Asian Journal of Medical and Pharmaceutical Sciences
ISSN: 2348-0165
Journal Home Page: www.pharmaresearchlibrary.com/ajmps

Formulation and In-Vitro Evaluation of Fast Dissolving Oral Film of Sumatriptane by Using Natural Polymers

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A B S T R A C T

The objective of the present investigation was to formulate and evaluate fast dissolving tablets of Sumatriptane by solvent casting method. Xanthane gum, sodium alginate and guar gum were used as polymers for the preparation of Sumatriptane oral dissolving films. Sumatriptane selectively binds to and activates serotonin 5- HT1Dreceptors in the CNS, used to treatment of migraine headache. Around twelve formulations of Sumatriptane were developed as fast dissolving films using various Excipients which were found to be compatible using FTIR of films. Sumatriptane films were evaluated for quality control tests such as thickness, weight variation, folding endurance, SEM, surface pH, disintegration time, in-vitro dissolution, drug content, and stability study. The in-vitro drug study of F2 was found to give the highest % drug release then other formulations. Optimized formulation F2 made found to be stable at accelerated stability condition

Keywords: Sumatriptane, Solvent casting method, Xanthane gum, Formulation, Polymer

A R T I C L E I N F O

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JOURNAL QR-CODE

A R T I C L E H I S T O R Y: Received 19 Oct 2019, **Accepted** 28 February 2020, **Available Online** 19 June 2020

Citation: *K. Sunil kumar, et al.* Formulation and In-Vitro Evaluation of Fast Dissolving Oral Film of Sumatriptane by Using Natural Polymers.*A. J. Med. Pharm, Sci.*, 2020, 8(1): 01-06.

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1. Introduction

Recently developments in the technology Oral route of drug administration is a most suitable and preferred route due to its ease of administration, non-invasiveness, adaptability, patient compliance and acceptability.[1] Regarding oral route of drug administration, many substitutes have continuously been presented by using recent novel technologies for pediatrics, geriatrics, nauseous and non-compliance

patients. The Delivery of the drugs till date due to ease of ingestion, pain avoidance and versatility. Solid oral delivery system is less expensive to manufacture ,but oral drug delivery system still need some advancement to be made because of their some draw backs related to particular class of patients which includes geriatrics ,pediatrics and dysphasic patients associated with many medical conditions as they have difficulty in swallowing or chewing solid dosage forms.

Silent features of fast dissolving oral films

- ✓ Ease of administration for patients who are mentally ill disabled and uncooperative
- ✓ Over comes unacceptable taste of the drugs.
- ✓ Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
- ✓ Ability to provide advantages of liquid medication in the form of solid preparation
- ✓ Adaptable and amenable to existing processing and packaging.
- ✓ Require no water.
- ✓ Cost effective.
- ✓ Thin elegant film.
- ✓ Available in various size and shapes.
- ✓ Un-obstructive
- ✓ Excellent Muco-adhesion.
- ✓ Fast disintegration and dissolution.
- ✓ Rapid drug release.
- ✓ Bypasses first pass effect.

Oral thin film:

Oral films, also called oral wafers in the relate literature, are a group of flat film which are administered into the oral cavity. Dissolvable oral thin film are oral strips evolved over the past few year from the convection and oral care markets the form of breath strips and became a novel and widely accepted form by consumer for delivering vitamins and personal care products . today ,OTFs are a proven and accepted technology for the systemic delivery of APIs for over –the –counter (OTC) medications and are in the early –to mind development stages for prescription drugs . This is largely as a result of the success of the consumer breath freshener products such as Listerine Pocket packs in the US consumer market. The film can reportedly incorporate soluble, insoluble or taste masked drug substances. The film is manufactured as a large sheet and then cut in to individual dosage units for packaging in a range of pharmaceutically acceptable formats.

Drug profile:

Sumatriptane is a selective 5-HT1B and 5-HT1D Receptor agonist in cranial arteries elicits vaso constrictive and anti-inflammatory effects, associated with anti-dromic neuronal transmission and relief of migraine headache.

2. Materials and Methods

Table 1: List of Chemicals

Name	Source	Grade
Sumatriptane	Gift sample by Mylion Laboratory	Laboratory Grade
Xanthane gum	Baskerville India Pvt.LTD	Laboratory Grade
Sodium alginate	Nice chemical Pvt.LTD	Laboratory Grade
Dehydrated banana powder	Holy Nature	Laboratory Grade
Propylene glycol	Nice chemical Pvt.LTD	Laboratory Grade
Citric acid	Avra Synthesis Pvt.LTD	Laboratory Grade
Sodium starch glycolate	Oxford Lab Fine Chem LLP	Laboratory Grade
Tween80	Avra Synthesis Pvt.LTD	Laboratory Grade
Aspartame	Foodvit	Laboratory Grade
Chocolate flavor	Keva flavors Pvt.LTD	-

Method used for the estimation of Sumatriptane in this present investigation:

A UV spectrophotometric method based on the measurement of absorbance at 282 nm was used in the present study for the estimation of Sumatriptane for the samples. Calibration curve were constructed for the Sumatriptane in 20-200µg/ml.

Construction of calibration curve of Sumatriptane by UV spectrophotometry:

Calibration graphs preparation in Phosphate buffer pH 6.8:100 mg of pure drug Sumatriptane was accurately weighed and transferred to 100 ml of volumetric flask. Drug was dissolved in phosphate buffer 6.8 and volume was made up to 100 ml. The concentration of drug was 1000 µg/ml.

Procedure for plotting calibration curve of pure drug:

From the standard solution of Sumatriptane was subsequently diluted with water to obtain a series of dilutions containing 20-200 µg/ml of Sumatriptane in 1ml solution. The absorbance of these solutions was measured at 221 nm UV spectrophotometer against corresponding blank. The concentration of Sumatriptane and the corresponding absorbance values are given in table . The calibration curves for the estimation of Sumatriptane were constructed by plotting linear best fit between concentration of Sumatriptane and corresponding mean absorbance value are shown in figure.

Preparation of sumatriptane mouth dissolving films:

Solvent casting method involves firstly the water soluble polymers are dissolved in water at 1,000 rpm and can be heated up to 60°C. All the other Excipients like colors, flavoring agent, sweetening agent, etc., are dissolved separately. Then both the solutions obtained are mixed thoroughly stirring at 1,000 rpm. The obtained solution is incorporated with the API dissolved in suitable solvent. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into

pieces of the desired size. The formulation codes are given in the table.

Drug-Excipient compatibility Studies:

Before formulation of a drug substance into a dosage form, it is essential that it should be chemically and physically compatibility. Compatibility studies give the information needed to define the nature of the drug substance and provide a frame work for the drug combination with pharmaceutical Excipients in the fabrication of a dosage form. One of the requirements for the selection of suitable Excipients or carrier for pharmaceutical formulation is its compatibility. Therefore in the present work, a study was carried out by using infrared spectrophotometer to find out if there is any possible chemical interaction between Sumatriptane and Excipients. Weighed 3 mg of drug was mixed with 100 mg of potassium bromide (dried at 40-50˚c). The mixture was taken and compressed under 10-ton pressure in hydraulic press to form a transparent pellet. The pellet was scanned from 4000-400cm-1 in IR spectrophotometer.

Characterization of Films

Scanning electron microscope:

The surface morphology of optimized formulation was studied using scanning electron microscopy. A scanning electron microscopic sample holder with a double sided taps and coated with a layer of gold of 150˚A for 2 min using a sputter coater in a vacuum of 3×10-1atm of organ gas. The samples were then examined using a scanning electron microscope.

Weight variation:

2.25cm^2 films were cut at 5 different places in the cast film. The individual weight of the film were measured using Shimadzu electronic weight balance the average weight and standard deviation weight then calculated .

Thickness of Films:

By using micrometer screw gauge the thickness of the film was measured at five different places; an average of three values was calculated. This is essential to ascertain uniformity in the thickness of the film this is directly related to the accuracy of dose in the film.

Folding endurance:

Folding endurance was determined by repeated folding of the strip at the same place till the strip breaks. The number of times the film was folded without breaking is computed as the folding endurance value.

Drug content uniformity:

This is determined by any standard assay method described for the particular API in any of the standard pharmacopoeia. Content uniformity is determined by estimating the API content in individual strip. Limit of content uniformity is 85-115%.

Surface pH:

The film to be tested was placed in a Petri dish and was moistened with 0.5ml of distilled water and kept for 30 s. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibration for 1 min. The average of three determinations for each formulation was done.

In vitro disintegration test:

Disintegration time is the time when an oral film starts breaking when brought in contact with water or saliva. For a fast dissolving film, the time of disintegration should be in range of 5-30s. United State Pharmacopoeia (USP) disintegration apparatus was used to study disintegration time. In another method, the disintegration time was visually determined by dipping the film in 25 ml water in a beaker. The beaker was shaken gently and the time was noted when the film starts to breaks or disintegrates.

In vitro diffusion studies:

The in-vitro dissolution studies were conducted using three media namely distilled water (500 ml), simulated gastric fluid (900 ml) and simulated saliva (500 ml). The dissolution studies were carried out using USP dissolution apparatus at 37 + 0.5°C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm2) was placed on a stainless steel wire mesh with sieve opening 700 µm. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 2, 5, 10, 15, 30, 60, 120 min time intervals and filtered through 0.45 µm what man filter paper and were analyzed spectrophotometrically at 231 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches.

Stability study:

The samples were kept for stability studies in aluminum foil packaging at different temperature and humidity conditions namely room temperature(deep freezer (4-8°C), refrigeration (20°C) and stability chamber (40°C/75% RH).

3. Results and Discussion

Estimation of Sumatriptane using UV Spectrophotometry:

Estimation of Sumatriptane measured at 282 nm in phosphate buffer (pH 6.8) using UV spectrophotometry. It was observed that the concentration range of 2-10µg /ml obeyed the Beer's Lambert's law. The correlation coefficient was found to be R = 0.998816.

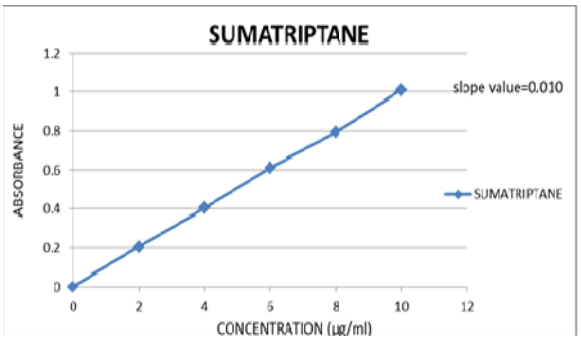

Fig 1: Calibration curve of Sumatriptane

Compatibility Studies:

The physical mixture of Sumatriptane and Excipients was subjected to FTIR to identify any interaction between them. There was no appearance or disappearance of any

characteristic peak of the drug, which confirms the absence of chemical interaction between drug and carrier. Hence the Excipient which was observed to be compatible with Sumatriptane was selected for further development of the formulation.

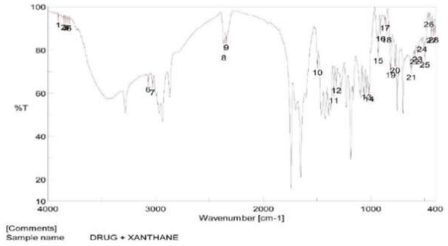

Fig 2: FTIR spectrums of Sumatriptane + Xanthane gum

Evaluation of Films

Surface morphology:

Sample of PMDF prepared by fracturing the films in liquid nitrogen, mounted on aluminum stubs, and sputter coated with platinum and surface morphology of PMDF was studied by scanning electron microscopy (SEM).

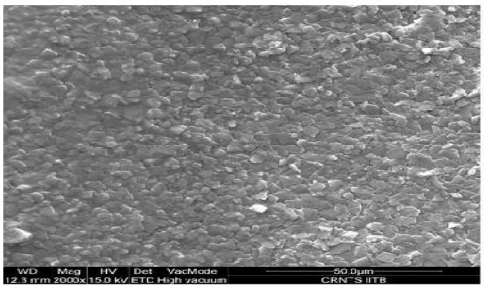

Fig 3: Scanning electronic microscopy of Sumatriptane

Surface PH of Films:

The surface pH of films was determined to investigate the possible side effect because of change in pH in vivo, since an acidic or alkaline pH may cause irritation to oral mucosa. The film to be tested was placed in a test tube and was moistened with 1.0 ml of distilled water and kept for 30 second. The pH was noted after bringing the electrode of the pH meter in contact with the surface of the formulation and allowing equilibrating for 1 min. The average of three determinations for each of the formulation was taken and standard deviation was also calculated. Surface pH of all films was found to be within the limits 6-7.

Disintegration Time:

Disintegration test for all prepared formulations was carried out using disintegration test apparatus as prescribed in USP. F1-F15 showed a Results & Discussion disintegration time of 7-58minutes. From the results obtained, by increasing the concentration of polymer, disintegration time was increased. The disintegration time of F2 was found to be 5 seconds which took less time as compared to all other formulations (F1-F12). From the results obtained from the above formulations, other thanF7, F12 disintegration time of all films was found to be within the limit as 5-30 seconds as per specification. Based on the disintegration time alone, F2 can be lead to develop Sumatriptane as fast dissolving delivery system.

Drug Content Uniformity: Percentage of drug content for different formulations was calculated and the results were shown in the table. Percentage of drug content of F2 was considered as best formulation compared to the other formulation. The formulations showed percentage drug content 85-113%. From the results obtained from the above formulations. The drug content of films should be complies with the limit as 90.1 to 100.2. The drug content of film should be 85-100%. As per IP specifications.

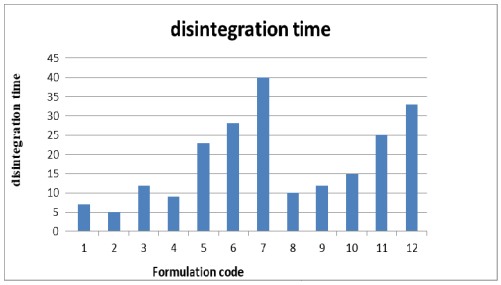

Fig 4: Disintegration Time

In-vitro dissolution studies:

The in-vitro dissolution studies were conducted using three media namely distilled water(500ml), simulated gastric fluid (900 ml) and simulated saliva (500 ml). The dissolution studies were carried out using USP dissolution apparatus at 37 + 0.5°C and at 50 rpm using specified dissolution media. Each film with dimension (2 x 2 cm2) was placed on a stainless steel wire mesh with sieve opening 700 µm. The film sample placed on the sieve was submerged into dissolution media. Samples were withdrawn at 1,2,4,6,8,10 min time intervals and filtered through 0.45 µm what man filter paper and were analyzed spectrophotometrically at 231 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained by experiment. The dissolution testing studies were performed in triplicate for all the batches.

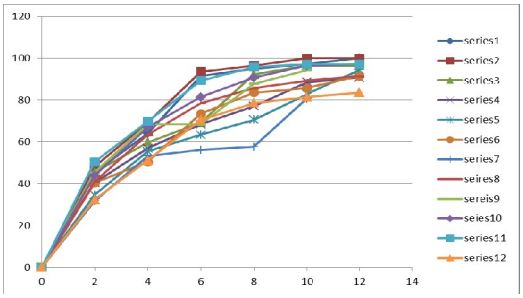

Fig 5: Cumulative % drug release of fast dissolving oral film

Stability Studies for (F2) optimized formulation: The optimized film (F2) did not show any significant change in appearance and weight loss on storage, disintegration time and % drug content. From these results it was concluded that, formulations F2 containing Sumatriptane Succinate is stable and retained their original properties.

Table 2: Composition of fast dissolving films of Sumatriptane using Xanthane gum F1-F12

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Sumatriptane (g)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
Xanthane gum(g)	0.3	0.4	0.5	0.6	0.3	0.4	0.5	0.6	0.3	0.4	0.5	0.6
Propylene glycol(ml)	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Citric acid(g)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Dehydrated banana powder(g)	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
sodium starch glycolate (g)	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.02
Tween80(ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame(g)	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
Flavor	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Water	10	10	10	10	10	10	10	10	10	10	10	10

Table 3: Calibration data of Sumatriptane

S. No	Concentration (µg/ml)	Absorbance at 282nm
1	20	0.2045±0.0045
2	40	0.4021±0.0021
3	60	0.6125±0.0025
4	80	0.7923±0.052
5	100	1.0100±0.083

Table 4: IR spectrum of Sumatriptane with Excipients (Xanthane gum)

Functional group assignment	Standard wave number (cm-1)	Test wave number (cm-1) of drug	Test wave number (cm-1) of Excipients
			Drug + Xanthane
N-H stretching	3000-3600	3432.67	3067.23
CH stretching	2700-3300	2964.05	3026.73
N-H bending	1500-1700	-	1498.42
COOH stretching	1500-1760	1743.33	1648.95
Alkanes (bending)	1340-1470	1429.96	1415
C-N stretching	180-1360	1186.97	1321.1
O-H bending	1200-1400	1228.43	1346.64
C-F stretching	1100-1250	1162.87	1016.0
N-H rocking	700-900	816.706	815
Mono sub benzene ring(rocking)	730-770	754.55	750.69
C-O stretching	1050-1300	1278.57	1058.73

Table 5: Determination of thickness, weight variation and folding endurance for Different formulations of Sumatriptane films (F1-F12)

Formulation	Thickness (µm)± SD	Weight variation	Folding Endurance
F1	90±2	42.06	110±2
F2	92±4	56.16	112±1
F3	90±5	54.75	108±1
F4	92±3	43.8	106±0
F5	96±2	41.4	112±0
F6	70±1	52.2	111±0
F7	68±2	41.6	105±2
F8	64±2	52.98	108±2
F9	67±3	40.4	104±1
F10	54±4	53.65	109±1
F11	62±1	42.6	107±1
F12	55±2	53.30	105±3

Table 6: Determination of Surface pH, Disintegration time and Drug content uniformity for Different formulations of Sumatriptane films (F1-F12)

Formulation	Surface pH	Disintegration time	Drug content uniformity
F1	6.77±0.1	7	97.4
F2	6.81±0.01	5	100.2
F3	6.68±0.02	12	98.3
F4	6.92±0.02	9	99.5
F5	6.67±0.01	23	96.6
F6	6.75±0.00	28	96.4
F7	6.78±0.01	40	99.7
F8	6.72±0.05	10	97.5
F9	6.68±0.03	12	96.4
F10	6.09±0.02	15	99.7
F11	6.28±0.01	25	95.5
F12	6.76±0.01	33	90.1

Table 7: Cumulative % drug release of oral fast dissolving film

Time (hr)	Cumulative % of drug release of oral fast dissolving films											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1	45.36%	48.24%	45.36%	40.32%	34.56%	40.32%	31.68%	41.04%	45.36%	43.92%	50.4%	32.4%
2	64.08%	69.12%	59.76%	56.88%	55.44%	50.4%	53.28%	63.36%	68.4%	66.96%	69.84%	51.12%
4	91.44%	93.6%	69.12%	68.4%	63.36%	73.44%	56.16%	78.48%	87.12%	81.36%	89.28%	70.56%
6	95.04%	96.48%	92.16%	77.04%	70.56%	83.52%	57.6%	85.68%	87.84%	90.72%	95.76%	78.48%
8	97.2%	97.2%	96.48%	88.56%	82.8%	85.68%	80.64%	89.28%	94.32%	96.48%	97.2%	81.36%
10	99.92%	99.92%	96.48%	90.72%	94.32%	91.44%	83.52%	91.44%	96.48%	97.2%	97.2%	83.52%

Table 8: Accelerated stability testing data of optimized formulation (F2) kept for stability at 40 ºC /75 %RH

Retest Time For F2	Disintegration Time (sec	Percent Drug Content/ Assay (%)	Transparency
1 week	9±4	100.1±0.2	Transparency
2 weeks	10±4	100.2±0.2	Transparency
1 month	10±4	99.1±0.2	Transparency
2 months	10±4	99.0±0.2	Transparency

4. Conclusion

Sumatriptane fast dissolving films have been successfully prepared by solvent casting method. Sumatriptane is an anti-migraine drug was selected for the preparation of fast dissolving films. Xanthane gum sodium alginate and guar gum were used as polymers for the preparation of Sumatriptane oral dissolving films. FTIR spectroscopic studies were carried out in order to establish compatibility between drug and polymer the result were concluded that that there were no chemical interactions between drug and the polymer used, so they could be used for the formulation of Sumatriptane fast dissolving films. Around twelve formulations of Sumatriptane were developed as fast dissolving films using various Excipients which were found to be compatible using FTIR of films. Formulations F1-F12 was Sumatriptane fast dissolving films prepared using three different polymers such as Xanthane, sodium alginate and guar gum. Sumatriptane films were evaluated for quality control tests such as thickness, weight variation, folding endurance, SEM, surface pH, disintegration time, in-vitro dissolution, drug content, and stability study. The thickness of all formulations complies with the limit. Weight variation of all formulations complies with the standard. Folding endurance of all formulations within the limit 100-150 as per standard. Surface pH of all formulations complies with the limit. Scanning Electrode Micrograph of the optimized formulation F2 are shown of the magnification ration of X5000 at 20kv. The drug content of all formulations of found to be within the limit. Disintegration time of all formulations complies with in the limit. The in-vitro drug study of F2 was found to give the highest % drug release then other formulations. From the in vitro dissolution study of fast dissolving films it was observed that F2 showed 99.92% of drug release at 10 minutes.Optimized formulation F2 made found to be stable at accelerated stability condition.

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