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FORMULATION AND EVALUATION OF ORO-FLASH RELEASE FILMS OF ANTI-MIGRAINE DRUG

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ABSTRACT:

Recently, fast dissolving films are gaining interest as an alternative of fast dissolving tablets. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without need for additional liquid. Flunarizine is a selective calcium channel blocker and coupled with its antihistaminic property it is claimed to be effective in prophylaxis of migraine, but it has poor solubility. Oro-flash release films containing solid dispersion of Flunarizine were prepared to enhance the water solubility, dissolution, oral bioavailability coupled with faster onset of action. Solid dispersions of Flunarizine were prepared using PEG-6000 as carrier in different ratios by fusion method. The selected solid dispersion with enhanced solubility was then utilized for the preparation of Oro-flash release films by solvent casting method by varying the concentrations of film forming polymer HPMC- K4M & disintegrating agent Sodium Starch Glycolate. Formulations (F1-F9) were prepared and evaluated for their physicochemical properties like uniformity of mass, thickness, folding endurance, transparency, swelling index, surface pH, disintegration time, drug content, *In vitro* release study. Among the all Formulation, Batch F9 with HPMC K4M 30% and SSG 8% showed minimum disintegration time of 34 sec, highest dissolution rate of 99.01% and satisfactory physicochemical properties, hence selected as best formulation. It is evident from the above results that the developed formulation can be an innovative dosage form to improve the drug delivery, onset of action as well as improve patient compliance.

KEYWORDS: Oro-flash release films, Flunarizine, Solid dispersion, Solvent casting method, HPMC- K4M.

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1. INTRODUCTION:

The fast dissolving drug delivery systems came to existence in the late 1970's as a form different to tablets, capsules and syrups for children and aged patients who experience difficulty in swallowing oral solid doses. These can overcome the issues related with oral administration of drugs like minimizing the risk of partial loss of active ingredients due to tablet or capsule crushing or imprecise liquid administration which leads to dosage inaccuracy and drug therapy overdosing or inefficiency. Recent technological advancements in the oral drug delivery system has led to change of dosage forms from oral disintegration tablet (ODT) to wafer to the latest development of fast dissolving oral films (FDOFS), Oro-flash release films (OFRF). Between the plethoras of avenues for the quick drug release products, Oro-flash release films are gaining much attention. Nowadays, there has been significant development in transmucosal routes of drug administration because this route has a potential to fathom such problems associated with oral administration of the drugs. They consist of the solid doses to disintegrate and dissolve rapidly in the oral cavity without taking of water. Absorption of drug by oral mucosa into systemic circulation is an attractive approach because it is highly vascularized and hence highly permeable. Therefore fast dissolving films have become a popular oral dosage form for various medicaments which provide rapid disintegration due to large surface area and hence improve patient compliance[1,2].

Migraine is a condition marked by recurring moderate to severe headache with throbbing pain that usually lasts from four hours to three days, typically begins on one side of the head but may spread to both sides, is often accompanied by nausea, vomiting, and sensitivity to light or sound, and is sometimes preceded by an aura and is often followed by fatigue[3]. Flunarizine, a piperazine derivative, is a selective Ca++ channel blocker coupled with its antihistaminic property claimed to be effective in prophylaxis of migraine. It is effective in migraine by reducing intracellular Ca++ overload due to brain hypoxia and thus prevents the deleterious effects of cellular calcium overload. Flunarizine is BCS Class-II drug, has low aqueous solubility and dissolution hence it exhibits poor in vivo bioavailability (18-27%), it has a long half life of 18-19 days[4,5,6].

In view of these facts this drug can be considered as a suitable candidate for Oro-flash release films. In order to enhance the solubility of Flunarizine and subsequently dissolution and absorption, solid dispersions of Flunarizine with Poly Ethylene Glycol-6000 (PEG-6000) as carrier were prepared and evaluated. The optimized solid dispersion was used in preparation of Flunarizine Oro-flash release films. In this study, an attempt is made to investigate the feasibility of Oro-flash release films as a medium for the fast delivery of Flunarizine with better bioavailability and enhanced patient compliance.

2. MATERIAL AND METHODS:

Flunarizine was obtained as gift sample from Vital Pharma Ltd, Hyderabad, INDIA. PEG-6000, HPMC K4M were obtained from S.D. Fine Chemicals, Mumbai. All other ingredients were used of analytical grade.

2.1. Preparation of Flunarizine Solid Dispersions by Fusion Method:

Solid dispersions of Flunarizine were prepared using PEG-6000 as hydrophilic carrier in different ratios i.e, 1:1, 1:2, 1:3, & 1:4 by fusion method. PEG-6000 was taken and heated to a molten state at 60°C and to this mass, the weighed amount of Flunarizine was added with continuous stirring with a glass rod until dissolved. Solidification was allowed to occur at room temperature. The product was stored in Desiccators for 24 hrs and then pulverized using mortar and pestle. The pulverized powder was passed through 80-mesh sieve to get uniform particle size[7]

2.1.2. Solubility studies:

The solubility studies were conducted by taking excess amount of pure drug and prepared solid dispersions in separate conical flasks containing phosphate buffer pH 6.8. Then the samples were kept in the water bath shaker for 24hrs, at 100 rpm in room temperature. The samples were filtered and were analyzed spectrophotometrically at 225 nm. Best drug: carrier ratio was found out based on the

improvement of water solubility and was used for further study[6].

2.2. Preparation of Flunarizine Oro-flash release film:

The fast dissolving films of Flunarizine were prepared by solvent casting technique by varying concentrations of film forming polymer Hydroxy Propyl Methyl Cellulose- K4M (HPMC-K4M) in 20%, 25%, 30% and superdisintegrant Sodium Starch Glycolate (SSG) in 2%, 5%, 8% as illustrated in table no.1. The calculated amount of HPMC-K4M was added in a 3/4th volume of water with continuous stirring on magnetic stirrer and the solid dispersion containing Flunarizine was incorporated in the polymeric solution. SSG was then added to the polymeric solution and stirred vigorously. In another beaker citric acid, sodium saccharin, Tween-80, DMSO and glycerin were added in a 1/4th volume of water with continuous stirring on magnetic stirrer. The two solutions were added and mixed well using a magnetic stirrer to obtain a homogenous solution. This solution was sonicated for 10 min for deaeration, the resulting bubble-free viscous solution was cast on a petridish and dried using a hot air oven for about 35-40 minutes at 70ºC. Once the film is set, it is air dried for one hour and then the film is carefully removed, wrapped in an aluminum foil and stored in a desiccator until further use.

Table 1: Formulation of Oro-flash release films of Flunarizine

Ingredients	Solid Dispersion (mg)	HPMC K4M (mg)	Citric acid (mg)	Sodium saccharine (mg)	Tween-80 (ml)	Glycerol (ml)	SSG (mg)	DMSO (ml)	Water (ml)
F1	350	200	38	57	1	0.375	20	2	8
F2	350	200	38	57	1	0.375	50	2	8
F3	350	200	38	57	1	0.375	80	2	8
F4	350	250	38	57	1	0.375	20	2	8
F5	350	250	38	57	1	0.375	50	2	8
F6	350	250	38	57	1	0.375	80	2	8
F7	350	300	38	57	1	0.375	20	2	8
F8	350	300	38	57	1	0.375	50	2	8
F9	350	300	38	57	1	0.375	80	2	8

2.3. Evaluation parameters of Oro-flash release films [8-12]:

2.3.1. Uniformity of mass:

Films of 2 cm^2 were cut from the different places of the casted film and were weighed on digital balance. Then, average mass were calculated. A large variation in weight indicates the inefficiency of the method employed and is likely to have non-uniform drug content.

2.3.2. Thickness:

The thickness of the drug films was measured with the help of vernier calipers at different strategic locations like four corners and center of each film. Mean is calculated. The standard range of film thickness should not be less than 5%. This is essential to assure uniformity in the thickness of the film as this was directly related to the accuracy of

dose. The thickness of film should be in the range of the 5-200 micrometer.

2.3.3. Folding endurance:

Folding endurance is to determine mechanical properties of film and was measured by repeatedly folding of the film at the same place to the extent where film breaks. The number of times the film is folded without breaking is calculated as the folding endurance value.

2.3.4. Transparency: It was checked simply by visual inspection of films.

2.3.5. Swelling index:

Initial weight of film is determined and is placed in pre-weighed stainless steel wire mesh. This mesh containing film is then dipped into simulated saliva solution. Increase in the weight of film is noted at constant pre-determined time intervals until no more increase in weight.

$$\% \text{ Swelling} = \frac{\text{Final weight [W2]} - \text{Initial weight[W1]}}{\text{Initial weight[W1]}} \text{ X } 100$$

2.3.6. Drug content:

2X2cm² of film is cut evenly. It is then added to 100 ml volumetric flask and diluted using 2ml DMSO and makeup with phosphate buffer pH 6.8. It is then sonicated for 15–20 min. Then it is filtered and absorbance was measured using UV-visible spectrophotometer at 225 nm.

2.3.7. *In-Vitro* Disintegration test:

A small strip of film 2x2cm² is placed in beaker containing 15 ml of phosphate buffer pH 6.8 and continuously shaken until the strip disintegrates completely. Time taken for complete disintegration was noted.

2.3.8. Surface pH:

Surface pH of film was determined by placing the film in Petri dish and film was made wet with distilled water and note pH by touching the film surface with a pH meter.

2.3.9. *In–Vitro* Dissolution studies:

The in vitro drug dissolution study was carried out in 100 ml of phosphate buffer pH 6.8 at 37.0±0.5°C, using mechanical stirrer. The film 2x2cm² was placed in the beaker with the help of forceps. The mechanical stirrer is used to provide stirring speed of 100 rpm. Samples of dissolution medium (1ml) were withdrawn for specific intervals and replaced immediately with equal volume of fresh medium. The collected samples were filtered and analyzed by UV visible spectrophotometer at 225nm by using phosphate buffer as blank.

3. RESULTS & DISCUSSION:

3.1. Solubility Studies:

Results of this study suggested the poor aqueous solubility of Flunarizine in phosphate buffer pH 6.8 (0.0017mg/ml) as depicted in table no 2. However solid dispersions have shown significant improvement in solubility. SD4 containing Drug: polymer ratio in 1:4 exhibited highest solubility of 2.516mg/ml, which is 148 folds higher than pure drug. This phenomenon can be ascribed due to the decrease in crystallinity of the flunarizine and also to a highly dispersed state of the drug resulting in its higher wettability in presence of hydrophilic carrier PEG-6000. Hence SD4 formulation was selected for preparation of Flunarizine Oro-flash release films.

Table 2: Solubility Studies of Flunarizine Solid Dispersions

Formulation code	Drug : Carrier ratio	Flunarizine (g)	PEG-6000 (g)	Solubility (mg/ml)
SD1	1:1	1	1	0.838
SD2	1:2	1	2	0.902
SD3	1:3	1	3	1.192
SD4	1:4	1	4	2.516
Pure drug	---	---	----	0.017

3.2 Post Formulation Evaluation Results:

Flunarizine Oro-flash release films of were evaluated for their uniformity of mass, thickness, surface pH, folding endurance, transparency, drug content and disintegration time. The results are tabulated in table no.3.

3.2.1. Thickness:

The thickness of the Flunarizine Oro-flash release films developed was found ranging from 0.275 mm to 0.325 mm. From the obtained thickness data it was observed that the thickness of the film was increased by increasing in the concentration of the film former.

Hence, the thickness of the film was directly proportional to its film former concentration.

3.2.2. Uniformity of mass:

The average mass of formulations was found to be in the range of 39.2 mg- 51.9mg. The mass of the film cut from the different places was found to be uniform.

3.2.3. Surface pH:

The surface pH of the film should be similar to that of saliva i.e. 6.8 as it is being kept in the oral cavity for dissolution for avoiding the irritation. The pH of formulations was measured in triplicate for each sample and found in the range from 6.65 – 6.9 with an average of around pH 6.80 which, indicated that pH range was well within the targeted pH and suitable in oral cavity.

3.2.4. Folding endurance:

The observed folding endurance data of the films was in the range of 45-154. The results indicated that the increase in concentration of the film formers lead to increase in the folding endurance of the films. Formulation F9 exhibited highest folding endurance as it has high concentration of HPMC K4M, where as formulations F1, F2, F3 with 20% HPMC K4M were fragile.

3.2.5. Disintegrating time:

The disintegration time of formulations ranged from 34-68 sec. The data of disintegration time indicates that increasing the concentrations of SSG tends to decrease the disintegration time of formulation. This may be attributed to super disintegrating nature of SSG. Formulation F9 showed least disintegration time of 34 sec as it has high concentration of SSG.

3.2.6. Drug Content:

The drug content of formulation ranged 93.99% to 98.87%. Results suggested a good uniformity of content in the formulations without any significant variation. All the formulations drug content within the specification range.

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Table 3: Results of Flunarizine Oro-flash Release Films Evaluations

Formulation Code	*Mean thickness (mm ± SD)	*Uniformity of mass (mg ± SD)	Transparency	*Surface pH (Avg ± SD)	*Folding endurance (Avg ± SD)	*Disintegration time (sec ± SD)	*Percent Drug content (%± SD)
F1	0.29±0.02	39.2±0.05	Semi transparent	6.7±0.03	45 ± 5	60±0.01	94.66±0.05
F2	0.31±0.01	40.6±0.03	Semi transparent	6.8±0.02	49 ± 6	54±0.02	98.2±0.03
F3	0.275±0.05	39.5±0.02	Semi transparent	6.7±0.03	50 ± 2	39±0.05	93.78±0.02
F4	0.325±0.02	41.2±0.04	Semi transparent	6.7±0.01	95 ± 1	65±0.06	94.94±0.06
F5	0.28±0.03	42.6±0.07	Semi transparent	6.8±0.04	97 ± 3	63±0.04	99.77±0.01
F6	0.311±0.01	44.7±0.05	Semi transparent	6.9±0.01	98 ± 2	40±0.03	95.92±0.04
F7	0.325±0.04	50.7±0.03	Semi transparent	6.6±0.05	144 ± 4	68±0.01	93.99±0.06
F8	0.31±0.02	49.6±0.04	Semi transparent	6.7±0.03	149 ± 5	53±0.03	95.05±0.05
F9	0.299±0.04	51.9±0.01	Semi transparent	6.8±0.02	154 ± 3	34±0.01	98.87±0.02

*Values are mean ± SD (n=3)

3.2.7. Swelling Index:

Percentage swelling of formulations was found to be in range of 24.5% - 51.4% as depicted in Fig no. 1. HPMC and SSG both have swelling property which resulted in higher percentage swelling in formulations. Higher percentage swelling suggests its suitability for rapid release of Flunarizine due to increased absorption of phosphate buffer pH 6.8. Formulation F9 exhibited highest % swelling index

of 51.4% due to synergistic effect of HPMC K4M and SSG.

3.2.8. *In-vitro* dissolution study:

The % drug release from formulations ranged from 87.52% - 99.01%, as depicted in Fig no. 2. It revealed that most of the formulations have more than 90% drug dissolution up to 5 min and thus indicated faster and almost complete drug dissolution. Formulation F9 has showed 99.01% drug release at the end of 5 min, this may be due to porous nature of HPMC K4M, rapid uptake of water, followed by rapid and enormous swelling of SSG

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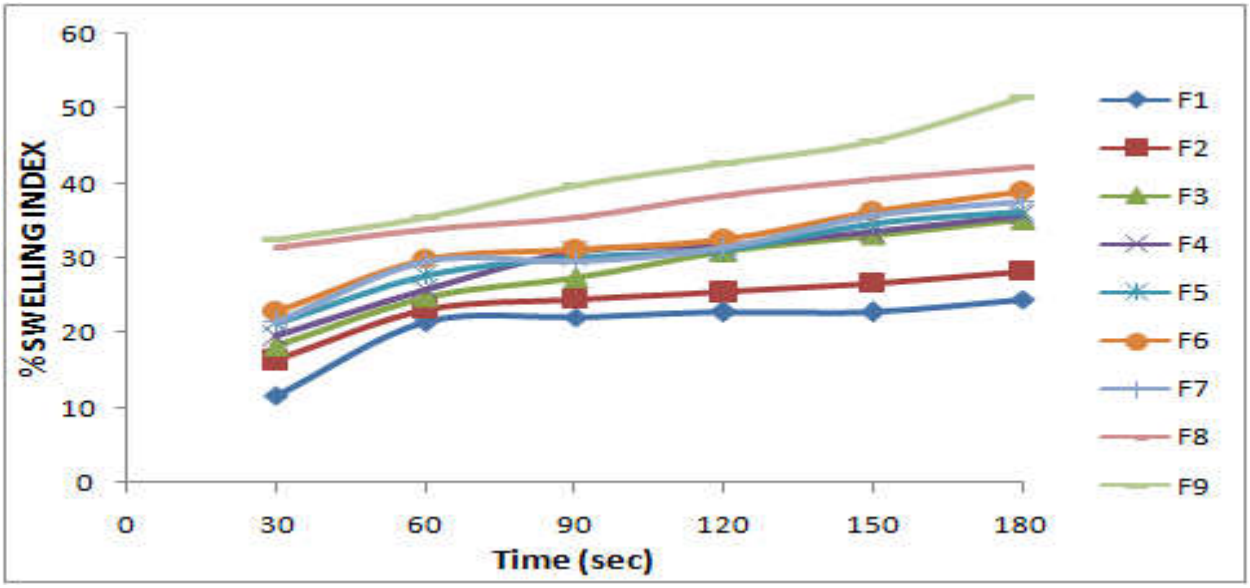

Fig.1: Comparative evaluation of swelling index of all film formulations.

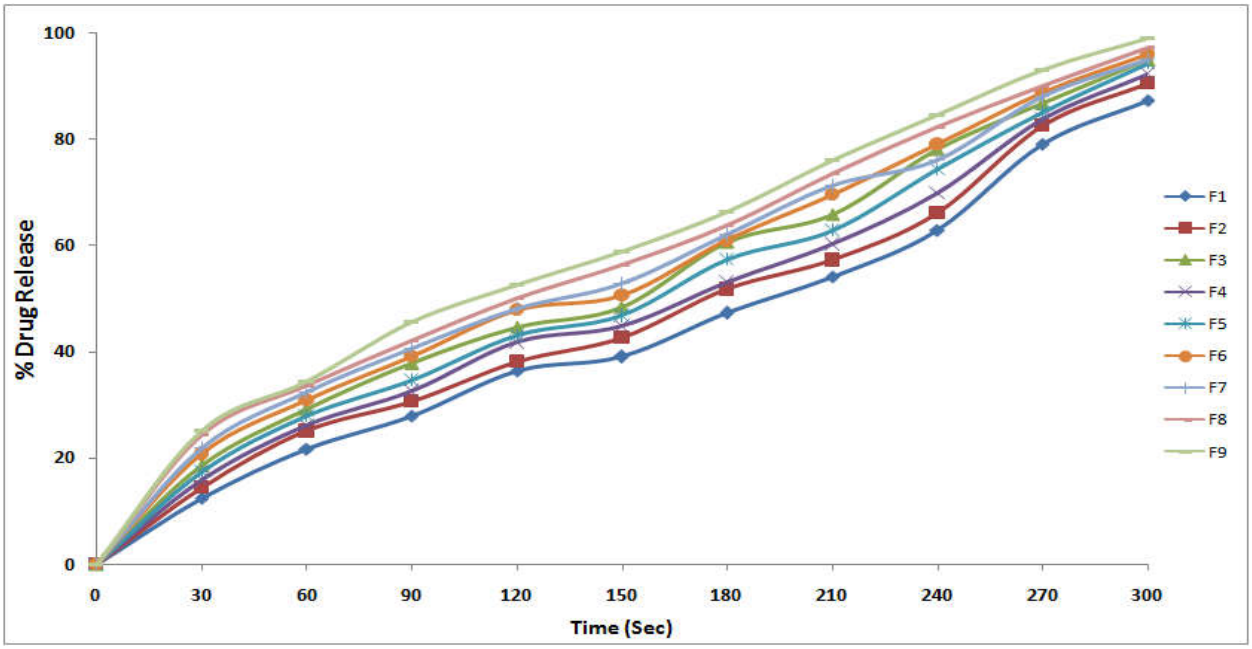

Fig. 2: *In-vitro* drug release profiles of Flunarizine Oro-flash release films

4. CONCLUSION:

The Oro-flash release films of Flunarizine solid dispersion were developed successfully via solvent casting technique with the intention of obtaining rapid drug release and enhanced solubility. Preparation of solid dispersions of the Flunarizine using fusion method with PEG 6000 up to 1:4 (drug to polymer ratio) found to remarkably increase the aqueous solubility of Flunarizine. Evaluation results of Flunarizine Oro-flash release films revealed good mechanical strength, uniformity of content, optimum surface pH, faster disintegration time and almost complete drug dissolution or release. Based on the characteristics of the film formulations F9 prepared with HPMC K4M (30 %) and SSG (8%) was selected as best formulation. Formulation F9 exhibited high folding endurance, good swelling nature, rapid disintegration of 34 sec and 99.01% drug release within 5 min. Thus it can be concluded that Oro-flash release films could be commercially exploited for the treatment of migraine using Flunarizine with merits of faster onset of action, avoidance of extensive first pass metabolism, low dosage regimen, enhanced bioavailability and improved patient compliance.

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6. REFRENCES:

1. Pandya Ketul, Patel K.R., Patel M.R., Patel N.M., Fast dissolving films: a novel approach to oral drug delivery., Asian Journal of Pharmaceutical Science & Technology., 2013; 3(1): 25-31.
2. Rajni Bala, Pravin Pawar, Sushil Khanna, Sandeep Arora., Orally dissolving strips: A new approach to oral drug delivery system., International Journal of Pharmaceutical Investigation., 2013; 3(2): 67-77.
3. Poojitha Mamindla, Sharanya Mogilicherla, Deepthi Enumula, Om Prakash Prasad and Shyam Sunder Anchuri., A Review on Migraine., Acta Scientific Pharmaceutical Sciences., 2019; 3(9): 29-42.
4. Bhupendra Shahand Dipesh Raj Pandey., Migraine., European Journal of Biomedical and Pharmaceutical Sciences., 2017; 4(4): 226-230.
5. Teresa Main M., Victoria Margarit M., Gloria E. Salcedo., Characterization and solubility study of solid dispersions of flunarizine and polyvinyl pyrolidone., IL Farmaco., 2002; 57(9): 723-727.
6. Hitesh V. Chavda, Ruchi I. Patel, Chhagan N. Patel., Preparation and characterization of ternary solid dispersion of flunarizine dihydrochloride., World Journal of Pharmaceutical Research., 2015; 4(5): 2506-2521.
7. Kumar B., Solid Dispersion- A Review., Pharma Tutor., 2017; 5(2): 24-29.
8. Pondugula Sudhakara Reddy, Ramana Murthy KV., Formulation and evaluation of oral fast dissolving films of poorly soluble drug ezetimibe using Transcutol-HP., Indian J of Pharmaceutical Education and Research., 2018; 52 (3): 398-407.
9. Pooja RD, Sayyad FJ., Design, development and evaluation of oxcarbazepine loaded fast dissolving oral films., International Journal of Drug Development and Research., 2018; 10: 12-24.
10. Muhammad Irfan, Sumeira Rabel, Quratulain Bukhtar, Muhammad Imran Qadir, Farhat Jabeen, Ahmed Khan., Orally disintegrating films: A modern expansion in drug delivery system., Saudi Pharmaceutical Journal., 2016; 24: 537-546.
11. Bikash Pandey, Arshad Bashir Khan., Enhancement of solubility and optimization of orally disintegrating films of acyclovir., Asian Journal of Pharmaceutical and Clinical Research., 2018; 11(9): 280-286.
12. Rahul A Jain and Atish S Mundada., Formulation, development and optimization of fast dissolving oral film of montelukast sodium., Int J Drug Dev & Res., 2015; 7(5): 40-46.

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