



Sublingual spray: a new technology oriented formulation with multiple benefits

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ABSTRACT

Sublingual drug delivery system was a well-established platform for delivering the drug that need to exhibit quick action without any first-pass metabolic effect, but various pitfall in the regular sublingual drug delivery systems such as a tablet, capsule etc., that can be overcome by novel sublingual drug delivery technology such as particulate sublingual spray. Sublingual spray for drug administration has gained attention in the market since it proved its propensity to by-pass the first-pass metabolism and to initiate a rapid onset of action due to its atomized micro particulate nature, which is significantly higher than the other sublingual formulations. The approval of sublingual spray by the regulatory agencies may commence further research in this field by subsuming various essential drugs for indications such as cancer pain, cardiovascular issue etc. This article comprises a detailed study on the drawback of conventional sublingual drug delivery system and the approach by which these drawbacks can be overruled by spray technology in the sublingual area and the, in-depth mechanism of drug delivery through sublingual with the help of atomization followed by the entire formulation strategy along with evaluation and industrial perspective of the sublingual spray dosage form as a future tool of patient-friendly drug delivery.



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INTRODUCTION

The sublingual spray (SL Spray) is an unprecedented pharmaceutical administration technology in which the drug can be atomized under the tongue which in-turn facilitate drug diffusion into the capillary network and often acts faster than the other oral administrations, with better bioavailability and so

there may be a proven improvement in the onset of therapeutic activity. General sublingual dosage form consists of tablet, film, mini pills, etc., and the advanced formulations include micro particulate spray, atomized liquid etc. The advanced formulation has a better penetrating ability than the conventional sublingual dosage forms. The capillary network absorbs the medication/drug, forwarding them directly into the bloodstream without entering the Gastro-intestinal system. Sublingual route is also advantageous for drugs with a high rate of hepatic first-pass metabolism. Rapid onset of action through immediate absorption, the convenience of administration, bypassing discordant gastrointestinal (GI) environment and first-pass metabolism are the crucial reasons for preferring sublingual delivery. Sublingual medications place a vital role in emergency situations like Myocardial infarction, where a sublingual drug proves as an undeniable approach (Poteet, 2017). This article discusses in detail about the need and development of sublingual

spray as a next-generation sublingual drug delivery system and its marketability towards potentially growing global pharmaceutical market.

Pitfall of conventional-sublingual delivery

In 2014, sales of Sublingual film (Suboxone) reached a total turnover of approximately \$1.3 billion in the US (United States) market while the total market has grown more than \$1.7 billion, driven by an 11 percent increase in prescriptions about 2017. Ergomar (ergotamine tartrate) marketed by Rosedale therapeutics was one among the sublingual tablets available in the US market, priced \$15 per pill also contributed its maximum in developing gross market of sublingual delivery products, Even with this dynamic growth thickness of the product, solubility leads to the slow onset of action. These drawbacks provided a path for next-generation pharmaceutical research towards the utilization of spray technology in the sublingual delivery.

Emerging of sublingual spray formulations

Sublingual spray delivery was a novel technological platform to overcome the drawbacks associated with the available sublingual drug delivery techniques. The application of SL spray formulation was initiated by using nitroglycerin as a sublingual metered spray, which has proved an improvement in the onset of action. Insys Therapeutics developed 'Subsys' (fentanyl), which was recently approved by the United States Food and Drug Administration (USFDA) for the treatment of cancer pain. Global pharma companies such as Teva, Sun Pharma Grunenthal, Neurax, Angelini, Sandoz, Ethy pharm, Arrow generics, Purdue and Actavispharma have a significant role in elaborating the application and utilization of sublingual delivery technology (Poteet, 2017). Intoxication or overdose of opioid can be treated by Naloxone Sublingual spray, which was introduced by the Insys Therapeutics and received fast track designation from the FDA (wired, 2015). Besides providing ease of administration, it also holds an advantage of increasing patient compliance by projecting as a non-invasive drug delivery device and also a delivery device with very less chance for cross-contamination. In sublingual spray, the drug will be present in the form of suspension or micronized dry powder or homogenous liquid that can be absorbed through the capillary network of the blood vessel on atomization. These spray system can also be utilized as an aid in the administration of paediatric vaccines, pain relievers and many other vitamin supplements. Comparatively, it possesses an effective, quick, and safe method of drug administration while comparing other oral and parental preparations. Globally, sublingual sprays

have been prescribed by physicians for the treatment of patients who are suffering from chronic cancer. Fentanyl Sublingual spray can take the edge off cancer pain on its single dose which has proven its ability to initiate absorption within 5 min after administration, and the plasma drug concentration increased over the first 30 minutes and remaining elevated level for 60–90 minutes in healthy subjects pharmacokinetic studies. Fentanyl sublingual spray provides linear dose proportionality with changes in the temperature or acidity of the oral cavity, which does not alter its pharmacokinetic properties. Statistically, significant breakthrough pain relief was observed after 5 minutes of the atomized product application on the sublingual region. The painrelieving effect persists at least for 60 min from the time of administration with mild to moderate intensity typically in opioid adverse events without reporting any new adverse effect stating the safety index of the modified delivery system. In summary, rapid onset of analgesia can be produced and justified by fentanyl sublingual spray that strives as an effective treatment for cancer pain (Taylor, 2013).

The global sublingual spray market is classified based on drug form (unit/bidose spray), distribution channel and geography (location – countries marketed). Sublingual route of drug administration is also preferred for Central nervous disorder such as depression, schizophrenia, migraine, insomnia, Alzheimer's disease, attention deficit hyperactivity disorder (behavioural disorders) and anxiety disorders that require non-invasive delivery of medication in a unit dose or bi-dose approach. In North America, demand for sublingual spray started elevating because of the growing cancer population. North America provides better availability of healthcare facilities and skilled professionals to the patients, and so they were largely supporting the development of sublingual spray market. Europe holds the second largest sublingual spray market. The sublingual spray market in the Asia Pacific and the Middle East regions are projected to grow faster because of increased government research funds and focus on better facilities on healthcare (Research, 2018).

Anatomy of sublingual mucosa and the existing barriers of absorption

The sublingual epithelium and connective tissue form the sublingual mucosa. The sublingual epithelium is comprised of squamous epithelial cells (stratified non-keratinized cells). The thickness of the sublingual epithelium (8-12 cells) is lesser than the buccal epithelial cells (40-50 cells). The non-keratinized nature allows the ease of entry of

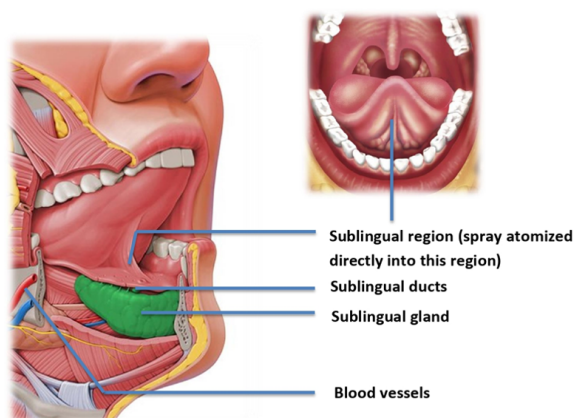


Figure 1: Anatomy of the sublingual gland

molecules through the sublingual route (Holsinger and Bui, 2007). The superficial cells of epithelia contain membrane coating material, secretions from the membrane coating material into the intercellular region exist as a vital obstacle for the drug entry through the sublingual region. The basal lamina connects the epithelium with connective tissues. The connective tissue region has a thickness of 150-500 μm and comprises of both lamina propria and submucosa (Shojaei, 1998; Hollinshead, 1982; Renee et al., 2018). Enormous blood vessels, nerve fibers and collagen fibrils are present in the lamina propria of the connective tissue, which enables rapid drug absorption from this region. Saliva moistens the sublingual region and also covers the tooth and the oral mucosa. The pH of saliva also has a role in sublingual drug delivery. Epithelial cells of the mucosa are covered with mucus, an intercellular substance, synthesized from salivary glands in the sublingual region, which is made of oligosaccharide molecules (Davis et al., 1958; Shojaei, 1998; Dawes et al., 2015). These oligosaccharides provide a net negative charge to the mucus in physiological pH. The sublingual mucosa possesses an enormous amount of polar lipids such as cholesterol esters, glycosylceramides and phospholipids (Chen et al., 1984). High fluidity of the membrane and increased permeability of water and hydrophilic molecules through the sublingual region is a result of the polar nature of the sublingual mucosa (Elizabeth and Martelli, 2005; Lea, 1996; Dawson et al., 2013). The structure of the buccal cavity was given in Figure 1

Cellular mechanism of drug absorption

In sublingual spray delivery system, the medication is spattered on the oral mucosa using spray devices over the sublingual region. Three layers of

the mucosal lining offer the simple diffusion process for the entry of drugs but also restricts the permeability of particular molecules. Glyceryl trinitrate, one of the best drugs which manifested a great success in the rapid symptomatic relief of angina. It has found that sublingual administration of glyceryl trinitrate reduced its onset of action to 1 – 2 minutes. The aerosol spray provides rapid relief for the symptoms. The extent of the first-pass metabolism was reduced to 48% with sublingual tablets and to 28% with the oral dose. Following sublingual administration, nitrates appear in plasma and persisted for 24h (Richman et al., 1965; Tarkin and Kaski, 2016). Sublingual Verapamil (a calcium channel antagonist prescribed for the management of angina, hypertension and certain supraventricular arrhythmias) was found to be effective in controlling the ventricular rate following sublingual administration (John et al., 1992; Balla et al., 2018). Absorption of a drug through the oral mucosa depends on the lipid solubility, permeability, pH and the molecular weight of the drug. For instance, absorption of some drugs via oral mucosa increases when carrier pH decreases (more acidic) and vice versa (more alkaline) (Mcelnay et al., 1995; Prachi and Varsha, 2017). Oral epithelial cells and epidermal cells are capable of absorbing the drug by endocytosis. This mechanism is used across the entire stratified epithelium. Active transport processes also operate in the oral mucosa. Acidic stimulation of the salivary glands, as well as the vasodilation, facilitates drug absorption in the systemic circulation. The buccal mucosal tissues and sublingual mucosal tissues are similar in their structure (Boer et al., 1984; Sah et al., 2016).

Biopharmaceutical consideration for sublingual administration

Following the absorption of the drug in the sublingual region, it diffuses into venous blood, then drains into a common trunk, followed by internal jugular vein, the subclavian vein and the brachiocephalic vein then directly enters into superior vena cava (Moore et al., 2013; Squier and Wertz, 1996; Saha et al., 2017). The thickness of the epithelial membrane is 100-200 μm in the sublingual region and is non-keratinized (Chen et al., 1984; Vilayat and Ashraf, 2014). On applying drug through the sublingual spray, it may reach systemic circulation through various mechanisms such as passive diffusion, active or carrier-mediated transport and endocytosis. Moreover, it's noteworthy that the sublingual region can be continuously washed by the movement of tongue and saliva; hence, these are not suitable for longer-acting (prolonged action) drugs. The rate of diffusion depends on the molecular weight and solubility of the drug substance, con-

Table 1: Hydrocarbons used as propellants in aerosol system

N- Butane	Propane	% composition		Designation
		Isobutane	Pressure (psig at 70 °F)	
Traces	99	1	108±4	A-108
3	1	96	31±2	A-31
98	Traces	2	17±2	A-17
49.2	0.6	50	24±2	A-24
2	12	86	40±2	A-40
2	20	78	46±2	A-46
2	28	70	52±2	A-52
1	51	48	70±2	A-70

centration gradient, temperature, surface area and proximity of the molecule to the membrane.

The unionized form of the drug can be absorbed by passive diffusion. Some substance can be transported by the carrier-mediated process. Some physical models have emerged to study the drug absorption from saliva to systemic circulation through the lipid bilayer. Hydrophilic drug substances may have the hassle to cross such lipid mucosa layer, and on the other hand, well-hydrated connective tissues can be a barrier for a hydrophobic drug. Hence the lipophilic and hydrophilic nature of the drug substance is essential during the developing stages of the drug product.

The drug must show hydrophobic properties, which will be good enough to the lipid bilayer but only to a minimal amount because of the partitioning problems. Oral absorption of drugs is good at a Log P value from 1 to 5. Beyond the value 5, the solubility of the drug substance to the saliva may decrease. Generally, a drug formulated for the sublingual delivery might possess a molecular weight of less than 500 (as free base) to improve its diffusion. pH should be from 5.6 to 7.6. Hence the basic drug absorption takes place when it exists as a free unionized form that occurs when the pH is above its pKa value and ensures its availability in circulation (Wehling *et al.*, 1993; Khan *et al.*, 2017). Hence the suitable buffer is added to the formulation which facilitates the optimal absorption from saliva. Drugs which does not have any ionizable groups may not be affected by changes in pH. Comparatively oral cavity (sublingual region) has a very less absorptive area. Hence very small doses can be absorbed, most preferably potent drugs. Also, the taste of the formulation/drug is an important consideration during formulation development. Unfavourable tastes should be masked because a drug is used in the oral cavity and has an impact on patient compliance (Vilayat and Ashraf, 2014). Drug Artemether

was formulated as a sublingual spray to overcome the first-pass metabolism, intolerable effects in the treatment of malaria. The drug was found to have lesser absorption than normal adults due to the severity of the disease. The unabsorbed fraction of the drug was absorbed through the upper intestine, which does not prevent the first-pass metabolism of the drug. The study could recognise that the sublingual Artemether spray can be preferentially suggested for children who have severe malaria with more compliance and equal effectiveness to oral therapy (Salman *et al.*, 2015).

Formulation considerations

Sublingual drug delivery system contains therapeutically active ingredients which can be dissolved or suspended in excipients which include preservatives, viscosity building or modifying agents, as well as buffering agents in a pressurized or non-pressurized dispenser. Each dose can be metered by a spray pump. A spray pump can be designed for both unit dose and multiple-dose delivery. The sublingual spray can be used for local and systemic action. Various dimensions and compositions are used to control the precision of drug delivery. These can be typically done by forcing the pharmaceutical formulation through the sublingual route from its orifices on actuation. The formulation can be developed by using a container closure system which includes a container, closure, pump, and any protective mechanism for packaging. Solution and suspension of pharmaceutical formulations can be formulated into sublingual sprays (Thorat, 2016).

The composition of Sublingual Spray

The sublingual spray consists of two essential components, the product concentrate, which include all the components of formulation except the propellants. The product concentrate may include dynamic constituents or a mixture of dynamic constituents and other necessary agents. For exam-

ple penetration enhancers, solvents, antioxidants, flavouring agents, sweeteners, hydrophilic polymers, preservatives, acidifying agents, cosolvents. Propellants used to expel out the active ingredients from the containers. Usual propellants are hydrocarbons, chlorofluorocarbons, hydro chlorofluorocarbons and hydro fluorocarbons and other compressed gases. The propellants used in the formulation should not produce any toxic effect in the system and should not interact with the active and inactive ingredients in the formulation.

Active Pharmaceutical Ingredient

An ideal drug for sublingual spray should possess the following characteristics such as aqueous solubility which is appropriate to provide desired dose in a volume of formulation, appropriate sublingual absorption properties that include absence of sublingual irritation, rapid onset of action, low dose generally below 25-30 mg per dose, no toxic sublingual metabolites production and no offensive aroma or taste associated with the drug ([Guidance For Industry, 2002](#)).

There are various types of excipients used in sublingual formulations. Most commonly used excipients are as follows. Selections of excipients are crucial in formulation development. For instance, Dihydroartemesinin drug was formulated as a sublingual spray, where the stability of the drug (reduction mechanisms) was increased by the incorporation of Miglyol® 810 (a medium-chain saturated chain saturated triglyceride). The glyceride can act mutually as a lubricant, viscosity enhancer as well as a stability enhancer in the spray formulation. Hence, the single excipient can play several roles in a formulation, thereby significantly reducing the number of excipients ([sublingual spray formulation comprising DihydroArtemesinin and patent application publication, 2017](#)).

Buffers

Sublingual secretions may alter the pH of the drug administered that will in turn influences the concentration of un-ionized drugs which will be ready for absorption. Hence adequate buffer capacity should be maintained. Examples of sodium phosphate buffer, sodium citrate buffer, citric acid buffer.

Solubilizers

The aqueous solubility of the drug is always a limitation for sublingual drug delivery in solution. Some of the conventional solvents or cosolvents can be used to enhance the solubility of the drug. Some biologically compatible solubilizers and stabilizers with the combination of some hydrophobic absorption enhancers can be used. Sublingual irritation

should be a factor of consideration.

Preservatives

For multi-dosing systems, the usage of preservatives is considered to be an important factor to prevent microbial growth. Methylparaben, ethylparaben, butylparaben, propylparaben, sodium benzoate, benzoic acid, or a mixture of these parabens with phenyl ethyl alcohol and other preservatives such as benzalkonium chloride, EDTA and benzyl alcohol are frequently used preservatives in the sublingual region as these are not irritant or harmful to the skin.

Antioxidants

Antioxidants are used in the formulation to prevent the oxidation in the formulation. Commonly used antioxidants are tocopherol, sodium bisulfite, sodium metabisulfite. Simultaneously it should not affect the drug absorption or should not produce any sublingual irritation.

Surfactants

To modify the permeability of the sublingual region and in some special case of nanotechnology incorporated sublingual spray, surfactants can be incorporated into the formulation. Example: Polysorbate.

Bioadhesive polymers

Drug compounds used in the sublingual region may be influenced by saliva through the elimination from the sublingual region. Hence some specific substances called bioadhesive polymers are used to retain the drug substance on the surface of the sublingual region. They are called mucoadhesive polymers. Forces of adhesion between the drug and membranes depend on the polymer nature, pH, disease state and mucin turn over. Sublingual irritation leads to the development of some carriers that is recommended for safety purposes.

Penetration enhancers

Some of the chemical penetration enhancers are widely used in sublingual drug delivery. They are able to modify the structure of the sublingual mucosa to enhance the drug permeation.

Aerosol systems

Aerosol denotes a pressurized system containing colloidal nature of very finely subdivided liquid or solid particles that are dispersed in gases (propellant). Meter dose inhalers are given more importance for ensuring dose accuracy. It is possible that the drug can be dispensed in a dose range varying from 25-100 μ l per actuation. The aerosol system provides a rapid onset of action, avoidance of degradation in the GI tract, use of doses can be used to

Table 2: Different Excipients used in the sublingual formulation

S.no	Category	Role	Example	Limits
1.	Tonicity adjustment	Used to adjust the tonicity of the formulation	Sodium chloride, Dextrose	Proven to be safe, 0.556 ± 0.050 grams of NaCl for 100 ml can be used to get optimum tonicity
2.	pH adjustment	Used to adjust pH same to physiological conditions and maximize drug stability	Sodium hydroxide.	0.004% w/w
3.	Antimicrobial Preservative	To avoid the microbial growth in the formulation	Benzalkonium chloride, chlorobutanol, Methylparaben	
4.	Buffer component	It gives the buffer capacity to the formulation at desired pH	Sodium citrate, Sodium Phosphate	Up to 0.0006% w/w
5.	Surfactant	Increases the suspendability and stability of the suspension	Polysorbate 80,20	Up to 3% but on with proper regulatory justification, this limit can be elevated.
6.	Cation chelating agent	Forms chelate with ions present in the formulation and increase the stability	Disodium EDTA	0.150 grams for 100 ml
7.	Suspending Agents	Increases viscosity and suspendability of suspension	Na CMC	2 % w/w
8.	Co-Solvent	Helps to improve solubility	Alcohol, PEG 400, Propylene Glycol	Upto 20 ml for 100 ml of solution
9.	Humectant	Used to maintain humidification in the formulation	Glycerin	Proven to be safe but for optimal effect 0.233 % w/w can be utilized

minimize the side effects, tamper-proof containers and value closure ([Gennaro, 2000](#)).

Different types of aerosol systems

Solution system - Two-phase system: vapor and liquid phase

[Pharmaceutical active ingredients are soluble in the propellant, no other solvents are used]

Water-Based system- Three Phase System: Propel-

lant, Water and Vapour

Certain amount of water can be used instead of non-aqueous solvent, Dispersion of active ingredients in the propellant or a mixture of propellants.

Suspension or Dispersion system

Dispersion of active ingredient in a suitable propellant or mixture of propellants, to decrease the rate of settling of dispersed particles- various surfactants or suspending agents can be used [Table 1](#).

Foam System

Foam System contains surfactants with active ingredients in aqueous or non-aqueous vehicles and propellants have been given as rapidly breaking foams. Hydrocarbons are used as propellants in aerosol systems that are mentioned in Table 2 and different excipients used in the sublingual formulation are listed in Table 3.

Spray Device

The structural multidisciplinary shape of the device is important in the dimension of the spray in which the drug can be atomized only into the required region. Hence, each of the components in the device plays a major role, which was diagrammatically explained in Figure 2 and Figure 3. For example, a different type of actuator and dip tube are used for a different state of formulation like powders, solutions.

Evaluation parameters for sublingual sprays

Qualitative Analysis

Spray Pattern

Selective colours can be used with the formulation (For example – Sudan red, Brilliant blue) and sprayed on the Whatman filter paper after which the pattern was observed, and the diameter and ovality ratio was calculated by the following formula (Par-mar and Patel, 2017; Baltzley et al., 2018).

$$Ovality = \frac{D_{max}}{D_{min}}$$

Where D_{max} and D_{min} are the maximum and minimum diameters of the spray pattern, respectively.

pH

After Calibration of pH meter with manufacturer direction, by using the recommended two buffers. The tip of the pH meter probe is dipped in a sample after rinsing with water. The pH is allowed to equilibrate, and the equilibrium state is noted.

Leak test

Crimping value (Available to prevent defective container) was checked by using leak test. Crimps dimensions are measured to ensure leak test value within the specifications. Leak testing of valve closure is performed by passing the filled containers through the water bath.

Quantitative tests for Sublingual spray

Vapour Pressure

Using Pressure gauge, the pressure was measured. It can be accessed through the role of a water bath, test gauges, and limited equipment which can give

detailed information about the maximum percentage of medicaments that can be loaded (Hoogstraate and Boddé, 1993).

Density

Density can be determined using pycnometer. Empty pycnometer is weighed and then filled with 25ml of product and then reweighed. The difference between empty and filled pycnometer is calculated to get the density of the product.

Prime Test

Prime test is performed by actuation of the container until the formulation is getting released. A number of actuation is counted for a container to release the formulation.

Flame projection

Indicates the effects of an aerosol formulation on the extension at an open flame. The product is sprayed for 4-8 S on the flame. Based on the formulation of nature, the flame is extended. By using a ruler, the exact length can be measured.

Aerosol valve discharge rate

The discharge rate can be determined by taking the known quantity of aerosol and allowing to discharge for a specific period of time using standard apparatus. Then the container is reweighed after a certain limit of time. Then the discharge rate is calculated and expressed in grams per second.

Net content

Containers are weighed before and after filling and compared to find the difference in net content, which will give us a clear idea about the uniformity of filling in bulk production.

Drug Content

1 ml of Spray solution is taken, and its absorbance is determined after adequate dilution using UV spectrophotometer, Concentration is determined from the standard calibration curve, and the drug content is calculated as % of the theoretical value.

$$Drug\ content = \frac{Actual\ drug\ content}{theoretical\ drug\ content} \times 100$$

Drug Content per Spray

Through the actuation from the container to the beaker containing diffusion media. The solution is kept for 15 minutes in sonication/ agitated/ shaken well. The drug content can be analysed by an analytical technique.

Spray Angle

The spray is actuated on the whole paper in the horizontal direction from the nozzle to measure the

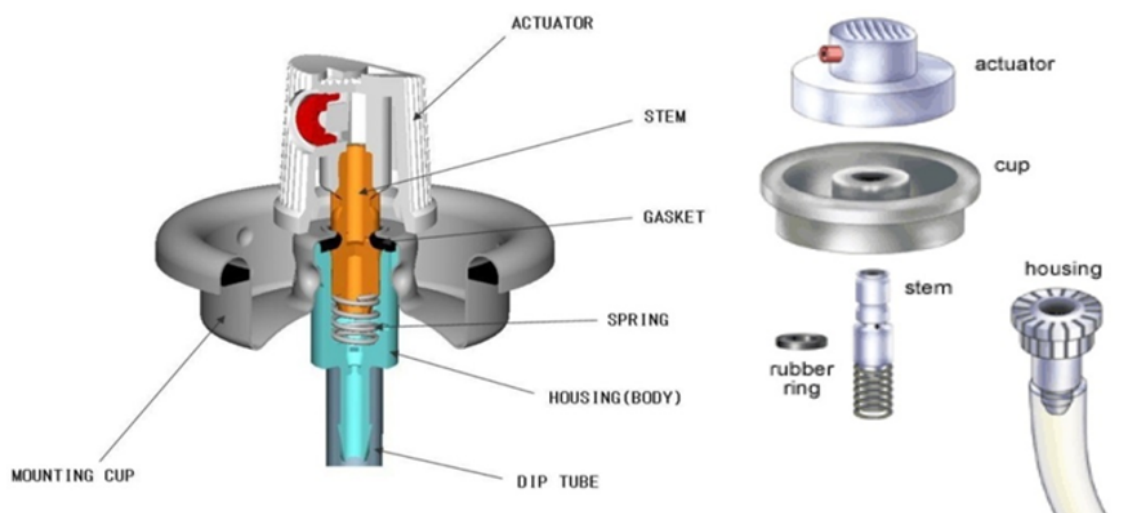


Figure 2: Basic components of the spray device

spray angle. Sudan red is dissolved in the formulation to facilitate visualization. The radius of the circle formed on the paper is measured. Then the spray angle is calculated by the following equation.

$$\text{Spray angle}(\theta) = \tan^{-1} \frac{D}{r}$$

Where D =Distance of paper from the nozzle

r = Average radius of the circle.

Spray profiling (delivered dose uniformity)

As per USP, reproducibility of the dose can be determined by the assay method. The mean quantity of active ingredient delivered through the actuator per spray is determined. The content uniformity of the spray at different points are validated. The content uniformity is calculated from starting, an intermediate and ending point approximately.

Flashpoint

Flashpoint is determined by the use of a standard Tag Open Cup apparatus. The aerosol product is cooled to a temperature of about -250°F and transfer to the test apparatus. The test liquid is permitted to increase slowly in temperature, and the temperature at which the vapor ignites is taken as a flashpoint. The obtained point is usually the flashpoint of the flammable component.

Ex-vivo drug diffusion studies

The *Ex-vivo* drug diffusion study of the optimized formulation can be carried out using Franz diffusion

cell apparatus. By using a goat sublingual mucosa in a buffer system. At each interval, the samples are collected, and the drug content is measured using UV spectrophotometric method.

Flux and Apparent Permeability Determination

Flux and apparent permeability can be calculated using the following formula.

$$J_{ss}(\text{Flux}) = \frac{\Delta Q_t}{\Delta t} \times S$$

Where, $\Delta Q_t/S$ is the cumulative drug permeation per unit of mucosal surface area ($\mu\text{g}/\text{cm}^2$) in time t(hours).

$$P_{app} (\text{Apparent permeability}) = \frac{J_{ss}}{C_d}$$

Where J_{ss} is the flux and C_d is the concentrate of the drug in the donor compartment.

Stability Studies

Two types of stability testing can be performed to calculate the shelf life of spray dosage forms, *i.e.*, electrochemical testing and long-term static testing. Though electrochemical testing provides only limited information, it stands as an effective screening method for stability studies, and on other side, Long-term stability studies provide the most important data such as weight loss, concentration changes, propellant saturation changes, vapour pressure measurement, maintaining original spray characteristics, corrosion has been seen. Long-term



Figure 3: Different types of actuator and dip tube

Table 3: Sublingual sprays available in the market

Name	Drug	Indication	Manufacturer
Subsys	Fentanyl	Breakthrough cancer pain	Insys Therapeutics
Sativex	Cannabinoid	treatment of spasticity due to multiple sclerosis	GWPharmaceuticals
Glytrin	Glyceryl Trinitrate	Treatment of acute angina pectoris.	Aspire Pharma Ltd
Nitromist	Glyceryl Trinitrate	Treatment of acute angina pectoris.	NovaDel
Nitrlingual pump spray	Nitroglycerin	acute relief of an attack or prophylaxis of angina	Espero Pharmaceuticals

stability studies can be performed as keeping 120° F, over a period of months to years.

Sublingual market and industrial perspective of spray

The general sublingual market consists of medications such as Nitroglycerin, Isosorbidedinitrate, Fentanyl citrate, Buprenorphine hydrochloride, Ergotamine tartrate, Ergoloidmesylates, Asenapine, Buprenorphine hydrochloride and naloxone hydrochloride and Zolpidem tartrate etc., Efficacy and utility of all the above-mentioned medicaments can be maximized by the sublingual spray formulations. Some of the detrimental factors for the formulation were the presence of open sores in the mouth and the effect of drinking, eating or smoking and industrial drawback includes cost, regulatory approvals etc., Thus on developing a strategy to overcome all minor drawback associated with SL spray formulation will pay a path for revolution in industrial scenario for more productivity-based utilization.

Summary

The sublingual spray is an unprecedented technology which possess a crucial role in delivering drugs in emergency situations and in case of chronic illness and pain where immediate drug action is required. Further, researches in the field offer delivery of more drugs with satisfying patient need and compliance. The consideration of patient perspectives and overcoming the industrial and technological barriers of SL spray system can contribute further widening of its application in drug delivery.

CONCLUSION

The sublingual spray offers a number of advantages in drug delivery over the normal sublingual formulations such as tablets and films. The drugs that can diffuse through the sublingual mucosa with the consideration of pH, molecular weight, clearance rate, and lipid solubility, can be formulated successfully into a sublingual spray. Understanding patient compliance, necessity and regulatory feasibility, further researches in the field to overcome the existing barriers can widen the SL spray application towards next-generation personalized medicine.

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