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FORMULATION AND EVALUATION OF RAPID DISSOLVING FILMS OF ZOLMITRIPTAN BY USING NATURAL POLYMER

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Abstract: The present study was aimed to formulate and evaluate rapidly dissolving films of Zolmitriptan by using naturally extracted banana powder which is act as a natural super disintegrant and Hydroxyl propyl methyl cellulose is used as film forming agent. Zolmitriptan is a 5-HT_{1B} and 5-HT_{1D} antagonist which is an antimigraine. Rapid dissolving films are meant to be dissolved in saliva and remain in oral cavity until swallowed. 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 99.6% 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. Hence it is concluded that zolmitriptan rapid dissolving films by using natural polymer are successfully developed and evaluated.

Keywords: Rapid dissolving film, Banana Powder Hydroxyl propyl methyl cellulose, Zolmitriptan

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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.

Extraction of banana Powder [5]

The collected fresh whole bananas were cleaned for any debris and weighed. The skin peeled bananas were dipped in ethanol in 5 minutes. Then banana was weighed and squashed to paste, this paste was added with citric acid (2-3%) to remove the sticky nature. Then water is

separate by centrifugation and processing. The pressed mass is subjected to drying in tray-dryer. The dried substances was milled and screened in sieve (#80) to get fine powder.

Formulation of drug films [6,7]:

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. All formulations were tabulated in table.No.1

Table.No.1: Composition of Zolmitriptan Formualtions

	F1	F2	F3	F4	F5	F6
Zolmitriptan	10mg	10mg	10mg	10mg	10mg	10mg
HPMC 5CPS	35mg	35mg	35mg	35mg	35mg	35mg
Banana Powder	2.5mg	5mg	-	-	2.5mg	5mg
PVA	-	-	2.5mg	5mg	2.5mg	5mg
Xylitol	40.5mg	38mg	40.5mg	38mg	38mg	033mg
Aspartame	2mg	2mg	2mg	2mg	2mg	2mg
Propylene glycol	5mg	5mg	5mg	5mg	5mg	5mg
Peppermint Flavor	5mg	5mg	5mg	5mg	5mg	5mg
Water*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Ethanol*	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

EVALUATION OF RAPID DISSLOVING FILMS[7]:

Thickness

The thickness of films was measured by digital Vernier calipers with least count 0.001mm. The thickness uniformity was measured at five different sites and average of five readings was taken with standard deviation.

Weight variation

The three films of 2*2 cm2was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch- to- batch variation.

Drug content

The Film of area 2x2 cm2 was cut and dissolved in distilled water. Then solvent ethanol and water, to make polymer soluble, were added to the mixture and the remaining volume was made up with distilled water to 100ml in 100ml volumetric flask. Then 1 ml was withdrawn from the solution and diluted to 10ml.The absorbance of the solution was taken at 226nm and concentration was calculated. By correcting dilution factor, the drug content was calculated.

Folding endurance

Folding endurance of the film was determined by repeatedly folding a small strip of film (2*2) at the same place until it broke. The number of times that the film could be folded at the same place without breaking gives the value of folding endurance.

Tensile Strength

The tensile strength was determined by the apparatus designed as shown in fig. The instrument was designed such that it had horizontal wooden platform with fixed scale and attachments for two clips that holds transdermal patch under test. Out of the two clips one was fixed and other was movable. Weights were hanged to one end of pulley and the other end of pulley was attached with movable clip. The wooden platform was such fitted that it would not dislocate while the test is running. Three strips of patch were cut having 2cm length and 2cm breadth. The thickness and breadth of strips were noted at three sites and average value was taken for calculation.

Percent elongation

The percent elongation at break was measured by formula given below.

Strain (E) = $\frac{\text{Total elongation}}{\text{Original lenth}} \times 100 = = \frac{L-Lo}{Lo} \times 100$

Where, L = length after force was applied

L0 = original length

In-vitro Disintegration

2ml of water was placed in a petriplates with a film on the surface of water the time taken for the disintegration of the film was measured.

In-vitro Dissolution

900ml of phosphate buffer(pH6.8)was used as a media, and was maintained at 37±0.5^{0}c 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 using a U.V Spectrophotometer at a wavelength of 226nm.

RESULTS AND DISCUSSIONS

The physical appearance of various formulations was determined by visual inspection under black and white background .All the prepared films showed transparency. Thickness is essential to ascertain uniformity. In the thickness of the film as this is directly related to the accuracy of dose in the strip**.** Low SD values in the film thickness measurements ensured uniformity of thickness in each formulation. Differences in thickness of films may due to differences of viscosities of polymeric solutions. The thickness was gradually increases with the amount of polymers. Thicknesses of the prepared films were in the range of 0.418±0.012 to 0.436± 0.006. The results indicated that the films would not break and would maintain their integrity with general folding when used. Folding endurance of the prepared films were in the range of 24 to 26. Lower folding endurance of films may due to less viscosity of the polymeric solution and formed films were very thin. Tensile Strength of the prepared films were in the range of 43.6 to 63. % Elongation of the prepared films were in the range of 5 to 17.5.

Table. No. 2: Evaluation data of Zolmitriptan films

Formulation	Thickness (mm)	Folding endurance	Tensile strength (gm/cm^2)	% Elongation
F-1	0.422±0.004	25±0.68	43.6	15
F-2	0.436±0.006	26±0.56	51.9	20

F-3	0.426±0.01	26±0.81	46.5	17.5
F-4	0.442±0.007	24±0.81	59.3	7.5
F-5	0.426±0.006	25±0.46	53	10
F-6	0.418±0.012	24±0.81	63	5

Weight variation of the prepared films were in the range of 0.97±0.004 to 0.99±0.04. As expected, increase in the polymer concentration increases disintegration time. While for a fixed polymer quantity, higher PVA content resulted in faster disintegration of the films. Films formed by combination of PVA and banana powder had shown good disintegration properties. Invitro Disintegration Time of the prepared films were in the range of 21 to 25 seconds. Homogeneous uniform drug distribution is one of the important characteristic of a fast dissolving film that ensures the uniform reproducible release of the drug from the film % drug content of the prepared films were in the range of 98.46 to 99.62%. Estimation of drug content indicated that the drug is uniformly distributed throughout the films, evidenced by the low values of the SD.

Table. No. 3: Evaluation data of Zolmitriptan films

Formulation trials	Weight variation(mg)	Invitro disintegration(sec)	Drug Content(%)
F1	0.97±0.004	25	98.46
F2	0.99±0.04	24	98.46
F3	0.986±0.04	23	98.32
F4	0.98±0.001	24	99.62
F5	0.98±0.002	22	98.6
F6	0.99±0.005	21	99.6

Being the fast disintegrating formulations the release rates of all the formulations were very rapid. It was noticed that the films got hydrated rapidly and began to dissolute the drug within minutes. This may be due to the water solubility of the drug and the polymer. Films formed by higher viscosity of polymer had shown slower dissolution, results in formation of high viscosity

gel layer caused by more intimate contact between the particles of polymer results in decreased in mobility of drug particles in swollen matrices, which leads to decrease in release rate. The release profiles of zolmitriptan from the films of formulae F1 to F6 in phosphate buffer pH 6.8 were in the range of 97.29±0.69 to 99.56±0.48. All resulted values were tabulated in table.no.4 and showed in Fig.No.1

Table.No.4: In vitro dissolution studies of all formulations

	F1	F2	F3	F4	F5	F6
0min	0	0	0	0	0	0
2min	15.43±0.22	15.42±0.32	24.65±0.41	28.67±0.34	20.43±0.42	19.35±0.22
4min	24.56±0.45	31.23±0.45	31.47±0.53	35.75±0.56	39.23±0.11	29.24±0.45
6min	37.54±0.38	42.36±0.67	47.26±0.63	56.21±0.12	52.26±0.26	58.62±0.62
8min	57.42±0.21	58.64±0.87	63.79±0.86	68.96±0.62	61.52±0.12	69.24±0.21
10min	71.32±0.35	73.93±0.94	74.72±0.35	79.79±0.36	72.61±0.34	87.61±0.45
12min	91.48±0.37	86.82±0.43	82.91±0.62	90.28±0.41	89.54±0.26	99.56±0.48
14min	98.46±0.44	97.63±0.27	97.29±0.69	99.46±0.28	98.16±0.48	

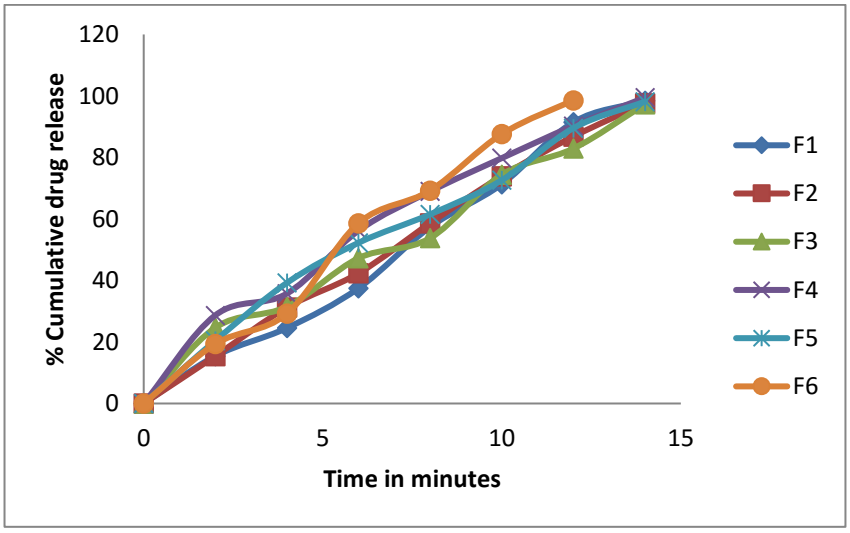

Fig. No. 1: Comparative In-vitro Drug release from all formulations

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. It is water soluble drug belongs to class III of BCS classification of drugs. Estimation of the drug by U.V method at 226nm. Preformulation studies involving FTIR study showed no interaction between drug and polymer. Formulation study involves F6 shows good mechanical properties and less disintegration time. The drug release from F6 formulation was good and follows first order kinetics. The present study resulted that the development of Zolmitriptan rapid dissolving films by solvent casting technique. Preformulation studies indicated that the drug and polymer were found to be compatible with each other. The release rate of drug was dependent upon the concentration ratio of polymers employed. All the formulated fast dissolving films followed first order release kinetics. The release rate of zolmitriptan from the fast dissolving films was found to be dependent on concentration of PVA and banana powder.

CONCLUSION

The fast-dissolving oral films of zolmitriptan prepared by using natural super disintegrants and film-forming material by the solvent-casting method which is simple and cost effective. Films showed satisfactory drug dissolution and acceptable physico-mechanical characteristics. Amongst all formulae, the formulation F6 showed the highest dissolution rate. Films were found to be stable at accelerated stability conditions. In the present work, it can be concluded that the fast dissolving films formulation can be an innovative and promising approach for the delivery of zolmitriptan by using natural polymer as a superdisintegrants for the treatment of migrane.

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