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Research Article

FORMULATION AND EVALUATION OF FAST DISSOLVING FILMS OF ZOLMITRIPTAN

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ABSTRACT
The present study was aimed to formulate and evaluate fast dissolving films of Zolmitriptan using hydroxyl propyl methyl cellulose. 5-HT_{1B} and 5-HT_{1D} antagonist which is an antimigraine. Hydroxyl propyl methyl cellulose is used as film forming agent. Fast dissolving films are meant to be dissolved in saliva and remain in oral cavity until swallowed. Hence taste masking becomes critically important. The films are prepared by solvent evaporation method and characterized by UV, FTIR studies. The suitable plasticizer and its concentration were selected on the basis of flexibility, tensile strength and stickiness of the film. In the present study propylene glycol was used as plasticizer. Films were evaluated for drug content and the drug loading capacity was found to be 98.62% per2cm^2 .The dissolution profile, disintegrating time and folding endurance were found to be satisfactory. Thermal stability of the film and drug-excipient interactions was investigated by FT-IR; results show that there is no interaction between drug and excipients used. Further, the optimized films were evaluated and it was found that the films disintegrate within 1 min and absence of bitterness in the film. Hence it is concluded that Zolmitriptan H.P.M.C fast dissolving films are successfully developed and evaluated.
Keywords: Fast dissolving film, Hydroxyl propyl methyl cellulose, Zolmitriptan

INTRODUCTION

For the last two decades, there has been an enhanced demand for more patient-compliant dosage forms. As a result, there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately $14.20 billion in 1995 and, according to industry reports; this is expected to grow to $60 billion annually. Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating, and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available.

Fast-dissolving drug-delivery systems were first developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing[1] traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphasia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules. Dysphasia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in geriatric and pediatric patients, as well as travelling patients who may not have ready access to water[1].

Research and development in the oral drug delivery segment has been led to transition of dosage forms from simple conventional tablets/capsules to oral disintegration tablet (ODT) to wafer to the recent development of oral films (ODF) can be considered as an ultra thin strip of postage stamp size with an active agent or active pharmaceutical ingredient and other pharmaceutical excipients. The advantage of convenience of dosing probability of ODF have led to wider acceptability of this dosage form by pediatric as well as geriatric population equally.

Salient features of fast dissolving drug delivery systems

1. Ease of administration for patients who are mentally ill disabled and uncooperative.
2. Require no water.
3. Over comes unacceptable taste of the drugs.
4. Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging
7. Cost effective.

Advantages [2]

These rapid dissolving films offer several advantages like,

- Convenient dosing.
- Fast disintegration or dissolution followed by quick effect which is desirable in some cases such as pain.
- No water needed.

Disadvantages[3]

- The disadvantage of OTF is that high dose cannot be incorporated into the strip.
- Expensive packaging of oral film.

MATERIALS AND METHODS

Zolmitriptan, Hydroxy propyl methyl cellulose, xylitol, Acesulfame potassium, propylene glycol and peppermint flavor were arranged by pharmatrai, Hyderabad.

Formulation of drug films[4, 5]

The formulation of films by using solvent casting method. The following steps are used in the manufacturing of films by this method. The polymers was dissolved in hot water .The drug and other excipients were dissolved in ethanol. This solution was added to the polymeric solution. Then the solution was mixed by using mixing device for 45minutes with rotating speed 60-80rpm.The entrapped air is removed by vacuum. The resulting solution was casted slowly and with continuous flow on a glass plates. The plates were kept in a hot air oven at 60^0cfor 24 hours. The dried film was gently separated from glass plate and cut into desired sizes

RESULTS AND DISCUSSIONS

FTIR Studies

FTIR studies conducted on pure drug and physical mixtures of all ratios showed that there is no marked interaction between drug and selected polymers. The resultant graphs were showed in fig1-3.

Thickness:

The thicknesses of the films were calculated by using screw guage. The thickness was varied from 0.025 to 0.06 mm. The values obtained for all the formulations were given in the table 1.

Folding Endurance

The folding endurance was found to be in the range of 21± 0.57to 25 ± 0.57. The values for all eight formulations are given in the table1. This data revealed that the films had good mechanical strength along with flexibility

Tensile strength[6]:

The tensile strength was found to be in the range of 43.6 to 63. The formulation F4 and F8 showed the best tensile strength. The values for all the films were tabulated in the table 1.

% Elongation[7]:

The % elongation was found to be in the range of 5 to 17.5%. The formulation F4 and F8 showed minimum % elongation among all the other films. The results obtained for all the formulations are tabulated in the table 1.

In vitro disintegration:

2ml of pH6.8 phosphate buffer was placed in a petryplates with a film on the surface of buffer the time taken for the disintegration of the film was measured. The results obtained all the formulations were tabulated in the table no.1

Drug content: This test was performed by dissolving a $4cm^2$ area of film in 50mlof pH6.8 phosphate buffer with stirring. This solution was filtered using a Whattmann filter paper, and the filtrate was diluted to 100ml with the same buffer in a volumetric flask. This solution was analyzed by U.V. Spectrophotometer and all vales were tabulated in the table no. 12.

In vitro dissolution Time:

900ml of phosphate buffer(pH6.8)was used as a media, and was maintained at 37 ± 0.5^0c while the basket was set at 100 rpm a film sample of $4cm^2$(2*2cm)was cut and taken in to the basket.5ml of the sample were taken every 2 minutes and the same amount was replaced with fresh buffer. The withdrawn samples were filtered and analyzed by using a U.V Spectrophotometer at a wavelength of 226nm. The results obtained for all the formulations are tabulated in the table 13-21.

Stability studies

The stability studies were carried according to ICH to assess the drug formulation stability. Optimized formulation was sealed in aluminium packaging laminated with polyethylene. Sample were kept at 40 ^{0}C and 75% RH for 3 months. At the end of the study period, the formulation was observed for change in physical appearance, color, drug content and drug release characteristics. The optimized formula was subjected for the stability studies and the values are tabulated in the table 5-6

SUMMARY AND CONCLUSION

The Zolmitriptan is a serotonin (5-HT1) agonist used for the treatment of migraine with or without aura. The half-life of Zolmitriptan is 2.5 to 3 hrs and it undergoes hepatic metabolism, the absolute oral bioavailability is about 40 to 50%. So, in order to improve the bioavailability and efficacy, we have prepared rapidly dissolving films of Zolmitriptan. In the present research work, films were prepared using H.P.M.C 5cps polymer by Solvent Casting Technique.. Zolmitriptan is water soluble drug belongs to class III of BCS classification of drugs. Estimation of the drug by U.V method at 226nm. Preformulation study involving FTIR study showed no interaction between drug and polymer. Formulation study involves F-4 and F-8 shows good mechanical properties and less disintegration time. The drug release from these two formulations were good and follows zero order kinetics.. Later stability studies of these two formulations were indicating that there was no degradation of the formulation at high temperature and humidity conditions. It was indicating that these two formulations were stable.

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Table1: Composition of all Formulations

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8
Drugs	125	125	125	125	125	125	125	125
H.P.M.C 5cps	625	750	875	1000	1125	1250	875	1000
Xylitol	1375	1250	1125	1000	875	750	875	750
Propylene glycol	250	250	250	250	250	250	500	500
Acesulfame potassium	100	100	100	100	100	100	100	100
Peppermint flavour	25	25	25	25	25	25	25	25
Total	2500	2500	2500	2500	2500	2500	2500	2500

Table2: Physicochemical evaluation data of Zolmitriptan films

Formulation	**Thickness (mm)**	**Folding endurance**	**Tensile strength(gm/cm^2)**	**% Elongation**	**Invitro disintegration (sec)**	**Content of the drug**
F-1	0.344±0.004	21±057	43.6	15	23	**Assay (%)**
F-2	0.385±0.006	25±0.57	51.9	20	20	87.7
F-3	0.376±0.01	25±0.81	46.5	17.5	20	90.8
F-4	0.54±0.007	22±0.81	59.3	7.5	18	93.3
F-5	0.518±0.006	24±0.57	53	10	22	98.62
F-6	0.55±0.012	25±0.81	63	5	23	97.6
F-7	0.428±0.008	25±0.57	52.5	12.5	21	95.6
F-8	0.545±0.012	25±0.57	59.3	7.5	18	95.5

Table3: In vitro dissolution studies of all formulations

	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
2min	27.7	27.2	20.4	26.2	30.16	16.03	23.2	29.7
4min	39.2	35.8	38.9	41.2	46.6	34.1	37.4	46.6
6min	50	52.2	55.5	57.2	58.3	47.09	53.65	62.69
8min	62.6	64.2	69.4	76.3	71.4	61.23	70.71	81.64
10min	80	73	79.02	84.4	85.5	74.35	86.1	93.31
12min	88.8	86.4	88.93	99.34	91.12	87.48	93.7	97.5
14min	93.6	91.8	96.08		95.5	96.0		

Table4: Regression coefficient (R^2) values for different kinetic models for all formulations

Formulation	R^2	R^2	R^2	R^2
	Zero order	First order	Higuchi	Peppas
F1	0.985	0.945	0.971	0.984
F2	0.984	0.828	0.979	0.984
F3	0.973	0.938	0.970	0.990
F4	0.996	0.756	0.962	0.994
F5	0.968	0.921	0.99	0.993
F6	0.991	0.902	0.944	0.995
F7	0.991	0.941	0.951	0.995
F8	0.971	0.943	0.976	0.993

Table5: Stability studies for F-4

Parameters	Stability data	
	Initial	3 months(40^0C±75%RH
Thickness(mm)	0.54±0.07	0.52±0.008
Folding endurance	22±0.01	20±0.01
Tensile strength(gm/cm^2)	59.3	57
Invitro disintegration(sec)	23	26
Invitro dissolution (%)	99.4	99.1

Table6: Stability studies for F-8

Parameters	Stability data	
	Initial	3 months(40^0C±75%RH)
Thickness(mm)	0.545±0.07	0.52±0.008
Folding endurance	25±0.057	20±0.01
Tensile strength(gm/cm^2)	59.3	58.2
Invitro disintegration(sec)	22	25
Invitro dissolution (%)	97.5	96.1

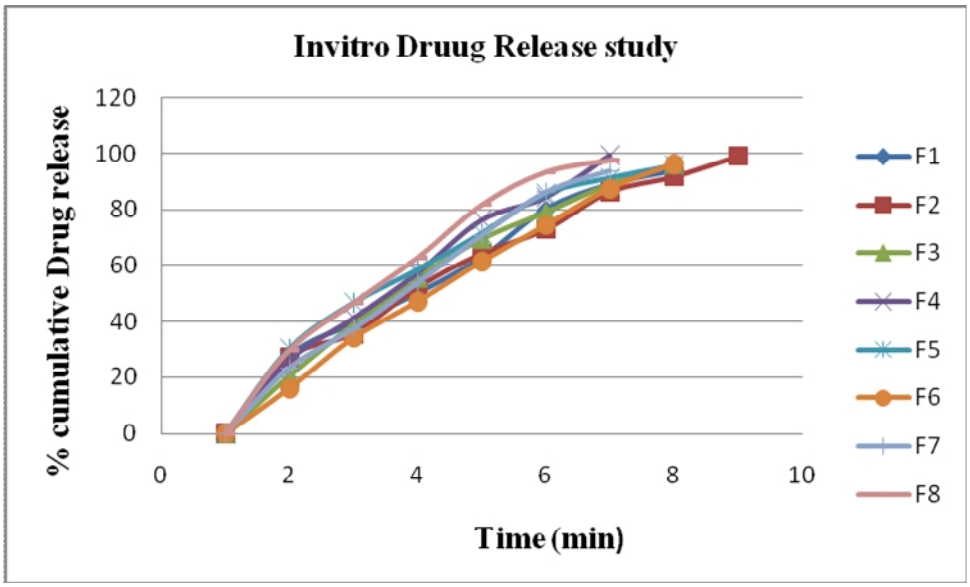

Fig1: Comparative Invitro Drug release from all formulations

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