The bases used for the manufacture of pessaries are such that at room temperature they retain the original shape but when inserted into the cavity either melt or dissolve in the cavity fluids to release the medicament. They may be prepared either by moulding or by compression. Examples are lactic acid pessaries, nystatin pessaries.

Powders

Powders are solid dosage form of medicament meant for internal and external use. The powders meant for internal use are known as oral powders whereas those meant for external use are known as dusting powders. The powders may be simple or compound. When the powders are dispensed in large quantities in a container and the patient is asked to measure a specified quantity as a dose then these powders are known as bulk powders. Examples are compound rhubarb oral powder, compound sodium chloride and dextrose oral powder, talc dusting powder etc.

Solutions

Solutions are liquid preparations meant for internal or external use. They contain one or more than one ingredient usually dissolved in water. They may be sterile when intended for parenteral administration or unsterilized when intended

for oral administration. Examples are strong ammonium acetate solution, aqueous iodine solution, cetrimide solution etc.

Solution tablets

Solution tablets contain a medicament or medicaments required to dissolve completely in the liquid to produce solutions of definite concentration. The solutions prepared by dissolving the soluble tablets may include mouthwashes, gargles, skin lotions, douches, antibiotics and certain vitamins. Examples are effervescing mouthwash tablets, benzyl penicillin solution tablets.

Spirits

Spirits are solutions of medicament or medicaments in alcohol (90 per cent). Examples are chloroform spirit, lemon spirit, compound orange spirit.

Sprays

Sprays are the liquid preparations of medicaments in aqueous, alcoholic or glycerin containing vehicle and are meant for application to the nose or throat by means of an atomiser or nebuliser. Examples are compound adrenaline and atropine spray, isoprenaline spray.

Suppositories

Suppositories are special shaped solid dosage form of medicament for insertion into body cavities other than mouth. They may be inserted into rectum, vagina or urethra. These products are so formulated that after insertion, they will either melt or dissolve in the cavity fluids to release the medicament. Suppositories vary in shapes, sizes and weights. Generally suppositories from 1 to 2 gm are prepared with either cocoa butter or glycerogelatin base. Examples are aminophylline suppositories, glycerol suppositories etc.

Suspensions

Suspensions are the biphasic liquid dosage form of medicament in which the finely divided solid particles ranging

from 0.5 to 5.0 micron are suspended or dispersed in a liquid or semisolid vehicle. Suspensions are mainly used for oral administration, external application or parenteral use. Examples are barium sulphate suspension; chalk, kaolin suspension.

Syrups

Syrups are sweet, viscous, concentrated aqueous solutions of sucrose or other sugars in water or any other suitable aqueous vehicle. They are used as sweetening and flavouring agents. Examples are lemon syrup, raspberry syrup, tolu syrup etc.

Tablets

Tablets are unit solid dosage form of medicament or medicaments with or without suitable diluents. They are prepared by moulding or usually by compression. Tablets are generally meant for oral administration but may be used by other routes of administration. Examples are aminophylline tablets, chloroquine sulphate tablets, paracetamol tablets etc.

Tinctures

Tinctures are alcoholic liquid preparations containing the active principles of vegetable drugs. They are usually prepared by maceration or percolation, or may be prepared by dissolving the corresponding liquid extract or chemical substances in alcohol or hydroalcoholic solvent. Examples are belladonna tincture, aromatic cardamom tincture, nux vomica tincture etc.

Throat paints

Throat paints are viscous liquid preparations used for mouth and throat infections. Glycerin is commonly used as a base because of viscous nature and agreeable taste. Examples are boroglycerin, phenol glycerin and compound iodine paint (Mandl's paint).

DRUG DELIVERY SYSTEMS

With the advancement of technology, emerging concepts, new theories and their practical applications in the development

and production of previously termed as "dosage forms" are now more appropriately referred to as "drug delivery systems."

With the development of new drug delivery systems, new drugs were discovered. The production processes, machines for manufacture, new control methods for accurate definition of drug delivery and new and improved quality control procedures were developed. All these changes and improvements lead to the production of superior quality drug dosage forms at lesser costs. With the development of new techniques, processes and instruments like microprocessors and small computers, the production of modern drugs has further been revolutionized to a great extent.

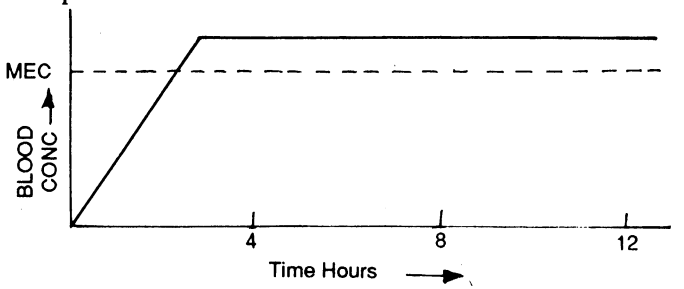
Majority of the drugs are administered to the body with the basic aim to achieve a stable blood or tissue concentration which is therapeutically effective and nontoxic for an extended period of time. This can only be achieved if proper dosage regimens are designed and attempt is made to attain a maximum rate and extent of drug absorption, however drug action can be controlled through formulation by controlling bioavailability to reduce drug absorption rates. By the use of new drug delivery systems one can enhance the bioavailability and therapeutic index of medicinal agents as well as reduce side effects and can improve acceptance and compliance by the patient. Following approaches to the formulation of drug delivery systems based on the deliberate control of drug availability are considered.

Sustained release, sustained action, prolonged action, extended action, controlled release, timed release, depot and repository dosage forms are terms used to identify drug delivery systems. These preparations are designed to achieve a prolonged therapeutic effect by continuously releasing the drug over an extended period of time after administration of a single dose of the drug. Now a days a large number of products are available in the market which are formulated for oral, parenteral, ophthalmic, transdermal, intravaginal and intrauterine administrations which act as sustained or controlled drug delivery systems. Research is being carried out to develop intranasal and rectal routes of administration.

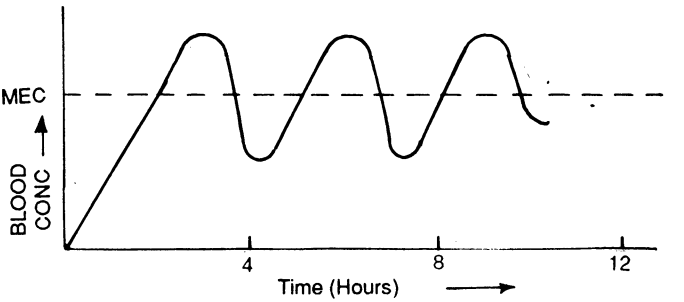
Sustained release or controlled release drug delivery systemsw are found more suitable for the treatment of chronic diseases which require a prolonged use of drugs. Some of the diseases which require such type of treatment include : asthma, diabetes, hypertension, peptic ulcer, rheumatoid arthritis, cancer, angina pectoris, depression, anxiety, bacterial infections etc.

1. Oral Drug Delivery Systems

Sustained action dosage form of medicament like tablets and capsules are meant for oral administration and release the drug slowly and continuously for a prolonged duration of action, thus maintaining a minimum effective connectration (MEC) of the drug in the blood at a constant level throughout the treatment period. Whereas in the conventional therapy i.e. administration of the drug in divided doses at a specified intervals of time, a constant blood concentration is not maintained but there is a considerable fluctuation in drug concentration. Graphically these two types of concentrations can be represented as follows :



The effect of oral administration of sustained action medication.



The effect of oral administration of medication in divided doses.

The sustained release or sustained action dosage forms release the initial dose immediately to cause a rapid onset of desired therapeutic action and the subsequent doses are released to maintain an effective concentration of the drug for the duration of the treatment. The initial desired therapeutic response is maintained because the rate of release of the desired therapeutic concentration is equal to the rate at which the drug is eliminated or inactivated. The products which release the drug for prolonged action are becoming more popular and are referred to as sustained-action, sustained-release, prolonged-action, prolonged-release, timed-release or repeat action products.

Advantages

1. They maintain the therapeutic effect for a longer period than obtained by the administration of single dose medication.
2. They are considered the most convenient dosage forms because the necessity of administering the doses serveral times a day are eliminated.
3. They eliminate the inconvenience caused to the patient for taking the dose during night hours when he is asleep. They control the level of sleep throughout the entire period of sleep and also control the migrain headache on awakening.
4. They reduce the chances of missed doses by forgetful patients.
5. They eliminate the undesirable side effects caused by high blood levels of drugs administered as conventional dosage forms.
6. They reduce or eliminate the gastrointestinal irritation caused by high concentrations of drugs administered orally.

Disadvantages

1. The long acting dosage forms may not release the drug as completely or effectively as those of conventional dosage forms.

2. Certain drugs are no more effective when administered in long acting forms.
3. They are comparatively costlier than the drugs in conventional dosage forms.

Principles Involved in the Development of Sustained Action Dosage Forms

When the drug is administered into the body, it is absorbed into the blood stream from the site of absorption, distributed, metabolised and eliminated out of the body in the original form or in the metabolised form. The amount of drug present in the circulation at any given time depends upon the rate of absorption, rate of biotransformation and rate of elimination of the drug. Thus the action of a drug can be prolonged by :

1. Decreasing the rate of absorption.
2. Decreasing the rate of biotransformation.
3. Decreasing the rate of excretion.

Out of the above mentioned factors, for the development of sustained action dosage forms it is not possible to either decrease the rate of biotransformation or the rate of elimination of drugs because both the factors involve the simultaneous administration of enzymes and other substances which interfere with the normal metabolic functions, therefore, cannot be administered. Thus the only factor which can be manipulated is to decrease the rate of absorption of drugs.

Design of Sustained Action Dosage Forms

It is the principle of sustained action dosage forms that the initial dose must be released immediately to the system to produce rapid action and the subsequent doses are released gradually and continuously at a specified time to maintain an effective blood concentration to produce the desired therapeutic effect for a specified period of time. Therefore the products so designed should conform to these requirements. Following are a few types of sustained action dosage forms generally used for the administration of drugs.

1. Coated Beads or Granules

The total quantity of the drug is divided into a suitable number of groups (generally 10 groups of pellets, 1-2 mm in diameter). The first group is kept uncoated to produce the rapid therapeutic effect and the other groups are coated with selected materials one by one to produce thickness of varying degrees. This can be done by giving two coating to the 2nd group, three coating to the 3rd group, four to the fourth and so on. The total thickness of these coatings should be about 0.1 mm. All these groups i.e. coated and uncoated are then mixed together. They may be compressed into tablets, filled in capsules or suspended in suitable liquids to produce liquid dosage forms. For coating, the materials may include cellulose esters, fats, keratin, and gluten. The other coating materials are mixtures of bees wax, carnuba wax with glyceryl monostearate. Stearic acid, palmitic acid and cetyl alcohol can also be used for coatings. Generally for coaring, beads of 12 to 40 mesh size are recommended and coating pans are used for coating the beads.

If the dose of the drug is small, then the blank granules or beads may be prepared from any inert material like lactose, starch or sucrose and the drug adsorbed on to them by dissolving the drug in a nonaqueous solvent mixture such as alcohol and acetone.

2. Matrix Embedding

In this process the drug is suspended in a melt of some water insoluble material such as carnauba wax or hydrogenated castor wax and the admixture is allowed to cool and solidify. The solidified mass is then ground to produce granules or coarse powder which can be used to prepare compressed tablets or filled into capsules. The grinding process often produces enough surface drug which is sufficient to release the initial dose. Too much grinding should be avoided because this may lead to uncover the drug thus rendering the embedding useless. The additional uncoated drug can be incorporated to release the initial dose immediately to produce the rapid therapeutic effect.

The inert, non-absorbable plastic materials such as polyvinyl chloride or ethylcellusose etc. can be used as matrix. The drug is mixed with the plastic materials and made in the form of granules or coarse powders which are then compressed or filled into capsules. Some channeling agents can be included which will help the drug to leach out of the matrix by body fluids and absorbed into the system, the plastic material remains unchanged and is excreted as such through the faeces.

3. Slowly Soluble Chemical Complex Formation

Some medicaments which possess very low solubilities may themselves act as sustained action preparation but the drugs which are very soluble may be chemically converted to complex forms which dissolve slowly thus acting as sustained action preparations. Griseofulvin, possess this property itself, whereas certain amine drugs combine with high molecular weight acids like tannic acid and polygalacturonic acid to form slightly soluble complexes which dissolve slowly in the body fluids thus increasing the time of release of the drug.

4. Use of Ion Exchange Resins

There are two types of ion exchange resins, one is known as cation or acid exchange resin and the other anion or base exchange resin. The cation exchange resin exchanges the cations in solution with hydrogen ions from resin whereas anion exchange resin removes the anions from resin. When a solution of the cationic drug is passed through the cation resin it forms a complex which is then washed with deionised water and compressed in the form oif tablets or filled into capsules. It may be dissolved in a suitable liquid to prepare a liquid dosage form. Before compression or filling into capsules a certian quantity of unbound drug sufficient to produce minimum effective concentration is incorporated to the resin complex. After administration the drug is released in greater amount in the acidic medium of the stomach than the alkaline medium of the small intestine.

Other Techniques of Producing Sustained Action of Drugs

The following are the other techniques by which sustained action of drugs can be produced.

1. Route of Administration

The absorption of a drug depends on the route by which it is administered. If it is administered by intravenous injection an immediate effect is produced whereas the effect is delayed if the sme drug in introduced by intramuscular injection. The effect can be prolonged which may last for months if the drug is placed under the skin as implant. Hence the route of administration can be used to produce sustained action of a drug.

2. Particle Size of the Drugs

Since the dissolution rate of a drug depends on its particle size the smaller the particle size more will be dissolution rate and bigger the particle size less will be dissolution rate. The absorption depends upon the dissolution rate of a drug therefore this parameter can be used to prolong the action of a drug.

3. Viscosity and Nature of the Vehicle

By increasing the viscosity of the vehicle the absorption can be slowed down to a desired extent. Gelatin, carboxymethyl cellulose, polyvinylpyrrolidone and polyvinyl alcohol have been used individually as thickening agents to prolong the action of intramuscular injections. Lipophilic solutions of a drug usually have longer therapeutic effect than the aqueous solutions of the same drug. Therefore oily vehicles may be employed to obtain sustained action of a drug.

Vaso-constriction, immiscibility, dissolution rate, ionization, polymorphism and surface tension of dissolution medium are still other parameters which can prolong the action of a drug.

Types of Sustained-Action Dosage Forms

(a) Long-acting Capsules (Spansules)

The coated beads or granules are filled into hard gelatin capsules which release the medication gradually and uniformly

over an extended period of time. They are available in the market under different trade names

(b) Long-acting Multilayer Tablets

In long-acting multilayered tablets the quickly disintegrating portions are compressed successively in the second and third layers. The first layer disintegrates immediately to produce rapid action whereas the other layers disintegrate slowly and continuously to produce prolonged action.

(c) Long-acting Core Tablets

These tablets consists of core tablets containing active medicament or medicaments. The cores are then coated with a substance like glyceryl ester of a higher fatty acid which does not allow the core to disintegrate in the stomach but disinegrates in the intestinal fluids. To this coated core is then applied another coating of active ingredients by means of pan coating. This outer layer disintegrates immediately to produce rapid therapeutic effect there-after the drug is slowly released from the inner core and the patient receives the second dose.

(d) Long-acting Liquid Products

The very finely coated particles of a drug are suspended in a suitable viscous aqueous vehicle to get a suspension.

(e) Repeat-action Tablets

These tablets consists of a core and a coat containing two doses of the medicament. The first dose is compressed or coated in the outer covering whereas the second dose is present in the core. In repeat action tablets the second dose of the drug is released only when the first dose has been completely used up and there is no continuous release of the drug.

Nanocapsules

Nanocapsules, the ultrafine drug delivery system have become very popular due to the reason that they are able to alter the drug distribution. Nanocapsules are quite commonly

used for this purpose because they are relatively easy to prepare, pharmaceutically stable and their biodegradation can be controlled. Nanocapsules or nanoparticles are less than a micrometer in dimensions. They consists of a solid or liquid core material containing one or more drugs which are enclosed in coating. The core is known as nucleus or fill whereas coating is known as wall or shell. When a distinct coating and core regions are present then they are known as nanocapsules but when there is no distinct coating and core regions present then they are known as nanoparticles. Materials like gelatin, albumin and casein obtained from natural sources and synthetic substances like diethylacrylates, cyanoacrylates, polyacrylamide etc are used to make nanocapsules or nanoparticles. The drugs which are nanocapsulated include antibiotics, analgesics, steriods, enzymes, toxins, anticancer agents etc.

2. Transdermal Drug Delivery Systems

These systems deliver drugs systamically through the skin but without the use or needle or any other instrument to inject them into the blood circulation. The system is applied to the skin and is absorbed by a process of molecular diffusion. This diffusion process begins as soon the system is applied to the skin. In the begining the process is quite fast till the binding sites of the skin are saturated, then the release of the drug settles at a constant rate.

The drugs to be administered by transdermal route should have the qualities that (1) It should show sufficient absorption through the skin to produce minimum effective concentration (2) It should not produce any harmful effects on the skin on continuous use for a long time. A large number of drugs are already available in the form of transdermal systems and there is a great scope for the further expansion of these systems. The transdermal drug delivery systems has the following advantages :

1. Effects on the liver are eliminated
2. Side effects are reduced
3. Duration of action is increased
4. Patient compliance is improved.

3. Ophthalmic Drug Delivery Systems

The use of conventional opthalmic preparations show lower bioavailability because of constant lacrimal secretion as well as naso-lacrimal drainage. These factors lead to frequent instillation of concentrated preparation into the eyes to obtain the desired therapeutic effects which sometimes leads to undesirable side effects. These difficulties can be overcome by the use of sustained release ophthalmic preparations. The therapeutic effects can be achieved by increasing the contact time between the drug and the corneal surfaces. The sustained action of ophthalmic formulations can be produced (i) by the use of viscous gels and (ii) by the use of some suitable inserts.

4. Contraceptive New Drug Delivery Systems

The new drug delivery systems used for contraception has the following advantages :

1. It eliminates the necessity of administration of the drugs daily.
2. it decreases the systemic or local side effects on the female reproductive systems.
3. It decreases the possible carcinogenic effects of steroids.
4. It allows complete privacy for the women.

The drug delivery systems used as contraceptives can be classified as :

(i) Monthly injections
(ii) Medicated intra-uterine or vaginal devices.
(iii) Implants.

Injections are given to the women which are repeated every month.

Medicated intra-uterine or vaginal devices are quite useful and have certain advantages that they reduce the side effects and possible development of cancer can be minimised or even eliminated. The contraceptive action of these devices can be terminated at any time by removing the device. However these devices has certain disadvantages that they may produce discomfort to the women and menstrual cycle may become irregular. Since intra uterine devices are special devices and

require technique for their insertion so a qualified doctor or nurse should insert such type of devices. Copper-T is the most commonly used device of this kind.

Contraceptive implant is a special type of tablet which is kept under the skin by giving a suitable surgical cut which is stiched after inserting the implant. These implants contain levonorgestrel which is continuously released to produce contraceptive action.