

# A Review Article on Self - Micro Emulsifying Mouth Dissolving Film

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**Abstract:** Article aims to formulate a self micro emulsifying mouth dissolving film (SMMDF) is a novel dosage form, an integration of the self microemulsifying drug delivery system (SMEDDS) in SMMDF. Preformulated SMEDDS increases the solubility of class - 2 and class 4 drugs biopharmaceutical classification and these SMEDDS incorporated into mouth dissolving film that are targeted for diseases like angina pectoris, congestive heart failure, Asthma, Parkinson's convulsions, Anti histamine etc, by enhancing absorption rate through oral absorption, avoid first pass metabolism, and show rapid/quick onset of action. SMEDDS are the isotropic mixtures of oil, surfactant, co - surfactants upon mild agitation followed by dilution with aqueous medium (gastro - intestinal fluids) this system can form oil - in - water (o/w) micro emulsion having small globular size they can provide large surface area for absorption and improve oral bioavailability of drug. SMEDDS are liquid, that improve the solubility of poorly water soluble drugs in aqueous medium having stability problems of liquid. To stabilize the liquid SMEDDS are incorporated into complex polymeric matrices oral fast dissolving films that can be disintegrate / dissolve in the mouth within 5 minutes.

**Keywords:** Integration, mouthfilm, preformulated, polymeric matrices, self microemulsifying drug delivery

## 1. Introduction

Every drug has its own physicochemical properties that ultimately facilitates solubility of the drug in water (blood stream) i.e. hydrophilicity and permeability of the drug to cross the cell membrane i. e. lipophilicity. Based on solubility and permeability, drugs are biopharmaceutically classified into four classes. About 30% drugs are insoluble in water, poor solubility and improper drug absorption leads to low bioavailability affect the efficacy and safety of the drug. the physio - chemical properties responsible for the poor solubility of the drug which include their complex structure size, high molecular weight, high lipophilicity, compound H - bonding to solvent, crystallinity, PH, their solubility, dissolution rate. Scientists adopt various strategies include particle size reduction, nanonization, cosolvency, hydrotrophy, sono crystallization supercritical fluid (SCF) process, self emulsifying systems (SMEDDS, SNEDDS), lipid - solid emulsions<sup>[1] [2]</sup> (SMMDF) is a novel drug delivery based on mouth dissolving film integrated with self - micro emulsifying components (SMEDDS) having great potential for oral dissolution of poorly water soluble

Liquid SMEDDS of drug was prepared, followed by strong SMEDDS must be organized by means of adding adsorbents to solidification of solid self micro emulsifying components into powder as solid - SMEDDS (S - SMEDDS) to minimize the liquid dosage problems like in stability, microbial contamination and transferring problems. but S - SMEDDS are administered into stomach must be disintegrate which is a time taken process and it should be pass through first pass metabolism. So based on the buccal route of administration of quick onset of action liquid SMEDDS are loaded with mouth dissolving film to produce Self - micro emulsifying mouth dissolving film (SMMDF)<sup>[1]</sup>

### A. Reasons for SMMDF formulation:

- 1) Liquid self micro emulsifying drug delivery systems have drawbacks such as high production, low cost stability, portability, low drug loading, excipients precipitation, storage, handling limited to lymphatics [3].
- 2) S - SMEDDS possess more time to give action due to the disintegration process.
- 3) SMMDF dissolves in saliva within 20minutes and form o/w microemulsion in mouth leads to buccal absorption thereby solubility enhances pre - systemic metabolism by pass, increasing oral bioavailability [3] [4].
- 4) SMMDF is a better choice for delivery of poorly water soluble drugs along with immediate action.

### B. Merits of SMMDF<sup>[5][6][7]</sup>:

- 1) Rapid onset of action as compared to tablets and other dosage forms.
- 2) Offers patients compliance.
- 3) Rapid disintegration and dissolution.
- 4) Avoids first pass metabolism.
- 5) Good stability.
- 6) Good mucoadhesion property.
- 7) Water insoluble drugs are incorporated.

### C. Demerits of SMMDF<sup>[6][7]</sup>:

- 1) Low dose drugs can be incorporated (less than 30mg).
- 2) Dose uniformity is a challenge.
- 3) It requires special packing from the atmosphere.

## 2. Classification of SMMDF<sup>[9]</sup>:

Oral strip/fast mouth dissolving films are classified into

- 1) Mucoadhesive films
- 2) Flash release wrappers

**A. Mucoadhesive melt - away wafer:**

Mucoadhesive film which is placed at buccal (or) gingival mucosa and adhesive to mucosal surfaces used polymers for the bio adhesion purpose. these are generally prepared by hot extrusion technique and solvent casting method. as per the function and disintegration time these are categorised in two parts

- 1) *Mucoadhesive melt away strip*: It sticks to the mucosa, totally dissolves within minutes and releases drug content over time, these are monolayer films.
- 2) *Mucoadhesive sustained release film*: These remains for several hours to show their action. for that duration, drug release is sustained and wafer must be removed at the time of medication. oramoist is a sustain release oral film that adheres to the mouth roof and enhances the salivary secretion to prevent the dry mouth condition like xerostomia

**B. Flash release wafers:**

Flash release dissolves in maximum of 60 seconds with instant drug release, immediate release. ad per site of application again these are two types.

- 1) *Oro - dispersible film (ODF)*: ultra thin strip which is similar to postage stamps in size, having larger surface area leads to the rapid disintegration of precise unit dosing. .
- 2) *Sublingual film*: same properties as ODF but these are placed under tongue rather in oral cavity

**3. Materials and Methods****a) Formulation Of SMMDF:**

It involves the following steps,

- Formulation of liquid SMEDDS
- Evaluation of L - SMEDDS
- Formulation of SMMDF by incorporation of L - SMEDDS into polymer to form SMMDF.
- Evaluation of SMMDF.

Self - Micro Emulsifying Drug Delivery System (SMEDDS) Various oils and surfactants are used as components to enhance the solubility of drug lead micro emulsions. Selected ingredients must be biocompatible, nontoxic, clinically acceptable and emulsifiers in appropriate concentration range that will result in good micro - emulsions. SMEDDS upto mild agitation formed by dilution in aqueous Medium, forms O/W micro - emulsions with small droplet size provides large surface area for drug release, absorption<sup>[9][10][11]</sup>.

**1) Formulation Of Liquid - SMEDDS:****a) Selection of oil and surfactants by solubility studies:**

Solubility studies have been carried by allocate an extra quantity of drug in a screw capped vials containing 1g of vehicles (oil, surfactants, co - surfactant) that suspension of vehicles have been heated on water bath at 40°C and facilitate the solubilization of drug by placing vial at vortex mixer, followed by constantly agitated on rotary shaker for 48hrs at ambient temperature. Obtained suspension centrifuged at 5000 rpm for 15 mins, collected supernatant made into successive dilutions with methanol and analyzed at uv to estimate drug content in oil & surfactants.

**b) Construction of pseudo - ternary phase diagram:**

Pseudo ternary phase diagrams were constructed by using triplot software version 4: 1: 2 for temperature by water titration method used to estimate the micro - emulsion Area. Based on solubility studies, the selected oil, surfactant/co - surfactant (Smix), and water undergo a pseudo - ternary phase diagram. Surfactant was mixed with co - surfactant in 4: 1, 3: 1, 2: 1, 1: 1 respectively to form Smix. mix the solutions at vortex shaker for 5 minutes and place at 50°C for 1 hr until isotropic mixture obtained. These Smix aliquots of surfactant /co - surfactant were mixed with oil in ratios like 9: 1, 8: 2, 7: 3, 6: 4, 5: 5, 4: 6, 3: 7, 2: 8, 1: 9 in different vials and titrated with water. Further keep a side for visual observation for 30 seconds to classify whether it is a Nanoemulsion, micro - emulsion, coarse dispersion, and gel phase. Turbidity sample indicates coarse dispersion, a clear isotonic sample indicates micro - emulsion, clear bluish transparent sample indicates Nano - emulsions<sup>[2]</sup><sup>[9]</sup>.

**c) Preparation of liquid - SMEDDS:**

Weight Estimated ratio of surfactant and co surfactant from the phase diagram with bigger area and vortex for 5 - 10 minutes place this Smix at oven for 1hr at 50°C, to this add oil with different ratio to Smix, again vortex for 5 - 10 minutes, place in oven at 50°C to form isotropic mixture, add drug to these isotropic formulation, mix by vortex shaker until a clear solution obtained<sup>[13][9][20][19]</sup>.

**2) Evaluation of L - SMEDDS<sup>[19][20]</sup>:****a) Globule Size, PDI, Zeta potential:**

Determine globule Size and PDI, Zeta potential formulated SMEDDS of 0.1 ml (1: 100) of SNEDDS in 10ml of double distilled water, vortex for 5 minutes to form a uniform solution, kept stand by overnight followed by analyse the sample of droplet size, poly - dispersity index, zeta potential by using malvern zetasizer under the principle of dynamic light scattering technique at 90 degrees angle.

**b) Phase separation and precipitation:**

As per ratio 1; 1000 that is 0.01ml in SMEDDS containing drug were diluted with 10 ml of distilled water, 0.1N HCL, 6.8pH of phosphate buffer respectively in a 3 vials at 37° C for visual observation and mix the preparation in a vortex for 5 minutes, keep a side for 24 hrs and observe the phase separation, precipitation for regular intervals of 2, 4, 6, 8, 10, 12, 24hrs.

**c) Self emulsifying efficiency test visual assessment test:**

self emulsifying or dispersity property was visual assessment by using dissolution apparatus 2 according to USP, for that (1: 1000) 0.25ml preformulated SMEDDS/SNEDDS were added to 250ml of distilled water, 0.1N HCL, 6.8 pH phosphate buffer stirred by using magnetic stirrer 100 rpm at 37C temperature. Observe the time taken for dropwise dispersity.

Grade A: rapidly forming micro emulsion having a clear bluish white appearance within min.

Grade B: rapidly forming, slightly less clear emulsion.

Grade C: fine milky emulsion formed within 2 minutes.

Grade D: Dull grayish white emulsion having a slightly oily appearance that is slow to emulsify.

Grade E: formulation exhibiting either poor or minimal emulsification.

Recommended Grade - A, Grade - B formulation as micro emulsion when dispersed in GIT.

**d) Percentage transmittance test:**

SMEDDS are diluted with water having ratio 1: 100 that is 100microlitres (0.1ml) in each 10ml water, 0.1N HCL, 6.8pH phosphate buffer and measuring percentage transmittance using UV – spectroscopy

**e) Robustness to dilution:**

Formulation is diluted to the ratio 1: 100, 1: 1000 with excess amount of water, 0.1N HCL, pH 6.8 phosphate buffer and kept for 24 hrs and observed for precipitation or phase separation.

**f) Thermo - dynamic stability test:**

Optimize formulation subjected to various thermodynamic stability study tests namely centrifugation and freeze thaw cycle.

**g) Drug content:**

Drug content percent in SMEDDS formulation is estimated by UV - spectroscopy.50mg of formulation is diluted with 100 ml of solvent and vertx for 5 mins analyse under uv. Drug loading efficiency =amount of drug is known amount of formulation \*100/initial drug load

**h) Viscosity:**

Viscosity of SMEDDS estimated with the help of a viscometer.

**3) Incorporation of L - SMEDDS into polymer to form SMMDF;**

L - SMEDDS are double formulated again formulated) incorporated in to the matrix polymer to form oral disintegrating mouth film by following the standard formula of mouth films.

**4) Formulation Of SMMDF [2]: Formulation consists of Materials and method.**

- Film forming polymer:* polymer plays a vital role in film formation; maximum hydrophilic polymers are used in preparation, either natural or synthetic, natural polymers are more preferable than synthetic polymers to avoid side effects. for hot extrusion technique they should have a suitable glass transition temperature in the range 50 - 180c 1, low hygroscopic, stability at extrusion technique and non toxicity.
- Natural polymers are pullulan, starch, pectin, sodium alginate, Maltodextrin, lycoat 473.
- Synthetic polymers are Hydroxypropyl methyl cellulose, poly vinyl pyridine, kollicoat, Hydroxypropyl cellulose, polyethylene cellulose.

**Properties:**

It should be expensive and readily available.

It should have good wetting and spreadabilityproperties.

- Plasticizers:* plasticizer selection is the another important parameter for the SMMDF, plasticizer improves flexibility and mechanical property of the film like tensile strength and elongation which reduces bitterness

of the strip, improves strip properties by reducing the glass transition temperature of polymer, plasticizer must compatible with drug finally improves flow property.

- Saliva stimulating agent:* This increases the selection of saliva so that oral film disintegrates and dissolves faster in the oral cavity. acids which are used in preparation of food are generally used as saliva stimulators. Example: citric acid, mali acid, lactic acid, ascorbic acid, tartaric acid.
- Sweetening agent:* Sweeteners are used to mask the bitterness of a drug and make it palatable. Natural and Artificial sweeteners are used for SMMDF. Natural sweeteners are xylose, ribose, glucose, sucrose, maltose, dextrose, steviosides, liquid glucose etc. Artificial sweeteners are sodium, calcium saccharine, neotame, Altilame. *Flavouring agents:* flavouring agents impart flavour to SMDMFmostcompatible with drugs. US FDA approved flavour can be added to Formulation according to choice of individual of different age groups.
- Anti - sticking agents:* During the extrusion technique, the shear force is generated due to the frictional forces which ultimately generate excessive heat and thermal fluctuations during process. so the addition of anti sticking agents like micro crystalline cellulose hypothesized the retain moisture exerts lubrication reduces the frictional forces
- Surfactant:* surfactant a solubilizing, wetting, dispersing agent that dissolves within seconds release active ingredients instantly. Ex: sodium lauryl sulphate

**Table I:** Formulation of SMMDF

S. No.	Ingredients used for SMMDF	Percentage
1	Drug	1 - 30%
2	Film forming polymer	40 - 59%
3	Plasticizers	0 - 20%
4	Saliva stimulating agent	2 - 6%
5	Sweetening agent	3 - 6%
6	Surfactant	q. s
7	Flavouring agents	q. s
8	Colour and filter	q. s

**Preparation of SMMDF:**

A mouth dissolving film forming solution was prepared by mixing selective water soluble polymer and plasticizerin a certain amount of water along with addition of flavouring or sweetening agent, colour in it. In additionto Formulated SMEDDS in another suitable solvent, mix both the solvent and pour film forming solution in a Petri dish and dried at 40°C and cut into dimensional mouth film.

**Preparation Methods of SMMDF:**

- Solvent casting method:* water soluble excipients are dissolved in water, drug added to water soluble polymer than this solution stirred with magnetic stirrer for 5 mins to form homogeneous solution. finally casting on Petri plate and dried at 40°C in hot air oven<sup>[2] [16] [17]</sup>
- Semi Solid casting method:* this method done to insoluble acid polymers, firstly a solution of water soluble films forming polymer premix with all excipients resultant solution, then the resultant solution is added to insoluble polymers like cellulose acetate phthalate (4: 1 ratio) prepared in Ammonium butyrate or hydroxide. to this solution plasticizer added do that a gel mass formed will

casted on films or heat controlled drums which was dried at 40°C and thickness of film must be 0.015 - 0.05 inches.

- c) **Hot melt extrusion:** this technique mainly used for formulate granules, sustained release tablets, transdermal patches. processing film involves shaping a polymer into film by heat process drug mixed with carrier insoluble form, then extruded having heaters which melt the mixture, thereby melting is shaped into films by dies fewer operation units Better content uniformity Anhydrous process. the two types hot extruders used for the preparation of mouth films.
- d) **Solid dispersion technique:** dispersion of one or more active ingredients in an inert carrier in a solid state in presence of Amorphous hydrophilic polymers. Drugs dissolved in suitable liquid solvent incorporate the solution into the melt of poly ethylene glycol below 70° C. Solid dispersion is shaped into films by means of dyes.
- e) **Rolling method:** A suspension of premix is prepared with the drug dissolved in water or organic solvent along with all mouth film related excipients fill ntl the fed holder, then this premix will be dried in a heat rollers.
- f) **Flexoprint or flexographic technology (FPT):** A rotary process, primix of the mouth film solution having a ink measure consistency by an anilox roller then they are printed into cylinder that prints the film after unwinding the daughter roll.

## 5) Evaluation of SMMDF:

### a) Mechanical properties<sup>[18] [2] [19]</sup>:

- Thickness: thickness of film is measured by micrometre screw gauge or calibrated digital vernier callipers. SM MDF thickness must be in 5 - 200micrometers and should be evaluated at five different locations (four corners and one at centre) because the thickness of film is directly proportional to dose distribution
- Tensile strength: The maximum stress applied to a point of which a strip breaks is called tensile strength.  
Tensile strength = load at break /strip break\*Strip width
- Folding endurance: Measured by repeated foldings of film at the same place till it breaks. The number of times it is Folded without breaking is known as folding endurance value.
- Young's modulus: Measure of stiffness of the strip is Young's modulus, measured by houn's field universal testing Machine.  
Young's modulus = Slope \* 100/strip thickness\* cross head speed.
- Percentage elongation: when stress applied a film sample stretches and referred as strain, basically deformation of film increases as a plasticizer content increases.  
Percentage elongation =  $L/L_0 \times 100/L$   
Where L=increase in length of film  $L_0$ =initial length of film.

- b) **Degree of swelling:** film swelling studies are conducted using simulated saliva solution. Each film sample is weighted and placed in a pre weighted stainless steel wire mesh containing film samples submerged into a 15ml medium in a plastic container. Estimate the increase in weight of the film at the present time interval until constant weight is observed.

Degree of swelling  $W = W_t - W_0/W_0$

Where  $W_t$ = weight of film at time  $W_0$ = weight of film at time zero

- c) **In - vitro dissolution:** In - vitro dissolution study is carried out in a simulated saliva solution pH 6.4 buffer using paddle apparatus at 37°C+ - 0.5°C. Samples are withdrawn at regular time intervals and analysed by UV - spectroscopy.
- d) **Assay / Drug content/Content uniformity:** Drug content is determined by any standard Assay method which is described for the particular API in any standard pharmacopoeia. Limit for content uniformity 85 - 115%. Another method by using X - RD.
- e) **Transparency:** The measurement of oral film transparency can be determined by using a simple UV - spectroscopy. Cut the film sample into rectangles and place it on the internal side of the spectrophotometer cell. Now determine the transmittance of film at 600nm.  
Transparency =  $(\log T_{600})/b = c$   
Where  $T_{600}$ = Transmittance  $b$ = film thickness  $C$ = concentration
- f) **In - vitro disintegration test:** Disintegration time is the time taken for an oral film to start breaking when brought in contact with water (or) saliva. Disintegration time must be 30secs - 5 mins. United State pharmacopoeia (USP) Disintegration apparatus can be used to study disintegration time. Another method for estimating disintegration time is visually by dipping in 25ml of water in a beaker followed by shaking the beaker gently and the time was noted when the film starts to break (or) disintegrate.  
Surface  $P^H$  test: Surface  $P^H$  test of mouth dissolving film can cause the side effects to the oral mucosa  $P^H$  should be 7 or close to neutral. For this purpose, a combined  $P^H$  electrode can be utilised to help with water, making SMMDF wet and  $P^H$  was measured by bringing electrodes in contact with the surface of oral film. This study should be to determine the surface of film  $P^H$ , changes in colour of  $P^H$  paper gives surface  $P^H$  of the film.
- g) **Morphological Analysis of SMMDF by SEM:** estimation of outer surface properties of SMMDF by SEM. Solid state characterization of SMMDF by FTIR, DSC, X - RD technology.
- h) **Droplet size of reconstituted micro - emulsion:** Assess the Average droplet size, size distribution poly dispersibility index of micro emulsion from liquid - SMEDDS and form SMMDF by correlation spectroscopy.

## 4. Conclusion

SMMDF are the oral mucosa drug delivery systems which are formulated by incorporation of Solubility Enhanced drug containing L - SMEDDS targeted for the rapid absorption rate with instant drug release which mainly aimed and focused to treat diseases those need immediate and instant medication with in seconds time like Angina pectoris, congestive heart failure, Asthma, Parkinson's convulsions, Antihistamines for allergies etc.

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