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Research Article

FORMULATION AND EVALUATION OF SUBLINGUAL FILM OF NATEGLINIDE

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ABSTRACT

Sublingual route is a very useful for rapid onset of action with better patient compliance. It provides better drug utilization and improves the efficacy of active pharmaceutical ingredients. The oral route is the most acceptable for patients. Fast dissolving oral drug delivery system is solid dosage form which disintegrates or dissolves within second when placed in the mouth without need of water or chewing. The current study presents the formulation aspects, manufacturing methods like solvent casting, evaluation parameters and applications of fast dissolving films by sublingual route by using polymers such as PVP K-30, PVA and PEG-400 as a plasticizer and Mannitol as a sweetener. A film formed in F3 formulation was transparent, smooth and homogenous with best film forming property among all the film forming agents.

Keywords: Nateglinide, Polyvinyl alcohol, Polyvinyl pyrrolidone, Polyethylene glycol, Mannitol, Sublingual film, Solvent casting

INTRODUCTION

For the last two decades, there has been an enhanced demand for more patient compliant dosage forms.The cost involved and time consumed in the development of a single new chemical entity has made it mandatory for pharmaceutical companies to reconsider delivery strategies to improve the efficacy of drugs that have already been approved.Therefore, pharmaceutical Industries are now directed towards reformulating existing drugs into new drug delivery systems.[1] Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medicines as prescribed. Difficulty in swallowing or dysphagia is seen to afflict nearly 35% of the general population. Other groups, who may experience problems in swallowing solid dosage forms, are the mentally ill, to develop mentally disabled, uncooperative patient and reduced liquid intake plans or nausea.[2] Dosage alternatives from oral route have been developed especiallyfor pediatric, geriatric, bedridden, nauseous or non-compliant patients. [3] Buccal routes are one of such alternatives which havelately become an important route of drug administration. As polymers and plasticizers forms the main body of MDF; therefore, their properties greatly affect the characteristics of MDF. [4, 5]

Concept of oral dissolving films[6]

- Oral dissolving film is flexible
- The dosage form can be consumed at any place
- Pain avoidance
- Available in various size and shapes
- Un Obstructive
- Fast disintegration
- Rapid release
- Excellent mucoadhesion

Ideal characteristics of a drug[7]

- The drug should have pleasant taste
- The drug to be incorporated should have moderate dose
- The drugs with smaller and moderate molecular weight are preferable
- The drug should have good stability and solubility in saliva
- It should have the ability to permeate oral mucosal tissue
- It should be partially unionized at the pH of oral cavity

The objective of the study was to prepare Fast Dissolving Films (FDF) of nateglinide which can be useful in hyperglycemia (Type 2 DM). Fast Dissolving Film was prepared by solvent casting method using various polymers such as PVP K30, PVA, PEG 400 and Mannitol as a sweetener. Prepared films were evaluated for thickness, tensile strength, folding endurance, disintegration time, surface pH, drug content uniformity, Invitro dissolution study and stability studies.

MATERIALS AND METHODS

Nateglinide as a gift sample from CIPLA, Mumbai and Polyvinyl Alcohol, Polyvinyl Pyrrolidone (PVP K 30), Polyethylene glycol 400 and Mannitol are purchased from Research Fine Chem Laboratory, Mumbai.

Preparation of sublingual film

Weigh PVA & PVP K30 and mix them in 10ml of water. Weigh required amount of drug and dissolve in 10ml of water. With the help of magnetic stirrer (40˚C – 50˚C) mix both the above solutions for 15 to 20min. Now add the solution in Petri plates and keep the solution at room temperature for 24hrs for drying.

Evaluation of sublingual film

Thickness

Thickness was measured using vernier calipers. The thickness was measured at 5 locations (one at center and four corners of the film) and the mean thickness was calculated.[8]

Folding Endurance

To determine folding endurance, a stripe of film was cut and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the value of folding endurance.[9]

Tensile Strength

The tensile strength was measured using analogy tensile tester. The two clamps of the tensile tester were adjusted such that the distance between them is 3 cm by moving the upper clamp. During measurement the films were pulled by top clamp. The force applied was measured until the film was broken.[10]

Tensile strength was measured using a formula:
Tensile Strength = Breaking Force (n) / Cross sectional area of sample (mm^2).

Disintegration Time

The disintegration time is the time when film starts to break or disintegrate. It was determined in a Petri plate of 25 ml distilled water with swirling every 10 seconds and the results were obtained.[11]

Drug Content

The film ($4cm^2$) is placed in 100ml of volumetric flask and dissolved in methanol and volume is made up to 100ml. The solution were filtered and analyzed at 217 nm in UV Spectrophotometer. The averages of drug content of 3 films were taken as final reading.[12]

In-vitro dissolution study

The studies were carried out in freshly prepared solution of pH 6.8 Phosphate buffer using USP paddle apparatus at 37˚C. Samples were withdrawn at every 1 min time interval. Samples were diluted by 6.8 phosphate buffer solution and analyzed by UV spectrophotometer.[13]

Stability Studies

The optimized formulations F3 were evaluated for its physical characteristics at intervals of 30, 60 and 90 days like appearance, pH, drug content and disintegration time.[14]

RESULT AND DISCUSSION

Thickness

The thickness of the drug loaded films F-1 to F-9 formulations were measured with the help of micrometer screw gauge at different strategic locations like four corners and center of each films. Mean SD were calculated. Thickness should be controlled within a ± 5 % variation of standard value.

Folding Endurance

The number of times the film fold until it breaks was reported. The studies reflex influence of concentration of PVA in the formulation. As the concentration of PVA is increased, folding endurance is also increased.

Tensile Strength

From the results it clears that when the concentration of the polymer increases, the tensile strength of the sublingual film also increases. The formulation. Presence of PEG- 400 as a plasticizer imparts flexibility to the Polymers. Tensile strength measures the ability of the sublingual film to withstand rupture.

Disintegration Time

In-vitro disintegration time is determined visually in a glass dish of 25 ml distilled water with swirling every 10 seconds. The disintegration is the time when sublingual film breaks or disintegrates. PVP K-30 is incorporated as a super-disintegrates. As the concentration of PVP K-30 increases, the disintegration time decreases**.**

Drug Content

Drug content of optimized batches were calculated by using sublingual film. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations are calculated. The drug content ranging from 97.05±2.160 to 99.39 ±2.460**.**

In-vitro dissolution study

In-vitro dissolution study shows maximum release i.e. 98.57% for F3 formulation this could be attributed to higher concentration of PVP and lower concentration of PVA in the formulation. This also resembles to the results of disintegration test.

Stability Studies

Optimized formulation F3 at 40ºC, 75% RH ± 5 % were found to be stable up to 90 days. There were no significant change visual appearances i.e. changes in color, disintegration time and drug content.

Table 1: Composition of Nateglinide sublingual film

Ingredients (Mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nateglinide	360	360	360	360	360	360	360	360	360
PVA	150	150	150	200	200	200	250	250	250
PVP K-30	200	250	300	200	250	300	200	250	300
PEG 400	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30	0.30
Mannitol	40	40	40	40	40	40	40	40	40
Water	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Evaluation data of various parameters

Batch	Thickness	Folding Endurance	Tensile Strength
F1	0.092±0.022	150 ± 1.945	1.1536± 0.032
F2	0.094±0.020	155± 2.201	1.3557± 0.026
F3	0.098±0.018	160± 2.515	1.7325± 0.031
F4	0.112±0.025	170± 2.640	1.2211± 0.010
F5	0.115±0.041	165± 2.431	1.4237± 0.050
F6	0.110±0.016	175± 2.709	1.6738± 0.040
F7	0.085±0.008	210± 3.135	1.3634± 0.045
F8	0.090±0.012	205± 2.820	1.5811± 0.038
F9	0.083 ±0.016	220± 3.210	1.5165± 0.036

Table 3: Evaluation data of various parameters

Batch	Disintegration time	Drug content
F1	36.7± 1.141	97.10± 2.160
F2	34.2± 0.580	98.35±2.350
F3	**33.0± 0.535**	**99.31± 2.455**
F4	37.3± 1.230	97.05± 2.155
F5	35.0± 0.860	98.20± 2.310
F6	33.3± 0.550	99.08± 2.425
F7	38.0± 1.130	97.40± 2.425
F8	35.5± 0.875	98.71± 2.390
F9	33.3± 0.400	99.15± 2.433

Table 4: Stability studies for F3 formulation

S.N	Observation	Before Stability Testing	After Stability Testing
1.	Drug content	98.57%	98.45%
2.	Visual appearance (Color changes)	Pale White	Pale White
3.	Disintegration time	33 Sec	34 Sec

Table 5: In-vitro dissolution study

Time In Min	% Cumulative drug release ± S.D								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	63.34± 0.300	69.94± 0.501	**77.85± 0.650**	55.95± 0.670	70.18± 0.550	75.10± 0.525	50.03± 0.740	65.51± 0.415	61.60± 0.190
2	71.43± 0.595	75.49± 0.550	**84.21± 0.830**	62.10± 0.250	77.28± 0.610	81.25± 0.826	56.54± 0.785	72.30± 0.540	68.50± 0.490
3	79.10± 0.670	85.51± 0.880	**90.65± 0.940**	70.48± 0 .560	84.59± 0.855	89.69± 0.895	64.80± 0.343	78.90± 0.630	75.27± 0.534
4	84.72± 0.861	89.92± 0.900	**94.85± 0.873**	79.20± 0.685	90.04± 0.911	93.80± 0.965	73.59± 0.651	83.82± 0.775	85.10± 0.870
5	88.51± 0.795	95.17± 0.971	**98.57± 0.993**	84.38± 0.842	94.49± 0.964	96.35± 0.984	80.10± 0.805	89.14± 0.890	91.85± 0.924

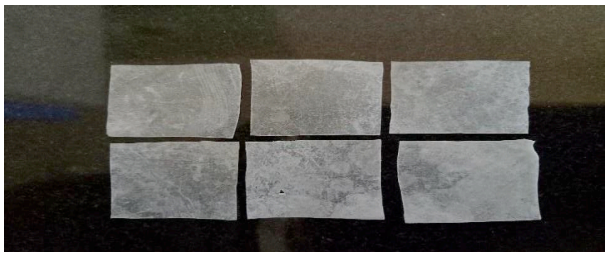

Figure 1: Desired shape of sublingual film

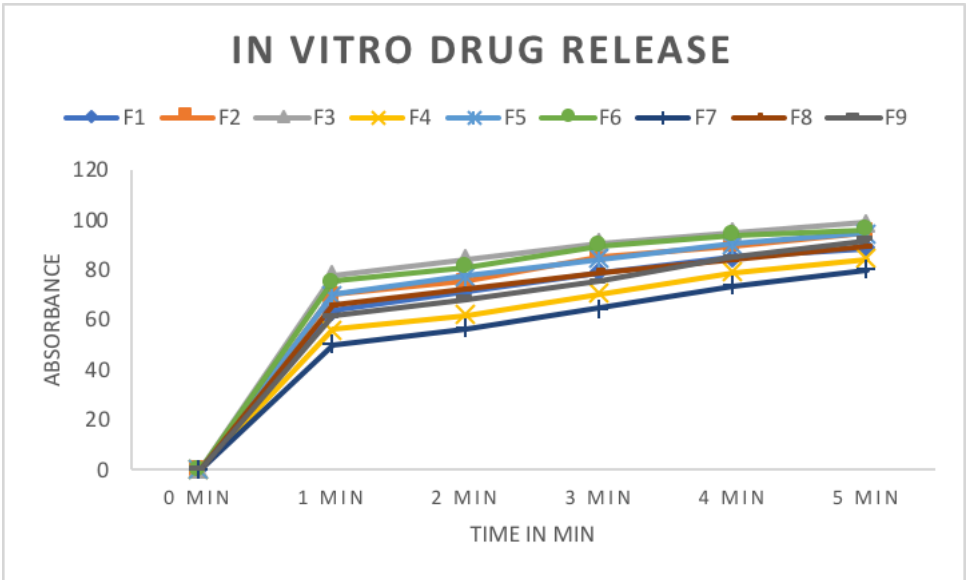

Figure 2: Evaluation of in-vitro drug release study

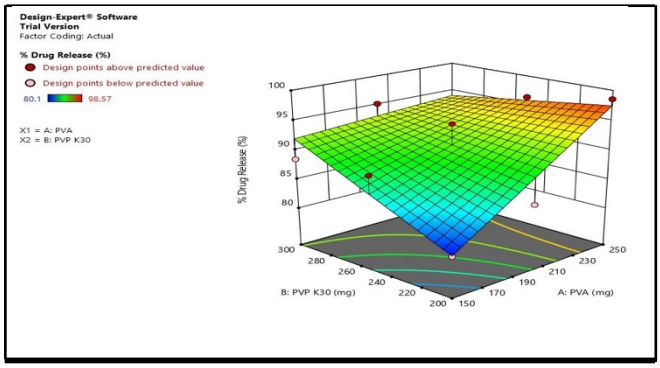

Figure 3: Surface response plot showing effect of polyvinyl alcohol and polyvinyl pyrrolidone K-30 on drug release

CONCLUSION

The Nateglinde sublingual films were prepared using different film forming polymers. Films formed with polyvinyl alcohol and polyvinyl pyrrolidone were found transparent, clear, smooth. While, least disintegration time for F3 (33 sec) formulation were observed. Also, the highest dissolution rate were observed for F3 (98.57%) formulation.

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