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FORMULATION AND EVALUATION OF SUBLINGUAL FILMS OF AMPHETAMINE SULFATE

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ABSTRACT

The present work was attempted to formulate and evaluate sublingual films of Amphetamine sulfate. Literature survey was carried out for selection of suitable excipients. Preformulation studies were conducted to identify Amphetamine sulfate by means of UV Spectrophotometric test and melting point determination. The results of compatibility studies were carried out by FTIR. The result of FTIR analysis showed compatibility without any significant interaction. Preliminary studies were conducted with an attempt to select suitable polymer and to see the effects of it on in- vitro disintegration time, % release of drug and mechanical properties like folding endurance, tensile strength etc. Polymer except Pullulan gives more thickness and requires more time to disintegrate and dissolved. So, it requires more time to give maximum drug release. From the results of preliminary studies, Pullulan was selected to optimize the rapidly disintegrating film and

gives fast drug release. It gives more than 90% drug release in 10 min and 21 sec Disintegration time.

KEYWORDS: Amphetamine sulfate, Pullulan, PEG 400, Sublingual Films.

INTRODUCTION

Amphetamine is indicated for the treatment of attention deficit/hyperactivity disorders (ADHD) as well as for the treatment of central nervous system disorders such as narcolepsy Amphetamine is well absorbed in the gut and as it is a weak base hence the more basic the environment the more of the drug is found in a lipid-soluble form and the absorption through lipid-rich cell membranes is highly favored Amphetamine, as well as other catecholamine's, is taken into presynaptic nerve terminals by the association with two sodium ions and one chloride ion.

It is available in the market as tablets and capsule dosage form with different strength of 5 and 10 mg. The Log P value of drug is 1.85 and its pKa value is 10.01. The drug has good water solubility which is 1.3 mg/ml. The peak plasma concentrations are attained at 9-14 hours. Hence, the present research work is aimed to prepare and evaluate the sublingual films of Amphetamine which gives quick onset of action and reach to the systematic circulation quickly as. The low molecular weight, low dose of drug, good water solubility and Log P value favors drug to formulate as sublingual dosage form which gives quick onset of action after taking with or without water and ultimately improves patient compliance.

Sublingual gland: Salivary organs are available in the floor of the mouth under underneath the tongue. They are otherwise called sublingual organs. They deliver mucine thusly creates salivation. The inside territory of the mouth stays lubed because of generation of the spit by the organs, which is important for biting and sustenance gulping. The liquid which is created by the organs gets blend with the nourishment, so the sustenance gets effortlessly bit. Because of low discharge of the spit it can make issue in gulping the sustenance and potential for nourishment hold up in the throat increments. The assimilation is exchange of the medication from its site of organization into fundamental dissemination, so it tends to be said that retention is specifically relative layer thickness. The ingestion of the medication following along these lines Sublingual >Buccal > Gingival >Palatal. Due to high penetrability and rich blood supply, the sublingual course can create quick beginning of activity so the medication with short conveyance period can be conveyed and portion regimen is visit. The

medication gets weakened in the salivation and from that point the medication is adsorbed over the oral cavity.

Sublingual drug delivery Sublingual means under the tongue. Sublingual route offers direct contact of drug with oral mucosa which wills leads to come directly in to systemic circulation which leads to enhance bioavailability of dosage foam. Complexity in swallowing which is a common problem of all age groups, children, elderly, uncooperative or on reduced liquid intake have difficulties in swallowing sublingual route is promising approach for overcoming this type of problems after the oral administration of drug the drug goes to hepatic first pass metabolism this will result in to decrease bioavailability of drug formulation. Sublingual route of drug delivery is promising approach to remove this type of problems.

Sublingual formulations A. Bio adhesive sublingual tablet **B.** Fast-disintegrating sublingual tablets **C**. Thin film drug delivery **D**. Lipid matrix sublingual tablet **E**. Sublingual immunotherapy **F.** Sublingual vitamin tablet

MATERIALS AND METHOD

MATERIALS

Amphetamine sulfate (API), Polyethylene Glycol Glycerine Propylene Glycol (Plasticizer), Pullulan Kollicoat IR HPMC E5 (Film forming polymer), Sucralose(Sweetener), Citric Acid (Saliva stimulating agent) and Water(Solvent) are used.

Formulation of Amphetamine sulfate Sublingual Films

Films were prepared by using solvent casting method. Amphetamine sulfate films were prepared by using different film forming polymers like HPMC E5 LV, HPMC E15 LV, HPMC E50 LV, Kollicoat IR and Pullulan. The required amount of film forming polymer was allowed to hydrate using fixed quantity of purified water for about 3-4 hours and then uniformly dispersed to get clear solution of film forming polymer.

To this polymeric solution, PEG 400 and other ingredients including sweetener, saliva stimulating agent were dissolved one by one in appropriate quantities. Drug was dissolved in small quantity of water and added to the above polymer plasticizer solution and mixed thoroughly using a magnetic stirrer at 80-90 rpm The solution was kept undisturbed condition till the entrapped air bubbles were removed and was sonicated. Finally, a measured quantity of the above solution was poured in to the Petri dish dried overnight at room temperature.

The dried films were cut into squares of 2 cm X 2 cm and stored in air tight containers wrapped in butter paper and aluminum foil for further analysis.

Table 1: Trial batch of Amphetamine sulfate Sublingual Films.

Ingredients (mg/film)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Amphetamine sulfate	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
HPMC E5 LV	200	-	-	-	-	100	-	-	-	-
HPMC E15 LV	-	200	-	-	-	-	100	-	-	-
HPMC E50 LV	-	-	200	-	-	-	-	100	-	-
Kollicoat IR	-	-	-	200	-	-	-	-	100	-
Pullulan	-	-	-	-	200	-	-	-	-	100
Citric Acid	4	4	4	4	4	4	4	4	4	4
Sucralose	5	5	5	5	5	5	5	5	5	5
PEG 400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Water (ml)	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s	Q.s

Here in this table no 1 drug loaded films were prepared by using different types of film forming polymers. Started with 200 mg amount of film forming polymer and it's decreased to 100 mg. Amount of polymer decreased to get desired drug dissolution profile and Fast disintegration time of film. Higher amount of polymer retard disintegration of film so dissolution time also increased.

EVALUATION OF AMPHETAMINE SULFATE SUBLINGUAL FILM

Compatibility Study by FTIR:- Amphetamine sulfate and physical mixture of Amphetamine sulfate with excipients were subjected to FTIR spectroscopic analysis, to characterize drug and to determine the compatibility of drug with the excipients used. The FTIR spectra obtained for pure drug and mixture with excipients is given in below figure 1.

Figure 1 FTIR Spectra of Pure Drug (Amphetamine sulfate) and Physical mixture of drug with

Excipients

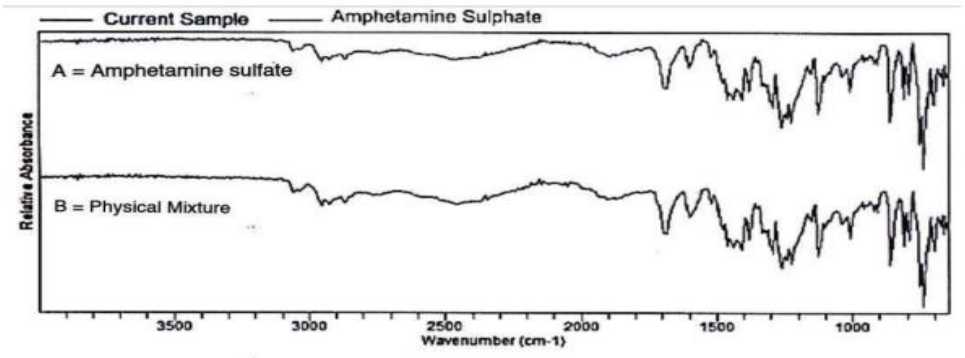

Table 2: Interpretation of FTIR data.

Stretching	Range (cm^{-1})	Drug (cm^{-1})	Physical Mixture(cm^{-1})
C-H stretching	2960-2850	2940.30	2941.51
C=C stretching (alkenes)	1680-1620	1634.82	1634.82
C=C stretching (aromatic)	1450-1600	1466.25	1463.68
C-O stretching	1310-1410	1305.39	1307.51
C-Nvibrations	1000-1400	1248.02	1250.76

Based on the above FTIR interpretation data, it confirms that the drug does not show any interaction with the selected excipients. Hence the selected excipients found compatible with the API.

Calibration curve of Amphetamine sulfate: The scanning of drug done using 6.8 phosphate buffer and the obtained spectrum was shown in below fig1. The absorbance maximum was found at 286 nm. Hence 286 nm was considered as λmax and the calibration curve to estimate Amphetamine sulfate was constructed at 286 nm.

Table 3: Standard Calibration curve of Amphetamine sulfate.

Sr. No.	Concentration (µg/ml)	Absorbance (average) ± SD
1	0	0.00
2	10	0.205± 0.005
3	20	0.398± 0.009
4	30	0.580± 0.007
5	40	0.750± 0.008
6	50	0.930± 0.005

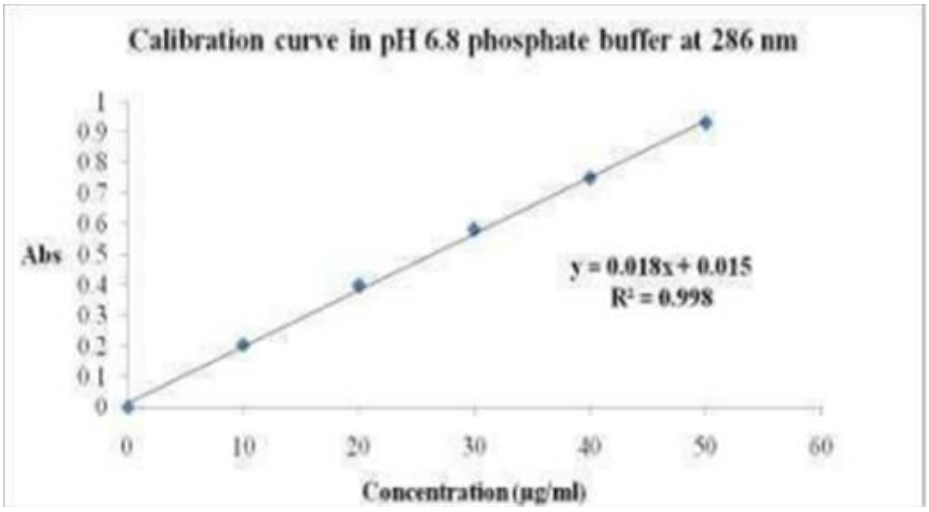

Figure 2 Evaluation of Trial Batches of Amphetamine Sulfate Sublingual Films.

Table 4: Evaluation of formulation F1-F10.

Batch	Average weight (mg) (n=20)	Thickness (mm) (n=3)	Folding Endurance (n=3)	% Drug content (n=3)
F1	204 ± 3.2	0.23 ± 0.03	98 ± 4.8	98.2 ± 1.9
F2	201 ± 2.5	0.24 ± 0.02	107 ± 5.7	97.5 ± 2.3
F3	205 ± 2.1	0.26 ± 0.05	148 ± 4.1	98.3 ± 1.5
F4	200 ± 3.5	0.25 ± 0.02	196 ± 5.2	97.5 ± 2.1
F5	203 ± 2.8	0.27 ± 0.05	269 ± 4.8	98.9 ± 1.9
F6	109 ± 1.9	0.19 ± 0.01	73 ± 3.2	96.7 ± 2.8
F7	105 ± 1.6	0.21 ± 0.03	89 ± 4.6	98.3 ± 3.1
F8	101 ± 2.5	0.22 ± 0.02	113 ± 2.8	98.2 ± 1.7
F9	108 ± 2.3	0.23 ± 0.03	167 ± 3.4	97.5 ± 2.0
F10	110 ± 1.4	0.20 ± 0.02	233 ± 2.7	98.1 ± 1.8

The weight of the batch F1-F10 was found in the range of 101 to 205 mg. the weight variation was found well within acceptable limit. The concentration of polymer affects the weight of the film, as the amount of polymer increase, weight of film increase. The thickness of F1-F10 was found in the range of 0.20-0.27 mm. As the polymer concentration of polymer was increased the thickness was increased. The folding endurance was affected by variable amount of polymer. The high amount of polymer gives more value of folding endurance and provides good mechanical strength. In above batches the folding endurance was in the range of 73 to 269. The pullulan batches show good folding endurance as compared to other polymers. The % drug content of all F1-F10 batches was found between of 97.5 to 98.9%. So, it shows that the drug is uniformly distributed throughout the film.

Table 5: Evaluation of formulation F1-F10.

Batch	Surface pH (n=3)	Disintegration time (Sec) (n=3)	Wetting time (sec) (n=3)	Tensile Strength (kg/cm^2) (n=3)	Percent Elongation (n=3)
F1	6.8 ± 0.2	71 ± 4.8	79 ± 5.4	0.34 ± 0.5	24.1 ± 2.3
F2	6.7 ± 0.4	76 ± 5.6	85 ± 4.9	0.35 ± 0.7	26.9 ± 3.1
F3	7.1 ± 0.1	84 ± 3.9	91 ± 5.7	0.37 ± 0.4	27.8 ± 2.5
F4	6.8 ± 0.2	90 ± 2.8	99 ± 4.6	0.40 ± 0.9	30.9 ± 1.8
F5	6.9 ± 0.2	63 ± 2.1	70 ± 3.8	0.36 ± 0.7	24.8 ± 2.5
F6	7.0 ± 0.1	39 ± 1.9	48 ± 4.5	0.28 ± 0.4	20.5 ± 1.2
F7	6.8 ± 0.3	43 ± 2.4	52 ± 3.7	0.29 ± 0.8	21.4 ± 1.6
F8	6.7 ± 0.2	49 ± 2.6	60 ± 2.9	0.31 ± 0.6	23.9 ± 2.2
F9	6.8 ± 0.3	57 ± 3.2	67 ± 4.6	0.33 ± 0.4	26.7 ± 1.4
F10	7.0 ± 0.1	21 ± 1.5	26 ± 2.1	0.29 ± 0.7	21.5 ± 1.1

The surface pH of all batches was well within acceptable range. It was found between 6.7 - 7.1. The disintegration time was found in the range of 21 to 91 sec. It was found satisfactory in terms of the dosage form requirement. The amount of polymer also affects the time required to disintegrate the film. Here the formulation batch F4 requires maximum disintegration time that is 90 sec and formulation batch F10 requires minimum disintegration time that is 21 sec. So, it shows increase the amount of polymers increase time requires disintegrating. The same behaviour was observed in wetting time results. The results of wetting time found between 26 to 99. The % elongation of F1-F10 batches was found in the range of 20.5 to 30.9. The elongation was increased with increased in polymer concentration. As well as tensile strength was also affect the variable concentration of polymer. In above batches the tensile strength was found to be in the range of 0.28 to 0.40 kg/cm2.

Table 6: Cumulative Drug Release Profile of Formulation F1-F10.

Time (min)	% Cumulative drug release (n=3)									
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
2	19.5	16.5	15.9	14.2	20.5	24.9	23.1	20.5	18.5	29.4
4	32.5	29.9	27.4	25.9	34.9	39.7	37.8	33.9	31.5	47.2
6	43.9	40.5	37.8	34.7	46.9	49.2	45.4	42.5	40.8	65.4
8	52.9	49.6	48.6	45.2	55.4	59.4	54.5	51.6	50.5	78.9
10	63.5	59.7	57.2	54.1	66.4	70.1	66.8	63.5	61.3	91.3
12	72.5	70.4	67.4	65.9	76.9	79.5	77.1	74.1	71.9	97.2
14	81.3	79.1	76.1	74.6	83.4	89.4	87.6	84.9	82.8	98.9
16	89.2	87.2	84.3	82.1	92.5	96.5	92.5	91.2	89.9	99.1
20	96.2	94.5	93.1	90.8	97.9	99.7	98.6	97.8	97.9	99.5

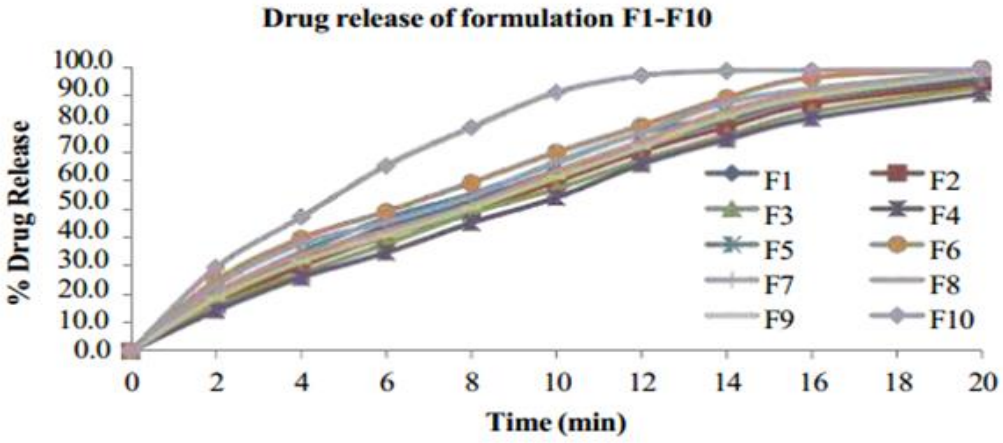

Figure 3: Cumulative Drug Release Profile of Formulation F1-F10.

Dissolution profile of formulation batches F1-F10 was tabulated in above table and comparison chart also prepared. Dissolution Profile of formulation Batch F1-F10 shows as the concentration of polymer is increase the % drug release is decrease. The high concentration of Pullulan required more time to give maximum drug release. F10 batch gives fast drug release as compared to all formulation. The formulation batch F10 gives 91.3 % drug release within 10 min. It contains low amount of polymer so it gives maximal drug release in minimum period of time and gives acceptable result.

CONCLUSION

The present work was attempted to formulate and evaluate sublingual films of Amphetamine sulfate. Literature survey was carried out for selection of suitable excipients. Preformulation studies were conducted to identify Amphetamine sulfate by means of UV Spectrophotometric test and melting point determination. The results of compatibility studies were carried out by FTIR. The result of FTIR analysis showed compatibility without any significant interaction. Preliminary studies were conducted with an attempt to select suitable polymer and to see the effects of it on in- vitro disintegration time, % release of drug and mechanical properties like folding endurance, tensile strength etc. Polymer except Pullulan gives more thickness and requires more time to disintegrate and dissolved. So, it requires more time to give maximum drug release. From the results of preliminary studies, Pullulan was selected to optimize the rapidly disintegrating film and gives fast drug release. It gives more than 90% drug release in 10 min and 21 sec Disintegration time.

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