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Formulation & Evaluation of Fast dissolving Buccal films of Sertraline

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Abstract

The hydrochloride of Sertraline is a white crystalline powder; slightly soluble in water and freely soluble in ethanol [1]. It is a drug of selective serotonin reuptake inhibitors (SSRI) that is chemically unrelated to other SSRIs, tricyclic, tetracyclic, or other available antidepressant drugs. Sertraline inhibit the inactivation of serotonin (5-hydroxytryptamine or 5-HT) by blocking its absorption in the central nervous system [2]. SSRIs are used to treat depressions and effective for obsessive-compulsive disorder, posttraumatic stress disorder, premenstrual dysphoric mood disorder, panic disorder, generalized anxiety disorder and bulimia. The films were prepared from polymers such as polyvinyl pyrrolidone, Carbopol 934P in different ratios by solvent casting method. Propylene glycol or PEG 400 as plasticizers and mannitol or sodium saccharin as sweeteners were also included. Satisfactory results were obtained when subjected to physico-chemical tests such as weight variation, thickness and folding endurance. Films were also subjected to *in vitro* drug release studies by using USP dissolution apparatus. *In vitro* release studies indicated 90-95% release within 1 hr.

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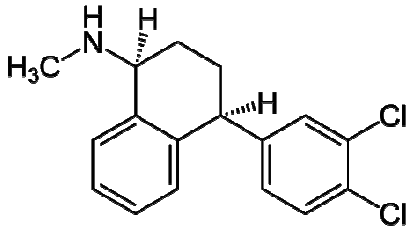
Introduction

The main question arises that what are fast dissolving buccal films. A fast-dissolving buccal film drug delivery system, in most cases, is a film containing active ingredient that dissolves or disintegrates in the saliva remarkably fast, within a few seconds without the need for water or chewing. Some drugs are absorbed well from the mouth, pharynx and

esophagus as the saliva passes down into the stomach. In such cases, bioavailability of drug is significantly greater than those observed from conventional tablet dosage form [2]. Most fast-dissolving delivery system films must include substances to mask the taste of the active ingredient. This masked active ingredient is then swallowed by the patient's saliva along with the soluble and insoluble excipients. Improved patient compliance is a primary benefit of the fast-dissolving drug delivery systems. Fast dissolving buccal films provide ease of administration for patients who are mentally ill, disabled and uncooperative; requires no water; have quick disintegration and dissolution of the dosage form. They can be unobstructive and can be designed to leave minimal or no residue in the mouth after administration and also provides a pleasant mouth feel. This delivery system has no risk of chocking. It allows high drug loading and has the ability to provide advantages of liquid medication in the form of solid preparation [3]. Fast dissolving buccal film is a drug delivery film that is placed on a mucosal or in oral cavity. They provide suitability for a wide variety of drugs. It has improved bio-availability for certain therapeutic ingredients. It has small size for improved patient compliance. As most of the drugs are unpalatable, fast dissolving buccal films usually contain a medicament in taste masked form. Films has ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders as a result of extremities and dysphasia, and to patients suffering from nausea, such as those patients receiving chemotherapy. It is the newest frontier in drug delivery technology that provides a very convenient means of taking medications and supplements. There are multiple fast-dissolving over the counter and prescribed products on the market worldwide, most of which have been launched recently. There have also been significant increases in the number of new chemical entities under development using a fast-dissolving drug delivery technology. Sertaline an antidepressant drug, which exhibits only 44% of oral bioavailability because of extensive first pass metabolism and has low solubility [4]. In view of all the above reasons, this study will be an attempt to optimize the therapeutic effect of sertraline by formulating as fast mouth dissolving films for sublingual use. Following are the structure and values of various parameters given for **Sertraline in Table 1.**



IUPAC NAME: (1S,4S)-4-(3,4-dichlorophenyl)-N-methyl-1,2,3,4--tetrahydronaphthalen-1-amine4.

Table 1: Determination of values of different parameters for Sertraline

Parameters	Value
Molecular weight	342.69
Melting point	246-249 °C[1]
Log P	5.06[3]
pKa	9.5[45]
Half life	26 hrs
Protein binding	98.5%[3-4]
Bioavailability	44%[4]
Dose	12.5- 200 mg daily[3]
Water solubility	4mg/ml[5]

The present study aims to improve the bioavailability of sertraline with reduced systemic effects by using a novel approach of fast dissolving buccal films

- To formulate a suitable delivery system for delivery of sertraline.
- To characterize and evaluate the delivery system for its efficacy.

Advantages of fast dissolving buccal films of Sertraline

The design of thin film, often referred to as PharmFilm, as an oral drug delivery technology

offers several advantages over other modes of drug delivery, such as ingestible tablets, chewable tablets, orally dissolving tablets, soft gels, liquids or inhalants: The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament. All tablet dosage forms, soft gels and liquid formulations primarily enter the blood stream via the gastrointestinal tract, which subjects the drug to degradation from stomach acid, bile, digestive enzymes and other first pass effects. As a result, such formulations often require higher doses and generally have a delayed onset of action. Conversely, buccal and sublingual thin film drug delivery can avoid these issues and yield quicker onsets of action at lower doses. Thin film is more stable, durable and quicker dissolving than other conventional dosage forms. Thin film enables improved dosing accuracy relative to liquid formulations since every strip is manufactured to contain a precise amount of the drug. Thin film not only ensures more accurate administration of drugs but also can improve compliance due to the intuitive nature of the dosage form and its inherent ease of administration. These properties are especially beneficial for pediatric, geriatric and neurodegenerative disease patients where proper and complete dosing can be difficult. Thin film's ability to dissolve rapidly without the need for water provides an alternative to patients with swallowing disorders and to patients suffering from nausea, such as those patients receiving chemotherapy. Thin film drug delivery has the potential to allow the development of sensitive drug targets that may otherwise not be possible in tablet or liquid formulations. From a commercial perspective thin film drug delivery technology offers an opportunity to extend revenue lifecycles for pharmaceutical companies whose drug patent is expiring and will soon be vulnerable to generic competition [6].

Problems associated with conventional dosage forms of sertraline

They have low bioavailability, have extensive first pass metabolism, often have low solubility, can lead to gastric distress, stomach upset and loose stools [5-7].

Methodology

Preformulation studies of sertraline including tests for identification, solubility studies, partition coefficient determination, melting point determination and other studies were carried out and compared with the specification as per literature.

Identification

Ultraviolet Absorption Maxima (λmax)

The organic molecules in solution form when exposed to light in the ultra-violet region of the spectrum absorb light of particular wavelength depending on the type of electronic transition associated with the absorption. 10 µg/ml solution of the sertraline in phosphate saline buffer pH 7.4 when scanned between 200-400 nm exhibited absorption maxima at nm respectively.

Preparation of calibration curves

The calibration curve of sertraline was prepared in phosphate saline buffer (PBS 7.4). The method estimated the drug concentration in the range of 2-20 µg/ml in all Medias and it followed the Beer's Lambert law in the same concentration range.

Ten mg accurately weighed drugs were dissolved separately in 100 ml with the different media resulting in a stock solution of 100 µg/ml. From the stock solution, aliquots of 0.2, 0.4, ..., 1.8, 2.0 ml were withdrawn in a series of 10 ml volumetric flasks and diluted to 10.0ml with media. This gave a range of 2, 4..... 18, 20 µg/ml. The absorbance of each solution was measured in at Shimandzu UV/Vis spectrophotometer at λ_{max}. The data was processed using Microsoft Excel computer program and various statistical parameters were determined [8].

Partition coefficient

Ten mg of drug was accurately weighed and taken in stoppered vials containing 10 ml each of two immiscible phases, n-octanol and aqueous phase (PBS 7.4). The vials were placed on water bath shaker for 24 h. Phases were separated using separating funnel and both the phases were analyzed for the amount of drug after suitable dilution spectrophotometrically. The partition coefficient was calculated by following formula:

$$P.C = Co/Cw$$

Where, P.C = Partition coefficient

Co = concentration of drug in n-octanol phase

Cw = concentration of drug in aqueous phase

This procedure was followed for both the drugs separately [9].

Solubility study

Sertraline was added in excess amount in PBS 7.4. Flasks were placed in water bath shaker for 48 h at 37°C. After 48 h solutions were analyzed spectrophotometrically and drug concentrations were calculated.

Formulation of fast dissolving buccal film:

Fast dissolving films were prepared by solvent casting method (Weinberger, 1987). Aqueous solution I was prepared by dissolving polymer in 20 ml hot water (80°C) with stirring to produce a clear solution and kept for 1 h to remove all the air bubbles. In the case of the FC formulations, Carbopol 934P was first dissolved in a small portion of distilled water, neutralized with triethanolamine and then added to the cooled Poly Vinyl Alcohol (PVA) solution. Aqueous solution II was prepared by dissolving pure drug, sweetener, and plasticizer in specific proportion in distilled water. The aqueous solutions I and II were mixed and stirred for 1 h. The solutions were cast on to 9-cm diameter Petri dish and were dried in the oven at 45°C for 24 h. The films was carefully removed from the Petri dish and checked for any imperfection and cut according to size required for testing (square film 2 cm length, 2 cm width) so that each film contained 4 mg of the drug. The samples were stored in a glass container maintained at temperature 30 °C and relative humidity 60% ± 5% until further analysis [Table 2] [10].

Table 2: Composition of sertraline fast dissolving buccal films [10]:

1. Formulation containing Carbopol as the polymer:

Ingredients	Formulations FA	
	FA1	FA2
Sertraline	0.09	0.07
PVA	52.62	43.95
Carbopol	13.15	10.99
Propylene glycol	34.14	28.51
PEG-400	--	--
Mannitol	--	16.48
Sodium saccharin	--	--

2. Formulation containing PVP as the polymer [10]:

Ingredients	Formulations FA	
	FA1	FA2
Sertraline	0.09	0.07
PVA	52.62	43.95
PVP	13.15	10.99
Carbopol	--	--
Propylene glycol	34.14	28.51
PEG-400	--	--
Mannitol	--	16.48
Sodium saccharin	--	--

Evaluation

Weight variation

Weight variation of the prepared films was studied by individually weighing 10 randomly selected patches. Such determination was performed for each formulation.

Thickness

Thickness of different films of all batches was determined by micrometer at five random points on the films.

Drug content determination

An accurately weighed portion of the film (100 mg) was dissolved in 100 mL of dichloromethane and then the solution was shaken continuously for 24 h in shaker incubator. After sonicaing and filtering, drug solution was estimated spectrophotometrically by appropriate dilution.

Folding endurance

Folding endurance of the film was determined repeatedly folding the film at the same place until it break. The number of times the film could be folded at the same place without breaking was the folding endurance value.

***In vitro* release studies**

The *in vitro* drug release studies were performed by using a modified US Pharmacopoeia paddle-type dissolution apparatus (using 900 ml of PBS 7.4 as dissolution medium). The dissolution studies are crucial because one needs to maintain the drug concentration on the surface of the

Stratum corneum consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation. A circular film with an internal diameter of 1 cm was used for the study and a stainless steel ring was employed to hold the patch at bottom. . All dissolution studies were performed at 32±0.5°C, at 50 rpm. Samples were withdrawn at different time intervals and analyzed spectrophotometrically. % drug released were plotted against time for different formulations [11].

Result and Discussion

Preformulation studies

The sample of sertraline was identified and characterized as per requirement by official compendia. The drug purity was identified by TLC and melting point, which was found to be 246-249° C. sertraline was found to be slightly soluble in water and alcohols (ethanol, isopropyl alcohol

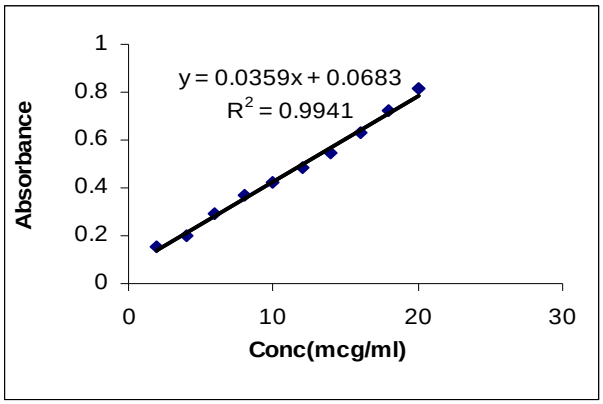
Selection of λ_{max} for determination

The UV scan obtained for sertraline in PBS 7.0. The drug showed λ_{max} 235nm.

Preparation of calibration curves and validation of analytical method

The prepared aliquots (2-20 µg/ml) were scanned for absorbance in PBS 7.4. The absorbance range was found to be 0.151-0.816. These solutions obeyed Beer-Lambert's law in above concentration range with regression of 0.999. This shows good linearity and range. The standard plot of sertraline is shown in Figure -1.

Figure 1



Partition Coefficient

The partition coefficient of sertraline in n-octanol: PBS (pH 7.0) was found to be 2.9.

Optimization and evaluation of transdermal patches

Good, transparent films were obtained by solvent casting method for both the batches FA and FB. But they were found to be brittle without plasticizer. Then glycerol was added as plasticizer to decrease the brittleness, which formed the films with good elasticity.

The average weights ranged between 168 to 177 mg, which indicates that different batches were relatively similar in weights. The thickness of the films was measured by micrometer and the film thickness was found to lie between 0.568 to 0.67 mm in all the cases. Good uniformity of drug content among the batches was observed with all formulations and ranged from 85 to 95%. The results indicate that the

process employed to prepare transdermal patches in this study was capable of producing formulations with uniform drug content and minimal patch variability. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus no constriction was observed indicating all patches had a smooth and flat surface. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied [12].

***In vitro* release studies**

Drug release from polymer matrix and drug dissolution ensured sustained reproducibility of rate and duration of drug release. The drug release from mixed polymers without permeation enhancer was found to be 90- 95% for batches FA and FAB respectively within 1 h. release profile of fast dissolving buccal films is shown in Table 3 & 4.

Table 3: Release profile of batch FA containing Carbopol [13]

Time(min)	Average	SD
0	0	0
5	23.65	0.098489
10	45.57	0.1253
20	50.48	0.213854
30	65.92	1.87788
45	78.76	1.562402
60	90.87	0.579511

Table 4: Release profile of batch FB containing PVP K30 [13]

Time(min)	Average	SD
0	0	0
5	23.63	0.718528
10	39.85	0.323407
20	49.82	1.725225
30	62.75	4.05237
45	79.56	2.153609
60	95.12	0.704651

Figure 2: Release profile of batch FA [14]

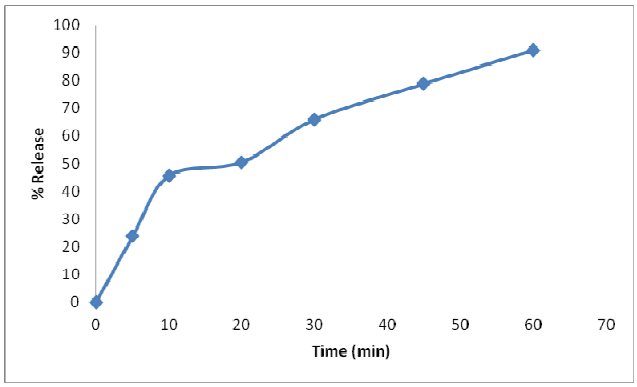
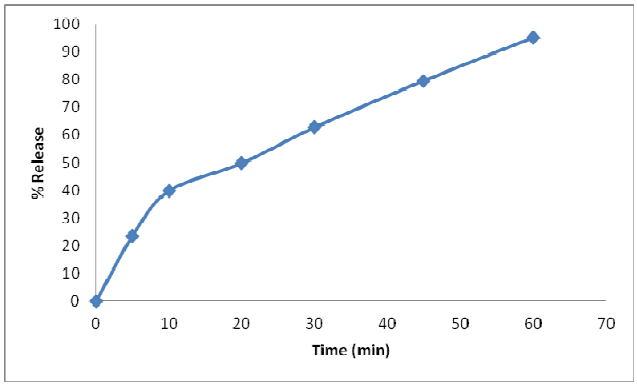


Figure 3: Release profile of batch FB [14]



Conclusion:

The use of water-soluble sweeteners, especially mannitol not only enhanced the taste of the sertraline containing films, but also increased drug release and drug permeation through oral mucosa. On the basis of data obtained from *in vitro* dissolution and *ex vivo* permeation studies that FA1 and FA2 are promising formulations suitable for the immediate release of sertraline for systemic use since they exhibited maximum drug release and permeation, respectively [15-16].

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