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A REPORT ON FORMULATION AND DEVELOPMENT OF DIFFERENT DOSAGE FORMS

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Abstract:

The new developed pharmaceutical formulation is related to the fact that it is able to deliverthe active substance to the target organ at therapeutically relevant levels, with negligible discomfort and side effects, increasing the patient compliance to the therapeutics. Regardingthis respect, the route of administration is of major relevance. Various methods of Novel Drug Delivery systems are used for the better patient compliance. During the recent decades several studies have suggested that novel drug delivery systems based on lipid nanoparticles have the potential of increasing cutaneous drug delivery of both hydrophilic and lipophilic drugs. Despite the substantial potential of transdermal and dermal drug delivery, only relatively few drugs are yet commercially available as topical formulations. The limitation lies in the barrier function of the skin function, which is considered one of the most impermeable epithelia of the human body to exogenous substances. The current review gathered information on the, formulation, advantages, and disadvantages of Tablet in Tabletor compression coating. The report also elaborates on the importance of Tablets in Tablet techniques in the development of a modified release system. And information on capsule types, formulation, advantages and disadvantages. And various instruments required in the laboratory practices.

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INTRODUCTION:

1. Tablets

Tablets is a solid unit dosage form containing one or more medicament prepared by compression of uniform particles with or without excipients. Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drug or a mixture of drugs, with or without diluents. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.[1]

1.1 Advantages of Tablet:

- Large scale production at low cost.
- Easiest and cheapest to pack and ship.
- More stable
- Lightest and most compact formulation aspect.

1.2 Disadvantages of Tablet:

- Problem with compression to crystalline drug.
- Hygroscopic drugs are not suitable for compressed tablets.
- Drugs with low or poor water solubility, slow dissolution, may be difficult to formulate.
- Cost of production may be increase.

1.3 Excipients used in tablet formulation:

- Diluents– Fillers used to make required bulk of tablet when drug dosage itself is inadequateproduce bulk. Dose of drug is sufficiently high that no filter is required.
- Granulating Agents - These are used to convert the fine powder into granules. It provides proper moisture to convert fine powder into damp mass.
- Binding Agents- Material added in wet or dry form to form granules or cohesive compact for directly compressed tablet.
- Disintegrating Agents- Facilitate breaking up of tablet in contact with water in GIT. Function by drawing water into the tablet, swelling and causing the tablet to burst apart. Lubricants - Reduces friction between tablet material and wall of die during tablet ejection.
- Glidant- Reduce interparticle friction and may improve rate of flow of tablet granulation.
- Colours, Flavours and Sweetening Agents- FDA approved colours and C dyes are used as colourants. The colours are used to improve the elegance of the tablet. Flavours are included in lozenges, effervescent and chewable tablets. Sweetening agents are used to improve the taste of tablets. These are used in lozenges and chewable tablets. Commonly used sweetening agents are Sucrose, Lactose and Mannitol.[1]

1.4 Method of Granulation:

- Wet Granulation: Drug is added with diluents. Then binder solution is added and blended till wet mass is formed. Wet Screening of material is done after that drying can be done by Tray Dryer, Fluid bed Dryer. Particle size is reduced by Dry Screening.
  Ex. Acetaminophen tablet.
- Dry Granulation: It is done when drug is sensitive to heat and moisture. Milling → Mixing → Screening → Blending →Slugging → Screening → GranulationEx. Aspirin tablet
- Direction Compression: The powdered material is directly compressed into tablet without physical nature of former being modified. Weighing → Mixing → Screening → Compression
  Ex. Ascorbic acid tablet.[2]

2. Capsules

Capsules are solid dosage form in which one or more medicinal and inert ingredient are enclosed in gelatin shell. They mask the taste and odour of unpleasant drug. Capsules are not use for administering extremely soluble material because of sudden release of such materialin stomach result in irritation.[3]

2.1 Advantages of Capsules:

- Better compatibility
- Least excipient required
- Attractive in appearance
- Easy to handle and carry

2.2 Disadvantages of Capsules:

- Expensive
- Highly water-soluble materials can't be given.
- Highly deliquescent and effervescent material can't be given.

2.3 Hard Gelatin Capsule:

A type of capsule that usually use to contains medicine in the form of dry powder or very small pellets. It consists of two pieces – a cap and a body.
Composition of shell:

- Capsule shell - Made of gelatin with other excipients like dies and plasticizer.
- Dyes - Color approved by D & C act. Most widely used dyes are erythrosine, indigocarmine.
- Opacifier - TiO2 use to make capsule opaque.
- Plasticizers - Sorbitol, glycerin.
- Preservatives- Methyl paraben and propyl paraben (4:1)

2.4 Soft Gelatin Capsule:

They are hermetically sealed as a single piece capsule. It is round, oblong or tube like in shape. The ratio of plasticizer to gelatin is 0.8:1. The disintegration time of soft gelatin capsule is 60 min. The moisture content is 6-9% w/w. The sealing and filling is done in combined operation.

Composition of Hard Gelatin Shell:

1. Gelatin
2. Preservative
3. Die and Pigment
4. Opacifying agent
5. Polar / Non polar Solvent
6. Sugar
7. Flavouring agent
8. Plasticizers

2.5 Capsule Shell Manufacturing:

Thickness depends on speed and time of dipping.

- Centrifugal casting method
- Dip pin method

Dipping → Rotating → Drying → Stripping → Trimming → Joining → Polishing [3]

3. Targeted Drug Delivery System

In targeted drug delivery system, the pharmacologically active medicament is selectively targeted or delivered to its action or absorption site. Targeting drugs to special cells and tissues of body without their involvement in systemic circulation is a highly remarkable and novel idea. It should have a predictable and controllable rate of drug release. Minimal drug leakage should occur during transit.

3.1 Liposomes:

Liposome are simple microscopic vesicles in which an aqueous volume is enclosed by a membrane composed of lipid molecule. It is a composite structure made of phospholipid and may contains small amount of other molecules. Liposome can be filled with drugs and used to deliver drugs for cancer and other diseases.[4]

3.1.1 Structure of liposome:

- Phospholipid: It is a major component of biological membrane. The most common natural phospholipid is phosphatidylcholine or lecithin, which is an amphiphatic molecule.
- Cholesterol: It insert into membrane with its hydroxyl group oriented towards aqueoussurface and aliphatic chain aligned parallel to acyl chain in centre of bilayer.

3.1.2 Types of Liposomes:

- Multilamellar vesicles: These liposomes have more than one Lamella, and their size variesbetween 100 to 1000nm.
- Small Unilamellar vesicles: These liposomes have a single lamella, and are smaller than 0.1µ in size. The size variation is small when liposome approach the minimum size.
- Large lamellar vesicles: they have a single lamella and their size ranges from 0.1µm to1000nm.

3.1.3 Method of Preparation:

- Mechanical dispersion method: Lipid is solubilized in an organic solvent, remove organic solvent under vacuum, film deposition, solid lipid mixture is hydrated by using aqueous buffer, lipids spontaneously swell and hydrate and liposome is formed.
- Detergent removal method: Phospholipid brought into intimate contact with aqueous phase, by addition optimized concentration of detergent, formation of micelles.
- Solvent dispersion method: Lipid is dissolved in an organic solvent, and then brought in contact with an aqueous phase that contains the material to be entrapped under rapid dilution and rapid evaporation of organic solvent.

3.1.4 Applications of Liposomes:

- They are used in antimicrobial, antifungal and antiviral therapy.
- They are used in immunology.
- They are used as radiopharmaceutical and radio-diagnostic carrier.
- They are used in cosmetic dermatology.[4],[5]

4.2 Nanoparticles:

Nanoparticles are 10-1000nm (1µm) sized, solid colloidal particles that comprise of macromolecular materials in which the active ingredient (drug or biologically active material)is dissolved, entrapped, encapsulated, adsorbed, and/or attached.

4.2.1 Types of Nanoparticles:

- Nanosphere - They have a matrix-type structure in which the drug is dispersed.
- Nano capsule – They have a membrane -wall structure in which the drug is contained within an oily core.

4.2.2 Method of preparation:

- Emulsification diffusion evaporation
- Salting out
- Solvent emulsification
- Spontaneous solvent emulsification diffusion
- Solvent displacement

4.2.3 Advantages of Nanoparticle:

- Nanoparticles have dimensions below the critical wavelength of light renders them transparent, a property which makes them very useful for applications in packaging's,cosmetics and coatings.
- Particle size and surface characteristics of nanoparticles can be easily manipulated to achieve both active and passive targeting.
- Release of the drug can be controlled or sustained so as to achieve increase in therapeutic efficacy of drug and reduction in side-effects.
- They are capable of being stored for a period of up to 1 year and hence have longer shelfstability.[6]

4.2.4 Disadvantages of Nanoparticle:

- They may alter physical properties and cause particle-particle aggregation, thus making physical handling of nanoparticles difficult in liquid and dry forms due to smaller size andlarger surface area.
- It has been observed that nanoparticles are very reactive in the cellular environment because their smaller particle size leads to greater surface area.[6]

5. Nasal Route of Drug Administration:

Introduction:

Administration of drug through nasal route is called as nasal route of drug administration. Nasal mucosa is considered a potential administration route to achieve faster and higher level of drug absorption. Drugs that are potent (active in low doses) and show no minimal oral bioavailability (proteins and peptides) are successfully delivered by the nasal route.

5.1.1 Advantages of Nasal Route of Drug Administration:

- Drug absorption through this route is rapid due to highly vascularized mucosa.
- Its onset of action is rapid.
- The characteristics of controlled release and particle degradation can be easly modulated by selecting the matrix constituents.
- Small drug molecules exhibit good nasal bioavailability.

5.1.2 Disadvantages of Nasal Route of Drug Administration:

- There is a chance of nasal irritation, hence it is inconvenient as compared to the oral route.
- Drugs with high molecular weight (mass cut off ~1 kDa) cannot be delivered through thisroute.
- The absorption surface is smaller than that of the GIT.
- Systemic toxicity occurs due to the absorption enhancers added in the formulation.

5.1.3 Mechanism of drug absorption through nose:

When a drug absorbs from the nasal cavity, it first passes through the mucus. This passage is difficult for large or charged particles; however, the small or uncharged particles can easily cross the mucus layer.

- The first mechanism involves slow and passive aqueous route of transport or the paracellular route. Drugs with molecular weight >1000 Daltons show poor bioavailability.
- The second mechanism involves transcellular process, i.e., transport through a lipoidal route. Drugs also cross the cell membranes via active transport route through carrier mediated transport through the opening of tight junction

5.1.4 Barriers to Nasal absorption:

- Low Bioavailability: Absorption of lipophilic drugs from the nasal cavity is much morethan that of polar drugs. Pharmacokinetic profiles of lipophilic drug are similar to those obtained after an intravenous injection and bioavailability approaching 100%.
- Low Membrane Transport: This significant factor involves rapid clearance of the administered formulations (drugs not easily absorbed across the nasal membrane) from the nasal cavity due to mucociliary clearance mechanism.
- Enzymatic Degradation: possibility of enzymatic degradation of the molecule either within the nasal cavity lumen or while passing through the epithelial barrier. These sites contain exopeptidases that can cleave peptides at their N – and C-termini and endopeptidases (such asserine and cysteine) that can attack internal peptide bonds.

5.1.5 Strategies to improve nasal absorption:

- Nasal enzyme inhibitors, e.g., bestatin, amastatin, boroleucine, fusidic acids, and bile salts.
- Nasal permeation enhancers, e.g., cyclodextrins, surfactants, saponins, fusidic acids, and phospholipids. Prodrug approach, e.g., cyclic prodrug, esters, and derivatisation of C and N terminal. • Nasal mucoadhesives in nasal drug delivery, e.g., carbopol, polycarbophil, cellulose derivatives, lecithin, and chitosan. • Particulate drug delivery, e.g., microspheres, nanoparticles, and liposomes.

5.1.6 Applications of Nasal Route of Drug Administration:

- Delivery of Non-Peptide Pharmaceuticals: Delivery of non-peptide pharmaceutical with extensive pre-systemic metabolism such as progesterone, estradiol, nitroglycerin etc can beeasily absorbed through nasal mucosa with a systemic bioavailability of approx. 100%.
- Delivery of Peptide: Based Pharmaceuticals: Peptides and proteins have low oral bioavailability due to their physicochemical instability and susceptibility to hepatogastrointestinal first -pass elimination. Insulin, calcitonin, pituitary hormones, etc.
- Delivery of vaccines: Nasal route is considered to be suitable for vaccine deliver becauseNasal mucosa is the first site of contacts with inhaled pathogens, Nasal passages are rich inlymphoid tissue, Creation of both mucosal and systemic immune responses, and Low cost, patient friendly, non-injectable, and safe.
- Delivery of Diagnostic Drugs: Nasal drug delivery system also plays an important role in the delivery of diagnostic agents for diagnosing various diseases. The intranasal route offers better systemic release of medicament, Thus it causes less toxicity.[7]

6. Sustained Release Drug Delivery System:

Sustained release system is a type of modified drug delivery system that can be used as an alternative to conventional drug delivery system. These systems sustain the release of drug and maintain the plasma drug concentration in therapeutic window except any fluctuation and increase the therapeutic efficacy of drug. They show their action by avoiding peak and trough in dosing and show constant plasma drug concentration in therapeutic window. Sustained release systems include any drug delivery system that achieves slow release of drug over an extended period of time. If the systems can provide some control, whether this is of a temporal or spatial nature, or both, of drug release in the body, or in other words, the system is successful at maintaining constant drug level in target tissue or cell, it is a controlled release system.

6.1 Advantages of Sustained Release Drug Delivery System:

- Decrease local and systemic effect.
- Better drug utilization and reduction in total amount of drug. Improve patient compliance
- Improved efficiency in treatment, optimized therapy, more uniform blood concentration.

6.2 Disadvantages of Sustained Release Drug Delivery System:

- Decreased availability in comparison to immediate release conventional dosage forms.
- Poor in vitro-in vivo correlation.
- Retrieval of drug is difficult in case of toxicity, poisoning or hypersensitivity reactions.
- Reduced potential for dose adjustment of drugs normally administered in varying strengths.

6.3 Types of Sustained Release Drug Delivery System:

6.3.1 Diffusion controlled system

- Reservoir devices: Core drug is surrounded by polymeric membrane. Rate of drug release depends on the nature of membrane.
- Its characteristics are-
- Zero order drug release is possible.
- High molecular weight compounds are difficult to deliver.
- Matrix devices: Drug is homogenously dispersed in matrix. Its characteristics are-
- Zero order release cannot be obtained.
- High molecular weight compounds can be delivered.

6.3.2 Dissolution controlled system

- Matrix dissolution-controlled system: Spherical agglomeration, Aqueous dispersions areused.
- Encapsulation dissolution-controlled system: Particles, seeds, granules can be coated by this technique

6.3.3 Diffusion and dissolution-controlled system: ug is dispersed in bio erodible matrix and released by swelling or hydrolysis.

6.4 Characteristics of Drug for formulation as Sustained Release Drug Delivery System:

- Drug should exhibit neither very fast rate of absorption nor excretions.
- Drug should be uniformly absorbed throughout GI tract.
- They should have good margin of safety.
- The drug should not show any cumulative action, any undesired side effect as in case ofdose dumping it might produce toxicity.

6.5 Factors affecting Sustained Release Drug Delivery System:Physicochemical factors

- Dose size: In general, a single dose which contains drug about 500mg-1.0g is considered maximal for a conventional dosage form Compounds which having large dosing size that can sometimes be given in multiple amounts or formulated into liquid systems Same criteria also hold for sustained release dosage form.

• Ionization, pka and aqueous solubility: Low soluble Compounds are inherently sustained, since their release over the time course of a dosage form in the GI tract will be limited by dissolution of the drug.

• Partition coefficient: It is common to consider that these membranes are lipidic; therefore, the partition coefficient of oil soluble drugs is important in determining the effectiveness of membrane barrier penetration.

• Stability: For a drug in solid state degradation will continue at a reduced rate thus, this is the preferred composition of delivery for problem cases. For the dosage forms that are unstable in stomach, systems that prolong delivery over entire course of transit in the GI tract are beneficial.

▪ **Biological factors**

• Half-life: The half-life of a drug is an index of its residence time in the body. If the drug has short half-life (less than 2 hours) the dosage form may contain a prohibitively large quantity of the drug. Ideally, the drug should have half-life of 3-4 hours for formulation of drug delivery system.

• Therapeutic effect: If the dose of a drug in the conventional dosage form is high, then it is less suitable candidates for Sustained Release Drug Delivery System.

• Absorption Window: Absorption of drug need dissolution in fluid before it reaches to systemic circulation. The rate, extent and uniformity in absorption of drug are important factor when considering its formulation in to controlled release system.

• Plasma Concentration Response Relationship: Generally, plasma drug concentration is more responsible for pharmacological activity rather than dose. But the drug having pharmacological activity independent of plasma concentrations, are poor candidate for oral SR drug delivery system.

• Concentration Dependency on transfer of drug: Transfer of drug from one compartment to other, if follows zero order kinetic process then such drugs are poor candidate for oral SR delivery system. It should be of first order kinetics.[8],[9],[10],[11]

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