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RECENT METHODOLOGIES ON BUCCAL TRANSDERMAL PATCH

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ABSTRACT

The drugs which held and applied in area of buccal cavities are known as buccal transdermal patches. A **transdermal patch** is a patch that is placed on the skin of mouth to deliver a specific dose of medication through the skin and into the bloodstream. The patch is removed from the mouth and disposed of after a specified time. The highest selling transdermal patch in world is the nicotine patch, which releases nicotine in controlled doses to facilitate with termination of tobacco smoking. There are different methods used for preparation of buccal patch such as solvent casting method, Spray drying and Melt granulation etc. This paper aims to review the advances in the buccal adhesive drug delivery systems to provide basic principles to the formulation, which will be useful to avoid the difficulties associated with the formulation design.

KEYWORDS: Transdermal patch, Buccal cavities, Bloodstream.

INTRODUCTION

Hydrophobicion pairing (HIP) has been proven to be the most effective technique to obtain hydrophilic macromolecules in the oil phase of SEDDS. Use the most appropriate hydrophobic counterion & drug-counterion ratio even charges greater than 10% can be achieved.[1] The ability of HIP has been demonstrated for peptide, protein, polysaccharide and DNA drugs. The combination of fat lipophilic molecules and hydrophilic macromolecule can increase lipophilicity. For example, insulin, which represents perhaps the most hydrophilic macromolecule described in the literature, can be converted into lipophilic complexes by various methods. Lee et al. The complexation of surfactants such as distearyldimethylammonium bromide and soybean phosphatidylcholine with insulin and its loading into SEDDS is described.[2] In another study, Karamanidou et al. Grieser et al. Many have not been studied in detail to achieve the high burden of ion pair therapy peptides in SEDDS. Important parameters include the type of suitable surfactant, the number of surfactant molecules bound to the peptide, and the selection of the appropriate solvent to dissolve the complex in SEDDS. When all these precautions are taken into account, the load of chemical peptides can exceed 10%.[1] Zupancic et al. reported the HIP of daptomycin, an anionic peptide antibiotic, combined with the cationic surfactant dodecylamine hydrochloride to increase its hydrophobicity and incorporate into SEDDS. A change in log P from -5.0 to +4.8 corresponds to an approximately 1010 fold increase in lipophilicity. In another study, Zupančič et al. explained that the combination of desmopressin with docusate sodium caused the drug's log P value to

initially change from 6.13 to 0.33. At the same time, the ability of HIP in polysaccharides was also found. For example, the low molecular weight heparin enoxaparin was successfully ionized with dodecylamine. In another study, HIP was created from lipophilic cationic polymers of heparin and β-cyclodextrin.

Additionally, HIP for pDNA has been well established since the 1980s. Haupstein et al. Possibly the first to create pDNA HIP and incorporate the lipophilic complex into SEDDS. On the one hand, the diameter of the fat droplets formed in the intestine should be in the nanometer range, on the other hand, the diffusion coefficient of the macromolecule should be below 10-8 cm2/s and HIPs per second. According to their distribution coefficients, they are released from the lipophilic phase until the balance between the lipophilic and aqueous phase is achieved. Therefore, the partition coefficient (expressed as log D SEDDS/RM) between the lipophilic phase (SEDDS) and the hydrophilic phase (release medium = RM) can be considered a key factor for drug release.[3] Considering the volume of SEDDS preconcentrate administered and the volume of gastric fluid, log D SEDDS/RM > 2.5 appears to be effective in providing a controlled release through drug absorption alone rather than delivery. For example, assuming 1 ml of SEDDS concentrate and 30 ml of gastric juice are administered orally, only about 10% of the drug with a Log D of 2.5 will be immediately released. However, from the designer's perspective, the beneficial properties of SEDDS (such as protection or penetration of the mucus support) may not be effective in immediate evacuation of 10%. In the case of D SEDDS/RM>4, drug release will not be sufficient, but in this case, SEDDS must be rapid and controlled with lipase degradability.[4] SEDDS containing HIP have important properties including small water droplets (10 to 500 nm) and kinetic stability. SEDDS (SandimmunNeoral), which contains the only peptide marketed to date, is used in the form of soft gelatin capsules. However, the disadvantage of this form is the difficulty of managing the process, leakage of the closed process and limited storage capacity. Additionally, unless packaged in a blister pack, non-uniform components of SEDDS tend to evaporate from the capsule shell resulting in precipitation of the compound.

To overcome these shortcomings, SEDDS products have been developed that provide the benefits of food packaging while retaining the properties of most liquid SEDDS. Liquid SEDDS preconcentrates are converted to solids by adding adsorbents or porous supports such as cross-linked porous silica, magnesium aluminum silicate, and microporous calcium silicate.[5,6] For example, SEDDS containing low molecular weight heparin is solidified with microporous calcium silicate. In another study, Sander and Holm developed liquid SEDDS tablets containing cyclosporine. The pharmacokinetics of cyclosporine administered to dogs in these tablets are similar compared to soft gelatin capsules containing liquid SEDDS concentrate (Neoral®). Because cyclosporine is a unique molecule (essentially a peptide that behaves as a small lipophilic molecule unsuitable for HIP), this document rarely demonstrates the use of SEDDS products for oral peptide delivery. Release of drug from this solidification process is often incomplete and unstable over time due to differences in drug/structure in deep pockets. Additionally, the stability of HIPs may decrease due to adsorption binding to weak sites. Alternatively, SEDDS products can be prepared using composites or semi-finished products and processed by processes such as melt granulation, spray drying or hot melt extrusion. However, the hydrophilic macromolecule must have sufficient thermal stability when incorporated into molten lipids.[7]

BARRIERS FOR ORAL DELIVERY OF HYDROPHILIC MACROMOLECULAR DRUGS

The digestive system provides an environment that protects against external attacks. The local or systemic effectiveness of oral SEDDS depends on its ability to overcome intestinal infections. The following sections describe functional

parameters, including various pH values, enzymatic degradation, sulfhydryl barriers, mucus gels, and intestinal epithelial cell layers.

1] pH barrier

2] Enzymatic barrier

3] Sulfhydryl barrier

4] Mucus barrier

5] Intestinal epithelial barrier

1] pH barrier

Absorption of oral drugs occurs mainly in the small intestine (pH 5.5-8.0). However, the hydrophilic macromolecule must withstand the very low pH of the stomach (pH 1.0-2.0) before reaching the intestines. Therefore, unless provided in an enteric-coated form, SEDDS must not only be resistant to acid secretions but also provide resistance to encapsulated acid instability. Mercuri et al. The stability of SEDDS for fruit juice was investigated and the stability of fruit juice was demonstrated for all clinical trials.

2] Enzymatic barrier

In the intestine, the hydrophilic macromolecule is broken down by various enzymes. Therapeutic peptides and proteins are rapidly digested by luminal secretory enzymes such as trypsin, chymotrypsin, elastase, and carboxypeptidase A and B. Most therapeutic polysaccharides (such as heparin or chondroitin sulfate) are stable in the gastrointestinal tract because they mostly have stable sulfate substructures. It covers the known regions of polysaccharases. The result of SEDDS disruption (DEGRADATION) is often that the drug is released too quickly and the system loses its protection against the harsh environment of the intestine.

3] Sulfhydryl barrier

The sulfhydryl barrier contains reduced thiols such as glutathione, homocysteine, and/or cysteine, either intracellularly or in the diet. GI thiol content in foods varies from ≤ 350 nM/g in vegetables to ≤ 135 nM/g in fruits. Therefore, oral SEDDS (containing peptides and proteins) should protect against transient(TEMPORARY) thioldisulfide exchange reactions with sulfhydryl moieties that could lead to failure of this drug.

4] Mucus barrier

Mucus covers most of the body surface, and epithelial cells carry cells on their surfaces. The 3 dimensional mucus gel layer not only traps bacteria and xenobiotics, but is also an important problem that oral drug delivery must face. The mucus layers intertwine (twisted together), creating a mesh size of approximately 10-200 nm in its microstructure, blocking all very large particles. In general, the average size of oil droplets produced by SEDDS falls within this size range. However, the semipermeability of mucus gels allows the release of water, ions, nutrients, some proteins, and <50 nm particles/droplets without changing their structure**.**

5] Intestinal epithelial barrier

The epithelium in the gastrointestinal tract is the largest and most significant barrier to drug delivery by SEDDS. Permeability and diffusion across the cellular lining depend on physicochemical properties. The selective permeability of the epithelial barrier is determined by transcellular or paracellular pathways and is controlled by a network of

proteins that seal adjacent cells through adhesive complexes (e.g., desmosomes, adherens junctions, and/or tight junctions).[7]

Mucoadhesive SEDDS

Mucoadhesive drug delivery systems are designed to increase residence time on the mucosal surface. In most cases, SEDDS does not adhere to the mucosal area. However, like many nanoparticle drug delivery systems, SEDDS can achieve mucoadhesion through the addition of hydrophobic mucoadhesive polymers. For SEDDS, it is important to select the appropriate mucoadhesive polymer based on lipophilicity and compatibility. In addition to polymers that follow hydrogen bonding or weak electrostatic interactions, options exist for next-generation mucoadhesive polymers, such as thiol polymers with enhanced adhesion through covalent bonds. In this context, Bonenger et al. Thiolated alkyl substituted carbomers have been developed and proven for their emulsifying and mucoadhesive properties.Dosage forms designed for the administration of mucoadhesive drugs should be small, easily changed by the patient, and should not cause irritation. Other requirements for mucoadhesive labels include high drug loading, controlled drug release, good mucoadhesive properties, smooth surface, odorless, and easy application. Many mucoadhesive drug applications have been developedfor various drugs. Many peptides, including thyrotropin - releasing hormone (TRH), insulin, octreotide, leuprolide, and oxytocin, have been delivered via the mucosal route but have low bioavailability (0.1–5%).

Advantages

- Targeting and localization of the dosage form at a specific site.
- Also, the mucoadhesive systems are known to provide intimate contact between dosage form and the absorptive mucosa, resulting in high drug flux at the absorbing tissue.

Self Emulsifying Drug Delivery System

Selfemulsifying drug delivery systems (SEDDS) are isotropic mixtures of oils, surfactants, solvents, and cosolvents/surfactants that can be used in formulations to improve the oral absorption of highly potent drugs. Lipophilic drug compounds. Oral administration is the preferred method for long term treatment. Approximately 35-40% of new drug candidates have poor water solubility. Oral administration of these drugs is often associated with low bioavailability, high intra- and intra-individual variability, and dose disproportionality. Efforts are ongoing to improve the oral bioavailability of lipophilic drugs to increase their therapeutic efficacy. To overcome these problems, new strategies to increase solubility and bioavailability have been published, including complexation with cyclodextrins, soliddispersion (augmentation), agitation, micronization, salt formation, emulsions, use of micelles, and co-milling.

Emulsions are used as drug delivery vehicles, particularly due to their ability to improve the oral bioavailability of malabsorbed drugs. SEDDS formulations can be simple binary systems: lipophilic phase and drug or lipophilic phase, surfactant and drug. The formation of SEDDS requires the use of co-surfactants to form microemulsions. SEDDS formulations are characterized by an in vitro lipid droplet size of 200 nm-5 mm and the appearance of a turbid distribution. Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, preferably isotropic and sometimes cosolvents, that self-emulsify when introduced into an aqueous phase with gentle mixing and form a good Oil-in-Water lotion. Recently, SEDDS has been developed using non-toxic neutral triglyceride oil and nonionic surfactants. After each oral administration, these systems form a fine emulsion (or microemulsion) in the gastrointestinal tract (GIT) and increase the pressure from the stomach.[8]

The first SEDDS oral product (Sandimmun Neoral) entered the market more than two years ago. However, since then, the pharmaceutical industry, on the one hand, has considered SEDDS to be used only for the delivery of lipophilic drugs, while on the other hand, academia has been dedicated to the research of nanocarriers. However, the transfer of a lot of information collected over the years regarding the use of nanocarriers for SEDDS has brought them back to the agenda in recent years.

The introduction of a variety of new materials, such as acid-inert compounds and cell peptides, and the selection of appropriate materials can help eliminate the limitations associated with oral SEDDS technology for the delivery of hydrophilic macromolecules. Therefore, improved SEDDS provides new nanoemulsions with better performance such as intestinal stability, intestinal residence time, improved mucus permeability, improved permeability, and improved cellular uptake, thereby significantly increasing the hydrophilicity of the polymer material. This review highlights the overall role and future potential of next-generation SEDDSs.[7]

Properties of SEDDS

As the name suggests, they can rapidly self-emulsify in gastric fluid to form oil-in-water emulsions under the influence of gentle agitation provided by the peristaltic movement of digestive tract rice. They can mix chemicals (hydrophobic or hydrophilic) into the oil-surfactant mixture. They are available in both liquid and food forms. They require less medication than prescription drugs.[9]

ADVANTAGES

1. Protect sensitive APIs.
2. Similar drug absorption.
3. Protect the drug from the intestinal environment.
4. Check delivery.
5. High drug loading efficiency.
6. Quick start
7. Reduce the amount of medication
8. Easy to create and scale
9. Increase Oral Bioavailability
10. Inter- and Intra-Subject Variability and Food effects
11. Ability to deliver peptides subject to enzymatic hydrolysis in the GIT
12. It is not affected by the lipid digestion process
13. Increase drug transport[10]

DISADVANTAGES

1. Traditional extraction methods do not work because these methods may rely on digestion before the drug is released.
2. This in vitro model requires further development and validation to evaluate its power.
3. Further development will be in vitro-in vivo correlations and therefore there will be a need for the development of lipid prototype-based formulations and in vivo testing in animal models.
4. Disadvantages of this system include instability of the drug and high surfactant content in the sample (about 30-60%), GIT.[10]

Excipients used in sedds formulation

The self-emulsification process depends on:

1] Nature of the oil-surfactant pair

2] Surfactant concentration

3] Temperature at which self-emulsification occurs

1] Oils

Oils can dissolve special lipophilic drugs. It is one of the most important excipients because it promotes self-emulsification and increases the rate of lipophilic drugs transported by the intestinal lymphatic system, thus increasing intestinal absorption. SEDDS is made using long-chain triglyceride and medium-chain triglyceride oils at various levels of saturation. Modified or hydrolyzed vegetable oils have contributed to the success of SEDDS due to their structure and beneficial effects on the body. New semi-synthetic medium-chain triglyceride oil with surfactant properties is widely being replaced by conventional medium-chain triglycerides.[11]

Oils	Drugs
Poloxy castor oil	Simavastatin
Maisine oil	Lercanidipine
Soya bean oil	Ibuprofen
Oleic oil	Puerarin
Peanut oil	Griseofulvin

2] Surfactant

Nonionic surfactants (Tween, Labrasol, Labrafac CM 10, Cremophore, etc.) with high hydrophile-lipophile balance (HLB) value are used in SEDDS formulations. To create stable SEDDS, the active surfactant is usually between 30-60% w/w of the sample. Surfactants with high HLB and hydrophilicity facilitate the formation of oil droplets in water and/or rapid dispersion of formulations in aqueous media. Surfactants are amphiphilic in nature and can dissolve or dissolve large amounts of hydrophobic chemical compounds. This prevents the drug from precipitating in the intestinal tract and increases the time available for drug molecules.[12]

Surfactant	Drugs
Tween 85	indomethacin
Cremophor EL	loratadine
Labrafil M 1944 CS	probucol
TPGS	tacrolimus
Tween 80	Ketoprofen

3] Cosolvents

Many organic solvents are suitable for oral administration. Some examples are polyethylene glycol, ethanol, and propylene glycol, which help dissolve large amounts of hydrophilic surfactants or drugs in liquid matrices. Add a hydrophilic solvent such as triacetin or another suitable solvent as the solvent mixture. Triacetin is often used because it is miscible with the oil or lipid phase and can also be used to solubilize hydrophobic substances. The use of volatile solvents such as alcohol in selfemulsifying systems is prohibited as they may cause precipitation of hydrophilic substances. Therefore, selfemulsifying drug delivery systems that do not contain alcohol and other solvents can also be investigated.[11,12]

Co-Solvents	Drugs
Glycerine	Sandimmune soft gelatine capsule
Poly ethylene glycol	Targretin soft gelatine capsule
Ethanol	Sandimmune soft gelatine capsule

SELF systems are available: Self-emulsifying drug delivery systems (SEDDS) - Microemulsifying drug delivery systems (SMEDDS). Both SEDDS and SMEDDS have specific features related to the development of distribution systems. SEDDS formulations can be simple binary systems: lipophilic phase and drug or lipophilic phase, surfactant and drug. SMEDDS formulation requires the use of surfactants to form microemulsions. SEDDS formulations were characterized by an in vitro lipid droplet size of 200 nm-5 mm and the appearance of a turbid distribution. However, SMEDDS has a small lipid droplet size (<200 nm) and the dispersion has a clear appearance in visible light. Both are associated with the formation of large-area distributions that provide favorable conditions for the absorption of harmful substances. Whether SEDDS or SMEDDS is the appropriate choice depends mainly on the interaction between the components of the compound and its solubility and dissolution profile when tested in vitro using various excipients.[13]

Self microemulsifying drug delivery system

Selfmicroemulsifying drug delivery system (SMEDDS) is a drug delivery system that provides microemulsification with drugs instead of machines. That is, it is due to the beneficial properties of the drug formulation rather than the specific composition and function. Many anise-flavored wines benefit from the ouzo effect known to be caused by anethole. Microemulsions have great application potential in drug delivery, and SMEDDS is the best of these systems described to date. SMEDDS is particularly valuable in enhancing the absorption of oral lipophilic drugs.

The first drug to be marketed under SMEDDS is cyclosporine, which has been shown to be more effective compared to conventional solutions. Over the years, many SMEDDS-loaded antiretroviral drugs (ritonavir, saquinavir) have been tested for HIV treatment, but the relative improvement in treatment has not been significant. SMEDDS formulations (soft gel capsules) of ritonavir have been discontinued in some countries. In recent years, SMEDDS has also been used for oral administration of biological agents. Many hydrophilic macrodrugs can be incorporated into the lipophilic phase of SMEDDS due to ion coordination with suitable surfactants.

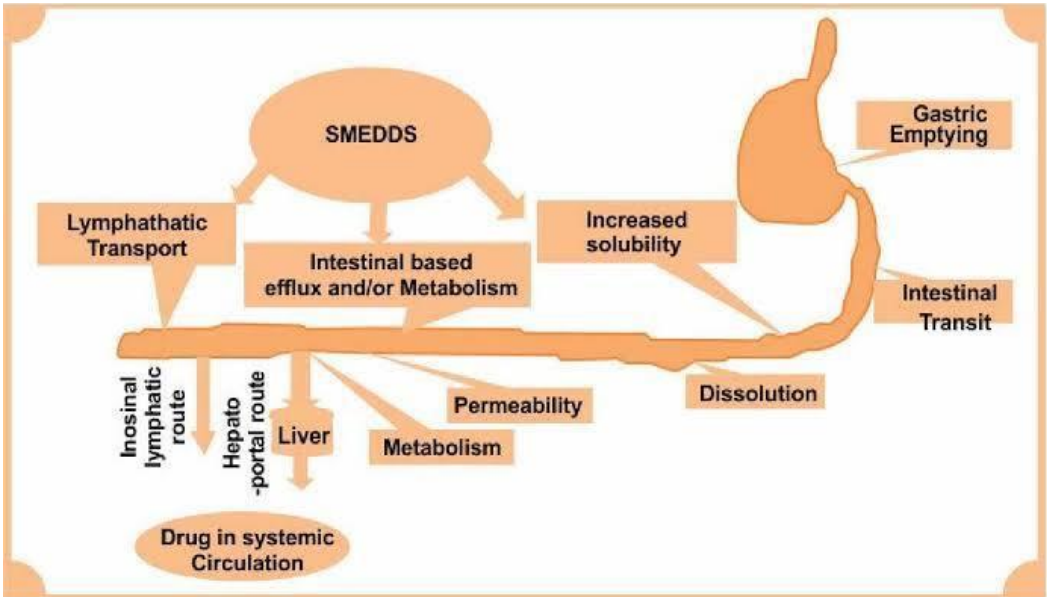


Fig. 1: Mechanism of action of self-micro-emulsifying drug delivery system on oral administration of drug.

For oral use, SMEDDS can be formulated as a liquid or solid packaged in capsules or tablets. Limited studies comparing them indicate that liquid SMEDDS is superior to solid SMEDDS in terms of bioavailability, and solid SMEDDS is superior to conventional tablets. Liquid SMEDDS has also been shown to be of value in injectable (liquid and urine) medications and topical (oral) medications.

Formulation Techniques

1] Spray Drving

Cocept of spray drying

In recent years, products produced during spraying have attracted great attention. These efforts have led to the use of spray technology in the production of products such as the direct compression of excipients and/or granules into microencapsulated flavors. The two main technologies are spray drying and spray coagulation. The main effect in drying is evaporation, while spray condensation is the phase change from liquid to solid. Other than power flow, the two systems are similar. In the case of spray drying, energy is applied to the droplets to cause evaporation of the medium, resulting in the transfer of energy and mass into the droplet. In spray condensation, only energy is extracted from the droplets, causing the melt to freeze. Drying is the most widely used industrial process involving production and drying. It is suitable for the production of dry products in powder, granule or agglomerate form from liquid raw materials such as solutions, emulsions and pumpable suspensions. Spray drying is the best process where the final product should achieve good distribution pattern in terms of moisture content, density and shape.[14]

Principle

Drying involves three simple steps.

1) Atomize the liquid feed into the water well.

2) Mix this spray with hot air to evaporate the liquid and leave the dry material.

3) Separate the dry powder from the air flow and collect it.

The drying method consists of atomizing the liquid feedstock into droplets and contacting the droplets with hot air in the drying chamber. Spraying is produced by rotation (wheel) or nozzle atomizer. Evaporation of water from droplets and formation of dry matter depending on temperature and air flow. Dust is constantly coming out of the dryer. Select the operation and design of the dryer according to the drying characteristics and the specific powder of the product.

Advantages of Dry Chemicals

1. Ability to work in a wide variety of applications, from sterile chemicals to ceramic powders.
2. It can be designed for almost any capacity needed. (Varies from a few pounds per hour to over 100 tons per hour).
3. The spray drying process is very fast, with most of the evaporation occurring in less than an hour.
4. It is suitable for all automatic control systems that can monitor and record many different processes simultaneously.
5. Different types of spray dryers can meet different product specifications.
6. It has little movement, and careful selection of various materials can ensure that the body is motionless in direct contact with the material, thus reducing corrosion problems.
7. Electrical equipment and heating equipment can be used.

Disadvantages of spray drying

1. Equipment is large and support is expensive.
2. The total thermal efficiency is low and a large amount of heated air passes through the drying chamber without coming into contact with the drying chamber is granular and therefore does not directly promote drying.

Application

The degree of application determines the importance of the process. Spray dryers are widely used in commercial and non-medical fields.

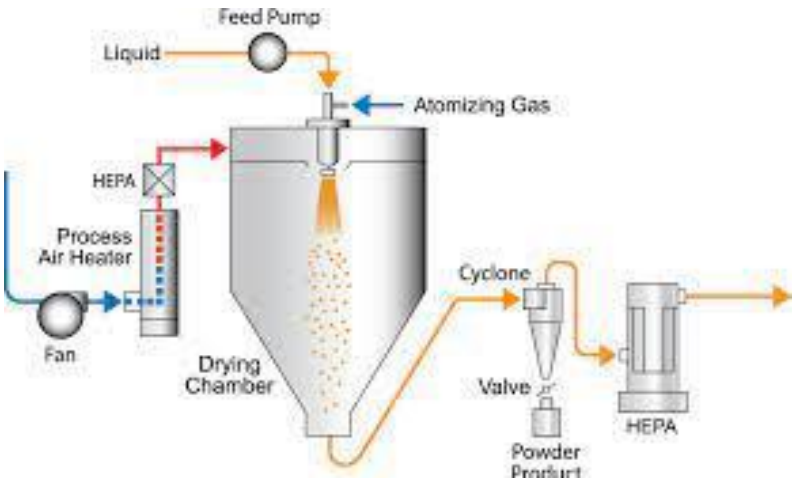


Fig. 2: Spray Drying.

2] Melt Granulation

Melt granulation is the process of obtaining powder agglomeration by adding glue that melts or softens at high temperatures. As a "one-step" process, melt granulation has many advantages over wet granulation models because the additional liquid and subsequent drying step are eliminated. It is also a good choice for solvent use. The main parameters controlling the granulation process are impeller speed, mixing time, binder particle size and binder viscosity.

Advantages of Melt Granulation

1] Time and Cost

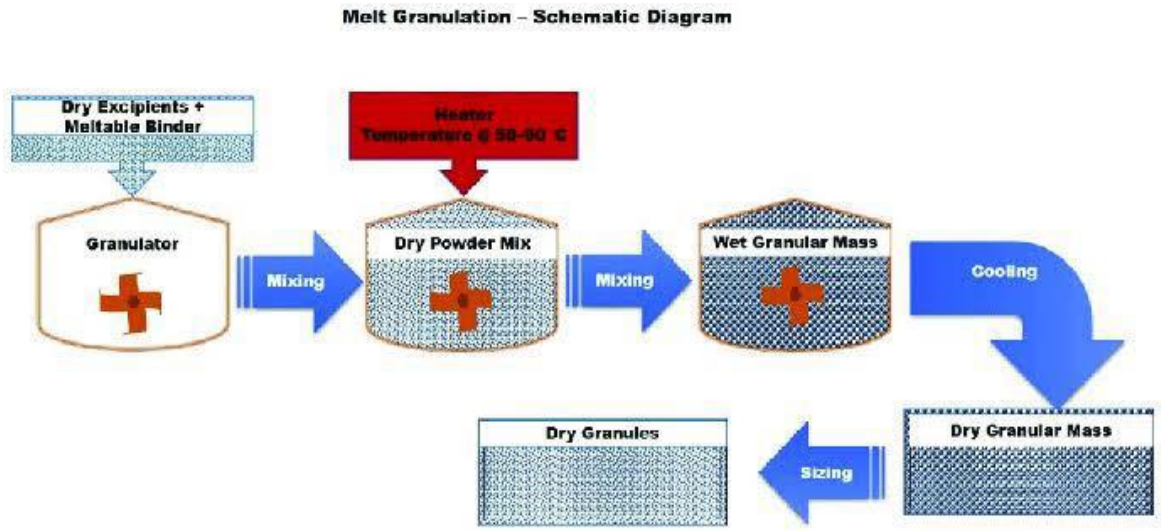
2] Control and modification of drug release

3] Water-sensitive drugs are good candidates.

Disadvantages of Melt Granulation

1] Not suitable for heat sensitive materials

2] Low melting point adhesives will melt/soften when used or stored.

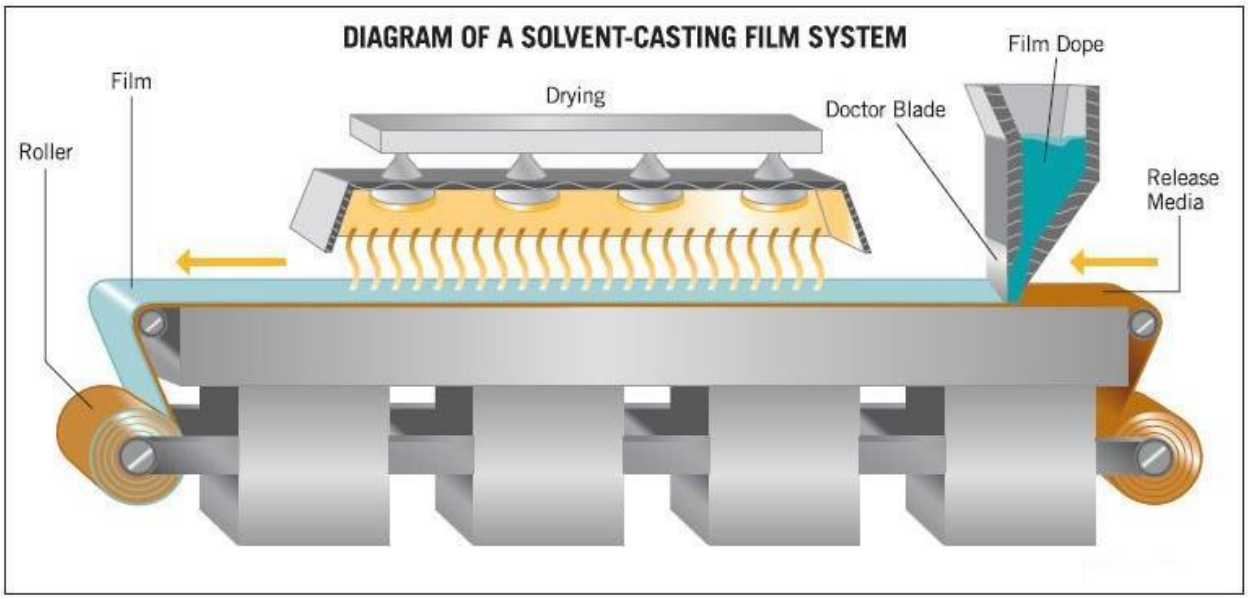


Preparation Buccal Films

Solvent casting method

Many individuals prefer to use the solvent casting approach while making buccal films. The following steps are involved in this process:

- Ingredients that dissolve in water (polymers) are used to
- API and other excipients are dissolved in an appropriate solvent resulting in a clear viscous solution, which is uniform in viscosity.
- After combining the two solutions, the mixture is poured into a film and let to dry.[15]



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