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A REVIEW ON FORMULATION OF CONVENTIONAL DRUG DELIVERY SYSTEM AND NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

The formulation development is important part of pharmaceutical development and essential for therapeutic and commercial success of product by providing quality, safety and efficiency. Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. Novel drug delivery systems (NDDS) are carriers which maintain the drug concentration in therapeutic range for longer period of time. The amount of drug in a tablet can be a limiting step in formulation design. Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability. In formulation of any dosage form the various excipients such as coloring agent, flavoring agents, glidandants, binders etc. are added. Gastroretentive dosage forms greatly improved the pharmacotherapy of the Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, dextrose and boric acid etc. GIT through local drug release In this article formulation of conventional such as tablets, capsules, semisolids, etc. and in NDDS formulation of Controlled drug delivery system, GRDDS etc. are given. Nose to brain drug delivery system in which drug transport through nasal route to CNS(central nervous system). The main aim of these review is providing a needfull information of excipients and various apporoaches are used in conventional drug delivery system and novel drug delivery system.

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INTRODUCTION

DRUG DELIVERY SYSTEM:-

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunegenicity, bio recognition, and efficacy of drugs were generated[1]. These new strategies, often called drug delivery systems (DDS), which are based on interdisciplinary approaches that combine polymer science, pharma- ceutics, bioconjugate chemistry, and molecular biology.

CONVENTIONAL DRUG DELIVERY SYSTEM:-

Conventional drug delivery involves the formulation of the drug into a suitable form, such as a compressed tablet for oral administration or a solution for intravenous administration. These dosage forms have been found to have serious limitations in terms of higher dosage required, lower effectiveness, toxicity and adverse side effects[1].

NOVEL DRUG DELIVERY SYSTEM (NDDS):-

Novel drug delivery systems is the new system Recent advances in the understanding of pharmacokinetic & pharmacodynamic behaviour of drug have offer a more rational approach to the development of optimal drug delivery system. The novel drug delivery systems (NDDS) are carriers which maintain the drug concentration in therapeutic range for longer period of time[2].

FORMULATION OF CONVENTIONAL DRUG DELIVERY SYSTEMS

TABLETS FORMULATIONS

EXCIPIENTS:-

Tablet formulation design starts with a predetermined value, which is the dose size. The amount of drug in a tablet can be a limiting step in formulation design[3]. Tablet excipients can be classified on the basis of their functionality as listed below:

1. Fillers/diluents
2. Binders
3. Disintegrants
4. Lubricants
5. Glidants
6. Buffering agents
7. Sweeteners
8. Wetting agents
9. Coating agents
10. Matrix formers

FILLERS/ DILUENTS:

Depending on the physiological conditions and formulation, one needs a tablet of around 100 mg for ease of handling and administration, and therefore, fillers are used to increase bulk[3].

COMMONLY USED TABLET DILUENTS

1. Lactose-anhydrous and spray dried lactose
2. Directly compressed starch-Sta Rx 1500
3. Hydrolyzed starch-Emdex and Celutab
4. Microcrystalline cellulose-Avicel (PH 101and PH 102)
5. Dibasic calcium phosphate dehydrate
6. Calcium sulphate dihydrate
7. Mannitol and Sorbitol
8. Sucrose- Sugartab, DiPac, Nutab
9. Dextrose Lactose

BINDERS AND ADHESIVES:

Binders can be added as dry powders to form a matrix that will include the drug, as in the case of dry granulation or in direct compression. Sometimes, the binders are dissolved in liquids such as water or alcohol and then sprayed onto the powder mixture as with wet granulation[3].

Binders used in Tablet Formulation are:

- Poly vinyl pyrrolidone (PVP)
- Sodium carboxy methyl cellulose
- HPMC (Low molecular weight, 5 cps)
- Starch paste
- Simple syrup

DISINTREGRANTS:-

Disintegrants serve the purpose of facilitating the disintegration of tablets into its components either after administration in the GI tract or just before administration, such as in the case of the fast-disintegrating tablets[3].

LUBRICANT AND GLIDANTS :-

Pharmaceutical lubricants are materials used in tablet formulations to reduce the friction between the lower punch and the die and the tablet. Friction damages both the tablet and the tablet press during the ejection cycle[3]. Glidants are materials that reduce interparticular friction, covering the particle surfaces with a thin layer, and as a result helping in better granule flow. Colloidal silicon dioxide, talc, and starch can be used as glidants colloidal silicon dioxide is effective as low as 0.5% as a glidant[3].

COLOURING AGENTS:-

All coloring agents must be approved and certified by FDA. Two forms of colors are used in tablet preparation FD & C and & C dyes . These dyes are applied as solution in the granulating agent or Lake form of these dyes. Lakes are dyes absorbed on hydrousoxide and employed as dry powder coloring[4].

FLAVOURS AND SWEETENERS:-

Flavors are usually limited to chewable tablets or other tablets intended to dissolve in the mouth. Flavor oils are added to tablet granulations in solvents, are dispersed on clays and other adsorbents or are emulsified in aqueous granulating agents (i.e. binder) [4].

The use of sweeteners is primarily limited to chewable tablets. E.g. Sugar

• Mannitol– 72% as sweet as sugar, cooling & mouth filling effect

• Saccharin– Artificial sweetener, 500 times sweeter than sucrose

• Cyclamate– either alone or with saccharin– it is banned

• Aspartame (Searle) – widely replacing saccharin[4]

TABLET MANUFACTURING TECHNIQUES

DIRECT COMPRESSION:

Direct compression is the simplest and most economical method for the manufacturing of tablets because it requires less processing steps than other techniques such as wet granulation and roller compaction. However, most pharmaceutical active ingredients cannot be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore they must be blended with other directly compressible ingredients to manufacture satisfactory tablets[5].

Fig.1: Direct compression machine.

WET GRANULATION:

Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid required to be properly adjusted, 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 solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis[5].

Fig.2: Wet granulation machine.

DRY GRANULATION:

Dry granulation requires drugs or excipients with cohesive properties. Dry granulation is simpler than wet granulation, therefore the cost is reduced. 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 often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet[5].

Fig.3: Dry Granulators.

CAPSULE FORMULATIONS

HARD GELATIN CAPSULE FORMULATIONS

GELATIN:

It is prepared by hydrolysis of collagen obtained from animal connective tissue, bone and pork tissue. There are two types of gelatin[8].

- Type A (Acid hydrolysis of pork skin)(pH 9)
- Type B (Alkaline hydrolysis of bones) (pH 4.7)

The physiochemical properties of gelatin most interest to the shell manufactures are[8] :

1) Bloom strength
2) Viscosity

PLASTICIZER :

- In plasticizer sorbitol and glycerol is used.

COLORANT :

- Colour approved by D & C act.
- Soluble synthetic dye (coaltar dyes) & insoluble dyes (iron oxide),
- Colorant plays an important role in improving patient compliance.
- Those the colour of drug product may be selected in consideration of the disease state for which it is intended. E.g. White – Analgesics[8].

OPACIFIERS :

- it provide protection against light or conceal the content. E.g. Titanium dioxide.

WATER :
- Demineralized water is used.
- Finished capsule contain an equilibrium moisture content of 12-16 % .

PRESERVATIVES :
When preservatives are employed, parabens are often selected[8].

FLAVOURING AGENTS :
- If needed flavouring agents may be added to capsule shell. Eg. Ethyl vanillin, essential oil.

GELATIN CAPSULE FORMULATION

The formulation of hard gelatin capsule includes different substances which promotes the release of drug constituents from the hard gelatin capsule these includes:

1) Active ingredients
2) Fillers / Diluents
3) Glidents
4) Lubricants
5) Disintegrants
6) Surfactants
7) Hydrophilic agents
8) Protectives
9) Anti – dusting agents

DILUENTS:

The determination of amount of diluents are used on 1)the total amount material that can possibly be put in the capsule in relation to the amount of active ingredients to be supplied by the capsule and 2)the amount of lubricant and oil (generally in the order of 2% or less) that can be used[9].

GLIDANTS/LUBRICANTS:

Material that may be considered for improvement of flow characteristics may include the following: glycol esters, silicones, silicon dioxide, metallic stearates, stearic acid and talc[9].

ANTI-DUSTING:

Oils that may be considered for use in assisting in the control of dusting, as well as in providing additional cohesiveness to a powder mix, may include any inert, edible FDA approved material[9].

MANUFACTURING OF HARD GELATIN CAPSULE:
Hard gelatin capsules are manufactured using a dip-coating method and the various stages involved are as follows[7]:

STEPS:

1. DIPPING
2. SPINNING
3. DRYING
4. STRIPPING
5. TRIMMING AND JOINING :
6. POLISHING

- ✓ Pan Polishing : Acela – cata pan is used to dust and polish.
- ✓ Cloth dusting : Capsules are rubbed with the cloth.
- ✓ Brushing : Capsules are filled under the soft rotating brush[7].

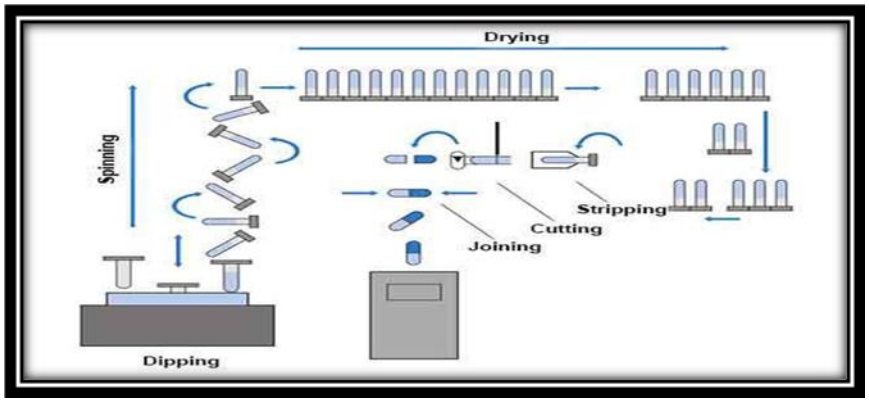

Fig.4: Steps of manufacturing of hard gelatin capsule

FILLING OF HARD GELATIN CAPSULE

The filling of hard gelatin capsules is an established technology, with equipment available ranging from that for very small-scale manual filling (e.g., Feton capsule filling machine), through intermediate-scale semi-automatic filling to large-scale fully automatic filling[6].

Fig.5: Capsule Filling Machine Fig.6: Automatic Capsule filling machine

SOFT GELATIN CAPSULE FORMULATION

- ✓ Formulation of soft gelatin capsule involves liquid
- ✓ Material generally formulated to produce the smallest possible capsule consistent with maximum stability, therapeutic effectiveness and manufacturer efficiency.
- ✓ The liquids are limited to those do those do not have adverse effects on gelatin walls.
- ✓ Emulsion can not be filled because water will be released that will affect the shell.
- ✓ The PH of the liquid can be between2.5 – 7.5[8].

CAPSULE SHELL

- ➢ Gelatin
- ➢ Plasticizer
- ➢ Preservatives
- ➢ Colorant
- ➢ Opacifier
- ➢ Flavoring agents
- ➢ Sugar

It manufactured by four methods:

1. Plate process
2. Rotary die process
3. Reciprocating die
4. Accogel machine[7]

PLATE PROCESS :-

- Place the gelatin sheet over a die plate containing numerous die pocket.
- Application of vacuum to draw the sheet into the die pockets.
- Fill the pocket with liquid or paste.
- Placed another gelatin sheet over the filled pockets.
- Sandwich under a die press where the capsules are formed and cut out[7].

ROTARY DIE PROCESS :-

- The material to be encapsulated flows by gravity. the gelatin sheets are feed on rolls contain small orifice lined up with the die pocket of the die roll.
- Two plasticized gelatin ribbons are continuously and simultaneously fed with the liquid or paste fill between the rollers of the rotary die mechanism where the capsule are simultaneously filled, shaped, hermetically sealed and cut from the gelatin ribbon.
- The sealing of the capsule is achieved by mechanical pressure on the die rolls and the heating(37-40 C) of the ribbons by the wedge[7].

RECIPROCATING DIE PROCESS

The early success of rotary die process led others to develop continuous methods of soft gelatin capsules manufacture. Was announced in 1949 and was developed by the Nortan Company, Worchester, MA[7].

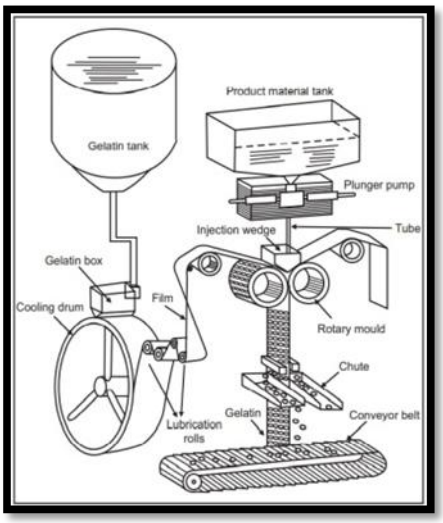

Fig.7: Rotary die Process.

FORMULATION OF ORAL LIQUIDS

Oral liquids are formulated as solutions, suspensions and emulsions depending on the nature of the active ingredient particularly solubility and stability. Liquid formulation needs various excipients including vehicle, solubilizer, stabilizer and viscosity builder, preservative and off course sweeteners, colour and flavour[10].

EXCIPIENTS FOR ORAL LIQUID FORMULATIONS:

Oral liquid formulation needs a meticulous blend of ingredients to perform various functions like wetting and solubilisation, stabilization and to impart suitable colour, taste and viscosity. The common excipients generally required for any liquid formulation are vehicles (base), viscosity builders, stabilizers, preservatives, colours and flavors[10].

WETTING AGENTS AND SURFACTANTS:

The use of a wetting agent allows removal of adsorbed air and easy penetration of the liquid vehicle into pores of the particle in a short period of time. For an aqueous vehicle, alcohol, glycerin, and PG are frequently used to facilitate the removal of adsorbed air from the surface of particles. Whereas for a non-aqueous liquid vehicle, mineral oil is commonly used as a wetting agent[10].

pH MODIFIERS AND BUFFERING AGENTS:

Control of the formulation pH, could prevent large changes during storage. Therefore, most formulations utilize a buffer to control potential changes in the solution pH. The amount of buffer capacity needed is generally between 0.01 and 0.1 M and a concentration between 0.05 and 0.5 M is usually sufficient[10].

SUSPENDING AGENTS AND VISCOSITY MODIFYING AGENTS :

Suspending agents impart viscosity, and thus retard particle sedimentation. Other factors considered in the selection of the appropriate agent include desired rheological property, suspending ability in the system, chemical compatibility with other excipients, pH stability, length of time to hydrate, batch-to-batch reproducibility and cost. Suspending agents can be classified into cellulose derivatives, clays, natural gums, and synthetic gums[10].

VEHICLES :

Vehicles, in pharmaceutical formulations, are the liquid bases that carry drugs and other excipients in dissolved or dispersed state. Pharmaceutical vehicles can be classified as under; Aqueous vehicles: Water, hydroalcoholic, polyhydric alcohols and buffers[10].

1. Water :

Water is intended for use in preparation of aqueous dosage forms except those intended for parenteral administration. Natural water contains large number of dissolved and suspended impurities. The dissolved impurities include inorganic impurities like salts of sodium, potassium, calcium, magnesium and iron as chlorides, sulfates and bicarbonates. Organic impurities present in purified water are either in soluble or insoluble state[10].

2. Alcohol (Ethyl Alcohol) :

Alcohol has been well recognized as a solvent and excipient in the formulation of oral pharmaceutical products**.** It is invariably used as hydro-alcoholic mixture that dissolves both water soluble and alcohol soluble drugs and excipients[10].

3. Glycerol:

Glycerol is called glycerin is a clear, colorless liquid with thick, syrupy consistency, oily to the touch, odorless, very sweet and slightly warm to taste. They are prepared by the decomposition of vegetable or animal fats or fixed oils and containing not less than 95% of absolute glycerin[10].

4. Propylene Glycol USP :

Propylene glycol has become widely used as a solvent, extractant and preservative in a variety of parenteral and non parenteral pharmaceutical formulations. PG is an important ingredient for a multitude of uses, including:

- Solvent for aromatics in the flavour-concentrate industry
- Wetting agent for natural gums
- Ingredient in the compounding of citrus and other emulsified flavours
- Solvent in elixirs and pharmaceutical preparations
- Solvent and coupling agent in the formulation lotion, shampoos, creams and other similar products[10]

PRESERVATIVES:

It prevent the growth of microorganisms during production and over storage time. In fact, it is desirable to develop a preservative-free formulation to avoid unwanted effects of these excipients. Preservatives must have following criteria: Effective against broad spectrum of microorganisms. Physically, chemically and microbiologically stable for lifetime of the product. Non toxic, non sensitizing, soluble, compatible and with acceptable taste and odour[10].

ANTIOXIDANTS :

The oxidation of an API in an oral liquid formulation is difficult to control due to low activation energies (2-12kcal/mol) for oxidation and photolysis compared to solvolysis, dehydration, and polymorphic transformations (10-56kcal/mol). Trace amounts of impurities, which are invariably present in the API or excipient catalyses the oxidation reaction[10].

FLAVOURING AGENTS :

Flavours used in formulation must be nontoxic, soluble (if for a clear product like syrup elixir) and stable and compatible with the preparation. Also sweetening agents that raise the blood sugar or increase caloric intake cannot be included in formulations for diabetics or patients or reducing diet respectively[10].

FORMULATION OF SEMISOLIDS

Semisolid pharmaceutical dosage form comprise a body of products, which when applied to skin or accessible mucous membranes tends to alleviate or treat a pathological condition or other protection against harmful environments. Ex. Ointments, Creams, lotion, etc[11].

INGREDIENTS ARE USED IN FORMULATION OF SEMISOLIDS

- Active pharmaceutical ingredients
- Bases
- Preservatives
- Humectants
- Anti oxidants
- Emulsifiers
- Gelling agents
- Buffers

BASES:

Ointments and suppository base do not marely acts as the carrier of the medicaments, but they also control the extent of absorption of medicaments incorporated with them[11]

IDEAL PROPERTIES OF BASES

- ✓ Compatible with skin pH and drug
- ✓ Inert, non irritating and non sensitizing
- ✓ Good solvent and/or emulsifying agents
- ✓ Adjective, protective, non greasy and easily removable
- ✓ Release medicaments easily at the sire of administration
- ✓ Pharmaceutically elegant and possess good stability[11]

CLASSIFICATION OF BASES

A. Hydrocarbon bases (oleaginous bases) (petroleum, paraffin, lanolin.)
B. Absorption bases (cold creams, anhydrous lanoline.)
C. Water removal bases (oil in water)
D. Water soluble bases (polyethylene glycol ointments.) [12]

PRESERVATIVES:

Commonly used preservative include[11]:

- ❖ Methyl hydroxyl benzoate
- ❖ Propyl hydroxyl benzoate
- ❖ Chorocresol
- ❖ Benzoic acid
- ❖ Phenyl mercuric nitrate

ANTIOXIDANTS :

Oxygen is highly reactive atom that is capable of becoming a potentially damaging molecules commonly called “free radicals”. Free radicals are capable of attacking the healthy cells of the body, causing them to lose their structure and functions. To prevent this anti oxidants are added. Examples : Butylated hydroxyl anisole, butylated hydroxyl toluene[11].

HUMECTANTS :

A humectants is a hygroscopic substance. It is often a molecule with several hydrophilic groups, most often hydroxyl group[11].

Humectants are used to :

- ✓ Increase the solubility of active ingredients
- ✓ To elevate its skin preparation
- ✓ Elevate the hydration of the skin.

1. **GELLING AGENTS :** Gelling agents form a gel dissolves in a liquid phase as a colloidal mixture that forms a weakly cohesive internal structure. Ex: Tragakanth, Sodium alginate, pectin, gelatin and cellulose derivatives[11].
2. **EMULSIFIERS:** An emulsifier is a substance that stabilizes an emulsion by increasing its kinetic stability. It must reduce surface tension for proper emulsification. It prevents coalescence. Ability to increase the viscosity at low concentration[12].

EMULSIFYING AGENTS

- ✓ Sodium lauryl sulfate : O/W emulsion
- ✓ Sodium stearate and calcium stearate
- ✓ Glycerol monostearate : weak W/O emulsifying agents and used as stabilization agents and emollient in the O/W emulsion[12].

BUFFERS:

- Compatibility with skin
- Drug stability
- Drug solubility
- Influence on ionization of drug

Example : Sodium acetate, Sodium citrate, Potassium meta phosphate etc[11].

METHOD OF PREPARATION OF OINTMENT:

Preparation of ointment mainly depend on nature of ingredients. Ointments are mainly prepared by two general method[13]:

a) Incorporation

b) Fusion

INCORPORATION:

In this finely subdivided insoluble medicaments are evenly distributed by grinding with a small amount of the base followed by dilution with gradually increasing amounts of the base[13]

FUSION :

In this method the ingredients are melted together in descending order of their melting points and stirred to ensure homogeneity[13].

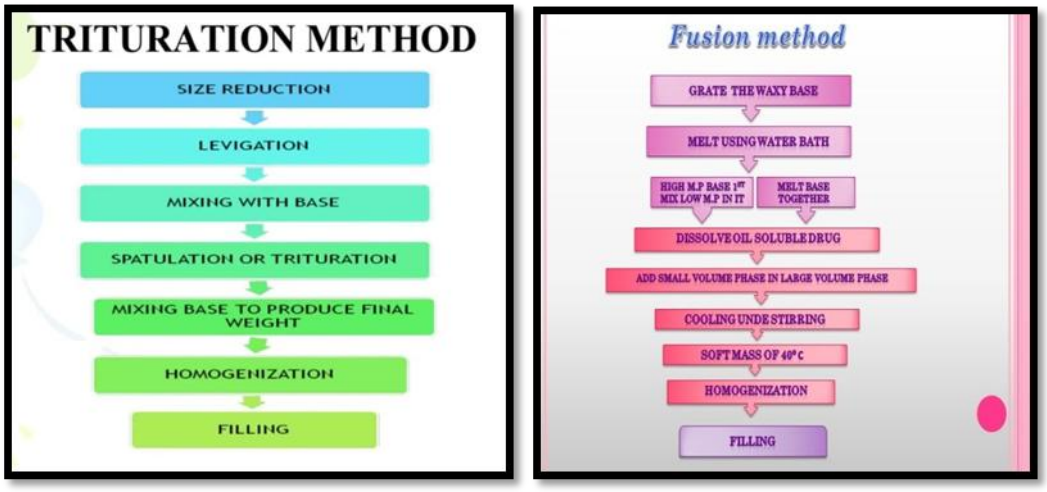

Fig.8: Trituration and Fusion method.

FORMULATION OF PARENTERALS

The aim of formulation development of parenterals product is to produce a safe effective and stable dosage form[15].

It includes :

1. Vehicles
2. Preservatives
3. Buffers
4. Tonicity adjusting agents
5. Surfactants
6. Chelating agents

VEHICLES :

Vehicle used for parenterals must be –

- Sterile (free from the presence of microbial contamination)
- Pyrogen free
- Free from any particulate matter
- Should be isotonic with blood plasma[15]

The vehicle for parenteral can be classified as aqueous vehicles and non-aqueous vehicles.

NON AQUEOUS VEHICLES:

Corn oil, cotton seed oil, peanut oil, and sesame oil are commonly used non aqueous vehicles Fixed oils are used as vehicles for certain hormone (e.g. progesterone, testosterone, deoxycorticosteron) and vitamin (e.g., Vitamin K, Vitamin E) preparations[15].

PRESERVATIVES:

- As a bacteriostatic to inhibit any microbes accidentally introduced while doses are being withdrawn.
- A must in multiple dose containers unless the drug itself is bacteriostatic.
- As adjuncts in aseptic filling.
- As adjuncts in intermittent heat sterilizations.
- Not permitted in single doses > 15 mL
- Not for routes reaching cerebrospinal fluid or intr-ocular.
- Not for oil-based parenteral products (due to the low water activity of this medium) [16].

BUFFERS:

- Added to maintain pH
- Results in stability
- Effective range, concentration, chemical effect[16]

TONICITY :-

Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, dextrose and boric acid etc[18].

SURFACTANTS:

- Surface-active agents enhance drug solubility to the required concentration to achieve solution clarity (>CMC).
- Surface-active agents may be incorporated into aqueous or oil-based vehicles for this purpose Examples:
- Nonionic SAA (e.g. tweens, Poloxamers)
- Lecithin from soybean and egg yolk[16].

CHELATING AGENTS:

Sequester heavy metals to prevent the catalysis of oxidation reaction. Example: Ethylene diamine tetra acetic acid derivatives and salts Citric acid tartaric acid**[18]**.

NOVEL DRUG DELIVERY SYSTEM (NDDS):

CONTROL DRUG DELIVERY SYSTEM:-

SELECTION OF DRUG CANDIDATES

- Short elimination half-life
- Long elimination half-life
- Narrow therapeutic index
- Poor absorption
- Active absorption
- Low or slow absorption
- Extensive first pass effect[19]

FACTORS INFLUENCING THE DESIGN AND ACT OF CONTROLLED RELEASE PRODUCTS[20]

(1) Physiological properties

(i) Aqueous Solubility's
(ii) Partition coefficient (P-value)
(iii) Drug pKa
(iv) Drug stability
(v) Molecular size & molecular weight
(vi) Protein binding

(2) Biological factors

(i) Absorption
(ii) Biological half-life
(iii) Dose size
(iv) Therapeutic window
(v) Absorption window
(vi) Patient physiology

Approaches to design controlled release formulations

1. Dissolution controlled release
   - Encapsulation Dissolution control
   - Seed or granule coated
   - Micro encapsulation
   - Matrix Dissolution control

2. Diffusion controlled release
   - Reservoir type devices
   - Matrix type devices
3. Diffusion and Dissolution controlled systems
4. Ion exchange resins
5. Osmotically controlled release[19]

MECHANISTIC ASPECTS FOR ORAL CONTROLLED RELEASE DRUG DELIVERY FORMULATION

Dissolution controlled release

Dissolution is defined as solid substance solubilized in a given solvent. It is a rate determining step when liquid is diffusing from solid. Several theories explain dissolution:

Diffusion layer theory, Surface renewal theory, Limited solvation theory.

Noyes Whitney Equation

$$dc/dt = kD.A\ (Cs - C)$$

$$dc/dt = D/h\ A.\ (Cs - C)$$

where, dc/dt = Dissolution rate, k = Dissolution rate constant (1st order), D = Diffusion coefficient / diffusivity, Cs = Saturation/maximum drug solubility, C =Conc. Of drug in bulk solution, Cs-C=concentration gradient, h =Thickness of diffusion layer[21,22].

Two common formulation system rely on dissolution to determine release rate of drugs are:

(i)Encapsulated dissolution system (ii) Matrix dissolution system

Encapsulated dissolution system

This is also known as Coating dissolution controlled system. Dissolution rate of coat depends upon stability & thickness of coating. It masks color, odor, taste and minimize GI irritation. Controlled release products by decreasing the dissolution rate of drugs which are highly water soluble can be formulated by preparing appropriate salt or derivatives, by coating the drug with a slowly dissolving material, or by incorporating the drug into a slowly dissolving carrier. Examples: Ornade spansules, Chlortrimeto Repetabs[21,23].

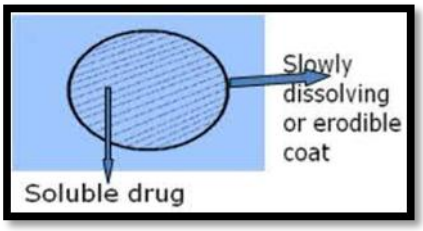

Fig.9: Encapsulated dissolution system.

Matrix dissolution system

It is also known as monolithic dissolution controlled system. In this dissolution is controlled by: Altering porosity of tablet, decreasing its wet ability, dissolving at slower rate. It follows first order drug release. The drug release can be determined by dissolution rate of polymer. Examples: Demeaned extencaps, Dimetapp extentabs[23,24].

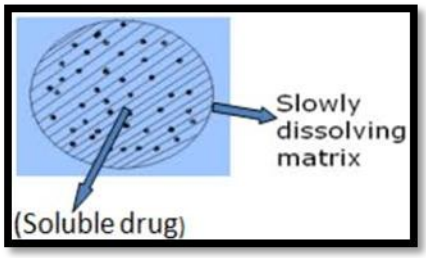

Fig.10: Matrix dissolution system.

Diffusion controlled system

It is a major process for absorption in which no energy required. In this drug molecules diffuse from a region of higher concentration to lower concentration until equilibrium is attained and it is directly proportional to the concentration gradient across the membrane. In this system release rate is determined by its diffusion through a water-insoluble polymer[19].

There are two types of diffusion devices:

- Reservoir diffusion system
- Matrix diffusion system

Reservoir diffusion system

It is also called as laminated matrix device. It is a hollow system containing an inner core surrounded by water insoluble membrane and polymer can be applied by coating or micro encapsulation. The Rate controlling mechanism is that drug will partition into membrane and exchange with the fluid surrounding the drug by diffusion. Commonly used polymers are HPC, ethyl cellulose & polyvinyl acetate. Examples: Nico-400, Nitro-Bid[25,26].

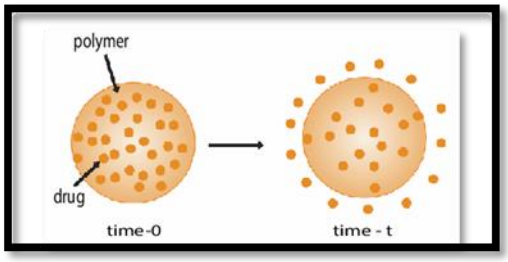

Fig.11: Reservoir diffusion system.

ii) Rate controlling steps: Polymeric content in coating, thickness of coating, hardness of microcapsule[19].

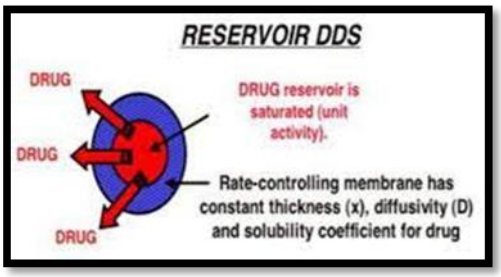

Fig.12: Rate controlling steps.

Matrix dissolution system

(a) Rigid Matrix Diffusion: Materials used are insoluble plastics such as PVP & fatty acids.

(b) Swellable Matrix Diffusion: it is also called as Glassy hydro gels and popular for sustaining the release of highly water soluble drugs. Materials used are hydrophilic gums. Examples:

Natural- Guar gum, Tragacanth. Semi synthetic -HPMC, CMC, Xanthum gum. Synthetic -Polyacrilamides. Examples: Glucotrol XL, Procardia XL

The Higuchi Equation describing the drug release from this system :

$$Q = [D\text{Ɛ}/T\ (2A\text{-Ɛ}\ Cs.t)]\ ½$$

Where Q=amt of drug release per unit surface area at time t, D=diffusion coefficient of drug in the release medium, Ɛ=porosity of the matrix, Cs=solubility of drug in release medium, T=tortuosity of matrix, A=concentration of drug present in matrix per unit volume[24].

Rate controlling step: Diffusion of dissolved drug in matrix.

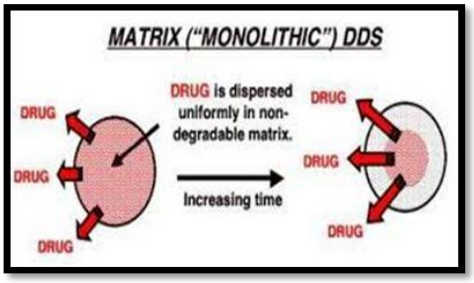

Fig.13: Matrix dissolution system.

Dissolution & Diffusion Controlled Release system

In this drug is encased in a partially soluble membrane and pores are created due to dissolution of parts of membrane. It permits entry of aqueous medium into core & drug is dissolved or diffused out of the system. Ex- Ethyl cellulose & PVP mixture dissolves in water & creates pores of insoluble ethyl cellulose[27].

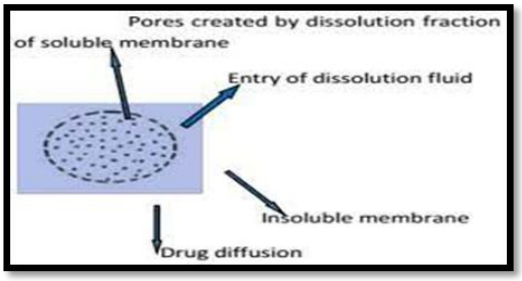

Fig.14: Dissolution & Diffusion Controlled Release system.

Ion exchange resins controlled release system

Ion exchange resins are cross-linked water insoluble polymers carrying ionizable functional groups. These resins are used for taste masking and controlled release system. The formulations are developed by embedding the drug molecules in the ion-exchange resin matrix and this core is then coated with a semi permeable coating material such as Ethyl Cellulose. This system reduced the degradation of drug in GIT. The most widely used and safe ion-exchange resin is divinylbenzene sulphonate. In tablet formulations ion-exchange resins have been used as disintegrant[28,29,30].

GASTRO RETENTIVE DRUG DELIVERY SYSTEM

GRDDS can be defined as a system which retains in the stomach for a sufficient period of time and releasing active moiety in a controlled manner, and finally metabolized in the body. Over the last two decades, numbers of GRDDS have been designed to prolong GRT. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery[31].

Gastroretentive drug delivery is prepared with the intention to retain drug in the gastric region for prolonged time and release incorporated drug candidates and thereby enable sustained and prolonged input of the drug to the upper part of the GIT thus leading its optimal bioavailability. Gastroretentive dosage forms greatly improved the pharmacotherapy of the GIT through local drug release, leading to high drug concentrations at the gastric mucosa making it possible to treat various diseases of GI[32].

FACTORS AFFECTING GASTRIC RETENTION[33]

1. Density
2. Size
3. Shape of the dosage form
4. Single or Multiple unit formulation
5. Fed/Unfed state
6. Nature of meal
7. Caloric content
8. Age
9. Frequency of feed
10. Gender
11. Posture
12. Concomitant drug administration
13. Disease state

CRITERIA FOR SELECTION OF DRUG CANDIDATE FOR GRDDS

1. Drugs those are locally active in the stomach (e.g. misroprostol, antacids)
2. Drugs those are unstable in the intestinal or colonic environment.
3. Drugs that have narrow absorption window in GIT (e.g. L-DOPA, paminobenzoic acid, furosemide, riboflavin).
4. Drugs exhibit low solubility at high Ph values (e.g. diazepam, chlordiazepoxide, verapamil).
5. Drugs that disturb normal colonic microbe such as tetracycline, clarithromycin, amoxicillin[34]

Approaches To Achieve Gastric Retention

1. Low density approach:

A. Effervescent system:

a. Gas generating system: Single layer floating tablet, Bilayer floating tablet, Multi- particulate system.
b. Volatile liquid/vaccum containing system: Intragastric floating gastrointestinal drug delivery, Inflatable gastrointestinal drug delivery, Intragastric osmotically controlled drug delivery.

B. Non effervescent system:

a. Colloidal gel barrier systems
b. Microporous Compartment System
c. Alginate beads,
d. Hollow microspheres.

2. High density approach.
3. Mucoadhesive approach
4. Expansion by swelling approach and
5. Raft forming system[35]

Low-Density Systems

To avoid premature evacuation of drug through the pyloric sphincter low density system (<1 g/cm3) with immediate buoyancy have been developed. They are made of lowdensity materials, entraping oil or air. Most are multiple unit systems, and are also called "microballoons" because of low-density core[35].

Floating Approach -Floating Drug Delivery Systems

This is mostly used approach of Gastroretntive drug delivery system .Floating drug delivery systems also known as hydrodynamically balanced systems. Have a bulk density lower than gastric fluids and thus remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the stomach. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the gastric retention time and a better control of fluctuations in the plasma drug concentration in some cases.These dosage forms are also known as gas powered system, which can float in the contents of the stomach and release the drug in a controlled manner for prolonged periods of time[35].

Based on formulation FDDS are classified in to following Types

Non-effervescent FDDS

Floating non effervescent matrix tablets were prepared by direct compression method employing various polymers like polypropylene foam powder (Accurel® MP 1000), Karaya gum and Chitosan ,gelicure is used for this system .Floating dosage forms involves intimate mixing of drug with a gelforming hydrocolloid, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than unity within the outer gelatinous barrier. The air trapped by the swollen polymer confers buoyancy to these dosage forms. In addition, the gel structure acts as a reservoir for sustained drug release since the drug is slowly released by a controlled diffusion through the gelatinous barrier[35].

Effervescent FDDS

Non only synthetic polymers but also natural polymers are used for this sysyem.These are matrix type of systems prepared with the help of swellable polymers such as Methylcellulose and chitosan and various effervescent compounds, e.g. sodium bicarbonate, tartaric acid and citric acid. They are formulated in such a way that when in contact with the gastric contents, CO2 is liberated and gets entrapped in swollen hydrocolloids, which provides buoyancy to the dosage forms. These buoyant delivery systems utilize matrices prepared with swellable polymers such as Methocel or polysaccharides, e.g., chitosan, and effervescent components, e.g., sodium bicarbonate and citric or tartaric acid or matrices containing chambers of liquid that gasify at body temperature. The matrices are fabricated so that upon arrival in the stomach, carbon dioxide is liberated by the acidity of the gastric contents and is entrapped in the gellified hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy. A decrease in specific gravity causes the dosage form to float on the chime[35].

Steps involved in floating of dosage form

1) Penetration of water
2) Generation of CO2 and floating
3) Dissolution of drug

High-Density Systems

These systems, which have a density of ~3 g/cm3, are retained in the rugae of the stomach and are capable of withstanding its peristaltic movements. Above a threshold density of 2.4–2.8 g/cm3, such systems can be retained in the lower part of the stomach[35].

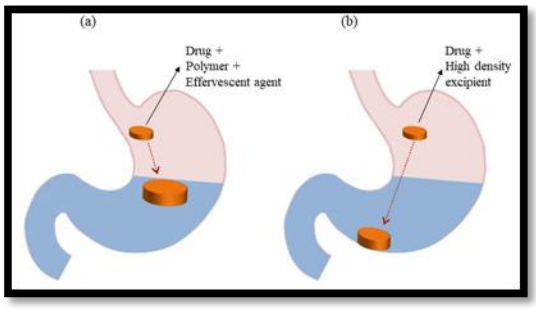

Fig.15 : GRDDS based on (a) at low density (b) at high density.

Bio/mucoadhesive system

In this system drugs bind to the gastric epithelial cell surface, or mucin, and extend the GRT by increasing the intimacy and duration of contact between the dosage form and the biological membrane. The concept is based on the self protecting mechanism of the GIT. The mucus not only protect the surface mucosal cells from acid and peptidases but also acts as a lubricant for the passage of solids and as a barrier to antigens, bacteria, and viruses. A bio/ mucoadhesive substance is a natural or synthetic polymer capable of adhering to a biological membrane or the mucus lining of the GIT. The epithelial adhesive properties of mucin are well known and have been applied to the development of GRDDS through the use of bio/mucoadhesive polymers. The adherence of the delivery system to the gastric wall increases residence time at a particular site, thereby improving bioavailability[35].

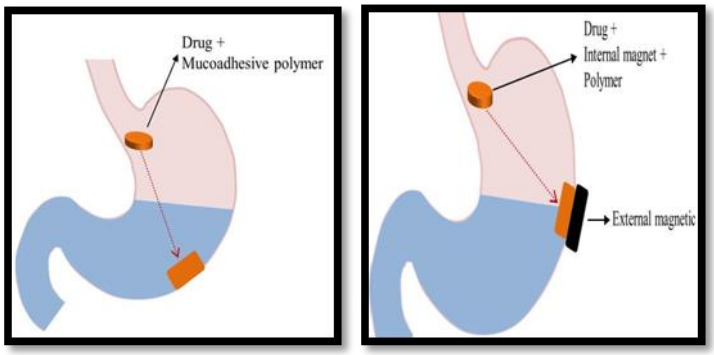

Fig.16: GRDDS based on mucoadhesion and GRDDS based on magnetic system.

There are various types of mucoadhesion like:

Hydration-Mediated Adhesion

This achieved by using hydrophilic polymers which imbibe large amount of water and become sticky, thereby acquiring mucoadhesive properties. The prolonged gastro retention of the bio/mucoadhesive drug delivery system is further controlled by the dissolution rate of the polymer[35].

Bonding-Mediated Adhesion

The adhesion of polymers to a mucus or epithelial cell surface involves various bonding mechanisms, including physical mechanical bonding and chemical bonding. Physical mechanical bonds can result from the insertion of the adhesive material into the crevices or folds of the mucosa. Chemical bond may be either covalent (primary) or ionic (secondary) in nature[35].

Receptor-Mediated Adhesion

Polymers can bind to specific receptor sites on the surface of cells, thereby enhancing the gastric retention of dosage forms. Certain plant lectins such as tomato lectins interact specifically with the sugar groups present in mucus or on the glycocalyx. Polymers used in Gastroretentive
mucoadhesive drug delivery system[35].

Synthetic polymers

(a) Various gardes Poly ethylene oxide like WSR 301, 301, N10, Coagulants.
(b) Cellulose derivatives (methylcellulose, ethylcellulose, +ydroxy-ethylcellulose, Hydroxyl propyl cellulose, hydroxy propyl methylcellulose, sodium carboxy methylcellulose.
(c) Poly (acrylic acid) polymers (carbomers, polycarbophil).
(d) Poly (hydroxyl ethyl methyl acrylate).
(e) Poly (vinyl pyrrolidone).
(f) Poly (vinyl alcohol).

Natural polymers

(a) Tara gum
(b) Sodium alginate
(c) Karaya gum
(d) Guar gum
(e) Xanthan gum
(f) Locust bean gum

Swelling system

After taking these swelling system it swell to a size that prevents their passage through the pylorus so that dosage form is retained in the stomach for a long period of time. These systems are sometimes referred to as plug type systems because they tend to remain lodged at the pyloric sphincter. These polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selecting a polymer with the proper molecular weight and swelling properties. Upon coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive swelling of these polymers is a result of the presence of physical–chemical cross links in the hydrophilic polymer network[35].

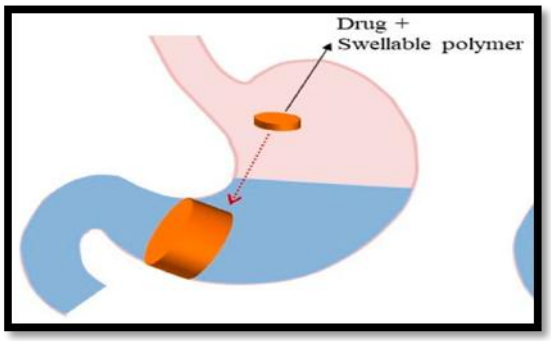

Fig.17: GRDDS based on polymer swelling.

Raft-forming System

Raft forming system is not only helpful for sustained drug delivery but also convenient for pediatric and geriatric patients. This system is helpful as an alternative of oral solid dosage form with the advantages of liquid dosage form. Sustained and prolonged release of the drug, good stability and bioavailability characteristics make the raft forming system very suitable candidate for gastric retention of the drug. Thus the raft forming system promises to be the potential approach for gastric retention drug delivery system In this gel forming solution (e.g., Sodium alginate solution containing carbonates or bicarbonates) swells and forms a viscous cohesive gel containing entrapped CO2 bubbles on contact with gastric fluid. Formulations also typically contain antacids such as aluminium hydroxide or calcium carbonate to reduce gastric acidity. Nowadays Raft Forming Systems have received much attention for the delivery of antacids and drug delivery for gastrointestinal infections and disorders[35].

POLYMERS AND OTHER INGREDIENTS USED IN THE FORMULATIONS OF GASTRORETENTIVE DOSAGE FORMS[35]

- Hydrocolloids (20%-75%)
- Inert fatty materials (5%-75%)
- Effervescent agents
- Release rate accelerants (5%-60%)
- Release rate retardants (5%-60%)
- Low density material
- Buoyancy increasing agents (up to 80%)

NOSE BRAIN DRUG DELIVERY SYSTEM

Nose to brain drug delivery system in which drug transport through nasal route to CNS(central nervous system). Via olfactory nerve pathway and trigeminal nerve pathway by passing through Blood Brain Barrier (BBB) and Blood Cerebrospinal fluid (BCB) barrier restrict the transport of drugs from systemic circulations into the central nervous system (CNS). The BBB serves to protect the brain and spinal cord from a variety of pathogens and toxicants, it also present a significant barriers to many of the xenobiotics in the treatment of CNS disorders[36].

FACTORS AFFECTING TO NASAL DRUG ABSORPTION

Crucial factors for nasal formulations[37]

1. Lipophillicity
2. Partition coefficient and pKa
3. Chemical form
4. Molecular weight
5. Particle size
6. Solubility and Dissolution rate

FACTORS RELATED TO FORMULATIONS

Physicochemical properties of formulation

1. **pH and mucosal irritation**: To avoid nasal irritation, the pH of the nasal formulation should be adjusted to 4.5–6.5. Avoiding irritation results in obtaining efficient drug permeation and prevents the growth of bacteria. Nasal secretions contain lysozyme, which, at acidic pH, destroys certain bacteria[38].
2. **Osmolarity**: Isotonic solutions are administered for shrinkage of the nasal epithelial mucosa, because of the effect of osmolarity on the absorption[39].
3. **Viscosity**: A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa, thereby increasing permeation time[40].
4. **Buffer capacity**: Nasal formulations are administered in small volumes ranging from 25 to 200 mL[41].
5. **Drug concentration, dose, & dose volume**: These are three interrelated parameters that impact the performance of the nasal delivery.
   - Therapeutic dose: upper limit 25 mg/dose
   - Higher the drug concentration, higher the permeation
   - Dose volume: 0.05–0.15 ml/dose[14].
6. **Gelling agents:** Increasing the viscosity may provide a means of prolonging the effect of nasal formulation[37].
7. **Solubilizers:** Conventional solvents or co solvents such as glycol small quantities of alcohol, transcutol (diethylene glycol monoethyl ether),medium chain glycerides and labrasol (saturated polyglycolyzed C8-C10 glyceride)can be used to enhance the solubility of drug[37].

NASAL FORMULATIONS:

The deposition and deposition area are mainly a function of the delivery system and delivery device. Different dosage forms and their application to deliver the drugs to the central nervous system following intransal drug delivery are discuss in this section[37].

Nasal Sprays:

Both solution and suspension solution can be formulated into nasal sprays. Due to the availability of metered dose pump and actuators, a nasal spray can deliver an exact dose anywhere from 25-200 µL. The particle size and morphology (for suspensions) of drug and viscosity of a formulation determines the choice of pump and actuator assembly. Solution and suspension sprays are preferred over powder sprays because powder results in mucosal irritations[37].

EXCIPIENTS USED IN NASAL FORMULATIONS[17]

- Buffers
- Solubilizers
- Preservatives
- Antioxidants
- Humectants

Surfactants

Nasal emulsions, Microencapsulation and Nanoparticles

NASAL GELS

Nasal gels are thickened solution and suspensions, of high viscosity. The advantages of the nasal gel include the reduction of post nasal dripping due to its high viscosity, reduction of the taste impact due to reduced swallowing, reduction of anterior leakage of the formulation, reduction of irritation by using soothing /emollient excipients, and target delivery to the mucosa for the better absorption. Vitamin B12 and apomorphine gel have been successfully employed to achieve desired therapeutic concentrations following nasal administration[37].

SOLID DOSAGE FORMS:

Solid dosage forms are also becoming popular for intranasal drug delivery, although these formulations are more suitable for pulmonary drug delivery and similar applications since it cover the vasculature within the epithelium of the nasal mucosa[37].

Nasal powders:

Powder dosage forms may be developed if solution and suspension dosage form cannot be developed, mainly due to the lack of drug stability. The advantages of nasal powder dosage form are the absence of preservative and superior stability of the drug in the formulation. However the suitability of the powder formulation is dependant on the solubility, particle size aerodynamic properties and nasal irritancy of the active drug and or excipients. An additional advantages of these system is local application of drug, but nasal mucosa irritancy and metered dose delivery are some of the challenges for formulation scientist and device manufacturer who are interested in powder dosage form[37].

CONCLUSION:

In formulation of both conventional and novel drug delivery system the excipints such as coloring agents, flavoring agents, pH modifiers, glidants, sweatning agents, buffering agents etc are used. In novel drug delivery system the selection criteria of exipients for formulation is important factor. For manufacturing of different dosage form different techniques and machines are used. The main aim of preparing GRDDS is to minimize the problem associated with existing oral sustained release dosage form and to develop patient benefited drug delivery. The new research should be focused towards better techniques in formulation in challanging time.

CONFLICT OF INTEREST:

None

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