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# Self Micro Emulsifying Mouth Dissolving Film (SMMDF) : A Novel Formulation for Poorly Water Soluble Drugs

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**Abstract :**
Self -microemulsifying mouth dissolving film (SMMDF) is a new dosage form, an integration of self-microemulsifying drug delivery system in a fast mouth dissolving film. Self microemulsifying drug delivery system(SMEDDS) is an isotropic mixture of oil, surfactant and co surfactant. Upon mild agitation followed by dilution in an aqueous medium (gastrointestinal fluids), this system can form fine oil-in-water (o/w) microemulsion. Due to their small droplet size they can provide large surface area of absorption and improve the oral bioavailability of drug than any other drug delivery systems. The composition of SMEDDS improve the solubility of poorly water soluble drugs in aqueous medium. Fast mouth dissolving films are complex polymeric matrices that can disintegrate/dissolve in the mouth within short time. After dissolution, the drug get available in the oral cavity for buccal mucosa absorption and reach the systemic circulation without undergoing pre-systemic metabolism of drug. These also have some advantages over other oral formulations including convenience to transport and store, availability of larger surface area for absorption, ease of swallowing without additional liquid especially for patients with dysphagia, vomiting, dyskinesia, and psychonosema.

**Keywords:** Oral Bioavailability, Poorly Water Soluble Drugs, Self-Microemulsifying Mouth Dissolving Film, Solvent Casting Method.

## INTRODUCTION:

More than 40% new chemical entities developed are practically insoluble in water. For absorbtion, drug must be present in the form of solution at the site of absorption. That means solubility is a major challenge for formulation scientist[1]. Poor solubility and improper drug absorption leads to low bioavailability, and also affect the efficacy and safety of the product[2]. A number of physicochemical properties contribute the poor solubility to drugs, which include their complex structure, size, high molecular weight, high lipophilicity, compound H-bonding to solvent, intramolecular H-bonding, intermolecular H-bonding (crystal packing), crystallinity, polymorphic forms, ionic charge status, pH, and salt form[3]. To improve their solubility, dissolution rate and absorption Formulation scientists adopt various strategies include Particlesize Reduction, Nanonization , Co-solvency , Hydrotropy, pH Adjustment , Sonocrystallization, Supercritical Fluid (SCF) Process , Solid Dispersion , Inclusion Complexation , Self-Emulsifying Or Self-Micro Emulsifying Systems , Liquisolid Methods etc..[4]

Self-emulsifying drug delivery systems is popular and commercially practicable formulation approaches for solving these problems. SMEDDs can effectively improve the solubility and oral bioavailability of poorly water-soluble drugs[5]. SMEDDS generally consists of drug, oil , surfactant, co-surfactant and co-solvents. The basic principle of this dosage form is to form fine oil-in-water (o/w) microemulsions under gentle agitation following dilution by aqueous phases [6] and improve bioavailability by affecting the drug absorption[7].

Oral route is the most convenient, usually the safest and least expensive route, also it is the one most often used. Per-oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract especially peptides and proteins. To over come this buccal mucosa drug administraton is used. Because advantages of this route include bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora for drug absorption[8].

For oral administration of drugs mainly solid and liquid oral dosage forms are used. Solid dosage form mainly include tablets and capsules. But they show poor patient compliance among pediatric and geriatric patients due to their difficulty in swallowing[9]. So that formulation of age-adapted and misuse-adapted dosage form is one of the priorities in the design of oral dosage forms. Liquid formulations exhibit greater patient compliance than solid oral dosage forms. They also allow an easier dose adjustment according to patient's age and weight. But on the other side, many drugs are not stable in liquid and the formulation must be palatable in order to retain patient acceptability[10].

To overcome these, oral fast dissolving drug deliveries have been developed. Oral fast dissolving dosage forms manufactured by variety of technologies, including direct compression, wet granulation and freeze drying, etc..[11]. Mouth dissolving film is a novel approach among oral drug delivery system as it provides convenience and ease of administration over other dosage forms such as orally disintegrating tablets, buccal tablets and sublingual tablets. That's why mouth dissolving films are gaining the interest of large number of pharmaceutical industries. Mouth dissolving film developed on the basis of technology of transdermal patch. Mouth dissolving films are thin solid dosage forms which dissolve within few seconds after placed in the oral cavity, without chewing and intake of water[12].

### Self micro emulsifying mouth dissolving film

A Self micro-emulsifying mouth dissolving film (SMMDF) is a new dosage form. Very few research

papers found during literature review . It showed in Table 1. In India only one research paper is reported. That paper is published by Seema Venkatrao Pattewar, Department of Pharmacy, Banasthali University, Banasthali, Rajasthan, INDIA [13]. SMMDF is based on mouth dissolving film integrated with self microemulsifying components [14] . This formulation show advantage of these 2 dosage forms. According to the survey found that SMMDF have greater potential for enhancing oral dissolution and bioavailability of poorly water soluble drug. Before this solid SMEDDS (S-SMEDDS) prepared by solidification of liquid/semisolid self-micro emulsifying ingredients into powder form. Because liquid formulation produce some disadvantages such as high production costs, low stability, portability, low drug loading, drugs/excipients precipitation[15], Storage, handling, Limited targeting to lymphatics [16]and few choices of dosage forms. Solid SMEDDS need more time to give action due to the disintegration process. But in the case of SMMDF, it dissolves in saliva within 20mint and form o/w micro-emulsion in mouth leads to the buccal absorption. Through this, solubility enhancement, pre-systemic metabolism bypass and increase in oral bioavailability can achieve. That is SMEDDF is a better choice for delivery of poorly water soluble drugs.

## MATERIALS AND METHODS :

### Steps involved in the formulation of SMMDF

Mainly 2 steps are involved in the preparation of SMMDF. First step include formulation of liquid SMEDDS by the selection of appropriate component selection and second incorporation of liquid SMEDDS to water soluble polymeric matrix [17].

### Formulation of SMEDDS

A large number of oils and surfactants can be used as components of microemulsion systems according to their compatibility with drug. But their toxicity, irritation potential and un-clear mechanism of action limit their use. The selected materials must be biocompatible, non-toxic, clinically acceptable and use emulsifiers in an appropriate concentration range that will result in good micro-emulsions. Early studies revealed that the self-microemulsification process is specific to the nature of the oil/surfactant pair, the surfactant concentration, oil/surfactant ratio, the concentration and nature of co-surfactant, surfactant/co-surfactant ratio and the temperature at which self-microemulsification occurs. From this can be concluded that only very specific combinations of pharmaceutical excipients could be used for the preparation efficient self- microemulsifying systems[18].

### Selection of oil, surfactant and co-surfactant

Selection of components done by drug solubility test. Excess amount of drug was added into each test tube containing 2 ml oils, surfactants, and co-surfactant. These mixtures mixed for 10 min with vortex mixer. After that samples were incubated in a shake water bath at 25°C for 48 -72h and then centrifuged at 3000 rpm for 10-15 min to separate the undissolved drug. The supernatants were filtered with a 0.45-µm filter membrane, and the drug content was quantified by high-performance liquid chromatography (HPLC) method or ultraviolet-visible (UV-VIS) spectrophotometer [19,20]. oil, surfactant and co surfactant in which drug show superior solubility are selected to achieve optimum drug loading and to minimize the final volume[21].

### Preliminary screening of surfactants for emulsification efficiency

Different surfactants were screened for its emulsification ability in the selected oily phase. Surfactant selection was done on the basis of transparency percentage and ease of emulsification [14]. Equal amount of each surfactant and selected oil are mixed. The mixtures were gently heated at 50°C for 2 min to achieve homogenization of components. From each mixture, 100 µl were then diluted with distilled water up to 50 ml in glass stoppered flask. The stoppered flasks were inverted several times and the number of flask inversions required to form a homogenous microemulsion (with no turbidity or phase separation) was counted. Additionally, the formed emulsions were allowed to stand for 2 h and their percentage of transmittance was estimated at UV-Vis Spectrophotometer by distilled water as blank. The percentage of transmittance was calculated for each sample in triplicates and the average values ± SD were calculated. The surfactant forming a clear emulsion per less inversions and a higher percentage of transmittance was selected.

### Preliminary screening of co-surfactants for emulsification efficiency

The selected oil and surfactant were used for further screening co-surfactant from different co-surfactants based on emulsification efficiency. Mixtures of each co-surfactant, selected surfactant and selected oil were prepared in the ratio of 1:2:3 and evaluated in the same manner as described in preliminary screening of surfactants[22].

### Construction of pseudo-ternary phase diagram

Construction of pseudo-ternary phase diagram helps to optimize the proportion of components that can form prefect SMEDDS. Values for constructing phase diagram obtained by water titration method at room temperature, using selected oil, surfactant, co-surfactant and DM water as an aqueous phase. Surfactant and co-surfactant were mixed in different weight ratios (1:1, 1:2, 1:3, 2:1,3:1 etc..), named as Smix by vortex mixer for 5min followed by place at 50ºC for 1hr. The Smix ratio was chosen in increasing concentration of one components with respect to other. Each of this Smix were mixed with oil in different weight ratios ranging from 1:0 to 0:1 (1:0, 0.9:0.1, 0.8:0.2, 0.7:0.3, 0.6:0.4, 0.5:0.5, 0.4:0.6, 0.3:0.7, 0.2:0.8, 0.1:0.9, 0:1) in different glass vials using vortex mixer for 5min and place in 50ºC for 1hr, for getting isotropic mixture. The water was titrated slowly with each isotropic mixture and visually observed for transparency or turbidity in the system. After every addition of water, the mixture was stirred on vortex mixer. If a clear and transparent mixture was obtained after stirring, the sample was considered monophasic. Every composition of monophasic emulsion was marked as a point in the phase diagram using Chemix software. The area covered by

these points was considered to be the microemulsion region of existence[23].figure 1 represent the pseudo ternary diagram.

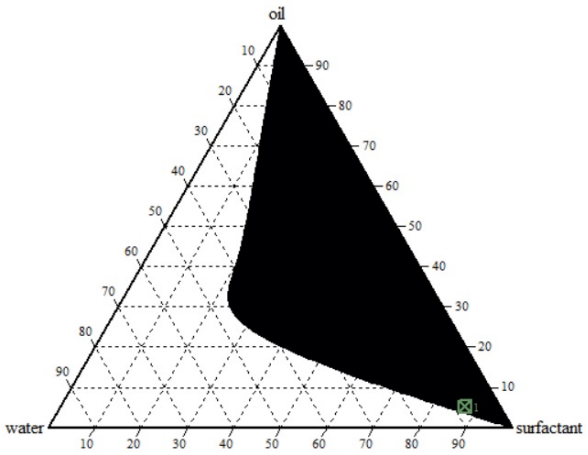


**Fig. 1 : Representation of pseudo-ternary diagram**

**Preparation of SMEDDS**

From the ternary phase diagram ratio of surfactant to co-surfactant (smix) was optimized with broad area. Optimized surfactant and co surfactant are accurately weighed and then vortexed for 5-10 min for smix preparation. After that, smix was placed in oven at 50ºC for 1 h. Then oil added to smix and vortexed for 5-10 min and placed in oven at 50ºC for 1 h with the purpose of an isotropic mixture was formed. Drug was loaded to these isotropic formulations at the end and vortexed by vortex shaker until clear solution was obtained[24]. Table 3 gives information related to the evaluation methods of SMEDDS.

**Preparation of SMMDF**

The film-forming solution was prepared by mixing selected water soluble polymer, plastisizer in a certain amount of water and added with flavouring agent, sweetening agent, and colour. Amount of all ingredients reported in table 2 . The emulsifier solution was added into the prepared film-forming solution, fixed the volume with water and stirred systematically until it form milky white mixture. The mixture then introduced into a special mold after removing the entrapped air and dried at 40°C in dark, the film was cut into desired sizes to get the final product[29].

**Methods of preparation**

One or more combinations of the following process can be used to manufacture the fast dissolving films-

**Solvent casting method**: In solvent casting method water soluble polymers are dissolved in water and the drug and other excipients is dissolved in suitable solvent . Then both the solutions are mixed with stirring and finally casted in to the Petri plates or mold, dried and cut in to uniform dimensions.

**Semisolid casting method**: In semisolid casting method, at first film forming solution is prepared using selected water soluble polymer. This polymer solution is added to a solution of acid insoluble polymer (e.g. cellulose acetate phthalate, cellulose acetate butyrate), which was prepared in ammonium or sodium hydroxide. To this appropriate amount of plasticizer is added to get a gel mass. Finally the gel mass is casted into the film or ribbon. The thickness of the film obtained by this method is about 0.015-0.05 inches. The ratio of the acid insoluble polymer to film forming polymer should be 1:4.

**Hot melt extrusion method**: In hot melt extrusion method, the drug is mixed with carriers in solid form. Then introduced into extruder having heaters, they melts the mixture. At the end, the melt is shaped in to films by the dies.

**Solid dispersion extrusion method**: In this method, immiscible components mixed with drug and then solid dispersions are prepared. Finally the solid dispersions are shaped in to films by means of dies.

**Rolling method**: In rolling method, solution or suspension of drug in suitable solvent is rolled on a carrier. The solvent is mainly water and water-alcohol mixture. The film is dried on the rollers and cut into desired shapes and sizes.[3031,32,33]

**Spray technique:**Drug substance, polymers and all other excipients are dissolved in a suitable solvent to form a clear solution. This clear solution is then sprayed onto suitable material such as glass, polyethylene film of non-siliconized Kraft paper or Teflon sheet.

**Flexoprinting or Flexographic printing technology (FPT)**: In this process drug transferred into thin films by contact printing. The flexographic printing is a rotary printing process. Measure ink solution or suspension consisting of drug by an anilox roller. Then it transferred to a printing cylinder that prints the film after unwinding the daughter roll. This process mainly used for heat sensitive products like proteins and peptides. The production efficiency is high as the production rate of 530 oral films per minute. Hence this used as scale-up process in production.

**Inkjet printing**: Inkjet printing is the recently developed technology, which is regarded as by its versatility, accuracy, repeatability and inexpensive method. Through this process, only deposits small volumes of solution in films. Inkjet printing is widely applicable for the preparation of low dose drug and also proposes a chance to fabricate personalized medicines. Dissolve the drug in ink with optimal properties (viscosity and surface tension) for printability. Deposition done by printing. After printing separate the printed patterns by cutting and inserting into capsule shells or folded to form the final therapeutic dosage forms or coated in an appropriate manner[34].

**Advantages of SMMDF**

a) Convenient dosing.
b) No water needed.
c) Enhanced stability.
d) Water insoluble drugs also incorporated
e) Improved patient compliance.
f) The drug enters the systemic circulation with reduced hepatic first pass effect.
g) Availability of large surface area that leads to rapid disintegration and dissolution within oral cavity.

h) There is no risk of chocking[35,36].
i) Bitter taste drugs can also encorporated due to taste masking capacity of SMEDDS [37s].

**Disadvantages of SMMDF**

a) Only low dose drug can be incorporated (less than 30 mg).
b) Dose uniformity is a challenge.
c) It takes moisture from atmosphere.
d) Packaging of films requires special equipments and it is difficult to pack[14,36].

**Drug selection criterias for SMMDF**

SMMDF is useful for poorly water soluble and low oral bioavailability drugs. That means BCS Class II and IV drugs are good candidates for SMMDF. Drug lipophilicity (log P) is a main criteria for design of SMMDF. Drug with log P value 2 to 4 is desirable. Drugs which have low solubility in lipids are difficult to deliver through SMMDF. Drugs which are administered in very high dose are not suitable for formulation. Otherwise they have extremely good solubility in at least one of the components of SMEDDS, preferably in oil phase. The drug should have smaller and moderate molecular weight[38,39]. Because that provide ease of buccal absorption of drug.

Melting point of drug can alter the product solubility and partition coefficient of drug. Low melting point drugs are more absorbed than high melting point ones. Chu KA et al, derived a relationship between melting point and passive transport for poorly soluble drugs. It based on expression derived from the General Solubility Equation (GSE) that relates melting point to the product of intrinsic solubility and partition coefficient. According to that study concluded that lower melting compounds are more likely to be well absorbed than higher melting compounds for any given dose. The fraction absorbed for drugs with high melting temperatures is limited by the dose to a greater degree than it is for low melting compounds.[40]

**Evaluation of SMMDF**

**Weight Variation**

Take 1 $cm^2$ film from different batches of the formulations and determine the weight on electronic balance. The estimations are carried out in triplicate.

**Film thickness**

Film thickness is measured by using micrometer screw gauge or calibrated digital vernier calliper. Measure the thickness of sample in ten different positions. Perform it in triplicate and calculate the average value. This evaluation is necessary to calculate the uniformity of thickness which is directly related to accuracy of dose in the film.

**Tensile strength**

Evaluation done by using Tensilometer. Tensile strength is defined as maximum stress required for the film breaking. This test is execute to measure the mechanical strength of film. It can be calculated by following equation:

Tensile strength = load at failure*100/ strip thickness*strip width

**Folding endurance:**

Determine folding endurance by repeated folding of the film at the same place till the film breaks. The number of times folded without breaking is noted as the value.

**Surface pH:**

Determination pH value by touching the surface of film is made wet by using distilled water with a pH meter electrode. Surface pH determination is important, because acidic or basic pH is liable to cause oral mucosal irritation.

**Petri dish method**

A film is place onto 2 ml distilled water in a petri dish. Time taken by the film to dissolve completely is measured as the disintegrating time.[41]

**Droplet size of re-constituted microemulsion:**

The average droplet size of liquid SMEDDS and from SMMDF is measure by correlation spectroscopy at a scattering angle of 90°at 25°C. Liquid SMEDDS or SMMDF is add to 25 mL of distilled water and shake gently to form a fine emulsion and keep it for 12 h at 25°C. Perform it in triplicate and calculate the average value .

**X-ray diffraction**

It perform to determine the physical state of drug in SMMDF. To identify this, powder X-ray diffraction (XRD) spectra of formulations are collected. A voltage of 36 kV and a current of 30 mA were applied with Copper tube as anode material. The solids were exposed to a Cu–Ka radiation, over a range of 2θ angles from 2°-50°, at an angular speed of 2 deg/min. sampling interval is about 0.02°.

**Morphological analysis of SMMDF**

The determination outer macroscopic surface characteristics of SMMDF by using SEM (scanning electrone microscopy). In this method fix the sample on a SEM-stub using double-sided adhesive tape and then coat with a thin layer of gold.

**In vitro dissolution test**

The dissolution test is perform on paddle type dissolution apparatus in 900 mL of phosphate buffer (pH 6.8) at 37°C with a paddle speed of 100 rpm and sink conditions must meet. The 2× 2 $cm^2$ film containing drug is used. Samples for analysis collect at equal intervals and filter. Concentrations of drug is determined by HPLC.

**Stability studies**:

Stability studies carried out according to ICH Q1A (R2) guidelines. Pack the films in aluminium foil, store at 30±2° and 75±5 % RH for several months for long-term testing in stability chamber.

**Table 1** : Research Work Related To SMMDF

| Title | Researcher | Journal name |
|---|---|---|
| 1. A new self-microemulsifying mouth dissolving film to improve the oral bioavailability of poorly water soluble drugs | L. Xiao et al | Drug Development and Industrial Pharmacy, 2012 |
| 2. Self-microemulsifying oral fast dissolving films of vitamin D3 for infants: Preparation and characterization | Zhang et al | Food Science and Nutrition, 2019 |
| 3. Fabrication and Characterization of Self-microemulsifying Mouth Dissolving Film for Effective Delivery of Piroxicam | Pattewar et al | Indian journal of pharmaceutical sciences,2019 |

**Table 2:** Composition of Mouth Dissolving Film

| Ingredients | Percentage |
|---|---|
| Drug | 5-30%w/w |
| Water soluble polymer | 45%w/w |
| Plastisizers | 0-20%w/w |
| Surfactants | q.s |
| Sweetening agents | 3-6%w/w |
| Saliva stimulating agents | 2-6%w/w |
| Flavors, colors, fillers | q.s |

**Table 3:** General Evaluation of SMEDDS

| Parameter | Evaluation |
|---|---|
| 1. Precipitation and phase separation | Visual inspection after diluted with 250ml distilled water at 37°C. Mix the preparation in vortex shaker for 5 minutes and store the mixture for 24 hours. Electoconductometer[25,26,27,28] |
| 2. Zeta potential | Photon correlation spectroscopy |
| 3. Droplet size | laser diffraction analysis using particle size analyzer |
| 4. Drug Content | calibration curve by using UV |
| 5. Percentage transmittance | Measure transmittance at 640.2 nm using UV-visible spectrophotometer after Reconstitute the SMEDDS with distilled water (1:100) |
| 6. Thermodynamic Stability studies | Centrifugation and freeze thaw stress test |
| 7. Cloud point measurement | Add 50 ml of water and placed on a water bath with gradually increase the temperature until the diluted formulation turned to cloudy. |
| 8. Efficiency of self-emulsification | Dispersibility test |
| 9. Electro conductivity Study | Electoconductometer[25,26,27,28] |

## CONCLUSION:

Self-emulsifying mouth dissolving film is hopeful approach for the formulation of drugs with poor aqueous solubility, pre systemic metabolism, Enzymatic degradation, gastric irritation, limited dissolution rate and low bioavailability. SMMDF is used to improve solubility of a poorly water soluble drug and provide quick onset of action. Solid –SMEDDS has ability to improve the stability of formulation and solubility, But it cannot bypass the first pass metabolism. SMMDF is commercial because it can incorporate small quantity of drug and needs less complicated machineries. So we can conclude that SMMDF is an exclusive and industrially practicable approach to overcome the problem of low solubility and low bioavailability of BCS class II and IV drugs.

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