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Research Article

A Recent Progresses and Manufacturing Techniques in Pharmaceutical Powders and Granulation

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ABSTRACT

Nowadays very few drugs are formulated as powders or granules, they are usually taken with some water in which they are readily dispersible in & somewhat rapidly dissolving in as a result of the large surface area provided by the small particles of the powder as well as high solubilitys of the other ingredients used in the formulation, leading to high drug absorption, their bioavailability could be similar to the suspensions form in general. This review covers the classifications of pharmaceutical powders, and recent advancements in granulation techniques with their desirable characteristics in enhancing drug bioavailability and manufacturing performance.

Keywords: Pharmaceutical Manufacturing Techniques, Powders and Granulation Pharmaceutical dosage forms.

Pharmaceutical powder

It is a mixture of finely divided drug and / or chemicals in a dry form that may be intended for internal use (oral powders) or external use (topical or dusting powder).

Powders are subdivided solid which are classified in BP (British pharmacopeia) according to size of their constituent particles of range from 1.25 µg to 1.7 mm in diameter. Another classification of powders is based on the manner of their dispensing[1].

Granules

are prepared aggregates of powdered materials to form a larger particle (2-4 mm) Granules may be used as such (granules of medicinal value) or in making tablets and capsules (because of better flowability of granules compared to powder)[2].

Advantages of powder [2, 3]

More rapid dissolution; because of small particle size causes more rapid dissolution in body fluids, increases bioavailability and decreses gastric irritations compared with tablet.

When it is not possible to dispense a drug as a solution or a suspension, because of its insolubility or because it is susceptible to microbial contamination if it is wetted, then it is a good idea to dispense as a powder.

When bulky drug that has a large dose is to be administrated, a powder is a good way of administrating it.

They are used for children and old patient who cannot swallow tablet or capsule.

They are more stable.

Limitations of powder

They are time consuming to prepare and pack.

They are bulky to carry about.

Powders may spill when are being opened.

Patient may misunderstand the correct method of use.

It is undesirable to take bitter or unpleasant tasting drug by oral administration.

Difficult to protect powders containing hygroscopic, deliquescent, or aromatic materials from decomposition.

Not accurate way of administrating drug[4].

Effect of powder and granules dosage forms on the bioavailability of the drug

Particle size and shape can influence a large variety of important physical properties, manufacturing processability and quality attributes, including:

Dissolution rate and bioavailability of active pharmaceutical ingredients:

The smaller the particle size, the faster is the dissolution and the higher the bioavailability.

Suspendability: ability to maintain uniform dispersion in liquid vehicle.

Uinform disrtribution: in a powder mixture or a capsule and tablets preparation, the ability of the drug to have uniform distribution is essential.

Penetrability; it is important for the intra-respiratory applications to reach the desired location. The size range of 1-5 micrometer is widely used.

Non-grittiness: should be used in dermal ointments, creams, and ophthalmic preparations. Fine particles of 50-100 micrometer in size can be used.

Drug release rate for sustained and controlled release formulations.

In vivo particle distribution and deposition, absorption rate and clearance time[4, 5].

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Methods to measure the particles size and size of distribution[1-6]
Sieving.
Microscopy.
Sedimentation rate.
Coulter counter.
Light Scattering.
Gas Adsorption
Why we prepare granules when we have powder?
Granules flow better than powder.
Granules increase compressibility.
Granules have smaller surface area than comparable volume of powder.
Granules have smaller surface area than a comparable volume of pow-ders. This makes granules more stable physically and chemically than the corresponding powders. Granules are less likely to cake or harden upon standing than are powders.
Granules produce particle - size uniformity, thus content uniformity[6].
Classification of powders according to the manner of their dispensing:
Bulk powders for external use.
Bulk powders for internal use.
Simple and compound powders for internal use.
Powders for reconstitute.
Effervescent granules.
Cachets.
Bulk powders for external use
External bulk powders contain non-potent substance for external application. These powders are dispensed in glass, plastic wide mouth bottles and also in cardboard with specific method of application.
Bulk powders for external use are of five types:
Dusting powder
Dusting powders usually contain substance such as zinc oxide, starch and boric acid ao natural mineral substance such as kaolin or talc. These are used externally for local application not intended for systemic action. They are employed chiefly as lubricant, protective, absorbent, antiseptics, antipruritic, astringent, antiperspirants[3,4,7].
Douche powder
These powders are intended to be used as antiseptics or cleansing agents for a body cavity; most commonly for vaginal use although they may be formulated for nasal, otic or ophthalmic use also. They usually are used after being dissolved in water.
Dental powder
Dental powderd are rarely prescribed. This preparation is a type of dentifrice meant for cleaning the teeth.
Insufflation
Insufflations are a class of powders meant for application to the body cavities e.g., ear, nose, vagina etc.
Sunffs
These are finely divided solid dosage forms of medicaments dispensed in flat metal boxes with hinged lid. These powders are inhaled into nostrils for decongestion, antiseptic, and bronchodilator action[3,6,8].
Bulk powder for internal use
They are non-potent substances such as antacid. They are dispensed in a wide mouth container so that the teaspoon can easily remove the powder[9].
Simple and compound powders for internal use
They are packed into properly folded papers and dispensed in envelopes, metal foil, small heat-sealed plastic bags or other containers. The modern packaging has replaced the foil and plastic laminates by paper wrapping, why? Because they offer superior protective qualities and are able to be used on high speed packing machine.
The preparation of simple powder involving weighing of the ingredients correctly and blending them. The mixture is either divided into blocks of equal size or each dose is weighed separately and placed into a powder paper, the paper is then folded and placed in an envelope or powder box.
Powder for reconstitution
These powders are intended to be reconstituted just before use. They are used to protect drugs against hydrolysis and enhance stability of the active constituents[9, 10].
Example
Oral antibiotic
Powder for injection
Oral antibiotic
They are prepared in dry form to prevent stability problems, and then packed into sealed bottles, and just before using it the powder is added. Once it is reconstituted the patient should be warned of the short shelf life (1-2 weeks)[9,10].
Powders for injection
They are sterile powders in ampoules are unstable in solution, so must be reconstituted just before use bu using sterile water for injection.
Effervescent granules
It is either prepared by compounding the ingredients as granules or dispensed in the form of salts.
They react in presence of water releasing carbon dioxide gas[9, 10].
Advantages
Attractive for the puplic.
The carbonated solution masks the undesirable taste of the drug.
The released CO2 can increase the gastric secretions and hence facilitate digestion.
Disadvantages
Instable in presence of moisture.
Problems in packing and storage.
Packaging and dispensing
As bulk powder.
As divided powder doses.
As bulk or divided granular powder.
The principle of effervescent granules preparation:
For releasing of the gas two constituents are essential:
Soluble carbonate such as sodium bicarbonate.
Organic acid such as citric or tartaric acid.
Preparation and requirements of effervescent granules:
Mixing the ingredients.
Formation of wet mass.
Passing through sieve to form granules.
Drying the granules[9,10,11].

Cachets

They are like capsules, contains larger quantity of the medication compared to capsules.

They are made of flour and water and they are easily damaged while handling.

The dosage form provides little protection against light and moisture.

Due to its size and shape, it is difficult to swallow.

The process of filling is similar to capsule.

Principals involved in powder preparation:

Drug content uniformity: the drug should have the same ratio or the same contents of the drugs involved in the prescription[9,10,11].

The size of the powder should be fine

Good test: it should be masked by adding sweetness

Amount: should be not too large or too small.

Method of mixing and powdering

Trituration: make coarse powders into small particles by rubbing them in a mortar with a pestle.

Pulverization by intervention: add a second material which helps in the powdering and which is latter removed. For example, powering camphor is difficult, so we add a small amount of alcohol to it and we then powder it, then we allow alcohol to evaporate.

levigation: this method is used to incorporate solid into dermatologic or ophthalmic ointments to prevent a gritty feel[11,12,13].

Procedure of powder preparation

geometric dilution: each time we add an amount that is equal to the amount in the mortar. When we take the material into the mortar in this way and mix them, we get very good mixing.

weighing: the final powder which prepared it is divided into individual doses, the final weight of a divided powder or bulk powder is not allowed to be in a fraction or of 100 mg.

packing: the packing of powders is done in very systematic and specific manner or envelopes against moisture.

dispensing

Flow properties of powder and powder flowability

The flow properties of the powder can be describe as good flow behavior properties or poorly flowing powder.

Good flowing powder means it does not consolidate much and flows out of a solo or hopper due to the force of gravity alone and no flow promoting devices are required

Products are poorly flowing if they have flow obstructions or consolidate during storage or transport.

Quantitative measurement of disability is possible[11,12,13].

Factors that affect the flow properties of powder

Particle size distribution.

Particle shape.

Chemical composition of the particles .

Moisture.

Temperature[11,12,13]

Adhesive forces and relationship between adhesive force, particle size, and flowability

The flowability of a bulk powder depends on the adhesive forces between individual particles.

With fine grained, dry bulk powders, adhesive forces due to Vander Waals interactions play the essential role .

With moist bulk powders, liquid bridges between the particles usually are most important[13,14].

Both types of adhesive forces described above are dependent on the distance between particles and on particle size.

Influence of adhesive forces on flow behavior

Bulk powders flow more poorly with decreasing particle size as the adhesive forces increase .

Cohesive bulk powder is used to describe the fine grained bulk powder with moderate or poor flow behavior due to adhesive forces.

There are two methods to quantify the flow properties of a powder

Direct methods**.**

Indirect methods**.**

Indirect methods.

Angle of repose.

Shear cell determinations.

Bulk density measurements.

Direct methods

Hopper flow rate.

recording flow_meter

Improvement of powder flow ability

Alteration of particle size and size distribution

Because coarse particle are generally less cohesive than fine paticle and an optimum size for free flow exists.

The size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particle "granulation".

Alteration of particle shape or texture

Spherical particles have better flow properties than irregular particles. As particles with very rough surface will be more cohesive and have a greater tendency to interlock than smooth surfaced particles. The shape and texture of particle can also be altered by control of production method, such as crystallization condition[13,14,15].

Alteration of surface forces

Reduction of electrostatic charge can improve powder flowability.

Formulation additive (flow activators)

Flow activator improve the flowability of powders by reducing adhesion and cohesion

Packaging of dry powders[15,16]

Bulk powders for external use

Are often dispensed in a shaker-top container to facilitate topical application.

They might be also dispensed in a wide-mouth jar or plastic container with flip-top lid, these container should be closed tightly to provide increased stability and protection from light and moisture.

Bulk powder for internal use

They should be dispensed in an amber, wide powder jar with a tight fitting lid with an appropriate sized dosing spoon, and labeled with the concentration of the active ingredient per dose.

Divided dry powder

They are packaged in individual dose and dispensed in either folded paper or plastic bags.

Classification of powder according to pharmacopoeial standards

Pharmaceutical powder is a mixture of finely divided drugs and/or chemicals in a dry form that may be intended for internal use (oral powders) or external use (topical or dusting powder).

Powders are subdivided solids which are classified in the BP (British pharmacopeia) according to the size of their constituent particles of range from 1.25 µm to 1.7mm in diameter. Another classification of powders is based on the manner of their dispensing.

Granules are prepared aggregates of powdered materials to form a larger particle (2-4 mm).Granules may be used as such (granules of medicinal value) or in making tablets and capsules (because of better flow ability of granules compared to powders)[16].

Advantages of Powders

When it is not possible to dispense a drug as a solution or a suspension, because of its insolubility or because it is susceptible to microbial contamination if it is wetted, then it is a good idea to dispense it as a powder. In another word powders can be used to solve problems of insolubility and instability of some drugs. ex: crude vegetable drugs, were the most often prescribed drugs, dispensing them as powders was a good option. Also this is the reason that why most antibiotic and some injectable drugs are dispensed as powder to be dissolved just before use as the stability of these drugs in the solid state is much more than their stability in the liquid state.

When a bulky drug that has a large dose is to be administered, a powder is a good way of administering it. Several compound bulk powders used to be there and mostly these were given for stomach conditions, such as indigestion, constipation and diarrhea. They used to contain large amounts of light materials such as Magnesium Carbonate. When we are using powders for this type of use, we give the instruction "take a teaspoonful of the powder and swallow with water".

Small children and old people cannot swallow tablets and capsules. In such msituations powders are a good option.

Powders dispense fast in the Gastro Intestinal Tract (GIT) and the drugs are absorbed faster from these powders. Whereas tablets have to disintegrate first, the capsule shell has to dissolve first and then there may be some problems because excipients are included in these dosage forms.

When the patient has to mix the ingredients before administration, and dispensing. in separate divided powders is a convenient way, Ex: effervescent granules

Powders are very good from chemical stability point of view[16,17].

Disadvantages of powders

Powders have several disadvantages as a dosage form as described below:

They are time consuming to prepare and pack.

They are bulky to carry about

Powders may spill when they are being opened.

Patient may misunderstand the correct method of use. Without clear instruction, patients may inhale through the nose a drug intended for oral administration.

It is undesirable to take bitter or unpleasant tasting drugs by oral administration. Many herbal drugs (mainly infusions in boiling water) have very bitter tastes.

It is difficult to protect powders containing hygroscopic, deliquescent (tendingto melt or dissolve in humid environment), or aromatic materials from decomposition.

Uniform, individually wrapped doses of powders (sachets) are required and this may increase the manufacturing expense. (It is possible to include a spoon in a packet of powder drug. This may result in inaccurate amount of drug delivered).

Powder must be a homogeneous blend of the components must be of the most advantageous particle size. Drug Particle size influences the rate of solubility in water. It may also impudence the biological activity of a drug.

This is not an accurate way of administering medicines as the same weights of various medicaments often have different volumes. So potent substances should never be given in the form of bulk Powder[17, 18]

Advantages of granules over powders

A few advantages of granules over powders are listed below:

Granules are usually made as a step to prepare tablets.

Granules flow into the dies more evenly and more freely than particles from the hopper (the funnel-like container holding the drug to guide its flow into the tableting press).

Granules flow better than powders. The easy flow characteristics are important in supplying drug materials from the hopper or feeding container into the tableting presses. For this reason powder mixtures are usually granulated if they are intended to be compressed into tablets. Granules also eliminate or control dust.

Granules increase compressibility.

Granules have smaller surface area than a comparable volume of powdery This makes granules more stable physically and chemically than the corresponding powders also they are more stable against humidity and atmosphere.

Granules are less likely to cake or harden upon standing than arepowders.

Granules are more easily wetted by a solvent than are certain powders, so thatgranules are also preferred in making solutions.Example: Principen® (ampicillin) for Oral Suspension (Squibb). Ampicillin is unstable in aqueous solution, so it is usually prepared as granules and reconstituted by a pharmacist with purified water just prior to dispensing. The granules also contain colorants, flavorants, and other pharmaceutical ingredients, so the resulting solution or suspension has all the desired medicinal and pharmaceutical features of a liquid pharmaceutical.

Granules produce particle-size uniformity, thus content uniformity.6) Segregation of the constituents of the powder mixture could be avoided by granulation segregation occurs due to difference in particle Size or densities (small particles and denser particles concentrated in the base of the container and vice versa), by granulation

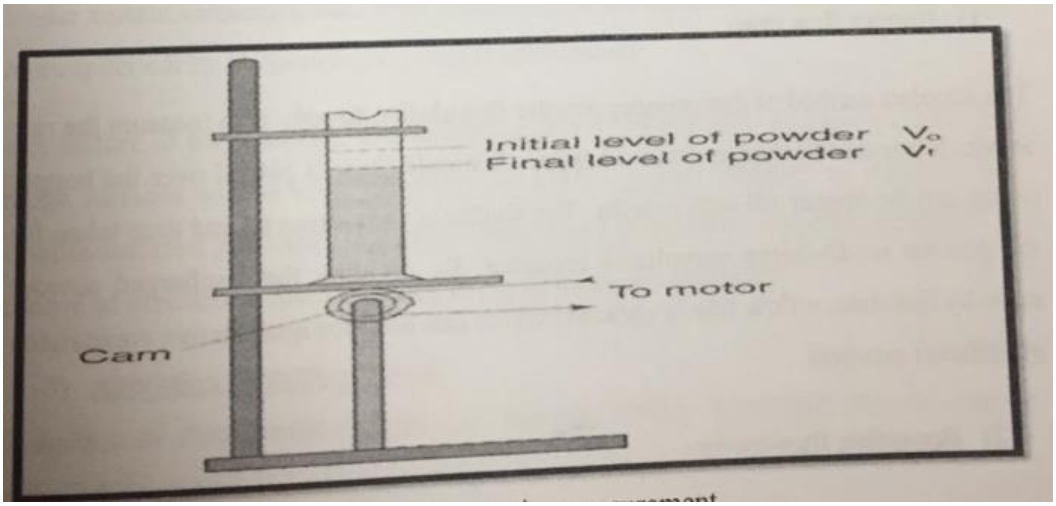

Figure: Bulk density measurement

same particles i.e. narrow range of particle size distribution, so that no segregation[18,19].

Classification of powders.

According to the manner of their dispensing Powders may be provided to the patient in bulk or divided.1) Bulk powders for external use.2) Bulk powders for internal use.3) Simple and compound powders for internal use.4) Powders for reconstitution5) Effervescent granules6) Cachets

Bulk powders for external use External bulk powders contain non-potent substances for external applications. Thesepowders are dispensed in glass, plastic wide mouth bottles and also in cardboard with specific method of application. Bulk powders for external used are of five types. (a)Dusting powders (b)Douche powder (c) Dental powder(d)insufflations (e) Snuffs

(a) Dusting powders

Uses: Dusting powders usually contain substances such as zinc oxide, starch and boric acid or natural mineral substances such as kaolin or talc. These are used externally for local application not intended for systemic action. They are employed chiefly as lubricants, protective, absorbents, antiseptics, antipruritics, astringents and antiperspirants [18, 19, and 20]. *Characteristics and requirements*

Homogeneity.

Non-irritability, also it should not be applied to broken skin

Free flow ability.

Good spreadability and covering capability

Adsorption and absorption capacity

Very fine state of subdivision. If desired, powders should be micronized

Capacity to protect the Skin against irritation caused by friction, moisture

And chemical irritants.

In some cases, powder should be sterilized such Talc, it may be contaminated with pathogenic microorganisms such as clostridium tetani and hence It should be sterilized by dry heat[18, 21].

Packaging and dispensing

Dusting powders should preferably be dispensed in Sifter-top containers. Such containers provide the protection from air, moisture and contamination as well as convenience of application. Currently some foot powdersand talcum powders have been marketed as pressure aerosols.

Douche powder

Uses: these powders are used as antiseptic for a body cavity, they are used after being dissolved in water

e.g: vaginal, nasal or otic use

Characteristics & requirements:

douchepowder formulation often include aromatic oils

To ensure complete mixing they should be passed through a sieve #40 or #60

Packing & dispensing: in sachets or wide mouth glass bottle[22]

Dental powders

Uses: it is a type of dentifrice for cleaning the teeth

Characteristics & requirements:

they contain detergents, antiseptics, coloring & flavoring agents

the base is calcium carbonate

essential oils are added to provide freshness to the mouth as well as antiseptic action

essential oils are easily absorbed by calcium carbonate & pumice

Packing & dispensing: in wide mouth jars or bottle

Insufflations

Uses: they are class of powders, for application to the body cavities e.g ear, vaginal

Characteristics & requirements

the powder has to be fine and must find an entry to the cavity deep enough to bring about its action at the site

it is delivered to the affected part in a stream with the help of a device called an insufflator

some of insufflations contain volatile liquid ingredients which may require uniform distribution in the powder

Packing &dispensing: they are packaged in pressurized form[22, 23]

Snuffs

These powders are inhaled into nostrils for decongestion & antiseptic action, they dispensed in flat metal boxes with hinged lid

Bulk powders for internal use

The non potent substances are used in bulk powder form such as; antacids, laxatives etc. they contain many doses in wide mouth container

Simple and compound powders for internal use

Simple powders are similar to bulk powders but individual doses are separated wrapped. These are unit dose powders normally packed in properly folded papers and dispensed in envelops, metal foils or other containers.

Powders for reconstitution

They are bulk powders intended to be reconstituted just before use. They are used to protect drugs against hydrolysis by water. Examples are**:** a) oral antibiotics: for stability problems the antibiotic is prepared in a dry form (powder or granules) and packed in a sealed bottle , a given amount ofwater is added before use.

b) Powder for injection: They may be classified as bulk or divided powders. Sterile water for injection is added from a second ampoule and the injection is used immediately.

Effevescent granules

The ingredients of this class whether in granular form or as salts, react in the presence of water evolving co_2 gas.

Advantages of effervescent granules:

Attractive dosage form for the public

The carbonated solutions masks undesirable taste of the drug.

The liberated co2 gas is used as a therapeutic agent, it acts as antinauseant.

Disadvantages of effervescent granules:

Instability in presence of moisture.

Problems in packaging and storage

Packaging & dispensing:

As bulk powder: the ingredients are mixed uniformly and directions stated on the label to add the prescribed quantity to water, before use.

As divided powder doses: The ingredients which cause effervescence on mixing with water are enclosed separately in papers of different colors .The patient is advised to take one powder of each color and add to water, before use.

As bulk or divided granular powder: The product contains all the ingredients mixed together in granular form[24, 25].

Principle of effervescent granules preparation

Forevolution of the gas two constituents are essential, a soluble carbonate such as sodium bi carbonate and an organic acid such as citric or tartaric acid

(Sodium bi carbonate) + (citric acid)

$3NaHCO_3+C6H_8O_7.H_2O = C_6H_5Na_3O_7 + 3CO_2 + 3H_2O$

(Sodium bi carbonate) + (tartaric acid)

$2NaHCO_3+C_4H_6O_6=C_4H_4Na_2O_6+2CO_2+2H_2O$

Quantities of the sodium bicarbonate & the organic acids are equimolecular in proportion.

*Preparation of effervescent:

Ingredient → mixing → mass formation → pass through sieves → dry → mix sodium bi carbonate and citric acid in the same quantity

mix sodium bi carbonate and citric acid both together, citric acid will produce water that will be enough to make mass, also produce carbon dioxide

mixing process can be done on water bath by keeping all ingredient in a dish, then heat the ingredients tell become mass, should be heated for short time to prevent drying the lump

tartaric acid and citric acid both should be used to form good granules

citric acid and tartaric acid are taken suitable properties and little acid access quantity required needed to neutralized sodium bi carbonate to give acidic taste

press the mass through sieve and don't change the position of paper to prevent lump formation

dry granules below 80c

if granules not in appropriate size or some granules are sticky should pass through sieve

drying lead to losing weight one seventh because water evaporated and loss of carbon di oxide

this process should be done with experienced

**Cachets:*

Its unit dosage form easily filled and sealed and it's replaced by capsule. It holds large quantity of medicine in comparing withcapsule. It made of flour and water, but its offer little protection against light and moisture. Due to size and shape it difficult to be swallowed. Process of filling same as capsules, it made of two flanges, upper one should be moistened, sealing take place due to moisture between upper and lower flanges &press over it, then allow drying for 15 minutes. Press the middle portion slightly to complete sealing.In absence of machine this process can be done with two bottles. keep upper and lower flanges on the mouth of bottles then add the drug to one of the bottles, rest the empty flange over the filled which should be moisture, pressed both then allow to dry. Cachets has different shapes. It should remain un touched & dispensed in bottles of glass or plastic then keep bottles closed[23, 25].

**Powder preparation*

Principle involved in powder preparation

dry content uniformity: mix drug then take 100mg sample from any corner then place it in the mixture, should have same ratio of drug in the prescription

fine size: should be fine to be easily swallowed

free flowing: powder should be in lumps not wet

good taste: if unpleasant should add sweetness

amount: not be large or small

**Method of mixing*

titration: make coarse powder fine by using mortar and pestle, we use this method to mix two dry powder

Pulverization by intervention: for soft powder should add second material to help in powdering

Lavigation: powdered the substance by adding suitable non-solvent to form paste like; paraffin

**Procedure of powdered preparation:*

-Geometric dilution: put drug in mortar &powder it with pestle then add amount with higher weight mix then add the remain quantity with mixing

-Weighing: powder prepared into individual doses

-packing: done with systemic and specific manner, now this process done automatically by machine

-dispensing: envelop is taken and labeled

**Quality control of powder[24, 25]*

Properties relevant to ideal formulation are' single particle properties, bulk properties, particle -particle interaction, powder morphology mixing and blending properties

-particle size: according USP such as fine- very fine and its affect some factors which affect properties

#Dissolution rate: small particle size more dissolution

#suspend ability: suspension preparation important to have good suspend ability

#uniform distribution: ability of drug to have uniform distribution as a capsule

#penetrability: for intra respiratory application, its of inhaled particles to reach desired location within respiratory tract range {1-5 Mm}

#non-grittiness: in dermal ointment, non-gritty fine powder should be used. Particle size {50-100 Mm} can be used

Granulation: Recent techniques in pharmaceutical industries

Definition: granulation is the process in which powder particles are made to adhere to form larger particles called granules.

There are many reasons for granulation such as:

Improving flow properties of the dose

Controlling the rate of drug release

Increasing the bulk density of a product

Improving product appearance

Types of granulation

Dry granulation: it is granules formation by compress powder particles together mechanically into slugs or roller compression to form flakes without using any liquids.

Wet granulation: this process involves powder adding to an adhesive to form granules. The wet mass is dried sized to get granules. The bonds between the granules is formed during drying, and this process is used mostly in granules formation[24, 25].

Wet granulation techniques

High sheer mixture granulation

In this process the particles are set into movement by an impeller rotating at high speed. The liquid is added by pouring from the top. After that the wet mass is sieved, dried and sieved again to form granules.

Advantages: short processing time, lesser amount of liquid compared with fluid bed granulation.

Disadvantages: over wetting of granules leads to large size lumps formation, and high temperature leads to chemical degradation of thermo-labile material.

Fluid bed granulation

Is a process include spraying a binder solution onto a fluidized powder to form granules? The system involves the heating of air and then directing it through the material to be processed.

Advantages: it reduces dust formation during processing, it reduce product loss and it improves worker safety[19,24,25].

Disadvantages: difficulty of assuring reproducibility and it is unsuitable for heat sensitive materials.

Extrusion-spheronization

5 steps: 1- dry mixing to have homogenous dispersion. 2- Apply wet granulation to have wet mass 3-extrusion of wet mass to form rod shaped particles 4- rounding off 5-drying

Advantages: 1-particles with high bulk density, dust free and smoother surface can be produced 2- physical characteristics of the active ingredients can be modified.

Disadvantages: have more time intensive than other methods.

Spray drying

In this process the product is made from solution or suspension instead of primary powder particles. Steps:

atomization the liquid feed into droplets

Mix the droplets with heated gas to evaporate and leave dried solids

Separate the liquid from the gas stream.

Advantages: rapid process, reduce cost by avoid granulation steps and it is suitable for heat sensitive product

Liquids in wet granulation

water is used in most preparation because it is nonflammable. But it affect drug stability and need more drying time. So organic solvents used in water-sensitive drugs or to have rapid drying.

Partical-size analysis

The Particle size and the size distribution can be measured by a number of methods

Sieving

Sieving is the simplest and probably the most commonly used method for determining the particle-size distribution. A powder mass is placed on top of a Sifter (mechanical shaker) that is made of a series of screens with sequentially smaller apertures. The horizontal sieve motion loosens the packing of particles allowing subsieve particles to pass through.

Most widely used screens are woven-wire screns ranging in size starting from 400 openings per inch. In the United States, Tyler standard and US standard (ASTM E11-70) are commonly used. The two standards are different slightly, but can be used interchangeably.

Microscopy

Particle size is measured using a calibrated grid background. The microscopic images of particles can be forwarded to a computer and the size and size distribution can be analyzed by an image analyzer. The resolution limit by light microscopy is 0.2. Electron microscopy can be highly useful for the particles smaller than 0.2[8,17,24,25].

Sedimentation Rate

The terminal settling velocity of particles through a liquid medium in a gravitational and centrifugal environment can be used to calculate the particle size based on Stokes' law, which is:

$$dx/dt = d^*2(ps — p_0)g/18n_0$$

where

dx/dt: is the rate of settling in cm/s,

d: is the diameter of the particle in cm,

ps: is the density of the particles (g/cm3), p_0 is the density of the medium (g/cm3),

g: is the acceleration due to gravity (981 cm/s2), and n_0 is the viscosity of the medium in poise (g/(cm.s))[17].

Coulter Counter

Coulter counter determines the volume distribution of particles suspended in an electrolyte-containing solution. When a particle passes through a small orifice, it blocks the

Table: Relationship between Hausner ration, compressibility index & Powder Flowability

Hausner Ratio	% Compressibility Range	Flow Description
1.00-1.11	`5-15	Excellent Flow
1.12-1.18	`12-16	Good
1.19-1.25	18-21	Fair
1.26-1.34	23-28	Poor
1.35-1.45	28-35	Poor
1.46-1.59	35-38	Very poor
≥ 1.6	> 40	Extremely Poor

electric current. The information on particle volume is used for calculating Particle size assuming a spherical shape.

Light Scattering

Other automatic particle-size measuring instrument employs the light scattering principle. This can be performed either in solution or in the dry powder state.

Gas Adsorption

The surface area of powdered materials can be measured by adsorption of solute from
solution or of a gas. This method results in the specific surface area (area/unit mass).

Usually, an inert gas, such as nitrogen, is adsorbed as a monolayer and the total volume of gas adsorbed is used to calculate the specific surface area, which in tum provides information on the particle size.

Flow Properties of Powders and Powder Flowability

The descriptions "good flow behavior" or "poorly flowing powder" are usually used to describe the flow properties of the powder. Good flowing powder usually means that bulk powder flows easily, i.e., it does not consolidate much and flows out of a silo or a hopper due to the force of gravity alone and no flow promoting devices are required. Products are poorly flowing if they have flow obstructions or consolidate during storage or transport. Along with these descriptive statements, a quantitative measurement of flowability is possible[18, 25].

The flow properties of powders depend on several parameters, e.g:

Particle size distribution
Particle shape
Chemical composition of the particies
Moisture
Temperature

Adhesive forces and relationship between adhesive force, particle size,and flowability

The flowability of a bulk powder depends on the adhesive forces between individual particles. Different mechanisms create adhesive forces. With fine-grained, dry bulk Powders, adhesive forces due to vander Waals interactions play the essential role. With moist bulk powders, liquid bridges between the particles usually are most important. Liquid bridges are formed by small regions of liquid in the contact area of particles, in which due to surface tension effects a low capillary pressure prevails. Both types of adhesive forces described above are dependent on the distance between particles and on particle size. Whether a bulk powder flows well or poorly depends on the relationship of the adhesive forces to the other forces acting on the powder. It can be shown that the influence of adhesive forces on flow behavior increases with decreasing particle size. Thus, as a rule a bulk powder flows more poorly with decreasing particle size. Fine-grained bulk powder with moderate or poor flow behavior due to adhesive forces are called cohesive bulk powder [24,26].

Characterization of powder flow

When examining the flow properties of a powder it is useful to be able to quantify the type of behavior and many different methods have been discribed, either indirectly, generally by measurements carried out on static beds. Or directly using dynamic or kinetic methods.

lndireet methods

Angle of repose

Angles of repose have been used as indirect methods of quantifying powder flowability, because of their relationship with inter-particular cohesion.

There are many different methods of determining angles of repose. The different methods may produce different values for the same powder. It is also possible that different angles of repose could be obtained for the same powder, owing to differences in the way the samples were handled prior to measurement.

For these reasons, angles of repose tend to be variable and are not always representative of flow under specific conditions[26,27].

The most popular method of detemiination of the angle of repose is the Funnel Method. The powder is allowed to flow freely through a funnel which height was
adjusted in such a way that the tip of the funnel just touched the apex of the heap of
the powder. The diameter of the powder cone was measured and its angle of repose was calculated using the following equation: Tan q = h/r

Where q is the angle of repose, h & r are the height & radius of the powder cone, respectively. Values of the angle of repose gives indication of the powder flowability according to the following table[24,28].

Shear cell determinations

It is possible to characterize flowability indirectly from the behavior of powder in a shear cell by determine the FLOW FACTOR of powder.

The relationship between flow factors and powder flowability is shown in Table:

Bulk density measurements

Thebulkdensityofapowderisdependentonparticlepackingandchangesasthe powder consolidates. Consolidated powder is likely to have a great erarch strength than a les consolidated on *e* and may therefore be more resistant to powder flow. The ease with which a powder consolidates can be usedas an indirectmethod of quantifying powderflow.

Bulk density can be determined by mechanical tapping device or jolting volumeter which can be used to follow the change in packing volume that occurs when void space diminishes and consolidation occurs. The powder contained in the measuring cylinder is mechanically tapped by means of a constant velocity rotating cam and

increases from an initial bulk density *Do* (also known as fluff or poured bulk density) to a final bulk density *Dr* when it has attain edits most stable ,i.e. unchanging arrangement.

Hausner found that the ratio Df/D0 was related to inter-particular friction and as such, could be used to predict powder flow properties. He showed that powders with low inter-particular friction such as coarse spheres, had ratios of approximately 1.2, whereas more cohesive, less free flowing powders, such as flakes have Hausner ratio greater than 1.6, another indirect method of measuring powder flow from buck densities was developed by carr[24,27].

The percentage compressibility or Carr`s index of a powder is measured from the bulk density as follow; Df/ D0*100/Df

The following table shows the generalized relationship between descriptions of powder flow and both of Husner ratio and percent compressibility.

Directmethods

Hopper flow rate

The simplest method of determining powder fiowability directly is to measure the rate at which powder discharges from a hopper. A simple shuts is placed over the hopper outlet and the hopper fill with powder. The shutter is then removed and time taken for the powder to discharge completely recorded. By dividing the discharged powder mass by this time, a flow rate is obtained which can used for quantitative comparison of different powders.

Recording Flow-meter

A recording flow-meter is essentially similar to the method described above except that powder allowed to discharge from a hopper or container on to a balance.

In the case of analoguebalances a chart recorder is used to produce a permanent record of increase in powder mass with time. In some systems, the signal from the balance is digitized at processed by a microcomputer. Recording flow-meters allow mass flow rates to be determined and provide a means of quantifying uniformity of flow[24,28].

Alteration of particle size and size distribution

Because coarse particles are generally less cohesive than fine particles and an optimum size for free flow exists, there is a distinct disadvantage in using a finer grade of powder than is necessary.

The size distribution can also be altered to improve flowability by removing a proportion of the fine particle fraction or by increasing the proportion of coarser particles, such as occurs in granulation.

Alteration of particle shape or texture

In general, for a given particle size more spherical particles have better flow properties than more irregular particles. The process of spray-drying can be used to produce near-spherical excipients, such as spray-dried lactose.

Under certain circumstances. Drug particles that are normally acicular can be made more spherical by temperature-cycling crystallization.

The texture of particles may also influence powder flowability, as particles with very surfaces will be more cohesive and have a greater tendency to interlock than smooth-surfaced particles.

The shape and texture of particles can also be altered by control ofproduction methods. Such as crystallization conditions[27,29].

Alteration of surface forces

Reduction of electrostatic charges can improve powder flow ability and this can be achieved by altering process conditions to reduce frictional contacts. For example, where powder is poured down the speed and length of transportation should be minimized. Electrostatic charges in powder containers can be prevented or discharged by efficient earth connections.

The moisture content of particls is also of importance to powder flowability as absorbed surface moisture films tend to increase bulk density and reduce porosity. In cases where moisture content is excessive powders should be dried and, if hygroscopic, stored and processed under low-humidity condition

Formulation additives: flow activators

Flow activators are commonly referred to pharmaceutically as `glidant`, although some also have lubricant or anti-adherent properties.

Flow activators improve the flowability of powders by reducing adhesion and cohesion. Some commonly used glidant include talc, maize starch and magnesium stearate, which may have their effect by reducing or altering electrostatic interactions

Bulk Powders for external use

They, sometimes called dusting powders, are often dispensed in a shaker-top container to facilitate topical application. They may also be dispensed in a wide· mouth jar or a plastic container with a flip-top lid.

The jar or plastic container can be closed tightly and provides increased stability and protection from light and moisture, especially for compounds that contain volatile ingredients[29,30].

Bulk Powders intended for internal use

They should be dispensed in an amber, wide-mouth powder jar, with a tight-fitting led.

They should be accompanied by an appropriately sized dosing spoon, or cup and adequate direction for removing and administering a correct dose.

Internal bulk powders should be labelled with the concentration of the active ingredient per dose (e.g: Potassium chloride 600mg per tablespoonful).

Divided Dry powders

They are packaged in individual doses and dispensed in either folded papers or plastic bags. If the individual dose of the compound is below the minimum weighable quantity of the prescription balance be in gused, orisso small in mass that it will be difficult for the patient to handle, diluents should be added to make the dose more manageable. This can be accomplished by preparing an aliquot to attain the proper concentration.Foldedpowderpapersareverytime-consumingandrarelyused.Plastic bags that either have a zipper closure or can be heat-scaled arc more frequently used to package individual doses of dry powders for internal use. Amber bags are available for products that are light-sensitive, and the filled bags can be dispensed in alight- resistant container.

Granulation

Granulation is the process of collecting particles together and converting fine or coarse particles into physically stronger and larger agglomerates by creating bonds between them. Bonds are formed by compression or by using a binding agent.

The art and science for process and production of granules is known as Granulation Technology

Primarily granules are prepared to improve flow and compression characteristics of the blend but there are many other reasons and sometimes multiple reasons for granulation such as:

Improving flow properties of the mix and hence the uniformity of the dose.

Increasing the bulk density of a product.

Facilitating metering or volumetric dispensing.

Controlling the rate of drug release.

Decrease dust generation and reduce employee exposure to drug product.

Improving product appearance.

Types of granulation

Granulation Technology can be broadly classified into 2 types based upon the type of processing involved:

Dry Granulation

Dry granulation involves granule formation without using liquid solution as the product may be sensitive to moisture and heat. In this process dry powder particles may be brought together mechanically by compression into slugs or by roller compression to obtained flakes.

Wet Granulation

Wet granulation is the most widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction. The wet mass is dried and then sized to obtained granules. The liquid added binds the moist powder particles by a combination of capillary and viscous forces in the wet state. More permanent bonds are formed during which leads to the formation of agglomerates[31].

Wet granulation techniques

High shear mixture granulation

High shear mixture has been widely used in pharmaceutical industries for and granulation. In this type of equipment, the particles are set into movement by impeller rotating at a high speed (Approx 50- 100 rpm). Equipment also contains a chopper which rotates at around 1500 — 4000 rpm. The primary function of chopper is to cut large lumps into smaller fragments thus increases the binder distribution into the blend. The binder liquid is added by pouring, pumping or spraying from the top.

After the wet mass is produced, the granules are wet sieved, dried and sieved again. The liquid amount is critical, because the process is susceptible for over-wetting, which leads to uncontrollable agglomerate growth.

Advantages

Short processing time

Lesser amount of liquid binders required compared with fluid bed granulation.

Highly cohesive material can be granulated.

Disadvantages

Mechanical degradation could take place in case of fragile particles.

Due to increase in temperature chemical degradation of thermo-labile material could be resulted.

Over wetting of granules can leads to large size lumps formation[32].

Fluid bed granulation

Fluidization is the operation by which fine solids are transformed into a fluid like state through contact with a gas. At certain gas velocity, the fluid will support the particles giving them free mobility without entrapment.

Fluid bed granulation is a process by which granules are produced in single equipment by spraying a binder solution onto a fluidized powder bed. The material processed by fluid bed granulation are finer, free flowing and homogeneous. The system involves the heating of air and then directing it through the material to be processed. Later, the same air exit through the voids of the product.

Advantages

It reduces dust formation during processing, thus improves housekeeping.

It reduces product loss.

It improves worker safety.

Disadvantages

The Fluid Bed cleaning is labor-intensive and time consuming.

Difficulty of assuring reproducibility.

It is unsuitable for heat sensitive materials.

Extrusion-Spheronization

This process is primarily used as a method to produce multi-particulates for controlled release application. It is a multiple step process involving at least 5 steps capable of making uniform sized spherical particles.

Dry mixing of materials to achieve homogeneous dispersion.

Wet granulation ofthe resulted mixture to form wet mass.

Extrusion of wet mass to form rod shaped particles.

Rounding off (in spheronizer)

Drying

These dried rounded particles can be optionally screened to achieve a targeted mean size distribution.

Advantages [31, 33]:

Ability to incorporate higher levels of active components without producing excessively larger particles.

Two or more active agents can be easily combined in any ratio in the same unit.

Physical characteristics of the active ingredients and excipients can be

Modified.

Particles having high bulk density. Low hygro-scopicity, high spheroid. dust free, narrow particle size distribution and smoother surface can be produced.

disadvantages:

This process is more labor and time intensive than other commonly used granulation techniques.

Spray drying

Spray Drying as a process has been used to produce microcapsules, food ingredients, flavors.and various

biotechnological preparations. This process differs from the methods discussed above in that it is a continuous process in which a dry granular product is made from a solution or a suspension rather than initially dried the primary powder particles. The solution or suspension may be of drug alone, a mixture of different excipients or a complete formulation. As long as the liquid solution or suspension reed to the drying system, dry powder product continues to be produced[31, 33, 34].

The spray drying process involves three fundamental steps

Atomization of a liquid feed into fine droplets.

Mixing of these sprays droplets with a heated gas stream, allowing the liquid to evaporate and Ieave dried solids.

Separation of the dried powder from the gas stream.

Advantages

Rapid and continuous process.

Reduces overall cost by avoiding labor intensive drying and granulation steps.

Offers minimal product handling and operator exposure to dust.

Suitable for heat sensitive product

Typical liquids included in wet granulation

Water is commonly used for economical and ecological reasons. The primary advantage of water is that it is non-flammable.

Its disadvantages as a solvent are that it may adversely affect drug stability, causing hydrolysis of susceptible products, and it needs a longer drying time than do organicsolvents. This increases the length of the process and again may affect stability because of the extended exposure to heat.

Organic liquids used mainly are Ethanol, Isopropanol, or combination. The granulation liquid may be used alone or, more usually, as a solvent containing a dissolved adhesive (also referred to as a binder or binding agent) which is used to ensure particle adhesion once the granule is dry. Organic solvents are used when water-sensitive drugs are processed, as an alternative to dry granulation, or when a rapid drying time is required[33].

REFERENCES

1. Libberman, H.A. and Lechman, L. 1981). Pharmaceutical Dosage Forms (Tablet V1, V2 and V3). Marcel Dekker. Inc., N.Y., USA.
2. Stockton SJ. Calculations. International Journal of Pharmaceutical Compounding 2010;14:327.
3. Tolu Balsam Syrup N F. US Pharmacopeial Convention, Inc. United States Pharmacopeia 37-National Formulary 32 [book online]. Rockville, MD: US Pharmacopeial Convention, Inc.; 2014.
4. Florence A.T., Siepmann J. (2009) Modern Pharmaceutics, 5th Ed. Taylor & Francis.
5. Rockville, MD: US Pharmacopeia, annual. (2007) United States pharmacopeia/national formulary: USP/NF.
6. British pharmacopoeia 2007. London, England: Her Majesty's Stationery Office.
7. Bisharat, Lorina, Alberto Berardi, Diego R. Perinelli, Giulia Bonacucina, Luca Casettari, Marco Cespi, Hatim S. AlKhatib, Giovanni F. Palmieri. "Aggregation of zein in aqueous ethanol dispersions: effect on cast film properties." International Journal of Biological Macromolecules: available online 12 August 2017.
8. Berardi Alberto, Lorina Bisharat, "Nanotechnology systems for oral drug delivery: challenges and opportunities." in Nanotechnology in Drug Delivery (2016), One Central Press (UK), Editor: Salam Massadeh.
9. Bisharat, Lorina, Diego R. Perinelli, Alberto Berardi, Giulia Bonacucina, Serena Logrippo, Feras W. Darwish Elhajji, Marco Cespi, and Giovanni F. Palmieri. "Influence of Testing Parameters on In Vitro Tramadol Release from Poloxamer Thermogels using the Immersion Cell Method." AAPS
10. Rang,H.P.;Dale, M.M. and Ritter,J.M. In: Pharmacology(4th ed.), Churchill Livingstone, London, 2003; 244.
11. Matthias, P. W. and Roger, S.: lipid signaling in disease. Natural reviews molecular cell biology. 2008; 9: 162-176.
12. Shriner, R.L.; Hermann, C.K.F.; Morrill, T.C.; Curtin, D.Y.and Fuson, R.C.: The Identification of Organic Compounds (8th ed.). John
13. Snyder AM, Markowsky SJ, Deleo J, Black EW. (Submitted) Pharmacokinetic Team-Based Learning Experience: Phenytoin. Curriculum submitted to AAMC MedEdPortal. MEP-2014-0211.R1
14. Black, EW, Davidson, RA, Rosenberg, E, Snyder, A, McCormack, W. An interdisciplinary team-based learning experience in ambulatory patient safety. AAMC MedEd Portal. MEP-2013-0005.R6
15. Hae-Sun Prk, Hee-Jeon Choi, Hea-Soon Shin, Sang Kook Lee and Myung-Sook Park: Synthesis and Characterization of Novel Hydantoins as Potential COX-2 Inhibitors:1,5-Diarylhydantoins. Bull. Korean Chem. Soc. 2007; 28(5): 751-757.
16. Berardi, Alberto, George P. Lomonossoff, David J. Evans, and Susan A. Barker. "Plant-expressed Hepatitis B core antigen virus-like particles: Characterization and investigation of their stability in simulated and pig gastro-intestinal fluids." International journal of pharmaceutics 522, no. 1 (2017): 147-156.
17. Berardi, Alberto, Lorina Bisharat, Marco Cespi, Iman A. Basheti, Giulia Bonacucina, Lucia Pavoni, and Hatim S. AlKhatib. "Controlled release properties of zein powder filled into hard gelatin capsules." Powder Technology 320 (2017): 703-717.
18. AbuRuz S, Al-Ghazawi M, Snyder AM. Pharmaceutical care in a community-based practice setting in Jordan: where are we now with our attitudes and perceived barriers? Int J Pharm Pract. 2012; Apr;20(2): 71-9. doi: 10.1111/j.2042-7174.2011.00164.x. Epub 2011 Oct 13
19. Snyder AM, Klinker K, Orrick J, Janelle J, Winterstein AG. In-depth Analysis of Medication Errors in Hospitalized patients with HIV. Ann Pharmacother 2011; 45: 459-468. DOI 10.1345/aph.1P477

20. Eckhardt M, Snyder A, Backes N, Homann J, Jaehde, U. Der "Teacher-Practitioner" als Brücke zwischen Universität und Patient: Patientenorientierte Pharmazie in der Apothekerausbildung. Krankenhauspharmazie. 2007; 28: 5-10.
21. Development and Validation of Newer High Performance Thin Layer Chromatographic Method for Quantification of Eflornithine Hydrochloride in Pharmaceutical Formulations, American Journal of Pharmacological Sciences, 2013, Vol. 1, No. 4, 47-52, Available online at http://pubs.sciepub.com/ajps/1/4/1 Science and Education Publishing, DOI:10.12691/ajps-1-4-1.
22. Berardi, Alberto, Lorina Bisharat, Giulia Bonacucina, Luca Casettari, Serena Logrippo, Marco Cespi, Hatim S. AlKhatib, and Giovanni F. Palmieri. "Formulation, swelling and dissolution kinetics study of zein based matrix tablets." Powder Technology 310 (2017): 241-249.
23. Smith DE, Brater DC, Lin ET, Benet LZ. Attenuation of furosemide's diuretic effect by indomethacin: Pharmacokinetic evaluation. J Pharmacokin Biopharm 7:265-274, 1979.
24. Lin ET, Smith DE, Benet LZ, Hoener BA. High-performance liquid chromatographic assays for furosemide in plasma and urine. J Chromatogr 163:315-321, 1979.
25. Smith DE, Benet LZ. Relationship between urinary excretion rate, steady-state plasma levels, and diuretic response of furosemide in the rat. Pharmacology 19:301-306, 1979.
26. Development and Characterization of Muco-Adhesive Microcapsules Containing Hypoglycemic Drug, Asian Journal of Biomedical & Pharmaceutical Sciences, 16th Issue (Jan - Feb, 2013).
27. Design, synthesis and anticonvulsant evaluation of novel N-(4-substituted phenyl)-2-[4-(substituted) benzylidene]-hydrazinecarbothio amides. European Journal of Medicinal Chemistry 2012, 47, 153 -166.
28. A new class of anticonvulsants possessing 6 Hz psychomotor seizure test activity: 2-(1H-Benzotriazol-1-yl)-N'-[substituted] acetohydrazides. Medicinal Chemistry, Bentham Science Publishers 2012, 8.
29. Smith DE, Gee WL, Brater DC, Lin ET, Benet LZ. Preliminary evaluation of furosemide-probenecid interaction in humans. J Pharm Sci 69:571-575, 1980.
30. Smith DE, Lin ET, Benet LZ. Absorption and disposition of furosemide in healthy volunteers, measured with a metabolite-specific assay. Drug Metab Dispos 8:337-342, 1980.
31. Wu SP, Smith DE. Impact of intestinal PepT1 on the kinetics and dynamics of N-formyl-methionyl-leucyl-phenylalanine, a bacterially-produced chemotactic peptide. Mol Pharm 10:677-684, 2013.
32. Huh Y, Hynes SM, Smith DE, Feng MR. Importance of peptide transporter 2 on the cerebrospinal fluid efflux kinetics of glycylsarcosine characterized by nonlinear mixed effects modeling. Pharm Res 30:1423-1434, 2013.
33. Sun D, Wang Y, Tan F, Fang D, Hu Y, Smith DE, Jiang H. Functional and molecular expression of the proton-coupled oligopeptide transporters in spleen and macrophages from mouse and human. Mol Pharm 10:1409-1416, 2013.