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Novel Stratergies Used To Formulate Buccal Films

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ABSTRACT:
The present study provides design and development of recent strategy such as carrier system like liposomes, niosomes, nanoparticle and Aquasomes as well as formulation dispersions of microemulsion and nanosuspension are used to formulate the buccal films in order to increase the safety, efficacy and patient compliance. This technology emerged as an advanced alternative to other conventional types of drug delivery system. It is proven technology for the systemic delivery of Active pharmaceutical ingredients. The buccal mucosa is the best studied site for local as well as systemic delivery of drugs due to its physiological features. The buccal film has an elegant and effective dosage form with improved bioavailability, when compared to other dosage form as it bypasses the hepatic first pass metabolism. It is the most acceptable and palatable dosage form due to its small size, small dose and thickness of the film and it does not require swallowing of the drug, which is most suitable for paediatric as well as geriatric patients. In this various issue like benefits of buccal films, manufacturing methods, evaluation parameters and also reviews on the market potentiality of dosage form and its future scenario on global market as an effective pharmaceutical dosage form.

Keywords: Buccal films, Liposomes, Niosomes, Aquasomes, Microemulsion, Nanoemulsion.

I. INTRODUCTION

Transmucosal medication distribution, for example, has different advantages to oral administration in terms of systemic effect. Buccal mucosa is the best route for local and systemic drug administration among the numerous transmucosal routes. The buccal mucosa is a suitable route for mucoadhesive drugs due to its unique physiological characteristics. These benefits include avoiding presystemic elimination and bypassing the hepatic first-pass impact[1,2] within the gastrointestinal tract It is generally known, that drugs are absorbed through the mouth mucosa avoids first-pass hepatic metabolism and allows the medication to enter the systemic circulation directly. Drug degradation in the gastrointestinal tract, both of which are linked to peroral delivery. [3-5]

Buccal films:

Buccal films are designed to adhere to the buccal mucosa and can be prepared to have both local and systemic effects. In terms of flexibility and comfort, buccal film may be favored over buccal tablet. Buccal films have direct access to the systemic circulation via the internal jugular vein, bypassing the hepatic first pass metabolism passing through metabolism, resulting in enhanced bioavailability Furthermore, these dosage forms are self- administrable, cost-effective and have a higher level of patient adherence [6,7]. The film can be classified as a water-dispersible dosage form. When placed on the tongue or in the mouth, the polymer causes the dosage form to swiftly hydrate, adhere, and dissolve Systemic medication administration is achieved through the mouth cavity [8].

Figure 1: Mucoadhesive buccal film

Potential Benefits of Buccal Films

Buccal films provide large surface area that leads to rapid disintegration and dissolution in the oral cavity due to which it promotes the systemic absorption of Active pharmaceutical ingredient. No need of chewing and swallowing and No risk of chocking, Drug can be protected from degradation by GI enzymes and the acidic environment. The film increases the systemic bioavailability of the drugs, as it bypasses the hepatic first pass metabolism. Rapid onset of action and minimum side effects, Self- administration is possible, Accurate dosing compared to liquid dosage forms and Taste masking is possible.

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Prolongs the residence time of the dosage form at the site of absorption, hence increases the bioavailability. Ease of administration to pediatric, geriatric patients, and also to the patients who are mentally retarded, disabled or non-cooperative.

Anatomy and Physiology of Oral Mucosa

The oro-mucosal region is sticky and functions as a lubricant, allowing cells to move more freely relative to one another. For medication administration, four locations were used: the buccal cavity, the lingual area, the palate, and the gingival region. The buccal mucosa is the most regularly used of the four locations indicated above for medication delivery. The buccal mucosa is the anatomic location for medication delivery between the cheek and gingiva [11]. There are three layers to the oral mucosa. The stratified squamous epithelium is the top layer, with the stratified squamous epithelium beneath it. The basement membrane is laid down in this layer. The lamina propria and submucosa are covered by the basement membrane.The epithelium's composition varies depending on where in the oral cavity it is found. Because the epithelium of the soft palate, buccal, and sublingual areas is not keratinized, it lacks ceramides and acylceramidesm, which are linked to barrier function [12]. When compared to other areas of the oral cavity, it contains lesser levels of ceramidem and is thus more permeable [13]. The epithelial layer of cells has a mucus layer on its surface. This is important for cell-to-cell attachment, Mucoadhesion of mucoadhesive drug delivery systems, as well as oral lubrication There is a lot of space in the buccal area.The buccal area features a large expanse of smooth, relatively static surface that is ideal for retentive system implantation [14]. Adhesion to the oral mucosa allows not only for intimate touch but also for buccal medication deliveryas well as the potential for increased medication absorption, but also the capacity to establish an optimal residence period at the site of administration[15] Because of these qualities, the buccal mucosa is a better choice for long-term systemic exposure

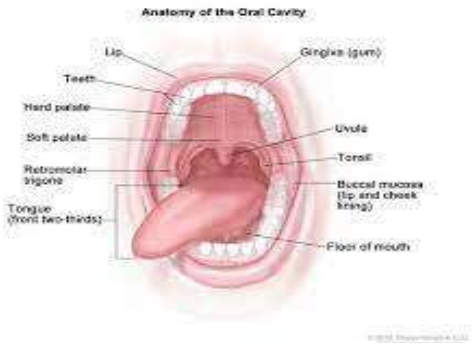

Figure 2: Anatomy and physiology of oral mucosa

RECENT TRENDS USED FOR THE BUCCAL DRUG DELIVERY:

Nowadays so much of recent technologies like carrier system are formulate to protect the drug such as degradation, presystemic circulation and first pass metabolism etc…

The carrier systems are

- Liposomes,
- Niosomes,
- Nanoparticles,
- Nanosuspension,
- Aquasomes,
- Micro emulsion.

1. LIPOSOMES ARE USED TO FORMULATE BUCCAL FLIMS

DEFINITION OF LIPOSOMES:

Liposomes are small artificial vesicles with a spherical form made from cholesterol and nontoxic phospholipids. Liposomes are attractive drug delivery devices due to their size, hydrophobic and hydrophilic properties (along with biocompatibility). Liposome characteristics vary greatly depending on lipid composition, surface charge, size, and manufacturing process. Furthermore, the choice of bilayer components influences the bilayer's 'rigidity' or 'fluidity,' as well as its charge.

Unsaturated phosphatidylcholine species from natural sources (egg or soybean phosphatidylcholine, for example) form much more permeable and less stable bilayers, whereas saturated phospholipids with long acyl chains (such as dipalmitoyl phosphatidylcholine) form a rigid, rather impermeable bilayer structure [16-18].

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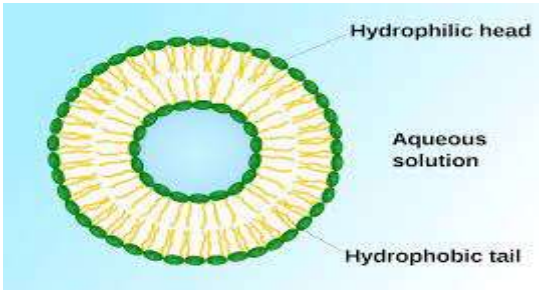


Figure 3: structure of liposome

Advantages of liposome

Liposomes increased efficacy, therapeutic index of drug, increased stability viaencapsulation. Liposomes are non-toxic, flexible, biocompatible, completely biodegradable, and non-immunogenic for systemic and non-systemic administrations, help reduce the exposure of sensitive tissues to toxic drugs. Flexibility to couple with site-specific ligands to achieve active targeting

Disadvantages of liposome

Liposomes are Low solubility, short half-life, sometimes phospholipid undergoes oxidation and hydrolysis-like reaction. Leakage and fusion of encapsulated drug/ molecules. Production cost is high.

Methods of liposome preparation

All the methods of preparing the liposomes involve four basic stages:

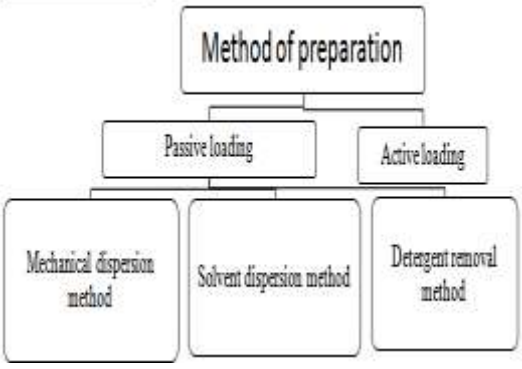
Drying down lipids from organic solvent.

Dispersing the lipid in aqueous media.

Purifying the resultant liposome.

Analyzing the final product.

Method of preparation:



APPLICATION OF LIPOSOMES LOADED IN BUCCAL FLIMS

Vitamins are prepared as liposomes

Improved delivery of water-soluble vitamins, to protect the vitamins from degradation, to enhance the permeability and help to mask taste and odour of the vitamins.

Ex: liposomal buccal mucoadhesion film for improved delivery and permeation of water soluble vitamins [20].

Increase the bioavailability of the drug having poor bioavailability.

Ex: silymarin are formulated as liposome loaded buccal flims for increasing thebioavailability of the drug [21]

To prolong systemic drug circulation, enhance drug accumulation at the target tissues.

Ex: increase level of cellular internalization and provide organelle -specific drug delivery.

Development and invitro evaluation of mucoadhesive patches of methotrexate for targeted delivery in oral cancer [22].

Easy and effective administration of liposomal therapy buccal flims.

Ex: Nonlabelled liposomal mucoadhesive flims for enhanced efavirenz buccal drug delivery [23]

To avoid first pass metabolism.

Ex: Self assembled liposome from multilayered fibrous mucoadhesion membrane for buccal delivery of drugs having first pass metabolism [24]

2. NIOSOMES USED TO FORMULATE BUCCAL FILMS:

DEFINITION OF NIOSOMES:

The medication is enclosed in a vesicle in the niosomes drug delivery mechanism [25]. Niosomes are vesicles that are made up of a bilayer of non-ionic surface-active substances. A non-ionic surfactant, such as Span – 60,forms amphiphilic vesicles in niosomes and is normally stabilized by the addition of cholesterol and diacetyl phosphate is an anionic surfactant [26].

ADVANTAGES OF NIOSOMES:

The characteristics such as size, lamellarity etc. of the vesicle can be varied depending on the requirement. The vesicles can act as a depot to release the drug slowly and offer a controlled release. Since the structure of the niosome offers place to accommodate hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs. The vesicle suspension being water based offers greater patient compliance over oil-based systems They are osmotically active, stable and increase the stability of the entrapped drug.

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DISADVANTAGES OF NIOSOMES

Niosomes undergoes fusion, Aggregation, Physical instability. Hydrolysis of encapsulated drugs which limiting the self-life of the dispersion.Leaking of entrapment.

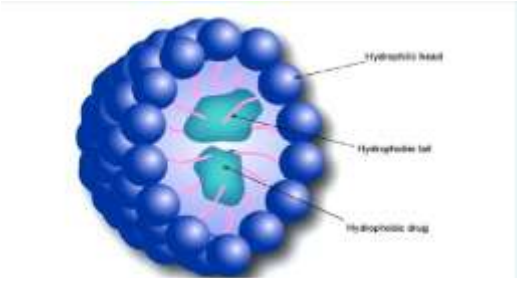
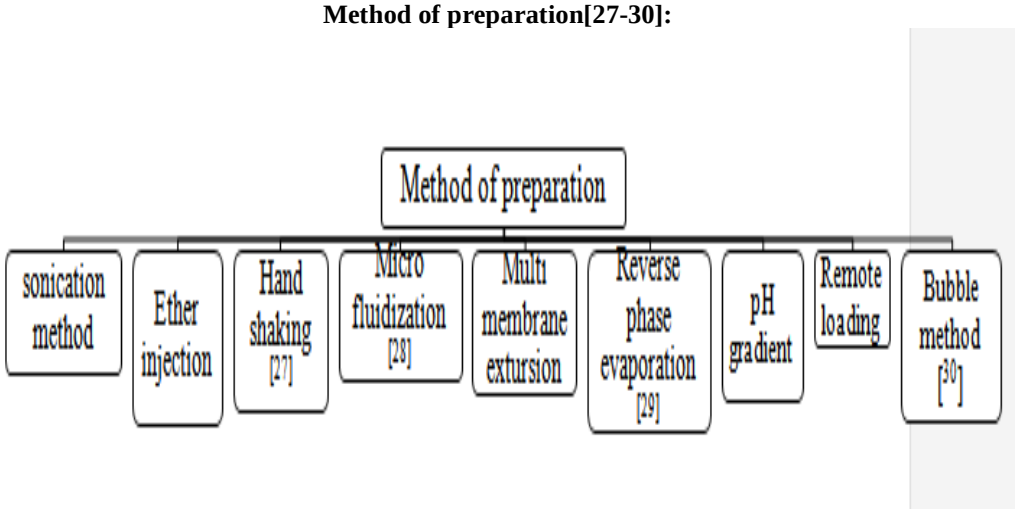


Figure 4: Structure of Niosomes

Method of preparation[27-30]:



APPLICATIONS OF NIOSOMES LOADED BUCCAL FILM:

For enhancement of bioavailability of the drug which having poorbioavailability.

Ex: Sublingual fast dissolving niosomal flims for enhanced bioavailability and prolong effect of metoprolol effect [31]

For targeted delivery.

Ex: Propolis -based niosomes as oromuco-adhesive flims, A randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous therapy[32]

For given prolonged effect.

Ex:Formulation and development and Invitro - Exvivo Assessment of Simvastatin niosomal flims[33]

To reduce dosage regimen:

Ex: Formulation and evaluation of niosomal suspension of cefixime[34]

To minimize side effects and reduce dosage of frequency.

Ex: Metformin loaded Non-ionic surfactant vesicles.optimization of formulation,effect of process variables and characterization.

To provide local effect on the oral cavity.

Ex:Formulation and evaluation of lignocaine hydrochloride Proniosomes loaded or a base for dental anesthesia.

3. NANOPARTICLES:

DEFINITION:

A particle is a small item that functions as a full unit in terms of attributes and transport in nanotechnology. It comes in a variety of sizes, including fine and ultra-fine particles. Fine particles have a diameter of 100 to 2500 nanometers, while ultrafine particles have a diameter of 1 to 100 nanometers. Nanoparticles, like ultrafine particles, are sized between 1 and 100 nanometers. Nanoparticles may or may not show characteristics that differ from those seen in bulk materials and fine particles [35]. Nanoparticles have a size of less than a few hundred nanometers, which causes considerable changes in their physical properties compared to bulk materials. They can be mineral or a metamaterial mix [36].

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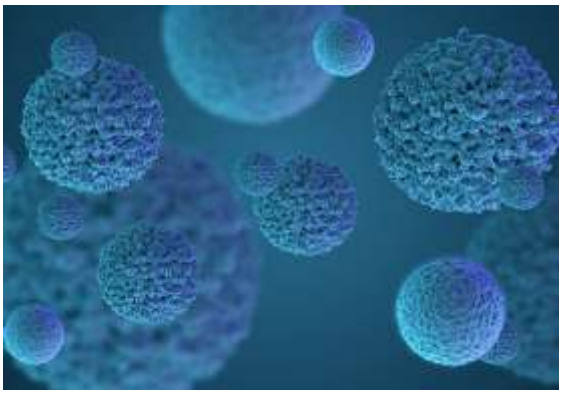


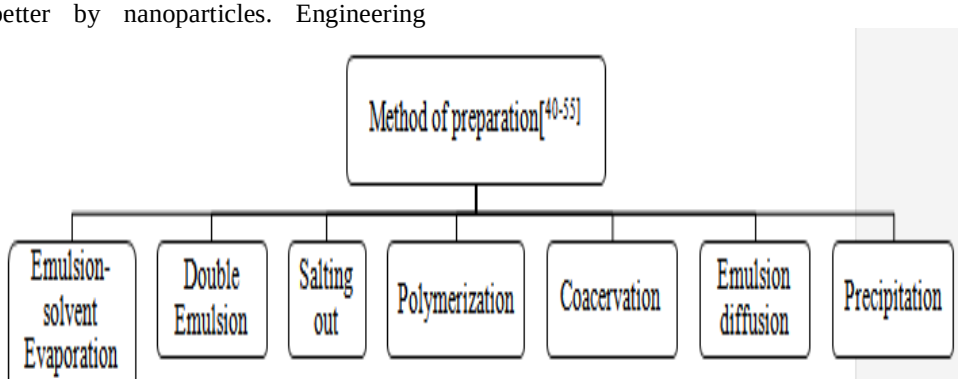
Figure 5: Structure of Nanoparticles

ADVANTAGES:

After parenteral administration to achieve both passive and active drug targeting particle size and surface characteristics of nanoparticles can be easily manipulated.To achieve high drug therapeutic efficacy and less side effects, during the transportation they control and sustain release of the drug and at the site of localization, altering distribution of the drug and subsequent clearance of the drug. By attaching targeting ligands to surface of particles or use of magnetic guidance site-specific targeting can be achieved. Including oral, intra-ocular,parenteral and nasal,the system can be used for various routes of administration. Within the body,drug delivery to tiny areas can be achieved better by nanoparticles. Engineering enables researchers to exercise precisely on this scale and previously control over the biomaterials and physical features of polymers.Over various anatomic extremities of body such as blood brain barrier (BBB) nano carriers holds potential to deliver biotech drugs.

DISADVANTAGES:

Nanoparticles, due to their small size, can cause inhalation problems and many other fatal diseases. Inhaling nanoparticles for 60 seconds can easily damage the lungs, now exceedingly expensive, and creating it can be very costly. It's also harder to manufacture, which is possibly why nanotechnology-based products are more expensive [38]. It has improved people's living standards, yet it has also increased pollutants, such as water contamination and air pollution. Nano pollution is the term for contamination caused by nanotechnology. This type of pollution is extremely harmful to living things.The drawbacks of nanoparticles are mostly unexplored. As a result, there are just a few more dependent on drug delivery.The use of polyvinyl alcohol as a detergent in the production of nanoparticles for medication delivery causes toxicity concerns.Particle growth, unanticipated gelation propensity, unexpected dynamic of polymeric transitions, and occasionally burst release are all observed in nanoparticles [37-39].



APPLICATIONS OF NANOPARTICLES USED TO FORMULATE BUCCAL FILMS:

To induce stability and increase the release of the drug.

Ex: Preparation and characterization of insulin chitosan -nanoparticles loaded in buccal films [56].

To reducing dosing of short half- life drug especially pediatric patients having cancer.

Ex: Design of Antiretroviral drug polymeric nanoparticles loaded buccal films for chronic HIV therapy in pediatrics [57].

vaccines are used to deliver this formulation because to avoid first pass metabolism, easy to administer and also needed of small quantity of vaccines for formulation purposes.

Ex: overview and future potential of fast dissolving buccal films as drug delivery system for vaccines [58].

To increase of bioavailability of the drug and also increase the permeability of the drug.

Ex: Formulation and evaluation of Nano-based drug delivery system for the buccal delivery of acyclovir[59].

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4. NANOSUSPENSION:

DEFINITION OF NANOSUSPENSION:

Nanosuspension is a colloidal dispersion of drug particles that is submicron in size. A pharmaceutical nanosuspension is defined as a very finely colloid, biphasic, dispersed, solid drug particles in an aqueous vehicle with a size below 1m, no matrix material, stabilized by surfactants and polymers, prepared by suitable methods for drug delivery applications, through the use of surfactants and polymers.Absorption and bioavailability have been reported to be improved by nanosuspension. It may be useful in lowering the dose of convectional oral dosage forms [60].

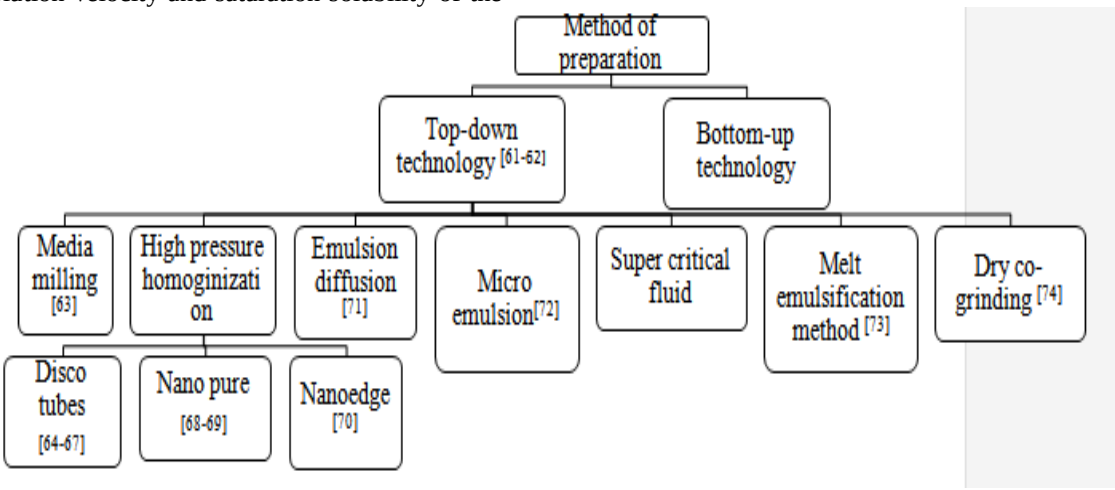
ADVANTAGES:

Nanosuspension increase in the dissolution velocity and saturation solubility of the drug,improved biological performance, Ease of manufacture and scale-up,Long-term physical stability, Versatility. Increase in the oral absorption, Improved dose proportionality**.** Its general applicability to most drugs & simplicity. It can be applied for poorly water- soluble drugs.Reduced tissue irritation in case of subcutaneous/intramuscular administration.

DISADVANTAGES:

Physical stability, sedimentation & compaction can cause problems. It is bulky sufficient care must be taken during handling & transport. Improper dose. Uniform & accurate dose cannot be achieved.

Method of preparation:



APPLICATIONS OF NANOSUSPENSION USED TO FORMULATE BUCCAL FILMS:

To avoid First pass metabolism.

Eg: Formulation and evaluation of Mucoadhesive films impregnated withcarvedilolNanosuspension: a potential approach for delivery of drugs having first pass metabolism[75]

To improve bioavailability and provide stability of the drug.

Eg:Development of stable Nanosuspension loaded oral films of glimepiride with improved bioavailability[76].

To improve the buccal absorption of the drugs having poor by water soluble drugs.

Eg:Particle size reduction to the monometer range: a promising approve to improve buccal absorption of poorly water-soluble drugs[77].

To improve solubility and gradual release of drug substances.

Eg:Clotrimazole Nanosuspension loaded hyaluronic acid catechol polyvinyl alcohol mucoadhesive films for oral candiasis treatment[78].

To provide stability of the drug.

Eg:Polymeric Nanosuspension loaded oral thin films of Flurbiprofen design,Development & Invitro Evaluation[79].

To increase solubility,permeability and also decreasing drug metabolism in the liver.

Eg:Formulation and development of oral fast dissolving loaded with Nanosuspension to Augment Paroxetine bioavailability;Invitro characterization,Ex-vivo permeation and pharmacokinetic evaluation in healthy human volunteers[80].

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5. Aquasomes Used To Formulate Buccal Films:

INTRODUCTION:

Aquasomes are a new type of spherical nano vesicular drug carrier with a size range of 60 to 300 nanometres. Different bonds, including as ionic, non-covalent, and van der Waals forces, act to self-organize these designs. Aquasomes are made up of three major components: a core substance, a covering material, and a medication that has been loaded. The coating material protects the loaded pharmacological bioactive chemicals from dehydration, while the core functions as a support for the polyhydroxy oligomers to improve the structural stability of the formulations.

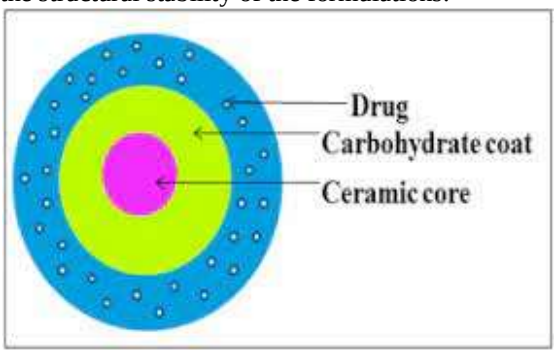

Figure 6: Structure of Aquasomes

ADVANTAGES:

Increases therapeutic efficiency of pharmaceutically active agents. Avoid multiple injection schedule.Offer favourable environment for proteins.Used for various imaging tests.Novel carrier for enzymes such as DNases and pigment\dyes.Act as a Vaccine delivery system.

DISADVANTAGES:

Poor Encapsulation efficiency for hydrophobic drugs,short half-life, Unstable membrane that results in leaky behaviour.

METHODS OF PREPARATION OF AQUASOMES:

The fabrication of Aquasomes is comparatively simple and straight forward synthesis with minimum use of solvents. In addition to that, for getting the required size, homogenization steps are not involved in their fabrication [81].

Step 1. Core fabrication

The first basic step for the establishment of Aquasomes is the fabrication of the core which is dependent on the material used for its preparation. Core can be prepared by means of colloidal precipitation, sonication, dendrimer method, plasma condensation, inverted magnetron sputtering, and other techniques. Preformulated cores are also available with different commercial suppliers [81-83]. Precipitation method Ceramic core can be prepared by coprecipitation with magnetic stirring under reflux conditions and self-precipitation technique. Coprecipitation by reflux: Diammonium hydrogen phosphate, (NH4)2HPO4, solution of 0.19 N is added into a calcium nitrate, Ca(NO3)2, solution of 0.32 M under continuous stirring in a drop-wise manner, maintaining the temperature at 75 °C. Then theobtained mixture isstirred&Shaked for six days. A precipitate of calcium phosphate forms. After filtering, washing thoroughly and airdrying overnight at 100 °C a powder form. The powder is then sintered to about 800-900°C using electric heater [84,85].

Step 2. Carbohydrate coating of the core

Several wet chemical analyses and lyophilization techniques are included in the coating process [82]. To achieve irreversible carbohydrate adsorption on the surface of the ceramics, carbohydrate is mixed into a dispersion comprising the core component, then sonicated and finally lyophilized. solvent addition and direct incubation are also mentioned as coating procedures [86]. Through agitated ultrafiltration cells, excess and unabsorbed carbohydrates are separated [87].

Step 3. Drug immobilization

The previous two methods, core preparation and coating are common for all aquasomal formulations. In this step the drug or the bioactive substance is adsorbed on the polyhydroxy oligomers.

Applications of Aquasomes used buccal flims:

1. Aquasomes are used to deliver the proteins and peptides.

Eg: Aquasomes a promising carrier for protein and peptides [88].

6. MICROEMULSION:

DEFINITION:

Microemulsions are characterized as "a single optically isotropic and thermodynamically stable liquid solution made up of water, oil, and amphiphile." Microemulsions develop spontaneously with droplet diameters ranging from 10 to 140 nanometers [89]. Surfactant is positioned

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at the definite boundary between the oil and water phases in microemulsions.

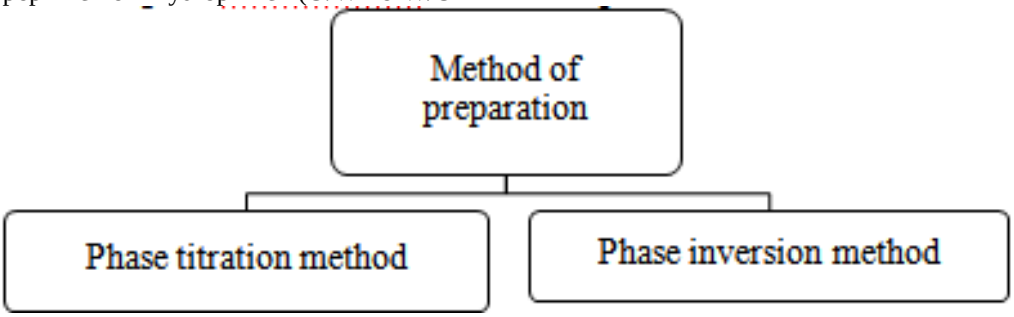
A polar head group area and a polar tail region were present in traditional surfactant compounds. Asymmetric microemulsions are common, taking on the shape of a prolate ellipsoid [90]. Microemulsions can be used to transport lipophilic chemicals through an aqueous medium or to transport hydrophilic substances across a lipoidal medium [91]. Microemulsions are translucent and the structure cannot be seen since the particle size is significantly smaller than the wavelength of visible light.

ADVANTAGES:

Microemulsions exhibit several advantages as a drug delivery system (94,95,96) Microemulsions are thermodynamically stable system and allows self-emulsification of the system. It act as supersolvents for drug, can solubilize both hydrophilic and lipophilic drugs including drugs that are relatively insoluble in both aqueous and hydrophobic solvents.The dispersed phase, lipophilic or hydrophilic (O/W orW/O microemulsions) can act as a potential reservoir of lipophilic or hydrophilic drugs, respectively. Drug release with pseudo-zero-order kinetics can be obtained, depending on the volume of the dispersed phase, the partition of the drug and the transport rate of the drug.The mean diameter of droplets in microemulsion is below 0.22 mm. This yield a large interfacial area, from which the drug is released rapidly into external phase when absorption (in vitro or invivo) takes place, maintaining the concentration in the external phase close to initial levels.

DISADVANTAGES:

Require large amount of S/Cs for stabilizing droplets.Limited solubilizing capacity for high-melting substances used in the system.The surfactant should be nontoxic for use in pharmaceutical applications.Microemulsion stability is influenced by environmental parameters such as temperature and pH.These parameters change as microemulsion delivered to patients.



Applications Of Microemulsion Loaded Buccal Films:

To improve bioavailability of the drug.

Eg: Assessment of improved buccal permeation and bioavailability of felodipine microemulsion based cross linked polycarbophill gel[97].

Increase the potential and efficacy of the drug.

Eg: Microemulsion containing triamcinolone acetamide for buccal administration[98].

To increase solubility,thereby increase bioavailability and hepatic pass metabolism.

Eg:Laminated sponges as challenging solid hydrophilic matrices for the buccal delivery of carvedilol microemulsion systems[99].

To avoid Irritancy of the drug.

Eg:Clotrimazole microemulsion and microemulsion based gel evaluation of buccal drug delivery and irritancy using chick chouoallantonic membrane as model[100].

II. CONCLUSION:

Buccal film has been identified as a suitable system for local as well as targeted drug delivery module. Carrier systems like liposomes, niosomes, Aquasomes and nanoparticles and other dispersion systems like nanosuspension and microemulsion are used to formulate buccal films in order to overcome the limitationsrelated todosing frequency,poor permeability,effects of first pass metabolism thereby increasing the bioavailability. Hencethe drug is being protected from the enzymatic as well as GIT irritation.As buccal films have good bioadhesive property, it gives rapid onset of action by increasing the contact time. The recent applications of the buccal film-based drug delivery system have been studied and are listed

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accordingly. Buccal film mediated delivery system holds immense possibility for future research with the aim of systemic delivery of orally inefficient drugs. It is feasible and alternative source for non-invasive delivery of low permeable,cytotoxic, enzymes, vitamins, proteins and peptides drug molecules. Hence the novel delivery system, employing buccal film as drug carrier, can be further investigated for its greatest contribution in improving the therapeutic efficacy of various drug candidates.

REFERENCE DETAILS:

[1]. 1.Akbari J, Nokhodchi A, Farid D, Adrangui M, Siahi-Shadbad MR, et al. (2004) Development and evaluation of buccoadhesive propranolol hydrochloride table formulations: Effect of fillers. Farmaco 59: 155-161.
[2]. Remunan-Lopez C, Portero A, Vila-Jato JL, Alonso MJ (1998) Design and evaluation of chitosan/ethyl cellulose mucoadhesive bilayered devices for buccal drug delivery. J Control Release 55: 143-152.
[3]. Rathborne M, Drummond B, Tucker I (1994) Oral cavity as a site for Systemic drug delivery. Adv Drug Deliv Rev 13: 1-22.
[4]. Hao J, Heng PWS (2003) Buccal delivery systems. Drug Dev lnd Pharm 29: 821-832.
[5]. Kurosaki Y, Kimura T (2000) Regional variation in oral mucosal drug permeability. Crit Rev Ther Drug Carrier Syst 17: 467-508.
[6]. Lee JW, Park JH, Robinson JR (2000) Bioadhesive-based dosage forms: the next generation. J Pharm Sci 89: 850-866.
[7]. Veuillez F, Kalia YN, Jacques J, Deshusses, Buri P (2001) Factors and strategies for improving buccal absorption of peptides. Eur J Pharm Biopharm 51: 93-109.
[8]. Sudhakar Y, Kuotsu K, Bandyopadhyay AK (2006) Buccal bioadhesive drug delivery- a promising option for orally less effective drug. J Control Release 114: 15-40.
[9]. Joseph RR, Vincent K L (1987) Lee controlled drug delivery. (2ndEdn), MarcelDekkerinc, New York, USA 42-43.
[10]. Pfister WR, Ghosh TK (2005) Drug delivery to the oral cavity molecules to market. Marcel Dekker, New York, USA.
[11]. Senel S, Ikinci G, Kas S, Yousefi-Rad A, Sargon M, et al. (2000) Chitosan films and hydrogels of chlorhexidine gluconate for oral mucosal delivery. Int J Pharm 193: 197-203.
[12]. Singh S, Jain S, Muthu MS, Tiwari S, Tilak R (2008) Preparation and evaluation of buccal bioadhesive films containing clotrimazole. AAPS Pharm Sci Technol 9: 660-667.
[13]. Danckwerts MP (2003) Intraoral drug delivery: A comparative review. Am J Drug Deliv 1: 149-224.
[14]. Squier CA (1991) The permeability of oral mucosa. Crit Rev Oral Biol Med 2: -32
[15]. Shojaei AH (1998) Buccal mucosa as a route for systemic drug delivery: A review. J Pharm Sci 1: 15-30.
[16]. Sahoo SK, Labhasetwar V: Nanotech approaches to drug delivery and imaging. DDT 2003, 8:24.
[17]. Gabizon A, Goren D, Cohen R, Barenholz Y: Development of liposomal anthracyclines: from basics to clinical applications. J Control Release 1998, 53:275–279.
[18]. Allen TM: Liposomes. Opportunities in drug delivery. Drugs 1997, 54(Suppl 4):8–14.
[19]. Chrai SS, Murari R, Imran A: Liposomes: a review. Bio Pharm 2001, 14(11):10–14.
[20]. Heba Abd El Azim,Noha Nafee,Alyaa Ramadana,Nawalk:liposomal buccal film for water soluble vitamins.International journal of pharmaceutics Volume 488pages 78-85
[21]. Gang Yang,Yaping Zhao,Yongtoi Zhang,Beilei Dang,Ying Liu and NianpingFeng:enhanced bioavailability of silymarin using liposomes.Int.j.Nanomedicines 2015;10:6633-6644.
[22]. Bao-Zhang jein,Xiao-qi Dang,Xin Xu Feng-Hezana:mucoadhesive patches of liposomal methotrexate for targeted delivery in oral cancer.Spandidos publications 2017pages 2541-2549.
[23]. Monica R.P.Roa,and Laxmi S.Babrekar:liposomal delivery of efavirenz buccal film.Int j pharm sci 2018;10(6):1115-1124.
[24]. Jianting Chen , Hao Pan , Yining Yang , Shihang Xiong , Hongliang Duan , Xinggang Yang , Weisan Pan:Self-assembled liposome for buccal delivery of drugs having high first-pass metabolism.Int.j.pharm 2018;547(1-2):303-314

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[25]. Baillie AJ., Florence AT., Hume LR., Muirhead GT., Rogerson A., The preparation and properties of niosomes non-ionic surfactant vesicles. J. Pharm. Pharmacol. 1985, 37: 863- 868.
[26]. Hunter CA, Dolan TF, Coombs G, Baillie AJ. Vesicular systems (niosomes and liposomes) for delivery of sodium stibogluconate in experimental murine visceral leishmaniasis. J Pharm Pharmacol 1988; 40:161-5.
[27]. Khandare JN., Madhavi G., Tamhankar BM., Niosomes Novel Drug Delivery System. The Eastern Pharmacist. 1994, 37: 61-64.
[28]. Rogerson A., Cummings J., Willmott N., Florence AT., The distribution of doxorubicin in mice following administration in niosomes. J. Pharm. Pharmacol. 1988, 40: 337-342.
[29]. Biju SS., Talegaonkar S., Misra PR., Khar RK., Vesicular systems: An overview. Indian J. Pharm. Sci. 2006, 68: 141-153.
[30]. Ijeoma F., Uchegbu., Suresh P., Vyas., Non-ionic surfactant-based vesicles (niosomes) in drug delivery. Int. J. Pharm. 1998; 172: 33–70
[31]. Ayat Allam,and Gihan Fetih.niosomal flims for enhancement of bioavailability of metoprolol.Drug Des Devel Ther.2016.10:2421-2433.
[32]. Mona G.Arofa,Dalia Ghalwash,Dina M.El - Keish &M.M.Elmazar propolis based niosomes as oromucoadhesion flims.Scientific reports 2018,18056.
[33]. Beeravelli,Akondi,Nimmathota.Invitro-Exvivoassesmentof simvastatin niosomal films.Bentham Science publisher.2012;150
[34]. Bhama Santhosh kumar,Rakhi Krishna,Lakshmi Ps,Deepa Vasudev,Sreeja c Nair.niosomal suspension of ceffixime.Asian journal of pharmaceutics &clinical Research.
[35]. Cristina Buzea, Ivan Pacheco, Kevin Robbie., Nanomaterials and Nanoparticles: Sources and Toxicity., Biointerphases.,2007; 2: MR17– MR71.
[36]. Paul JA, Borm and Wolfgang Kreyling., Toxicological Hazards of Inhaled Nanoparticles- Potential Implications for Drug Delivery., J Nanosci Nanotech., 2004; 4(6):1- 11. 3. Moh
[37]. Shinde N.C, Research Journal of Pharmaceutical, Biological and Chemical Sciences. Nanoparticles: Advances in Drug Delivery Systems,2012.
[38]. Nanogloss (2015,08). Retrievedfromhttp://nanogloss.com/nanotechnology/advantages-and-disadvantages-ofnanotechnology/#ixzz3hk6BD3SV.
[39]. Yadav N, (2013, 02 05). International Journal of Applied Pharmaceutics. Solid lipid nanoparticles- A Review.
[40]. Soppinath KS, Aminabhavi TM, Kulkurni AR, Rudzinski WE., Biodegradable polymeric nanoparticles as drug delivery devices., J Control Release., 2001; 70:1-20.
[41]. Tice TR, Gilley RM., Preparation of injectable controlled release microcapsules by solvent evaporation process., J Control Release., 1985; 2:343-352.
[42]. Vandervoort J, Ludwig A., Biodegradable stabilizers in the preparation of PLGA nano particles: a factorial design study., Int J Pharm., 2002; 238:77-92.
[43]. Ubrich N, Bouillot P, Pellerin C, Hoffman M, Maincent P., Preparation and characterization of propanolol hydrochloride nano particles: A comparative study., J Control release., 2004:291-300.
[44]. Catarina PR, Ronald JN, Antonio JR., Nano capsulation: Method of preparation of drug – loaded polymeric nanoparticles., Nanotech Bio med., 2006; 2:8-21
[45]. Quintanar-Guerrero D, Allemann E, Fessi H, Doelker E., Preparation techniques and mechanism of formation of biodegradable nanoparticles from preformed polymers., Drug Dev Ind Pharm., 1998; 24:1113-28.
[46]. Takeuchi H, Yamamoto Y., Mucoadhesive nanoparticulate system for peptide drug delivery., Adv Drug Del Rev., 2001; 47: 39-54.
[47]. El-shabouri MH., Positively charged nano particles for improving the oral bioavailability of cyclosporine-A., Int J Pharm., 2002; 249:101- 8.
[48]. Vargas A,Pegaz B, Devefve E, KonanKouakou Y, Lange N, Ballini JP., Improved photodynamic activity of porphyrin loaded into nano particles: an in vivo evaluation using chick embryos., Int J Pharm., 2004; 286: 131- 45.
[49]. Yoo HS, Oh JE, Lee KH, Park TG., Biodegradable nanoparticles containing PLGA conjugates for sustained release., Pharm Res., 1999; 16: 1114-8.

[50]. Fessi H, Puisieux F, Devissaguet JP, Ammoury N, Benita S., Nano capsule formation by interfacial deposition following solvent displacement., Int J Pharm., 1989; 55:R1-R4.
[51]. Chorney M, DAneuberg H, Golomb G., Lipophilic drug loaded nanospheres by nano precipitation: effect of the formulation variables on size, drug recovery and release kinetics., J Control release., 2002; 83: 389-400.
[52]. Puglisi G, Fresta M, Giammona G, Ventura CA., Influence of the preparation conditions on poly(ethylcyanoacrylate) nanocapsules formation., Int J Pharm., 1995; 125: 283-287.
[53]. Calvo P, Remunan-Lopez C, Vila-Jato JL, Alonso MJ., Novel hydrophilicchitosanpolyethylene oxide nanoparticles as protein CarrierJ Appl Polymer Sci., 1997; 63: 125- 132.
[54]. Calvo P, Remunan-Lopez C, Vila-Jato JL, Alonso MJ., Chitosan and chitosan/ethylene oxide-propylene oxide block copolymer nanoparticles as novel carriers for proteins and vaccines., Pharm Res., 1997; 14: 1431-1436.
[55]. Nusaiba.K. Al Nemrawi,Sara.S.M.Alsharif,Karem.H.Alzoubi,Rami Q Alkhatib. Insulin chitosan nanoparticles loaded in buccal films.Pharmaceutical Development &Technology.2018pages 967-974.
[56]. Design of Antiviral drug polymeric Nanoparticles loaded buccal films.Colloid and Interface science communications.2018,volume 27,pages 49-59.
[57]. Mohammad Nasi uddin,Amanda Allan,Monzurull A Roni,Samii Kowzi.vaccines of nanoparticles loaded in buccal films,Journal of pharmacy &pharmaceutical sciences 201922(1),388-406.
[58]. Bandel E Al.Dhubiab,Anroo P Nair,Rachna Kumria,Mahesh Attimarad.Colloidsand surface B:Bio interfaces 136 (12) :878-884.
[59]. Xiaohui P, Jin S, Mo L, Zhonggui H, Formulation of Nanosuspensions as a New Approach for the Delivery of Poorly Soluble Drugs, Current Nanoscience 2009; 5: 417-427
[60]. Patil SA, Rane BR, Bakliwal SR, Pawar SP, Nanosuspension: At A Glance, International Journal of Pharmaceutical Science, 2011; 3(1): 947-960.
[61]. Bansal.S, Bansal M, Kumria R, Nanocrystals: Current Strategies and Trends, International Journal of Research in Pharmaceutical and Biomedical Sciences, 2012; 3 (1): 406- 419.
[62]. Pandey S, Nanosuspension: Formulation, Characterization and Evaluation, International Journal of Pharma and Bio Sciences, 2010; 1(2): 1-10.
[63]. Kumar GP, Nanosuspensions: The Solution to Deliver Hydrophobic Drugs, International Journal of Drug Delivery, 2011; 3: 546-557.
[64]. Kumar BS, Review Article Increasing Possibilities of Nanosuspension, Journal of Nanotechnology, 2013: 1-12.
[65]. Battula SR, Nano Fabricated Drug Delivery Devises, International Journal of Pharmacy & Technology, 2012; 4 (1): 1974-1986.
[66]. Venkatesh T, Nanosuspensions: Ideal Approach for the Drug Delivery of Poorly Water- Soluble Drugs, Der Pharmacia Lettre, 2011; 3(2): 203-213.
[67]. Paun JS, Nanosuspension: An Emerging Trend for Bioavailability Enhancement of Poorly Soluble Drugs, Asian J. Pharm. Tech, 2(4), 2012, 157-168.
[68]. Vaghela A, Nanosuspension Technology, International Journal of Universal Pharmacy and Life Sciences, 2012; 2(2): 306-317.
[69]. Bhargavi A, Technical Review of Nanosuspensions, International Journal of Pharmacy & Technology, 2011; 3(3): 1503-1511.
[70]. Verma KAK, Nanosuspensions: Advantages and Disadvantages, Indian Journal of Novel Drug Delivery, 2012; 4(3): 179-188.
[71]. Srinivasa RK, an Overview of Statins as Hypolipidemic Drugs, International Journal of Pharmaceutical Sciences and Drug Research, 2011; 3(3): 178-183.
[72]. Koteshwara KB, Nanosuspension: A Novel Drug Delivery Approach, IJRAP, 2011; 2(1): 162-165.
[73]. Mudgil M, Gupta N, Nagpal M, Pawar P, Nanotechnology: A New Approach for Ocular Drug Delivery System, International Journal of Pharmacy and Pharmaceutical Sciences, 2012; 4(2): 105-112.
[74]. Priyanka Rana &R.S.R.Murthy,Mucoadhesive films impregnatedwith carvedilol

Nanosuspension,Drug delivery ,2013,pages 224-235.

[75]. VishaliKilor,Nindhi sapkal,Anwar Daud,Shruthi humne,Tushar Gupta,Nanosuspension loaded oral films of glimipride,International Journal of Applied Pharmaceutics,2017,Vol 9,issue 2.

[76]. Shasho Rao, Yumei song,Frank Peddie &Allan & evans,a promising approach to improve buccal absorption of poorly water - soluble drugs,Int.J.Nanomedicine 2011;6:1245-1251.

[77]. Chaiyakarn pornpitchanarong,Theerasak Rajanarata,Praneet Opanasopit,clotrimazole Nanosuspension loaded hyaluronic acid - Catechol/Polyvinyl alcohol Mucoadhesive films,Journal of Drug Delivery Science and Technology,Volume 60,Dec.2020,101927.

[78]. Jadhav Pankoja,Yadhav Adhikraov,Nanosuspension loaded oral thin films of Flurbiprofen,Research Journal of pharmacy and Technology,2020,Volume13,issue 4.

[79]. Almed Hassan,Elshafeey, Rania Moatoz El-Dahmy,oral fast dissolving films loaded with Nanosuspension of paroxetine,National Library of Medicine,2021 Nov 5;13(11):1869.

[80]. Narang, N., 2012. Aquasomes: Self-assembled systems for the delivery of bioactive molecules. Asian J. Pharm. 6, 95–100. https://doi.org/10.4103/0973-8398.102931

[81]. Jain, S.S., Jagtap, P.S., Dand, N.M., Jadhav, K.R., Kadam, V.J., 2012. Aquasomes: A novel drug carrier. J. Appl. Pharm. Sci. 2, 184–192.

[82]. Umashankar, M.S., Sachdeva, R.K., Gulati, M., 2010. Aquasomes: a promising carrier for peptides and protein delivery. Nanomedicine Nanotechnology, Biol. Med. 6, 419–426. https://doi.org/10.1016/j.nano.2009.11.002

[83]. Vengala, P., Aslam, S., Subrahmanyam, C.V.S., 2013a. Development and in vitro evaluation of ceramic nanoparticles of piroxicam. Lat. Am. J. Pharm. 32, 1124–1130.

[84]. VengalaP, Dintakurthi, S., Subrahmanyam, C.V.S., 2013b. Lactose coated ceramic nanoparticles for oral drug delivery. J. Pharm. Res. 7, 540–545. https://doi.org/10.1016/j.jopr.2013.06.015

[85]. Mukherjee, B., Satapathy, B.S., Bhattacharya, S., Chakraborty, R., Mishra, V.P., 2017. Pharmacokinetic and Pharmacodynamic Modulations of Therapeutically Active Constituents. Elsevier Inc. https://doi.org/10.1016/B978-0-323-52727-9.00019-4

[86]. Banerjee, S., Sen, K.K., 2018. Aquasomes: A novel nanoparticulate drug carrier. J. Drug Deliv. Sci. Technol. 43, 446–452. https://doi.org/10.1016/j.jddst.2017.11.011.

[87]. Marakanam s,Umashankar,Rajesh,Sachedeva,Monica,Aquasomes are used to deliver the protein delivery,Drug delivery,3Nov 2009.

[88]. Derle D V, Sagar B S H, Rohini Pimpale, Microemulsions as a vehicle for transdermal permeation of nimesulide,Indian J pharm sci., 68 (2006) 624-625.

[89]. Sushama Talegaonkar, Adnan Azeem, Farhan J. Ahmad, Microemulsions, A Novel Approach to Enhanced Drug Delivery., Recent Patents on Drug Delivery & Formulation., 2 (2008) 238- 257

[90]. Anna radomska soukharev, Joanna wojciechowska, Microemulsions as potential ocular drug delivery systems: Phase diagrams and physical properties depending on ingredients,Acta poloniac pharmaceutical drug research., 62 (2005) 465-471.

[91]. Sumedha Nadkar, Chandrakant Lokhand, Current Trends in Novel Drug Delivery an OTC Perspective, Pharma Times., 42 (2010) 17-23.

[92]. Vandamme Th F, Microemulsions as ocular drug delivery systems: recent developments and future challenges, Progress in retinal and eye research., 21 (2002) 15-34.

[93]. Kumar. K. Senthil, Dhachinamoorthi. D, Saravanan. R; Microemulsions as Carrier for Novel Drug Delivery: A Review; International Journal of Pharmaceutical Sciences Review and Research., 10 (2011) 37-45.

[94]. Patel R. Mrunali, Microemulsions: As Novel Drug Delivery Vehicle., 5 (2007).

[95]. Madhav. S, Gupta. D, A review on microemulsion based system, IJPSR., 2(8) (2011) 1888-1899.

[96]. Mahendra Singh,Jovita Kanorija,Poonam Parashar,Malti Arya,Assessment of improved buccal permeation and bioavailability of felodipine,Drug Delivery and Translational Research,8,591-601(2018)

[97]. C.padula,I.Telo,A.DiLanni,S.Pescina,S.Nicoli,P.Santi,Microemulsion containing triamcinolone acetamide for buccal administration,Pharmaceutical,Volume 115,pages 233-239.
[98]. Ahmed Abd-Elbary,Amina M.A.Makky,Mina Ibrahim Tadros,Ahmed Aloa -Eldin,Laminated sponges as challenging solid hydrophilic matrices for the buccal delivery of Carvedilol,European Journal of Pharmaceutics Sciences,Volume 82,2016,pages 31-44.
[99]. Jarika Kaewbonjong,Paul wan sia heng,Prapaporn Boonme,Clotrimazole microemulsion based gel evaluation of buccal drug delivery,Journal of pharmacy and pharmacology,Volume 69,Issue12,pages 1716-1723.