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MORPHINE SULFATE EXTENDED RELEASE TABLETS A SEMINAR REPORT

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ABSTRACT

Tablets are intended for oral administration. Some tablets are swallowed whole or after being chewed, some are dissolved or dispersion in water before administration and some are retained in mouth where the active ingredient is liberated. Preparation intended for administration by other routes, for example, in the form of implants and passerines may also be presented in the form of tablets but because they may required special formulations, methods of manufacture or from of presentation appropriate to the particular use they may not comply with all the requirement of this monograph. **Morphine** is a pain medication of the opiate family which is found naturally in a number of plants and animals. It acts directly on the central nervous system (CNS) to decrease the feeling of pain.It can be taken for both acute pain and chronic pain It is frequently used for pain from myocardial infraction and during labor. Morphine was first isolated between 1803 and 1805 by friedrichserturner. This is generally believed to be the first isolation of an active ingredientsfrom a plant. merck began marketing it commercially in 1827. Morphine was more widely used after the invention of the hypodermic syringe in 1853–1855. Serturner originally named the substance morphiumafter the Greek god of dreams, morpheus, as it has a tendency to cause sleep. The primary source of morphine is isolation from poppy strawof the opium poppy. In 2013, approximately 523 tons of morphine were produced. Approximately 45 tons were used directly for pain, a four-fold increase over the last twenty years. Most use for this purpose was in the developed world. About 70 percent of morphine is used to make other opioids such as hydromorphone, oxomorphone and heroine It is a Schedule II drug in the united states, Class A in the united kingdom and Schedule I in canada. It is on the medicinal health of organisation list of essential medicines, the most effective and safe medicines needed in a health system. Morphine is sold under many trade name. In 2016, it was the 158th most prescribed medication in the United States, with more than 3 million prescriptions.

EXTENDED RELEASE

Extended-release means the pill is formulated so that the drug is released slowly over time.
This has the advantage of taking pills less often. It also means that there may be fewer side-effects as the levels of the of drug in the body are more consistent in extended- release formulations.

KEY WORDS: Friedrich serturner, merck, hypodermic syringe, Morpheus, hydromorphone, oxymorphone.

INTRODUCTION

Tables are obtained by compression of uniform volumes of powders or granules by applying high pressure and using punches and dies. The particles to be compressed consist of one or more medicaments, with or without auxiliary substance such as diluents, binders, and disintegration agents, lubricant, glide ants and substances capable of modifying the behaviour of the medicaments inn the digestive tracts. Such substances must be innocuous and therapeutically inert in the quantities present.

Because of their composition, method of manufacture or intended use, tablets present variety of characteristics and consequently there are several categories of tablets.

Useless otherwise stated in the individual monograph, tablets are uncoated. Where coating is permitted the monograph directs coating the statement reads "The tablets are coated "Unless otherwise directed, tablets may be coated in one of different ways.

A **tablet** is a pharmaceutical oral dosage form (OSD). Tablets may be defined as the solid unit dosage form of medicament or medicaments with suitable excipients and prepared either by moulding or by compression. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose. The excipients can include diluents, binders or granulating agents, glidants(flow aids) and lubricants to ensure efficient tabletting; disintegrantsto promote tablet break-up in the

digestive tract; sweetnersor flavours to enhance taste; and pigments to make the tablets visually attractive or aid in visual identification of an unknown tablet. A polymer coating is often applied to make the tablet smoother and easier to swallow, to control the release rateof the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered sublingually, buccally, rectallyor intravaginally. The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions. Medicinal tablets were originally made in the shape of a disk of whatever color their components determined, but are now made in many shapes and color to help distinguish different medicines. Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified. Sizes of tablets to be swallowed range from a few millimeter to about a centimeters.

Generalcharacterstics

Tablets are usually solid, right circulars cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled, they may exist in others shapes like triangular, rectangular, etc also. They may have lines or break-marks and may bear a symbol or other markings. They are sufficiently hard to withstand handling without crumbling or breaking.

History

Pills are thought to date back to around 1500 BC.Earlier medical recipes, such as those from 4000 BC, were for liquid preparations rather than solids. The first references to pills were found on papyruses in ancient Egypt, and contained bread dough, honey or grease. Medicinal ingredients, such as plant powders or spices, were mixed in and formed by hand to make little balls, or pills. In ancient Greece, such medicines were known as katapotia ("something to be swallowed"), and the Roman scholar Pliny, who lived from 23-79 AD, first gave a name to what we now call pills, calling them *pilula* Pills have always been difficult to swallow and efforts long have been made to make them go down easier. In medieval times, people coated pills with slippery plant substances. Another approach, used as recently as the 19th century, was to gild them in gold and silver, although this often meant that they would pass through the digestive tract with no effect. In the 1800s sugar-coating and gelatin-coating was invented, as were gelatin capsules.

In 1843, the British painter and inventor William brockedon was granted a patent for a machine capable of "Shaping Pills, Lozenges and Black Lead by Pressure in Dies". The device was capable of compressing powder into a tablet without use of an adhesive.

TYPES

Pill

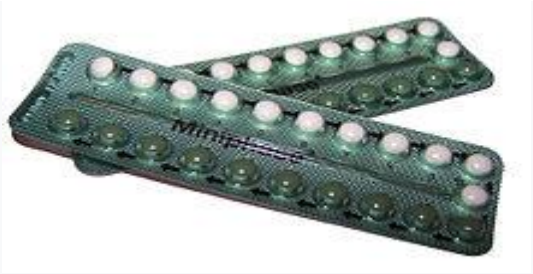


Figure 1: Pills.

Combined contraceptive pills were nicknamed "the pill" in the 1960s

A pill was originally defined as a small, round, solid pharmaceutical oral dosage formof medication. The oldest known pills were made of the zinc carbonates hydrozincite and smithsonite The pills were used for sore eyes, and were found aboard a Roman ship relitto del pozino which wrecked in 140 BC.Today, pills include tablets, capsules, and variants thereof like caplets — essentially, any solid form of medication colloquially falls into the pill category.

CAPLET

Figure 2: Caplet.

Variations on a common tablet design, which can be distinguished by both colour and shape

A caplet is a smooth, coated, oval-shaped medicinal tablet in the general shape of a capsule. Many caplets have an indentation running down the middle so they may be split in half more easily. Since their inception, capsules have been viewed by consumers as the most efficient method of taking medication. For this reason, producers of drugs such as otc analgesics wanting to emphasize the strength of their product developed the "caplet", a portmanteauof "capsule-shaped tablet", in order to tie this positive association to more efficiently-produced tablet pills, as well as being an easier-to-swallow shape than the usual disk-shaped tablet.

Orally disintigrating tablet (odt)

An orally disintegrating tablets or orodispersible tablet (ODT), is a drug dosage form available for a limited range of over – the -counter (OTC) and prescription medications.

Figure 3: Orally Disintegrating Tablet.

TABLETING FORMULATIONS

In the tablet-pressing process, it is important that all ingredients be fairly dry, powdered or granular, somewhat uniform in particle size, and freely flowing. Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity, but granulation should prevent this. Content uniformity ensures that the same API dose is delivered with each tablet.

Some APIs may be tableted as pure substances, but this is rarely the case; most formulations include excipients Normally, a pharmacologically inactive ingredient (excipient) termed a *binder* is added to help hold the tablet together and give it strength. A wide variety of binders may be used, some common ones including lactose, dibasic calcium phosphate, sucrose, corn (maize) starch, microcrystalline cellulose, povidone polyvinylpyrrolidone and modified cellulose (for example hydroxypropyl methylcellulose and hydroxyethylcellulose).

Often, an ingredient is also needed to act as a disintegrants to aid tablet dispersion once swallowed, releasing the API for absorption. Some binders, such as starch and cellulose, are also excellent disintegrants.

TYPES OF COATING

Compressed tablets

Compressed tablets represent a significant proportion of tablets that are clinically used to provide systemic administration of therapeutic agents either in an uncoated state (i.e., in their simplest form) or in a coated state. These tablets are designed to provide rapid disintegration in the gastric fluid following ingestion hence, allowing rapid release of the drug and, ultimately, systemic absorption of the dosage form.

Compressed tablets are formed by compression of powdered, crystalline, or granular materials into the required geometry by the application of high pressures, utilizing steel punches and die. In addition to the Active Pharmaceutical Ingredient(s) (APIs), compressed tablets usually contain a number of pharmaceutical excipients e.g., bulking agents, disintegrants, binders, lubricants, controlled-release polymers and other miscellaneous adjuncts such as colourants and flavourants which serve different and specialized purpose during tablet manufacture, storage, and use. Examples of compressed tablets include tablets for oral, buccal, sublingual, or vaginal administration.

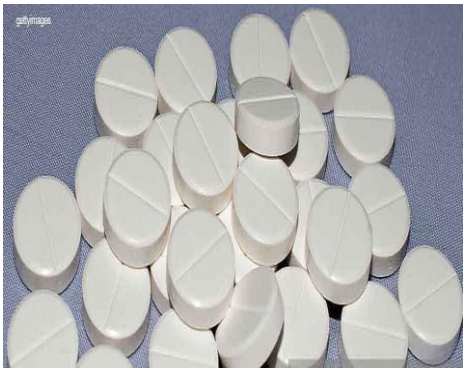


Figure 4: Compressed Tablets.

Sugar Coated Tablets

These are compressed tablets that have been coated with concentrated sugar solution to improve patient's compliance, increase aesthetic appeal, mask objectionable tastes or odours, increase stability and/or modify the release of therapeutic agent(s). Sugarcoating was once quite common but lost commercial appeal due to the time and expertise required in the coating process, the increase in size and weight of coated tablets, high cost of process validation and shipping.

The advent of film-coated tablets has also greatly decreased the use of sugar coatings due to the improved mechanical properties of the technique. Examples of sugar-coated tablets include Reasulf tablets – dried ferrous sulphate BP 200mg (Reagan Remedies Ltd.), Advil – Ibuprofen tablet BP 200mg (Pfizer Consumer Healthcare), Ebu-200 – Ibuprofen tablet BP 200mg (Me cure Industries Ltd) etc.

Figure 5: sugar coated tablet.

Film Coated Tablets

Film-coated tablets are conventional tablets coated with a thin layer of polymer (e.g., hydroxypropyl methylcellulose, hydroxypropyl cellulose) or a mixture of polymers (e.g., Eudragit E100) capable of forming a skin-like film. The film is usually coloured and also impacts the same general characteristics as sugar coating with the added advantage of being more durable, less bulky, and less time-consuming to apply. By its composition, the coating is designed to break and expose the core tablet at the desired location in the gastrointestinal tract.

Figure 6 film coated tablets.

Effervescent Tablets

Effervescent tablets are uncoated tablets that generally contain organic acids (such as tartaric or citric acid) and sodium bicarbonate in addition to the medicinal substance or API. They react rapidly in the presence of water by releasing carbon dioxide which acts as a disintegrator to produce either a drug suspension or an aqueous solution. These tablets are prepared by compressing granular effervescent salts (organic acid and bicarbonate) with the medicinal substances. A typical example of this tablet type is Ca C1000 Sandoz effervescent tablet (Novartis).

Figure 7: Effervescent tablet

Enteric Coated Tablets

Enteric-coated tablets are compressed tablets that have delayed-release properties. They are coated with polymeric substances (such as cellulose acetate phthalate/cellulose acetate butyrate; hydroxypropylmethylcellulose succinate; and methacrylic acid copolymers) that resist solution in gastric fluid but disintegrate and allow drug dissolution and absorption in the intestine.

Enteric coatings are primarily employed when the drug substance is inactivated or destroyed by gastric acid (e.g., erythromycin) or is particularly irritating to the gastric mucosa (e.g., non-steroidal anti-inflammatory drugs) or when bypass of the stomach substantially enhances drug absorption. Example of enteric-coated tablets includes Lofnac 100 – Diclofenac sodium delayed-release tablet USP 100mg (bliss GVS Pharma Ltd), Ecotrin tablets and caplets (GlaxoSmithKline Beecham).

Figure 8: Entric coated tablets.

Chewable Tablets

Chewable tablets are big sized tablets which are difficult to swallow and thus, are chewed within the buccal cavity prior to swallowing. They are especially useful for administration of large tablets to children and adults who have difficulty swallowing conventional tablets or antacid formulations in which the size of the tablet is normally large and the neutralisation efficacy of the tablet is related to particle size within the stomach.

Chewable tablets are not conventionally used if the drug has issues regarding taste acceptability. Examples of chewable tablets include Danacid – compound magnesium trisilicate tablet B.P. (Dana Pharmaceuticals Limited), Gestid – tasty chewable antacid (Ranbaxy) etc.

Figure 9: Chewable Tablets.

Buccal and Sublingual Tablets

Buccal and sublingual tablets are small, flat, oval tablets that are intended to be dissolved in the buccal pouch (buccal tablets) or beneath the tongue (sublingual tablets) for absorption through the oral mucosa to produce a systemic effect. These tablets are employed to achieve either rapid absorption into the systemic circulation e.g. glyceryl trinitrate sublingual tablets or, alternatively, to enable oral absorption of drugs that are destroyed by the gastric juice and/or are poorly absorbed from the gastrointestinal tract.

Figure 10: Buccal and Sublingual Tablets.

Lozenges or Torches

These are disc-shaped solid preparations containing medicinal agents and generally a flavouring substance in a hard candy or sugar base. They are intended to be slowly dissolved in the oral cavity, usually for local effects.

Examples include Strepsils Dry Cough Lozenges – Dextromethorphan Hydrobromide 5mg, Dichlorobenzyl alcohol 1.2mg, Amylmetacresol 0.6mg (Reckitt Benckiser), Dequadine – Dequalinium chloride BP 250mcg (Evans Medical PLC), Dr Meyer Coflin cough lozenges (Meyer Organics PVT Ltd), Cofta – Ammonium chloride/ Ipecacuanha tablet (Evans Medical PLC) etc.

Figure 10: lozenges or torches.

Advantages and Disadvantage

- Tablets are simple and convenient to use.
- They provide an accurately measured dosage of the active ingredient in a convenient portable package, and can be designed to protect unstable medications or disguise unpalatable ingredients.
- Coloured coatings, embossed markings and printing can be used to aid tablet recognition. Manufacturing processes and techniques can provide tablets with special properties, for example, sustained release or fast dissolving formulations.
- Some drugs may be unsuitable for administration by the oral route. For example, proteindrugs such as insulin may be denatured by stomach acids. Such drugs cannot be made into tablets.
- Some drugs may be deactivated by the liver when they are carried there from the gastrointestinal tractby the hepatic portal vein(the "first pass effect"), making them unsuitable for oral use.
- Drugs which can be taken sublingually are absorbed through the oral mucosa, so that they bypass the liver and are less susceptible to the first pass effect.
- The oral bioavailability of some drugs may be low due to poor absorption from the gastrointestinal tract.
- Such drugs may need to be given in very high doses or by injection. For drugs that need to have rapid onset, or that have severe side effects, the oral route may not be suitable.
- For example, salbutamol used to treat problems in the respiratory system,can have effects on the heart and circulation if taken orally; these effects are greatly reduced by inhaling smaller doses direct to the required site of action.
- A proportion of the population have difficulties swallowing tablets either because they just don't like taking them or because their medical condition makes it difficult for them (dysphagia, vomiting)
- In such instances it may be better to consider alternative dosage form or administration route.

General Properties

- A tablet must be strong and hard to withstand mechanical shock during manufacturing, packing, shipping, dispensing, and use.
- The drug content of the tablet must be bioavailable that is the tablet must be able to release its content in a predictable and reproducible manner.
- The label must be chemically and physically stable to maintain its physical and chemical attributes during manufacture, storage and use.
- The tablet should have the elegant product identity which is free from any tablet defects.
- Tablets must be uniform in weight and its drug content.

MANUFACTURING

Manufacture of tableting blend

In the tablet pressing process, the appropriate amount of active ingredient must be in each tablet. Hence, all the ingredients should be well-mixed. If a sufficiently homogenous mix of the components cannot be obtained with simple blending processes, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet. Two basic techniques are used to granulate powders for compression into a tablet: wet granulation and dry granulation. Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression.

Wet Granulation

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable. Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

Procedure

1. The active ingredient and excipients are weighed and mixed.
2. The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin and povidone.
3. Screening the damp mass through a mesh to form pellets or granules.
4. Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
5. After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state. High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process. Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

Dry Granulation

Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is sensitive to moisture and heat. Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation. Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.

Hot Melt Extrusion

Hot melt extrusion is utilized in pharmaceutical solid oral dose processing to enable delivery of drugs with poor solubility and bioavailability. Hot melt extrusion has been shown to molecularly disperse poorly soluble drugs in a polymer carrier increasing dissolution rates and bioavailability. The process involves the application of heat, pressure and agitation to mix materials together and ‘extrude’ them through a die. Twin-screw high shear extruders blend materials and simultaneously break up particles. The extruded particles can then be blended and compressed into tablets or filled into capsules.

Granule Lubrication

After granulation, a final lubrication step is used to ensure that the tableting blend does not stick to the equipment during the tableting process. This usually involves low shear blending of the granules with a powdered lubricant, such as magnesium stearate or stearic acid.

Manufacture of Tablets

Figure 11: Manufacture of tablet.

Tablets that failed due to capping and lamination compared to a normal tablet

Whatever process is used to make the tableting blend, the process of making a tablet by powder compaction is very similar. First, the powder is filled into the die from above. The mass of powder is determined by the position of the lower punch in the die, the cross-sectional area of

the die, and the powder density. At this stage, adjustments to the tablet weight are normally made by repositioning the lower punch. After die filling, the upper punch is lowered into the die and the powder is uniaxially compressed to a porosity of between 5 and 20%. The compression can take place in one or two stages (main compression, and, sometimes, pre-compression or tamping) and for commercial production occurs very fast (500–50 ms per tablet). Finally, the upper punch is pulled up and out of the die (decompression), and the tablet is ejected from the die by lifting the lower punch until its upper surface is flush with the top face of the die. This process is repeated for each tablet.

Common problems encountered during tablet manufacturing operations include:

- Fluctuations in tablet weight, usually caused by uneven powder flow into the die due to poor powder flow properties.
- Fluctuations in dosage of the Active Pharmaceutical Ingredient, caused by uneven distribution of the API in the tableting blend (either due to poor mixing or separation in process).
- Sticking of the powder blend to the tablet tooling, due to inadequate lubrication, worn or dirty tooling, or a sticky powder formulation
- Capping, lamination or chipping. This is caused by air being compressed with the tablet formulation and then expanding when the punch is released: if this breaks the tablet apart, it can be due to incorrect machine settings, or due to incorrect formulation: either because the tablet formulation is too brittle or not adhesive enough, or because the powder being fed to the tablet press contains too much air (has too low bulk density).
- Capping can also occur due to high moisture content.

MACHINES USED IN THE TABLETING PROCESSES

Tablet compaction machine

Tablet formulations are designed and tested using a laboratory machine called a Tablet Compaction Simulator or Powder Compaction Simulator. This is a computer controlled device that can measure the punch positions, punch pressures, friction forces, die wall pressures, and sometimes the tablet internal temperature during the compaction event. Numerous experiments with small quantities of different mixtures can be performed to optimise a formulation. Mathematically corrected punch motions can be programmed to simulate any type and model of production tablet press. Initial quantities of active pharmaceutical ingredients are very expensive to produce, and using a Compaction Simulator reduces the amount of powder required for product development.

TABLET PRESSER

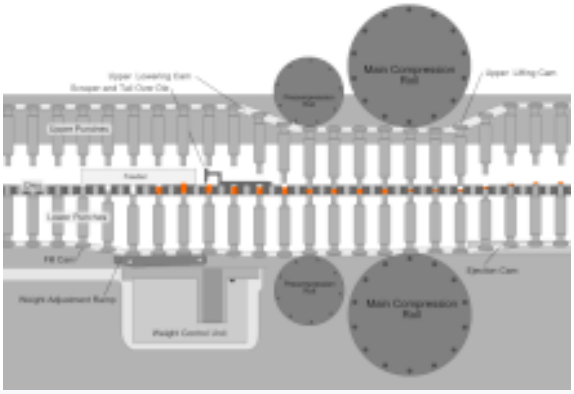


Figure 12: Tablet Presser.

AN OLD CADMACH ROTARY TABLET PRESS

Figure 13: Cadmach Rotary Tablet Press.

Tablet pressers, also called tableting machines, range from small, inexpensive bench-top models that make one tablet at a time (single-station presses), with only around a half-ton pressure, to large, computerized, industrial models (multi-station rotary presses) that can make hundreds of thousands to millions of tablets an hour with much greater pressure. The tablet press is an essential piece of machinery for any pharmaceutical and nutraceutical manufacturer. Common manufacturers of tablet presses include Natoli, Stokes, Fette Compacting, Korsch, Kikusui, Bosch-Manesty, B&D, PTK, Sejong, IMA and Courtoy. Tablet presses must allow the

operator to adjust the position of the lower and upper punches accurately, so that the tablet weight, thickness and density/hardness can each be controlled. This is achieved using a series of cams, rollers, and/or tracks that act on the tablet tooling (punches). Mechanical systems are also incorporated for die filling, and for ejecting and removing the tablets from the press after compression. Pharmaceutical tablet presses are required to be easy to clean and quick to reconfigure with different tooling, because they are usually used to manufacture many different products. There are 2 main standards of tablet tooling used in pharmaceutical industry: American standard 'TSM' and European standard 'EU'. TSM and EU configurations are similar to each other but cannot be interchanged.

Modern tablet presses reach output volumes of up to 1'700'000 tablets per hour. These huge volumes require frequent in-process quality control for the tablet weight, thickness and hardness. Due to reduce rejects rates and machine down-time, automated tablet testing devices are used on-line with the tablet press or off-line in the IPC-labs.

Tablet Coating

- Many tablets today are coated after being pressed. Although sugar-coating was popular in the past. The process has many drawbacks modern tablet coating are polymer and polysaccharide based with plasticizer and pigments included Tablet coatings must be stable and strong enough to survive the handling of the tablet, must not make tablets stick together during the coating process, and must follow the fine contours of embossed characters or logos on tablets.
- Coatings are necessary for tablets that have an unpleasant taste, and a smoother finish makes large tablets easier to swallow. Tablet coatings are also useful to extend the shelf-life of components that are sensitive to moisture or oxidation. Special coatings (for example with pearlescent effects) can enhance brand recognition.
- If the active ingredient of a tablet is sensitive to acid, or is irritant to the stomach lining, an enteric coating can be used, which is resistant to stomach acid, and dissolves in the less acidic area of the intestines.
- Enteric coatings are also used for medicines that can be negatively affected by taking a long time to reach the small intestine, where they are absorbed. Coatings are often chosen to control the rate of dissolutions of the drug in the gastrointestinal tract.
- Some drugs are absorbed better in certain parts of the digestive system. If this part is the stomach, a coating is selected that dissolves quickly and easily in acid. If the rate of absorption is best in the large intestine or colon, a coating is used that is acid resistant and dissolves slowly to ensure that the tablet reaches that point before dispersing.
- To measure the disintegration time of the tablet coating and the tablet core, automatic disintegration testers are used which are able to determine the complete disintegration process of a tablet by measuring the rest height of the thickness with every upward stroke of the disintegration tester basket.
- There are two types of coating machines used in the pharmaceutical industry: coating pans and automatic coaters. Coating pans are used mostly to sugar coat pellets. Automatic coaters are used for all kinds of coatings; they can be equipped with a remote control panel, a dehumidifier, and dust collectors. An explosion-proof design is required for applying coatings that contain alcohol.

Pill Splitter

It is sometimes necessary to split tablets into halves or quarters. Tablets are easier to break accurately if scored, but there are devices called pill splitters which cut unscored and scored tablets. Tablets with special coatings (for example enteric coatings or controlled release coatings) should not be broken before use, as this will expose the tablet core to the digestive juices, circumventing the intended delayed-release effect.

Evaluation of Tablets

Tablets are evaluated by a variety of methods.

- **Analyticaldeterminationoftabletcontent*:*** This probably will not be done due to the requirement of specialized equipment. However, the weight variation of the tablets can be measured by weighing each individual tablets and determining the percent difference from the intended amount. Guidelines in the USP 24/NF19 Supplement 1 indicate that each tablet "shall be not less than 90% and not more than

110% of the theoretically calculated weight for each unit."

- **Tablethardness*:*** The tablets must be hard enough to withstand mechanical stress during packaging, shipment, and handling by the consumer. Section <1216> of the USP 24/NF19 outlines a standard tablet friability test applicable to manufactured tablets. Most compounding pharmacy would not have the apparatus specified in Section <1216>. However, there are several hand operated tablet hardness testers that might be useful. Examples of devices are the Strong Cobb, Pfizer, and Stokes hardness testers. The principle of measurement involves subjecting the tablet to an increasing load until the tablet breaks or fractures. The load is applied along the radial axis of the tablet. Oral tablets normally have a hardness of 4 to 8 or 10 kg; however, hypodermic and chewable tablets are much softer (3 kg) and some sustained release tablets are much harder (10-20 kg).
- **Tabletdisintegration*:*** There are commercially available disintegration and dissolution apparatus. Most pharmacists will not have this equipment. However, a simple disintegration apparatus can be made. Start by supporting a 10 mesh screen about 2 inches above the bottom of a 1000 ml beaker. Fill the beaker with 1000 ml of water, add a stirring bar, and place the beaker on a magnetic stirring plate. Stir at a moderate speed. Drop the tablets onto the mesh screen and record the time needed for the tablets to disintegrate. A reasonable disintegration time should be between 15 and 30 minutes, although the time will depend on the product, the stirring speed, etc.
- **Tabletdissolution*:*** Disintegration time determination is a useful tool for production control, but disintegration of a tablet does not imply that the drug has dissolved. A tablet can have a rapid disintegration time yet be biologically unavailable. The dissolution rate of the drug from the primary particles of the tablet is the important factor in drug absorption and for many formulations is the rate-limiting step. Therefore, a dissolution time is more indicative of the availability of a drug from a tablet than the disintegration test. Even though this is an important parameter to measure, most pharmacies do not have the equipment needed to conduct these kinds of tests.

Morphine Sulfate

Morphine Sulphate tablets expose patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing Morphine Sulphate tablets, and monitor all patients regularly for the development of these behaviours and conditions.

MORPHOLOGY

Molecular formula

$C_{34}H_{40}N_20_{10}S$

Iupac name

(4*R*,4*aR*,7*S*,7*aR*,12*bS*)-3-methyl-2,4,4*a*,7,7*a*,13-hexahydro-1*H*-4,12-methanobenzofuro[3,2-e]isoquinoline-7,9-diol;sulfuric acid

Synoyms

duramorph
Astramorph
Avinza
Duramorph pf
Astramorph pf
Oramprphsr
kapanol

MOLECULAR WEIGHT: 668.8 g\mol.

STRUCTURE:

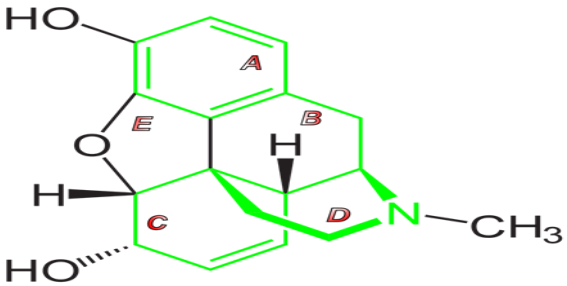
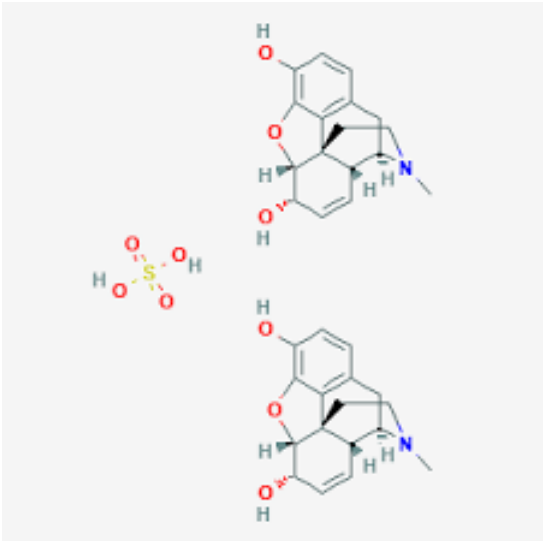


Figure 14: Structure of Morphine Sulphate.

CHEMISTRY



Morphine is a benzylisoquinolone alkaloid with two additional ring closures. It has:

- A rigid pentacyclic structure consisting of a benzene ring (A), two partially unsaturated cyclohexane rings (B and C), a piperidine ring (D) and a tetrahydrofuran ring (E). Rings A, B and C are the phenanthrene ring system. This ring system has little conformational flexibility.
- Two hydroxyl functional groups: a C3-phenolic OH (pK_a 9.9) and a C6-allylic OH.
- An ether linkage between C4 and C5,
- Unsaturation between C7 and C8,
- A basic, tertiary amine function at position 17,

- 5 centersof chirality (C5, C6, C9, C13 and C14) with morphine exhibiting a high degree of steroselectivity of analgesic action.
- Most of the licit morphine produced is used to make codeine by methylation. It is also a precoursor of many drugs like heroine, hydromorphone and oxomorphone(14-hydroxydihydromorphinone); many morphine derivatives can also be manufactured using thebaine or codeine as a starting material. Replacement of the *N*-methyl group of morphine with an *N*-phenylethyl group results in a product that is 18 times more powerful than morphine in its opiate agonist potency.
- Combining this modification with the replacement of the 6-hydroxyl with a 6-methylene group produces a compound some 1,443 times more potent than morphine, stronger than the bently compounds such as etorphine (M99, the Immobilon tranquilliser dart) by some measures.
- The structure-activity relationship of morphine has been extensively studied. As a result of the extensive study and use of this molecule, more than 250 morphine derivatives (also counting codeine and related drugs) have been developed since the last quarter of the 19th century. These drugs range from 25% the analgesic strength of codeine (or slightly more than 2% of the strength of morphine) to several thousand times the strength of morphine, to powerful opioid antagonists, including naloxone (Narcan), naltrexone (Trexan), diprenorphine (M5050, the reversing agent for the Immobilon dart) and nalorphine (Nalline).
- Some opioid agonist-antagonists, partial agonists, and inverse agonists are also derived from morphine. The receptor-activation profile of the semi-synthetic morphine derivatives varies widely and some, like apomorphine are devoid of narcotic effects.
- Morphine and most of its derivatives do not exhibit optical isomerism, although some more distant relatives like the morphinan series (levorphanol, dextorphan and the racemic parent chemical dromoran) do, and as noted above stereoselectivity in vivo is an important issue.
- Morphine-derived agonist-antagonist drugs have also been developed. Elements of the morphine structure have been used to create completely synthetic drugs such as the morphinan family (levorphanol, dextromethorphan and others) and other groups that have many members with morphine-like qualities. The modification of morphine and the aforementioned synthetics has also given rise to non-narcotic drugs with other uses such as emetics, stimulants, antitussives, anticholinergics, muscle relaxants, local anaesthetics, general anaesthetics, and others.

Most semi-synthetic opioids, both of the morphine and codeine subgroups, are created by modifying one or more of the following:

- Halogenating or making other modifications at positions 1 or 2 on the morphine carbon skeleton.
- The methyl group that makes morphine into codeine can be removed or added back, or replaced with another functional group like ethyl and others to make codeine analogues of morphine-derived drugs and vice versa. Codeine analogues of morphine-based drugs often serve as prodrugs of the stronger drug, as in codeine and morphine, hydrocodone and hydromorphone, oxycodone and oxymorphone, nicocodeine and nicomorphine, dihydrocodeine and dihydromorphine, etc.
- Saturating, opening, or other changes to the bond between positions 7 and 8, as well as adding, removing, or modifying functional groups to these positions; saturating, reducing, eliminating, or otherwise modifying the 7–8 bond and attaching a functional group at 14 yields hydromorphinol the oxidation of the hydroxyl group to a carbonyl and changing the 7–8 bond to single from double changes codeine into oxycodone.
- Attachment, removal or modification of functional groups to positions 3 or 6 (dihydrocodeine and related, hydrocodone, nicomorphine); in the case of moving the methyl functional group from position 3 to 6, codeine becomes heterocodenine, which is 72 times stronger, and therefore six times stronger than morphine
- Attachment of functional groups or other modification at position 14 (oxymorphone, oxycodone, naloxone)
- Modifications at positions 2, 4, 5 or 17, usually along with other changes to the molecule elsewhere on the morphine skeleton. Often this is done with drugs produced by catalytic reduction, hydrogenation, oxidation, or the like, producing strong derivatives of morphine and codeine.

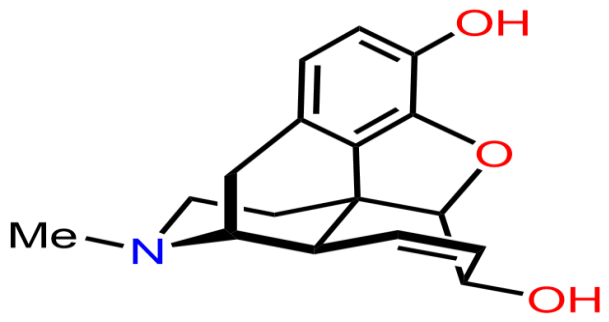
Structure and properties	
Molar mass	285.338 g/mol
Index of refraction, n_D	?
Acidity (pK_a)	Step 1: 8.21 at 25 °C Step 2: 9.85 at 20 °C
Solubility	0.15 g/L at 20 °C
Melting point	255 °C
Boiling point	190 °C sublimes

Both morphine and its hydrated form, $C_{17}H_{19}NO_3H_2O$, are sparingly soluble in water. In five liters of water, only one gram of the hydrate will dissolve. For this reason, pharmaceutical companies produce sulfate and hydrochloride salts of the drug, both of which are over 300 times more water-soluble than their parent molecule.

Whereas the pH of a saturated morphine hydrate solution is 8.5, the salts are acidic. Since they derive from a strong acid but weak base, they are both at about pH = 5; as a consequence, the morphine salts are mixed with

small amounts of NAOH to make them suitable for injection.

- A number of salts of morphine are used, with the most common in current clinical use being the hydrochloride, sulfate, tartrate, and citrate; less commonly methobromide, hydrobromide, hydroiodide, lactate, chloride, and bitartrate and the others listed below.
- Morphine diacetate, which is another name for heroin, is a Schedule I controlled substance, so it is not used clinically in the United States; it is a sanctioned medication in the united kingdom and in Canada and some countries in Continental Europe, its use being particularly common (nearly to the degree of the hydrochloride salt) in the United Kingdom.
- Morphine meconate is a major form of the alkaloid in the poppy, as is morphine pectinate, nitrate, sulfate, and some others. Like codeine, dihydrocodeine and other (especially older) opiates, morphine has been used as the salicylate salt by some suppliers and can be easily compounded, imparting the therapeutic advantage of both the opioid and the NSAID multiple barbiturate salts of morphine were also used in the past, as was/is morphine valerate, the salt of the acid being the active principle of valerian
- Calcium morphenate is the intermediate in various latex and poppy-straw methods of morphine production, more rarely sodium morphenate takes its place.
- Morphine ascorbate and other salts such as the tannate, citrate, and acetate, phosphate, valerate and others may be present in poppy tea depending on the method of preparation.
- Morphine valerate produced industrially was one ingredient of a medication available for both oral and parenteral administration popular many years ago in Europe and elsewhere called Trivalin (not to be confused with the current, unrelated herbal preparation of the same name), which also included the valerates of caffeine and cocaine, with a version containing codeine valerate as a fourth ingredient being distributed under the name Tetravalin.



Closely related to morphine are the opioids morphine-*N*-oxide (genomorphine), which is a pharmaceutical that is no longer in common useand pseudomorphine, an alkaloid that exists in opium, form as degradation products of morphine.

The salts listed by the united states drug enforcement administration for reporting purposes, in addition to a few others, are as follows:
ShowSelect forms of morphine as 'morphiniums' or *N*-protonated cations of morphine, i.e. ionic salts & chemical form with freebase conversion ratios:

Human Synthesis of Morphine Sulfate

Morphine is an endogenous opioids in humans that can be synthesized by and released from various human cells, including white blood cells. CYP2D6, a cytochrome p450 isoenzyme, catalyses the biosynthesis of morphine from codeine and dopamine from tyramine along the biosynthetic pathway of morphine in humans. The morphine biosynthetic pathway in humans occurs as follows:

The first morphine total synthesis, devised by marshall d. gates. jr in 1952, remains a widely used example of total synthesis. Several other syntheses were reported, notably by the research groupsof Rice, Evans, Fuchs, Parker, Overman, Mulzer-Trauner, White, Taber, Trost, Fukuyama, Guillou, and Stork. It is "highly unlikely" that a chemical synthesis will ever be able to compete with the cost of producing morphine from the opium poppy.

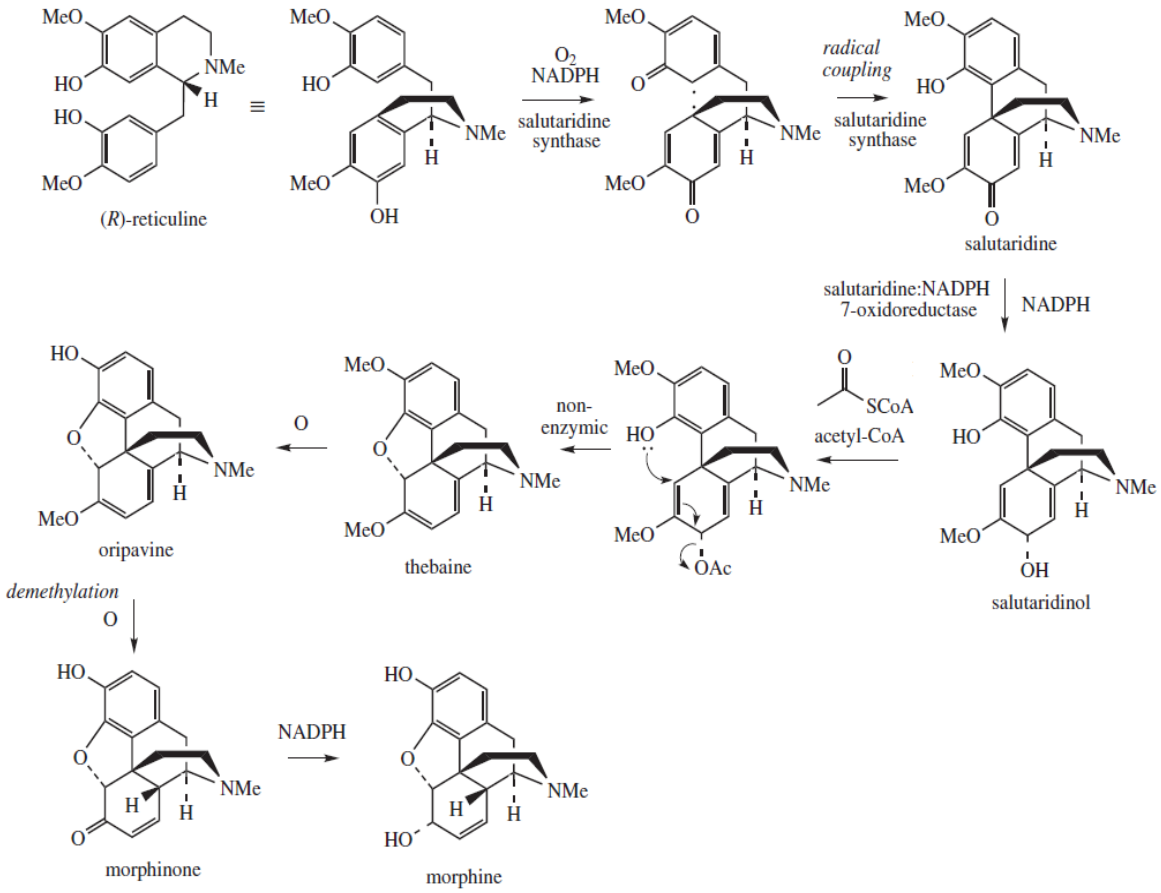


Figure 15: Human Synthesis of Morphine Sulphate.

Morphine is biosynthesized in the opium poppy from the tetrahydroisoquinoline reticuline. It is converted into salutaridine, thebaine, and oripavine. The enzymes involved in this process are the salts of salutaridinsalutaridine: NADPH 7- oxidoreductase and the codeinine reductase Researchers are attempting to reproduce the biosynthetic pathway that produces morphine in genitically engineered wastes. In June 2015 the *S*-reticuline could be produced from sugar and *R*-reticuline could be converted to morphine, but the intermediate reaction could not be performed. In August 2015 the first complete synthesis of thebaine and hydrocodone in yeast were reported, but the process would need to be 100,000 times more productive to be suitable for commercial use.

DOSAGE AND ADMINISTRATION

Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals

Initiate the dosing regimen for each patient individually, taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse

Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy and following dosage increases with Morphine Sulphate and adjust the dosage accordingly.

INITIAL DOSAGE

Use of Morphine Sulfate Tablets as the First Opioid Analgesic (Opioid-naïve or Opioid-non-tolerant patients) Initiate treatment with Morphine Sulfate tablets in a dosing range of 15 mg to 30 mg every 4 hours as needed for pain.

Conversion from Parenteral Morphine to Morphine Sulfate Tablets

For conversion from parenteral morphine to Morphine Sulfate tablets, anywhere from 3 to 6 mg of oral Morphine Sulfate may be required to provide pain relief equivalent to 1 mg of parenteral morphine.

Conversion from Other Opioids to Morphine Sulfate Tablets

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of Morphine Sulfate tablets. It is safer to underestimate a patient's 24-hour Morphine Sulfate tablets dosage than to overestimate the 24-hour Morphine Sulfate tablets dosage and manage an adverse reaction due to overdose. Initiate dosing using Morphine Sulfate tablets 15 mg to 30 mg every 4 hours.

Conversion from Morphine Sulfate Tablets to Extended-Release Morphine

For a given dose, the same total amount of Morphine Sulfate is available from Morphine Sulfate tablets, and extended-release morphine formulations. The extended duration of release of Morphine Sulfate from extended-release formulations results in reduced maximum and increased minimum plasma Morphine Sulfate concentrations than with shorter acting Morphine Sulfate products. Conversion from Morphine Sulfate tablets to the same total daily dose of an extended-release formulation could lead to excessive sedation at peak serum levels. Therefore, conversion to extended-release morphine formulations must be accompanied by close observation for signs of excessive sedation and respiratory depression.

Titration and Maintanace of Therapy

Individually titrate Morphine Sulfate tablets to a dose that provides adequate analgesia and minimizes adverse reactions. Continually reevaluate patients receiving Morphine Sulfate tablets to assess the maintenance of pain control and the relative incidence of adverse reactions, as well as monitoring for the development of addiction, abuse, or Frequent communication is important among the prescriber, other members of the healthcare team, the patient, and the caregiver/family during periods of changing analgesic requirements, including initial titration.

If the level of pain increases after dosage stabilization, attempt to identify the source of increased pain before increasing the Morphine Sulfate tablets dosage. If unacceptable opioid-related adverse reactions are observed, consider reducing the dosage. Adjust the dosage to obtain an appropriate balance between management of pain and opioid-related adverse reactions.

Discontuniation of Morphine Sulfate Tablets

When a patient who has been taking Morphine Sulfate tablets regularly and may be physically dependent no longer requires therapy with Morphine Sulfate tablets, taper the dose gradually, by 25% to 50% every 2 to 4 days, while monitoring carefully for signs and symptoms of withdrawal. If the patient develops these signs or symptoms, raise the dose to the previous level and taper more slowly, either by increasing the interval between dose decreases, decreasing the amount of change in dose, or both. Do not abruptly discontinue Morphine Sulfate tablets in a physically-dependent patient.

DOSAGE FORM AND STRENGTH

Morphine Sulfate tablets are supplied as

15 mg: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "15" and "273".

30 mg: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "30" and "274".

CONTRAINDICATIONS

Morphine Sulfate tablets are contraindicated in patients with

- Significant respiratory depression.
- Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment.
- Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days.
- Known or suspected gastrointestinal obstruction, including paralytic ileus.
- Hypersensitivity to morphine (e.g., anaphylaxis).

WARNING AND PRECAUTIONS

Addiction, Abuse, and Misuse

Morphine Sulfate tablets contain morphine, a Schedule II controlled substance. As an opioid, Morphine Sulfate tablets expose users to the risks of addiction, abuse, and misuse.

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed Morphine Sulfate. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient's risk for opioid addiction, abuse, or misuse prior to prescribing Morphine Sulfate tablets, and monitor all patients receiving Morphine Sulfate tablets for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as Morphine Sulfate tablets, but use in such patients necessitates intensive counseling about the risks and proper use of Morphine Sulfate tablets along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Consider these risks when prescribing or dispensing Morphine Sulfate tablets. Strategies to reduce these risks include prescribing the drug in the smallest appropriate quantity and advising the patient on the proper disposal of unused. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

Opioid analgesic risk evaluation and mitigation stratergy(rems)

To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a Risk Evaluation and Mitigation Strategy (REMS) for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to do all of the following:

- Complete a REMS-compliant education program offered by an accredited provider of continuing education (CE) or another education program that includes all the elements of the FDA Education Blueprint for Health Care Providers Involved in the Management or Support of Patients with Pain.
- Discuss the safe use, serious risks, and proper storage and disposal of opioid analgesics with patients and/or their caregivers every time these medicines are prescribed. The Patient Counseling Guide (PCG) can be obtained at this link: https://www.fda.gov/OpioidAnalgesicREMSPCG.
- Emphasize to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an opioid analgesic is dispensed to them.
- Consider using other tools to improve patient, household, and community safety, such as patient-prescriber agreements that reinforce patient-prescriber responsibilities.

Life-threatening respiratory depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient's clinical status. Carbon dioxide (CO2) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of Morphine Sulfate tablets, the risk is greatest during the initiation of therapy or following a dosage increase. Monitor patients closely for respiratory depression, especially within the first 24 to 72 hours of initiating therapy with and following dosage increases of Morphine Sulfate tablets.

To reduce the risk of respiratory depression, proper dosing and titration of Morphine Sulfate tablets are essentials. Overestimating the Morphine Sulfate tablets dosage when converting patients from another opioid product can result in a fatal overdose with the first dose.

Accidental ingestion of even one dose of Morphine Sulfate tablets, especially by children, can result in respiratory depression and death due to an overdose of morphine.

Neonatal Opiod Withdrawl Syndrome

Prolonged use of Morphine Sulfate tablets during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. Advise pregnant women using opioids for a prolonged period of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available.

Risks From Concomitant Use With Benzodiazepines Or Other Cns Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of Morphine Sulfate tablets with benzodiazepines or other CNS depressants (e.g., non-benzodiazepine sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because of these risks, reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties, it is reasonable to expect similar risk with the concomitant use of other CNS depressant drugs with opioid analgesics. If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with an opioid analgesic, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving an opioid analgesic, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid, and titrate based on clinical response. If an opioid analgesic is initiated in a patient already taking a benzodiazepine or other CNS depressant, prescribe a lower initial dose of the opioid analgesic, and titrate based on clinical response. Follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when Morphine Sulfate tablets are used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to drive or operate heavy machinery until the effects of concomitant use of the benzodiazepine or other CNS depressant have been determined. Screen patients for risk of substance use

disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs.

Adverse Reactions

The following serious adverse reactions are described, or described in greater detail, in other sections:

- Addiction, Abuse, and Misuse.
- Life-Threatening Respiratory Depression.
- Neonatal Opioid Withdrawal Syndrome.
- Interactions with Benzodiazepine or Other CNS Depressants.
- Adrenal Insufficiency.
- Severe Hypotension.
- Gastrointestinal Adverse Reactions.
- Seizures.
- Withdrawal.

The following adverse reactions associated with the use of morphine were identified in clinical studies or postmarketing reports. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Serious adverse reactions associated with morphine use included: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The common adverse reactions seen on initiation of therapy with morphine were dose-dependent and were typical opioid-related adverse reactions. The most frequent of these included: constipation, nausea, and somnolence. Other commonly observed adverse reactions included: lightheadedness, dizziness, sedation, vomiting, and sweating. The frequency of these events depended upon several factors including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual.

Other less frequently observed adverse reactions from opioid analgesics, including Morphine Sulfate included:

Body as a Whole: malaise, withdrawal syndrome

Cardiovascular System: bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia

Digestive System: biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst

Endocrine: hypogonadism

Hemic and Lymphatic System: anemia, thrombocytopenia

Metabolic and Nutritional Disorders: edema, weight loss

Musculoskeletal: skeletal muscle rigidity, decreased bone mineral density

Nervous System: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, depression, dry mouth, euphoria, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo, headache

Respiratory System: hiccup, hypoventilation, voice alteration

Skin and Appendages: dry skin, urticaria, pruritus

Special Senses: amblyopia, eye pain, taste perversion

Urogenital System: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention or hesitancy, anti-diuretic effect, amenorrhea

Serotonin Syndrome: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

Adrenal Insufficiency: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

Anaphylaxis: Anaphylaxis has been reported with ingredients contained in Morphine Sulfate tablets.

DRUG INTERACTIONS

Pregnancy

- Prolonged use of opioid analgesics during pregnancy can cause neonatal opioid withdrawal syndrome.
- There are no available data with Morphine Sulfate tablets in pregnant women to inform a drug-associated risk for major birth defects and miscarriage.
- Published studies with morphine use during pregnancy have not reported a clear association with morphine and major birth defects.
- In published animal reproduction studies, morphine administered subcutaneously during the early gestational period produced neural tube defects (i.e., exencephaly and cranioschisis) at 5 and 16 times the human daily dose of 60 mg based on body surface area (HDD) in hamsters and mice, respectively, lower fetal body weight and increased incidence of abortion at 0.4 times the HDD in the rabbit, growth retardation at 6 times the HDD in the rat, and axial skeletal fusion and cryptorchidism at 16 times the HDD in the mouse.
- Administration of Morphine Sulfate to pregnant rats during organogenesis and through lactation resulted in cyanosis, hypothermia, decreased brain weights, pup mortality, decreased pup body weights, and adverse effects on reproductive tissues at 3 to 4 times the HDD; and long-term neurochemical changes in the brain of offspring which correlate with altered behavioral responses that persist through adulthood at exposures comparable to and less than the HDD. Based on animal data, advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

CLINICAL CONSIDERATION

Fetal/Neonatal Adverse Reactions: Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth. Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea, and failure to gain weight. The onset, duration, and severity of neonatal withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly.

Labor or Delivery: Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid induced respiratory depression in the neonate. Morphine Sulfate tablets are not recommended for use in women during and immediately prior to labor, when use of shorter-acting analgesics or other analgesic techniques are more appropriate. Opioid analgesics, including Morphine Sulfate tablets, can prolong labor through actions that temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilatation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Human Data: The results from a population-based prospective cohort, including 70 women exposed to morphine during the first trimester of pregnancy and 448 women exposed to morphine at any time during pregnancy, indicate no increased risk for congenital malformations. However, these studies cannot definitely establish the absence of any risk because of methodological limitations, including small sample size and non-randomized study design.

Animal Data: Formal reproductive and developmental toxicology studies for morphine have not been conducted. Exposure margins for the following published study reports are based on human daily dose of 60 mg morphine using a body surface area comparison (HDD).

Neural tube defects (exencephaly and cranioschisis) were noted following subcutaneous administration of Morphine Sulfate (35 to 322 mg/kg) on Gestation Day 8 to pregnant hamsters (4.7 to 43.5 times the HDD). A no adverse effect level was not defined in this study and the findings cannot be clearly attributed to maternal toxicity. Neural tube defects (exencephaly), axial skeletal fusions, and cryptorchidism were reported following a single subcutaneous (SC) injection of Morphine Sulfate to pregnant mice (100 to 500 mg/kg) on Gestation Day 8 or 9 at 200 mg/kg or greater (16 times the HDD) and fetal resorption at 400 mg/kg or higher (32 times the HDD). No adverse effects were noted following 100 mg/kg morphine in this model (8 times the HDD). In one study, following continuous subcutaneous infusion of doses greater than or equal to 2.72 mg/kg to mice (0.2 times the HDD), exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted. The effects were reduced with increasing daily dose; possibly due to rapid induction of tolerance under these infusion conditions. The clinical significance of this report is not clear.

Decreased fetal weights were observed in pregnant rats treated with 20 mg/kg/day Morphine Sulfate (3.2 times the HDD) from Gestation Day 7 to 9. There was no evidence of malformations despite maternal toxicity (10% mortality). In a second rat study, decreased fetal weight and increased incidences of growth retardation were noted at 35 mg/kg/day (5.7 times the HDD) and there was a reduced number of fetuses at 70 mg/kg/day (11.4 times the HDD) when pregnant rats were treated with 10, 35, or 70 mg/kg/day Morphine Sulfate via continuous infusion from Gestation Day 5 to 20. There was no evidence of fetal malformations or maternal toxicity.

An increased incidence of abortion was noted in a study in which pregnant rabbits were treated with 2.5 (0.8 times the HDD) to 10 mg/kg Morphine Sulfate via subcutaneous injection from Gestation Day 6 to 10. In a second study, decreased fetal body weights were reported following treatment of pregnant rabbits with increasing doses of morphine (10 to 50 mg/kg/day) during the pre-mating period and 50 mg/kg/day (16 times the HDD) throughout the gestation period. No overt malformations were reported in either publication; although only limited endpoints were evaluated.

In published studies in rats, exposure to morphine during gestation and/or lactation periods is associated with: decreased pup viability at 12.5 mg/kg/day or greater (2 times the HDD); decreased pup body weights at 15 mg/kg/day or greater (2.4 times the HDD); decreased litter size, decreased absolute brain and cerebellar weights, cyanosis, and hypothermia at 20 mg/kg/day (3.2 times the HDD); alteration of behavioral responses (play, social-interaction) at 1 mg/kg/day or greater (0.2 times the HDD); alteration of maternal behaviors (e.g., decreased nursing and pup retrievals) in mice at 1 mg/kg or higher (0.08 times the HDD) and rats at 1.5 mg/kg/day or higher (0.2 times the HDD); and a host of behavioral abnormalities in the offspring of rats, including altered responsiveness to opioids at 4 mg/kg/day (0.7 times the HDD) or greater.

Fetal and/or postnatal exposure to morphine in mice and rats has been shown to result in morphological changes in fetal and neonatal brain and neuronal cell loss, alteration of a number of neurotransmitter and neuromodulator systems, including opioid and non-opioid systems, and impairment in various learning and memory tests that appear to persist into adulthood. These studies were conducted with morphine treatment usually

in the range of 4 to 20 mg/kg/day (0.7 to 3.2 times the HDD).

Additionally, delayed sexual maturation and decreased sexual behaviors in female offspring at 20 mg/kg/day (3.2 times the HDD), and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed at 20 mg/kg/day (3.2 times the HDD). Decreased litter size and viability were observed in the offspring of male rats that were intraperitoneally administered Morphine Sulfate for 1 day prior to mating at 25 mg/kg/day (4.1 times the HDD) and mated to untreated females. Decreased viability and body weight and/or movement deficits in both first and second generation offspring were reported when male mice were treated for 5 days with escalating doses of 120 to 240 mg/kg/day Morphine Sulfate (9.7 to 19.5 times the HDD) or when female mice treated with escalating doses of 60 to 240 mg/kg/day (4.9 to 19.5 times the HDD) followed by a 5-day treatment-free recovery period prior to mating. Similar multigenerational findings were also seen in female rats pre-gestationally treated with escalating doses of 10 to 22 mg/kg/day morphine (1.6 to 3.6 times the HDD).

Lactation

Morphine is present in breast milk. Published lactation studies report variable concentrations of morphine in breast milk with administration of immediate-release morphine to nursing mothers in the early postpartum period with a milk-to-plasma morphine AUC ratio of 2.5:1 measured in one lactation study. However, there is insufficient information to determine the effects of morphine on the breastfed infant and the effects of morphine on milk production. Lactation studies have not been conducted with Morphine Sulfate tablets and no information is available on the effects of the drug on the breastfed infant or the effects of the drug on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Morphine Sulfate tablets and any potential adverse effects on the breastfed infant from Morphine Sulfate tablets or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to Morphine Sulfate tablets through breast milk for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of morphine is stopped, or when breastfeeding is stopped.

Female and Male of Reproductive Potential

Infertility

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible.

In published animal studies, morphine administration adversely effected fertility and reproductive endpoints in male rats and prolonged estrus cycle in female rats.

Pediatric Use

The safety and effectiveness and the pharmacokinetics of Morphine Sulfate tablets in pediatric patients below the age of 18 have not been established.

Geriatric Use

Elderly patients (aged 65 years or older) may have increased sensitivity to morphine. In general, use caution when selecting a dose for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of Morphine Sulfate tablets slowly in geriatric patients and monitor closely for signs of respiratory depression. Morphine is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Hepatic Impairmment

Morphine pharmacokinetics have been reported to be significantly altered in patients with cirrhosis. Start these patients with a lower than usual dosage of Morphine Sulfate tablets and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension.

Renal Impairment

Morphine Sulfate pharmacokinetics are altered in patients with renal failure. Start these patients with a lower than usual dosage of Morphine Sulfate tablets and titrate slowly while monitoring for signs of respiratory depression, sedation, and hypotension.

DRUG ABUSE AND DEPENDANCE

Controlled Substance

Morphine Sulfate tablets contain morphine, a Schedule II controlled substance.

Abuse

Morphine Sulfate tablets contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. Morphine Sulfate tablets can be abused and are subject to misuse, addiction, and criminal diversion.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carry the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated "loss" of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating health care provider(s). "Doctor shopping" (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

Morphine Sulfate tablets, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of Morphine Sulfate Tablets

Morphine Sulfate tablets are for oral use only. Abuse of Morphine Sulfate tablets poses a risk of overdose and death. The risk is increased with concurrent abuse of Morphine Sulfate tablets with alcohol and other central nervous system depressants. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs, and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, nalbuphine), or partial agonists (e.g., buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Morphine Sulfate tablets should not be abruptly discontinued in a physically-dependent patient. If Morphine Sulfate tablets are abruptly discontinued in a physically-dependent patient, a withdrawal syndrome may occur. Some or all of the following can characterize this syndrome: restlessness, lacrimation, rhinorrhea, yawning, perspiration, chills, myalgia, and mydriasis. Other signs and symptoms also may develop, including: irritability, anxiety, backache, joint pain, weakness, abdominal cramps, insomnia, nausea, anorexia, vomiting, diarrhea, or increased blood pressure, respiratory rate, or heart rate.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs.

OVERDOSAGE

Clinical Presentation

Acute overdose with Morphine Sulfate tablets can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations.

Treatment of Overdose

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted

or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.

The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to morphine overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of morphine in Morphine Sulfate tablets, carefully monitor the patient until spontaneous respiration is reliably reestablished. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product's prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be initiated with care and by titration with smaller than usual doses of the antagonist.

MORPHINE SULFATE-CLINICAL PHARACOLOGY

Mechanism of Action

Morphine is a full opioid agonist and is relatively selective for the mu-opioid receptor, although it can bind to other opioid receptors at higher doses. The principal therapeutic action of morphine is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with morphine. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

PHARMACODYNAMICS

Effect on Central Nervous System

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effect on Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effect On The Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effect on The Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon.

Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date.

Effect on Immune System

Opioids have been shown to have a variety of effects on components of the immune system in in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration -Efficacy Relationship

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of morphine for any individual patient may increase over

time due to an increase in pain, the development of a new pain syndrome and/or the development of analgesic tolerance.

Concentration –Adverse Reaction Relationship
There is a relationship between increasing morphine plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions.

PHARMACOKINETICS
Absorption
Morphine, when administered as Morphine Sulfate is about two-thirds absorbed from the gastrointestinal tract with the maximum analgesic effect occurring 60 minutes post-administration. The oral bioavailability of Morphine Sulfate is less than 40% and shows large inter-individual variability due to extensive pre-systemic metabolism.
Administration of the 30 mg Morphine Sulfate tablet every six hours for 5 days resulted in a comparable 24-hour exposure (AUC). The steady-state levels were achieved within 48 hours. The mean steady state Cmax values were about 78 and 58 ng/mL for tablet and solution, respectively.
Food Effects: When Morphine Sulfate 30 mg tablet was administered 30 minutes after ingesting a high fat/high calorie meal, there was no change in the extent of absorption (AUC) of Morphine Sulfate. There was, however, an increase in the median Tmax from 0.5 to 0.75 hours and an 11% decrease in Cmax. The tablet can be administered without regard to meals.

Distribution
Once absorbed, Morphine Sulfate is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Although the primary site of action is the CNS, only small quantities cross the blood-brain barrier. Morphine Sulfate also crosses the placental membranes and has been found in breast milk. The volume of distribution of Morphine Sulfate is approximately 1 to 6 L/kg, and Morphine Sulfate is 20% to 35% reversibly bound to plasma proteins.

ELIMINATION
Metabolism: The major pathway of Morphine Sulfate detoxification is conjugation, either with D-glucuronic acid to produce glucuronides or with sulfuric acid to produce morphine-3-etheral sulfate. While a small fraction (less than 5%) of Morphine Sulfate is demethylated, virtually all Morphine Sulfate is converted by hepatic metabolism to the 3- and 6- glucuronide metabolites (M3G and M6G; about 50% and 15%, respectively). M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.
Excretion: Most of a dose of Morphine Sulfate is excreted in urine as M3G and M6G, with elimination of Morphine Sulfate occurring primarily as renal excretion of M3G. Approximately 10% of the dose is excreted.

STORAGE AND HANDLING SYSTEM
Morphine Sulfate Tablets
15 mg tablet: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "15" and "273".

Bottles of 100 tablets	NDC 0832-0273-11

30 mg tablet: white, round, flat-faced, beveled edge tablet; one side scored and one side debossed "30" and "274".

Bottles of 100 tablets	NDC 0832-0274-11

STORAGE
Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].
Dispense in a tight, light-resistant container with a child-resistant closure as defined in the USP.

Indication and Usage of Morphine Sulphate
Morphine Sulfate tablets are indicated for the management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Limitation of Use
Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses reserve Morphine Sulphate tablets for use in patients for whom alternative treatment options [e.g., non-opioid analgesics or opioid combination products]:

Side Effects of Morphine Sulphate
There are a number of things you can do to manage the side effects of morphine sulfate. Talk to your care team about these recommendations. They can help you decide what will work best for you. These are some of the most common or important side effects:

Slowed Breathing or Low Blood Pressure
You may experience low blood pressure or slowed breathing while taking an opioid painkiller. This usually only occurs when the dose of medication is too high or it is increased too quickly. This rarely happens to patients who have been taking opioid medications for a long time.

These side effects can also result from an overdose of opioids. If you suspect that you or someone you know has taken an overdose of opioids, call 911 immediately. If you feel extremely tired, lightheaded, dizzy, sweaty, nauseated, or short of breath, you need to see a doctor immediately. Sometimes patients who have taken too

much opioid medication will be so sleepy that they can't be awakened or aroused. These side effects are emergency situations. If any of these symptoms occur, you should seek emergency medical attention.

SLEEPINEES (Somnolence)
Feeling sleepy, drowsy or lightheaded may accompany the use of opioid pain medication. Some people just don't "feel like themselves" on these medications. Avoid driving or any other potentially dangerous tasks that require your concentration and a clear head until you feel normal again. Avoid alcohol or other sedatives while using these medications unless they are specifically prescribed by your care team. Most people will begin to feel like themselves after a few days on the medications. If you continue to feel "out of it" after a couple of days, talk to your healthcare provider about adjusting your dosages.

Constipation Caused By Pain Medications
Constipation is a very common side effect of pain medications that continues as long as you are taking the medications. This side effect can often be managed well with the following preventative measures:

- Drinking 8-10 glasses of water a day. Warm or hot fluids can be helpful.
- Increasing physical activity when possible.
- Attempting a bowel movement at the same time each day.
- Eating plenty of fruits and vegetables.
- Four ounces of prune juice or 3-4 dried prunes/plums can help promote bowel movements.
- However, high fiber foods (ex. bran flakes, high fiber cereals) and fiber supplements (such as Metamucil) can actually make constipation from pain medications worse and should be avoided.

NAUSEA
Nausea, with or without vomiting, can be a side effect of opioid pain medications. For some patients it lasts just a few days to weeks after starting the medication, but for some it is a long-term side effect. Nausea and vomiting can interfere with pain management if the nausea and/or vomiting affects the patient's ability to take the medication. You may find that eating or not eating when taking this medication may be helpful for you. Talk to your healthcare team so they can prescribe medications to help you manage nausea and vomiting.

Less common, but important side effects include

- **Serotonin Syndrome**: This medication can cause a high level of serotonin in your body, which in rare cases, can lead to serotonin syndrome. Symptoms can include shivering, agitation, diarrhoea, nausea and vomiting, fever, seizures, and changes in muscle function. Symptoms can arise hours to days after continued use, but can also occur later. This is a serious side effect and you should contact your care provider immediately if you have any of these side effects.
- **AdrenalInsufficiency*:*** Adrenal insufficiency (inadequate function of the adrenal gland) is a rare but serious side effect of taking this medication. It most often occurs after taking the medication for one month or longer. Symptoms are not very specific, but can include nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. It is important to contact your care provider if you experience any of these side effects.
- **Allergic Reaction*:*** Although it is uncommon, some people are allergic reaction to certain opioid preparations. If after taking morphine or other opioids, you experience chest tightness, swelling, wheezing, fever, itching, blue skin color or cough, you need to call 911. These side effects are emergency situations. If any of these symptoms occur, you should seek emergency medical attention. Reproductive Concerns
- Chronic exposure of an unborn child to this medication could result in the child being born small and/or early, or having symptoms of withdrawal (including respiratory distress, behavioural changes and seizures) after birth. Effective birth control should be used while on this medication. Even if your menstrual cycle stops or you believe you are not producing sperm, you could still be fertile and conceive. You should not breastfeed while receiving this medication as it is passed through a mother's milk.

Uses

- This medication is used to help relieve moderate to severe pain.
- Morphine belongs to a class of drugs known as opioids (narcotic) analgesics.
- It works in the brainto change how your body feels and responds to pain.
- Morphine sulfate is a narcotic used to relieve moderate to severe long-term pain
- While morphine in general can be used for both short and long-term pain
- Morphine sulfate is an extended-release form of the drug meant for people who need constant and long-term pain relief.

CONCLUSION
There is scientific evidence supporting the incorporation of probiotics in nutrition as a means of derivation of health benefits. This evidence seems adequate concerning the prevention and treatment of certain conditions while simply promising or even controversial when it comes to others. The best documented effects include bowel disorders such as lactose intolerance, antibiotic-associated diarrhoea and infectious diarrhoea, and allergy, and emerging evidence accumulates concerning their potential role in various other conditions. In the same time as relevant consumer awareness grows, such products are becoming increasingly popular and tend to represent one of the largest functional food markets. Dairy products,

particularly yoghurt, continue to be the most important vehicles for delivery of probiotic bacteria to the consumer with the nondairy sector continuously evolving as well, as a result of food technology advances and the growing demand. A virtuous circle is therefore created: as the range of new products with improved sensory appeal widens, consumer acceptance increases and the food industry invests more on this growing market by development of new processes and products. Nevertheless, the development of probiotics for human consumption is still in its infancy. Further research, in the form of controlled human studies, is needed to determine which probiotics and which dosages are associated with the greatest efficacy and for which patients, as well as to demonstrate their safety and limitations.

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