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FORMULATION AND *IN VITRO* EVAULATION OF FAST DISSOLVING ORAL FILMS CONTAINING SUMATRIPTAN SUCCINATE

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ABSTRACT

Sumatriptan Succinate is a potent anti-migraine agent with shorter half-life. It shows low oral bioavailability due to high first pass metabolism. Therefore, the current study wasfocussedto bypass first pass effect by formulating Sumatriptan succinate into oral films using solvent casting method. The fast dissolving oral films reduces the lag time, which in turn produces quicker onset of action. A natural polymer Pullulan along with synthetic polymers like HPMC E15, HPMC E10, PVA, is used in different proportions to formulate oral films. The physicochemical compatibility of the drug with different polymers was studied by FTIR spectroscopy. The results suggested no physicochemical incompatibility between the drug and polymers. The prepared films were evaluated for uniformity of weight, thickness, folding endurance, surface pH, drug content, tensile strength, % moisture content, % moisture uptake and *in vitro* dissolution studies.Formulation (F6) that contains Pullulan alone found to be releasing drug in a rapid manner, 96.5±1.02% for 30min with good releasing property. From the results F6 was taken as most satisfactory formulation and is subjected to stability studies for 60 days at 30±2 ºC 65±5 % RH. The results of stability studies showed no significant change in physicochemical properties, *in vitro* drug release. The drug release from films varied with the type of polymer used. Fast dissolving oral films of Sumatriptan succinate were made by solvent casting technique to bypass first pass effect with better compliance and effective therapy.

KEYWORDS: Sumatriptan succinate, Oral Films, Pullulan, HPMC E15, HPMC E10, PVA.

INTRODUCTION

Recently, Fast dissolving drug delivery system have start gaining popularity and acceptance as new drug delivery systems, due to better patient compliance. These delivery system either dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing[1]. In response to this need, a variety of dissolvable oral thin films (OTFs) evolved over the past few years from the confection and oral care markets in the form of breath strips and became a novel and widely accepted form by consumers for delivering vitamins and personal care products.[2] They also impact unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry are improved solubility/stability, biological half-life and bioavailability enhancement of drugs.[3]

Although oral disintegrating tablets have an advantage of administration without choking and fast disintegration; the disintegrated materials contained in them are insoluble and remain until swallowing. In such cases formulation of fast dissolving film will be advantageous.[4, 5]

Many pharmaceutical dosages are administered in the form of pills, granules, powders, and liquids. Generally, a pill design is for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills, which include tablets and capsules, are able to retain their shapes under moderate pressure. However, some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms[6]. Many pediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking[7].

Migraine is a familial disorder characterized by recurrent attacks of headache widely variable in intensity, frequency and duration. Attacks are commonly unilateral and are usually associated with anorexia, nausea and vomiting .The term migraine is derived from the Greek word hemicranias (Galen about 200AD). Migraine headaches are a common and painful experience for many young adults. They are two and half times more prevalent in women, occurring in 6% of all males and 15-17% of females.They are more likely to strike those aged between 25 and 44. With 90% of migraine patients reporting their first attack before age 40 .Migraine prevalence is similar in western countries and the USA.

Migraine prevalence varies by age, sex, ethnic origin, and income. Before puberty, migraine prevalence is about 4 %. After puberty, prevalence increases more rapidly in girls than boys. The headache classification committee of the international headache society (IHS) published the classification and diagnostic criteria for headache disorders (international headache society, 2004). The terms 'common migraine' and 'classical migraine' have been replaced by 'migraine without aura 'and 'migraine with aura' respectively[8].

The migraine aura was thought to be cause by cerebral vasoconstriction and headache by reactive vasodilation. However, it was later established that headache often begins while cortical blood flow is reduced thus, headache is not caused by simple reflex vasodilation. The immediate precursors of vasodilation are serotonin i.e. it is called as low-serotonin syndrome. Plasma serotonin levels decrease during increased platelet aggregation, leading to vasodilation with accompanying migraine headache[9].

Sumatriptan succinate is a potent and selective 5-hydroxytryptamine agonist chemically it is 3-[2-(dimethyl amino) ethyl]-N-methyl-1H-indol-5-methanesulfonamide butane -1,4-dioate it is an effective agent in the treatment of acute migraine attack. It provides rapid symptoms relief up to 85-90% of migraine patient within two hours of treatment. Sumatriptan succinate is white amorphous powder, freely soluble in water.Sumatriptan succinate is rapidly but incompletely absorbed following oral administration and undergoes first pass metabolism resulting in a low absolute bioavailability of 15%. The biological half-life of Sumatriptan succinate is about 2.5 h[10].

In the present work solvent casting method is used for making oral films using different water soluble polymers like, Pullulan, HPMC E10, E15, PVA, such are explored for this work.

MATERIALS AND METHODS

Sumatriptan succinate (Dr. Reddy's), HPMC E15, HPMC E10, PVA (Yarrow chem. Mumbai),Pullulan (Kumar organic PVT LTD. Bangalore), PEG 400, Tween 80, glycerin, aspartame.(Karnataka fine chem. Bangalore) were employed in present study.

METHOD OF PREPARATION OF SUMATRIPTAN ORAL FILMS

The fast dissolving strips of Sumatriptan succinate were prepared by solvent casting technique. Polymeric solution was prepared by using distilled water with continuous stirring. Calculated amount of Sumatriptan succinate was dissolved in the solvent, after complete

dissolution of the drug in water; polyethylene glycol 400 (plasticizer), tween 80 and glycerin are added and stirred to form a homogenous solution. The resultant viscous solution was filtered through gauze. Then both the solutions containing polymer and drug were mixed and kept for stirring for proper mixing. Then the solution was casted into petri plate and then kept in hot air oven at 40°C for 24 h (or at room temperature). The strips thus formed were cut into size of 2×2 cm^2. Each strip contains 12 mg ofSumatriptan succinate. The detailed compositions of the films are given in Table 1

The fast dissolving strips were prepared using polymers like Pullulan, HPMC E15, E10 and PVA. PEG-400 is used as plasticizer. The films were cut into size 2*2cm^2 containing 12mg of Sumatriptan succinate.

Table 1: FORMULATION CHART

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Sumatriptan succinate	210	420	210	420	210	420	210	420
HPMC E10(mg)	210	420	-	-	-	-	-	-
HPMC E 15(mg)	-	-	210	420	-	-	-	-
Pullulan(mg)		-	-	-	210	420	-	-
PVA(mg)	-	-	-	-	-	-	210	420
PEG 400(ml)	0.5	1	0.5	1	0.5	1	0.5	1
Tween 80(ml)	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Glycerin(ml)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Xantham gum (mg)	-	-	-	-	30	30	-	-
Aspartame (mg)	75	75	75	75	75	75	75	75

RESULTS & DISCUSSION

Drug – polymer compatibility studies by FTIR

Drug polymer compatibility studies are carried out by using FTIR and the results showed no major interaction between drug and various polymers used in the formulation. Graphs are shown in Fig 1.

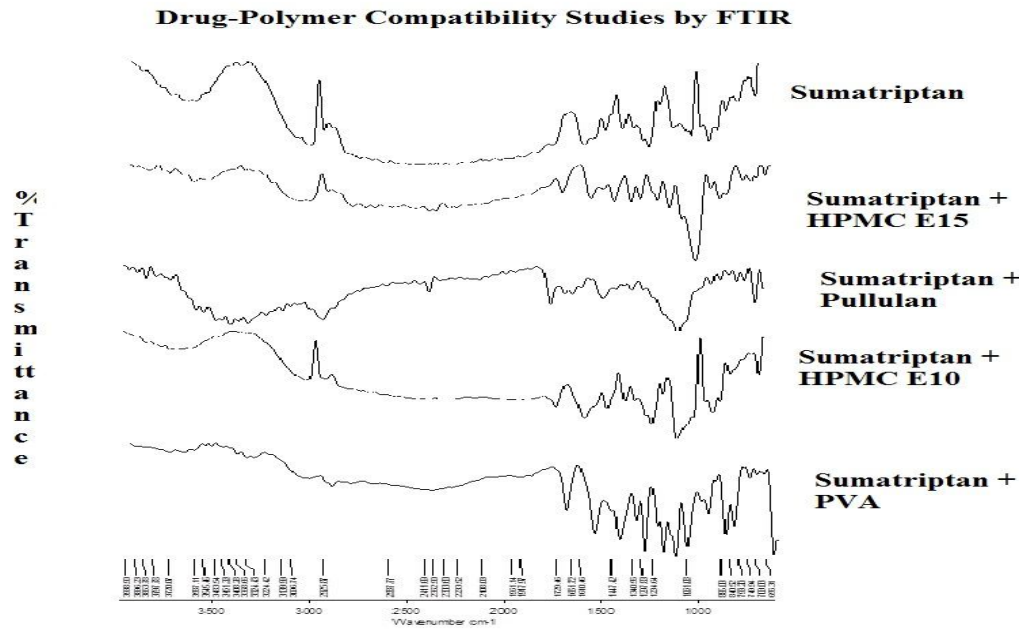

Fig 1: Drug – polymer compatibility studies by FTIR

EVALUATION PARAMETERS OF ORAL FILMS

Table 2: Film properties of Sumatriptan Succinate formulations

Formulation Code	ORAL FILM PROPERTIES			
	Weight variation ± SD	Drug content (%)	Disintegration test(sec) ± SD	Folding Endurance ± SD
F1	54.5 ± 0.45	89	23.63±0.44	184 ± 0.57
F2	65.1 ± 0.47	90	22.13±0.59	180 ± 0.57
F3	67.8 ± 0.251	91	20.45±0.47	185 ± 0.57
F4	71.9 ± 0.3	93	22.88±0.23	193 ± 0.57
F5	51.5 ± 0.66	94	21.16±0.43	190 ± 1
F6	61.1 ± 0.56	97	20.35±0.30	197 ± 1
F7	67.5 ± 0.55	81	22.70±0.56	184 ± 1
F8	81.3 ± 0.3	85	23.48±0.18	188± 0.57

All values are mean of 3 readings ± SD

Table 3: Film properties of Sumatriptan Succinate formulations

Formulation Code	Film properties			
	Thickness (mm) ± SD	Surface pH ± SD	% Moisture content ± SD	% Moisture uptake ± SD
F1	0.132± 0.002	6.65 ± 0.025	5.53 ± 0.32	5.84 ± 0.45
F2	0.144 ± 0.005	6.71 ± 0.015	6.28 ± 0.43	6.46 ± 0.12
F3	0124 ± 0.005	6 .84 ± 0.03	4.15 ± 0.11	5.61 ± 0.61

F4	0.131 ± 0.002	6.85 ± 0.020	4.54 ± 0.64	6.72 ± 0.23
F5	0.102 ± 0.028	6.66 ± 0.030	6.01 ±0.33	5.64 ± 0.16
F6	0.107 ± 0.028	6.71 ± 0.035	6.13 ± 0.42	5.98 ± 0.52
F7	0.186 ± 0.05	6.74 ± 0.045	5.61 ± 0.15	5.74 ± 0.89
F8	0.201± 0.015	6.84 ± 0.05	6.83 ± 0.12	7.09 ± 0.66

All values are mean of 3 readings ± SD

Tensile strength

GRAPH

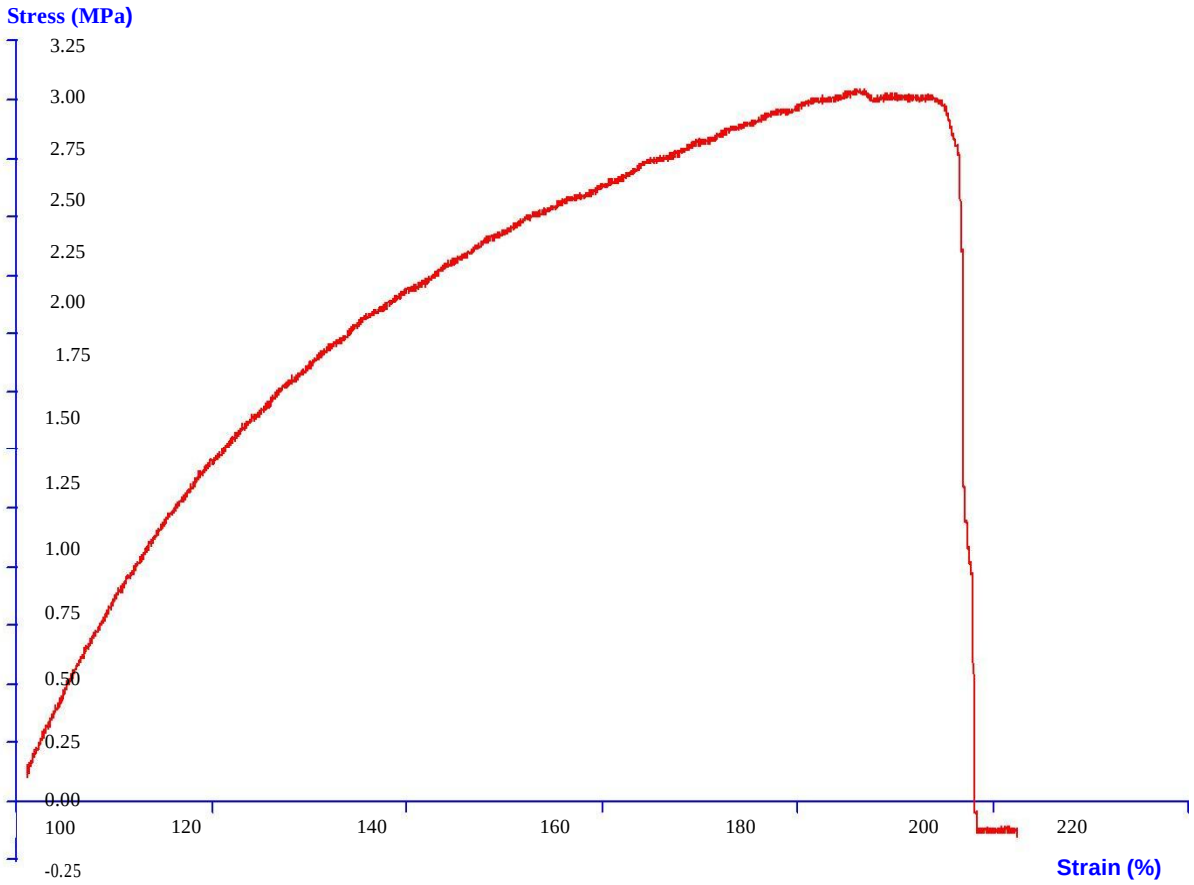

Fig 2: Tensile strength stress-strain graph of F6

RESULTS

Table 4: Result of tensile strength and % strain

Test ID	Tensile Strength	% Strain at Tensile Strength
	MPa	%
F6	3.153	191.85

***In vitro* drug release studies**

The release of Sumatriptan succinate oral films varied according to the types and proportion of polymers. Formulation (F1, F2) containing HPMC E10 alone showed release of 84.78± 1.02, 91.56±1.02 for 30 min. Formulations containing HPMC E15 (F3, F4) released the drug of 86.46± 1.02, 91.74± 1.33 for 30 min. Formulations (F5, F6) containing Pullulan showed release of drug (92.56 ± 1.32 and 96.5±1.02 respectively for 30 min). Formulation containing PVA (F7, F8) showed a release of 83.74±1.02,88.75± 1.15 for 30 min.

Formulation containing Pullulan 210mg (F5) showed good release pattern. Formulation (F6) containing Pullulan 420mg, showed release of drug. (96.5±1.02 respectively for 30 min) with good folding endurance and drug content. Formulation So F6 which has slight edge over F5 is selected as most satisfactory formulation.Results are shown in Fig 3&4.

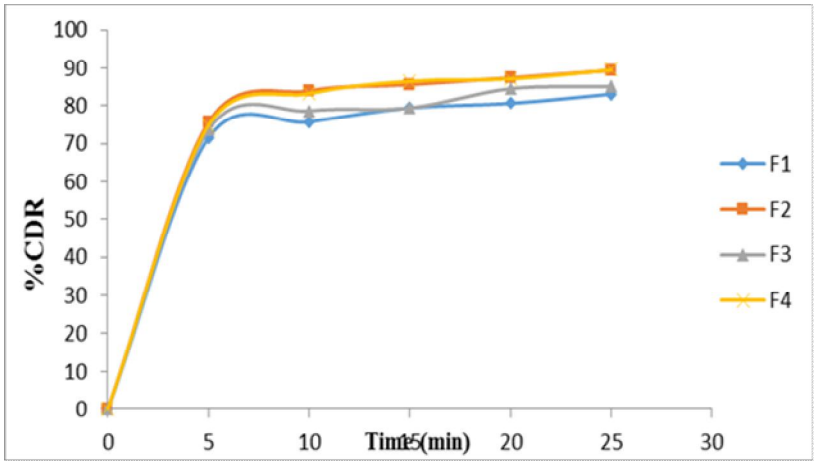

Fig 3: Percentage cumulative drug release profile of F1 – F4

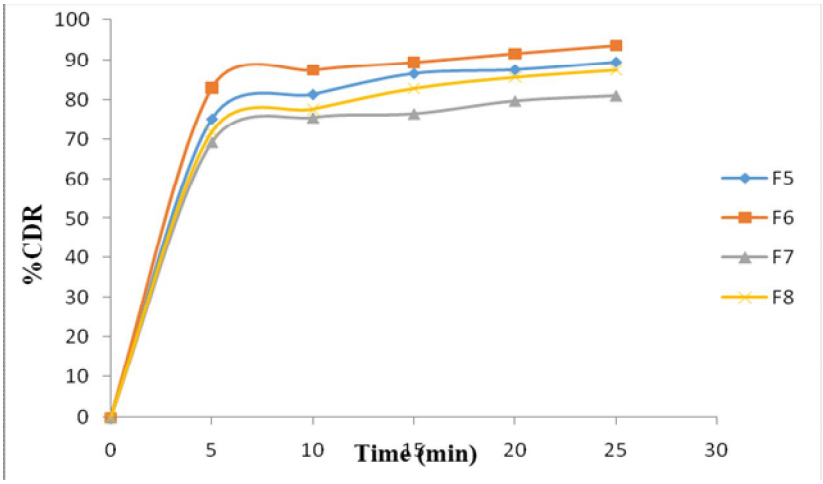

Fig 4: Percentage cumulative drug release profile of F5 – F8

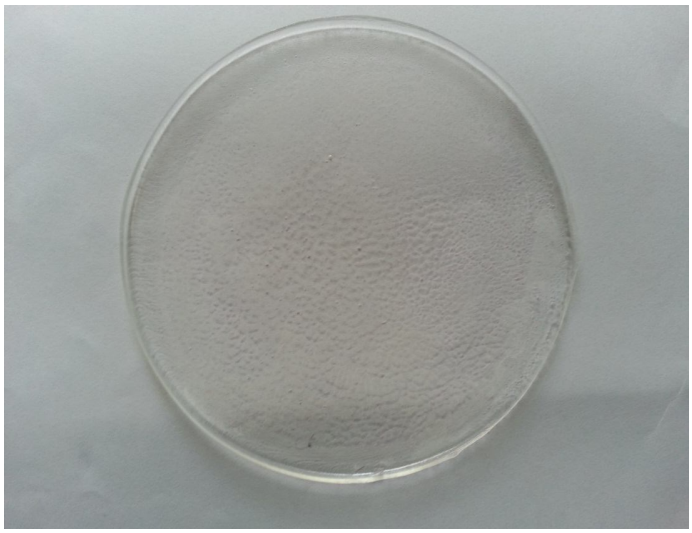

Fig 5:Fast dissolving oral film

Stability study

The optimized formulation (F6) was subjected for accelerated stability studies. Films arepacked in aluminium foil and kept in humidity chamber maintained at 30±2 °C / 65±5% RH for 60 days. The results of the stability studies showed that there was no significant difference in physical properties, drug content and *in vitro* dissolution pattern of F6 at various sampling points.

CONCLUSION

From this study it can be concluded that fast dissolving oral films containing Sumatriptan succinate are prepared by using natural and synthetic polymers using solvent casting method which provides good properties and provide immediate release of the drug. Over all studies indicated that the oral films prepared by employing natural polymer Pullulan (F6) showed good release characteristics with good tensile strength and *in-vitro* dissolution profile.

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