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FORMULATION DEVELOPMENT OF SUBLINGUAL FILM OF ANTIPSYCHOTIC DRUG WITH DIFFERENT POLYMERS AND PLASTICIZERS

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Abstract - Asenapine Maleate was selected for evaluation of different polymer for preparation of fast dissolving sublingual film. Asenapine Maleate, antagonist activity at Histamine 5-HT2A and dopamine D2 receptors is a new psychopharmacologic drug with high potency and affinity for blocking dopamine, serotonin, α-adrenergic and histamine receptors, which has oral bioavailability of only 2% due to first pass metabolism. This research work performed for developing Asenapine Maleate sublingual films with satisfactory drug dissolution in the oral cavity, thus bypassing hepatic first pass metabolism to provide rapid onset of action of the drug and comparable effect as reference listed drug product Saphris. The sublingual films were prepared by solvent casting method. Different combination of polymers was used with plasticizer to develop palatable and stable film. Cherry flavor is used as flavouring agent, Aspartame is used as sweetening agent and Poloxamer 188 was used as penetration enhancer. All the films formulations was evaluated for their thickness, weight variations, tensile strength, percentage elongation, folding endurance, surface pH, in-vitro disintegration, drug content and in-vitro drug release. Disintegration time showed by the formulations was found to be less than 2 minutes. Formulations showed 80% in-vitro drug dissolution within 4 min was finalized. The film showed an excellent stability for one month when stored at temperature 40˚C and 75% in humidity and room temperature.

Keywords: Asenapine, Schizophrenia, Bipolar disorder, drug substance

Introduction

Schizophrenia is rigorous chronic debilitating brain syndrome affecting around 1-2% of the world population, more affecting the urban population than rural population and affecting man and women equally.[1] In India, the figure of patient affect by the schizophrenia is just about 8.3 to 10.7 million. Age of onset is commonly between 20 year to 35 year and it is characterized by positive indication (e.g., hallucinations, delusions and thought disorder), negative indication (e.g., deficits in public interaction, emotional expression and motivation) and cognitive dysfunction (e.g., impairments of attention and working memory). Schizophrenia has shocking effects on several aspects of the patient's life. It is among the top ten causes of disability world-wide and reduces the life extent of those afflicted by normal of ten years. Suicide is the single greatest cause of early death among patients with this disorder. In schizophrenia treatment, patient non adherence is a main problem occurred as side effect related with drug and long term therapy regimen. More than 34% of patient demonstrate adherence problems during the first 4-6 weeks of treatment and within 2 years its reached up to 74%.[2,3,4] The common result of non-adherence are usually a remitting course with one or several relapses in 50-92% of cases. Patients on medication have a relapse rate of 40%, while those who break off their treatment have a 1-year decline rate of 65% and in 2-year rate more than 80%.[5]
Asenapine (ASN) is claim to be a novel psychopharmacologic agent with high affinity and power for blocking dopamine, serotonin, α-adrenergic and histamine receptors, and no significant activity at muscarinic cholinergic receptors. The mechanism of action of asenapine, like other atypical antipsychotics is believed to be mediated through a combination of antagonist activity at 5-HT_{2A} and D_2 receptors. It is accepted for the treatment of adults with schizophrenia and as an adjunctive treatment with lithium or valproate for the sharp treatment of hectic or mixed episodes linked with bipolar I disorder. [6]

Materials and Methods

Asenapine Maleate was received as gift samples from sun pharma Ltd, Baroda, India. Hydroxypropyl methyl cellulose E15LV was procured from Dow chemicals. Glycerin was obtained from Loba Chemie, Mumbai, India. Poloxamer 188 and PEG 4000 were procured from BASF. Cherry flavour from firminich and aspartame was purchased from Central Drug House, New Delhi.

Drug polymer compatibility studies [7,8]

Interaction of drug substance and excipients leads to generation of impurities in drug product. So drug excipients compatibility studies were studied by making physical mixture of drug and excipients in ratio of 1:1 and exposed to 40 ˚C/ 75 % RH. The sample was observed for any interaction leads to colour change.

UV Spectrum Analysis of Asenapine Maleate sublingual film

The solution was scan in the range of 200 to 400 nm to fix the highest wave length and UV spectrum was identified. Calibration curve was prepared and check for method suitability for method validation parameters.

The standard plot of Asenapine Maleate was prepared in Acetate buffer pH 4.5. Asenapine Maleate 14.06 mg was weighed accurately and dissolved in 100 ml of Acetate buffer. Appropriate dilutions were made with buffer to obtain test solutions ranging from 2 µg/ml to 20 µg/ml. The absorbance of the drug in the buffer was then measured on a double beam UV visible spectrophotometer at λ_{max} of 270 nm against the respective blank.

Method of preparation of fast dissolving sublingual film of Asenapine Maleate

Fast-dissolving film of Asenapine Maleate was prepared by the solvent-casting method.[9] Films with more flexible and elegant physical properties are produced by this method.[10] Aqueous solution I was prepared by dissolving the polymer, wetting agent, plastsizer and Asenapine Maleate in specific proportion-in distilled water and was allowed to remove all the air bubbles from solution. Aqueous solution II was prepared by dissolving Aspartame and Cherry flavor in specific proportion, in distilled water. Each aqueous solution I and II were mixed and stimulated for 1 hour. Then the mixture solution was casted onto a glass petri dish and it was dried up in the oven at 50˚C for 6 hours. The film was carefully removed from the petri dish, checked for appearance, and cut according to the size required for testing (square film: 2 cm length, 2 cm width). The samples were stored in a glass container maintained at a temperature below 25˚C in moisture protective container.

Evaluation of Sublingual film

Weight Variation **[11]**

Four centimeter square of the film was cut at three dissimilar places from the casted film. The weight of each film was carried out and weight variation was calculated.

Film Thickness

The thickness of the patch was measured using digital Vernier Calliper with a least count of 0.01 mm at three spots of the film. The thickness was calculated at three dissimilar spots of the patch and average was taken and SD was intended.

Folding endurance [12]

Folding endurance was calculated by repeated folding of the film at the same place till the film break. The number of times the film is folded with no breaking was computed as the folding endurance value.

Tensile strength

Tensile testing was done using a texture analyzer AG/MC1 (Acquati, Italy), equipped with a 5 N load cell. The film was cut into 2 × 2 cm film. Tensile tests were performing according to ASTM International Test Method for Thin Plastic Sheeting (D 882-02). Every test strip was positioned in tensile grips on the texture analyzer. First grip partition was 20 mm and crosshead speed was 1 inch/min. The test was considered accomplished when the film breaks. Tensile strength, was calculated with help of load need to break the film and cross sectional area to evaluate tensile property of the films. Tensile strength (TS) is the maximum stress applied to a point at which the film specimen breaks and can be calculated by dividing the maximum load by the original cross-sectional area of the specimen and it was expressed in force per unit area (MPa).[13]

Tensile Strength = Force at break (N)/ Cross sectional area (mm^2)

Percentage elongation

For the determination of percentage elongation of the film formulations, the distance between the tensile grips of the tensile strength testing machine was measured before and after the fracture of the film. Then the percentage elongation of the films was computed with the help of the method given under:-

% Elongation = $(D_f - D_0)/D_0 \times 100$

Where:-

D_0 = Distance among the tensile grips before the fracture of the film.

D_f = Distance among the tensile grips after the fracture of the film

pH film in water **[14,15]**

The pH of sublingual film was determined in order to investigate the possibility of irritation oral mucosa in vivo due to acidic or alkaline pH. It was unwavering to keep the surface pH as close to neutral as possible. A collective pH electrode was used for measurement film which was dissolved in water. The pH was measured. The formula was performed in triplicate and average, with standard deviation was reported.

Disintegration **[16]**

Disintegration time was resolute visually in a petri dish containing 25 ml of pH 6.8 phosphate buffer with swirling every 10 sec. The disintegration time of the film starts to break or it disintegrates.

Drug Content

Drug determination of the film was accepted by dissolving the film of 4 cm^2 in 100 ml of pH 6.8 phosphate buffer. The drug concentration was then evaluated spectrophotometrically at λmax of 270 nm. The determination was approved in triplicate for all the formulations and average with standard deviation was recorded.

In-vitro dissolution [17]

The dissolution study was carried out using USP Type II (paddle type) dissolution apparatus. The dissolution was carried out in 500 ml of pH 6.8 phosphate buffer maintained at 37±0.5 ^{0}C at 50 rpm. 5 ml aliquots of samples were taken at various time intervals which were replaced with same volume of fresh pH 6.8 phosphate buffer maintained at 37 ± 0.5 ^{0}C. Asenapine Maleate in the samples was then determined spectrophotometrically at λmax of 270 nm. Percentage drug dissolved was calculated.

Stability study [18]

Stability study was carried out at storage conditions; one was normal room conditions and 40˚C/75% RH for one month. Each piece of the films of formulation was packed in butter paper followed by aluminum foil and heat sealing. After one month, the films were evaluated for the physical appearance, surface pH, drug content, degradation and dissolution.

Table 1: Composition of Sublingual Film Prepared from Different Polymers and Plasticizers

Ingredients	F1	F2	F3	F4	F5
Asenapine Maleate	14.06	14.06	14.06	14.06	14.06
Hydroxypropyl Methyl Cellulose (E 15 LV)	25.94	25.94	-	-	12.97
Povidone (K-30)	-	-	25.94	25.94	12.97
Polyethylene oxide (POLYOX WSR N-80)	3.5	3.5	3.5	3.5	3.5
PEG 6000	4.00	-	4.00	-	-
Glycerine	-	4.00	-	4.00	4.00
Poloxamer 188	1.0	1.0	1.0	1.0	1.0
Aspartame	0.5	0.5	0.5	0.5	0.5
Cherry flavour	1.0	1.0	1.0	1.0	1.0
Purified water*	q.s.	q.s	q.s	q.s	q.s
Total	50.00	50.00	50.00	50.00	50.00

*****Evaporate during processing, does not remain in final formulation, once trace amount remain

Result and Discussion

Drug polymer compatibility studies

There was no colour change was observed in drug-compatibility sample, so there is no drug-excipient compatibility with selected excipients for formulation development.

Analytical method suitability

λ_{max} of Asenapine Maleate was 270 nm in UV Visible spectra. Proposed method of analysis is linear, accurate, precise and suitable for analysis of Sublingual film of Asenapine Maleate.

Evaluation of Sublingual film

Weight variations

Five films with dimension 4 cm^2 were cut at five different places from the casted film and weight variation was determined. Weight variation data are shown in Table 2.

Film Thickness

Different formulations contain different polymers and different amount; hence the thickness was change with type and amount of polymers. All the film formulations were found to have thickness in the range of 0.05 mm to 0.10 mm. The results are given in the Table 2.

Tensile strength, percentage elongation and folding endurance

Suitable film requires moderate tensile strength, acceptable percentage elongation and folding endurance. Learning of mechanical property was undertaken for all the chosen formulations. During the study the comparative mechanical properties of various prepared formulations is shown Table 2.The tensile strength of formulation F2 was found maximum 6.4. The percentage elongation of all the batches ranges from 5-18. It increased upon increasing the amount of polymer and plasticizer as shown by the formulations. Formulation F5 had highest percentage elongation. Folding patience increased with raise in the concentration of glycerine. The figure of time the film crease until it broke is reported in the Table 2.

pH of film

pH of the films was ranging from 5.5 to 6.8 as shown in Table 2. Since the surface pH of the films was found to be around the neutral pH as saliva, there will be no irritation to the mucosal lining of the oral cavity.

Disintegration Time

It was observed disintegration time varies from 30 to 120 sec for different formulations. Disintegration time of film containing HPMC E-15LV as polymer was affected by the thickness and plastsizer used in film. Disintegration time of the films was found increased with increase in the amount of the polymer. HPMC E-15 LV and Glycerin show less disintegration time as compared to other formulation.

Determination of drug content of films

The prepared film formulations were evaluated for assay and uniformity of dosage units. It was observed that all the formulations were satisfactory in drug content and uniformity of drug as given in Table 2.

In-vitro Dissolution study

Manufactured Sublingual films were evaluated for dissolution study as per OGD recommended media. The in vitro drug dissolution profiles of the formulations in pH 6.8 phosphate buffer show differences depending on their composition as given in Table 1. A rapid dissolution of all the film preparations was observed by the dissolution test, in which nearly 90% of Asenapine Maleate dissolved within 4 min. Sublingual film composition (F2) show above 90% drug release within 4 minutes. It is observed that HPMC E 15 LV with plastsizer glycerin show satisfactory physical properties and satisfactory dissolution.

Stability study

The chemical and physical stability study of the formulation F2 was carried out at controlled room temperature (25˚C/75 % RH) and Accelerated condition (40 ˚C/75% RH) for a period of one month as recommended by ICH guideline. The film does not show significant change in physical properties like appearance and flexibility. The drug content and pH of film was found almost constant for up to one month. The in vitro dissolution and disintegration time of the films after the stability study was also not found to be affected.

Table 2: Evaluation of sublingual film of prepared from different polymers andplasticizers

Parameter	F1	F2	F3	F4	F5
Thickness (mm)	0.05	0.052	0.053	0.049	0.052
Weight variation (%)	49.5-51.2	49.1-51.4	48.5-51.4	48.8-51.4	48.5-51.5
Folding endurance	100	125	80	90	84
Tensile strength (MPa)	6	6.4	3	4	4.5
Percentage elongation	5	6	4	3	6.3
pH film in water	6.4	6.5	6.0	5.8	6.5
Disintegration	1 min 20 sec	55 sec	1 min 5 sec	1 min 10 sec	1 min 6 sec
Assay (%)	97-102	98-103	99-104	97-102	99-103
Dissolution (at 4 minutes)	80	92	84	88	86

CONCLUSION

The conclusion of the present study is suggested that HPMC E15 and glycerin could be applicable as a film forming polymer for formulation of quick dissolving film containing Asenapine Maleate. Suitable mechanical properties were obtained for all the batches with *in vitro* collapse time of 120 second. On the base of data obtained from in-vitro dissolution is promising formulation appropriate for the sublingual urgent release of Asenapine Maleate for the systemic use since they exhibited greatest drug release and probable good absorption through sublingual route. The formulation batch was established to be steady for a period of one month at 40°C/75%RH.

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