Preparation and *in vivo* evaluation of oral dissolving films containing sumatriptan succinate

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ABSTRACT

The present investigation deals with the formulation of oral dissolving films (ODFs) of sumatriptan succinate which is used for the treatment of migraine. Rapidly dissolving films have acquired great importance in present scenario because of exclusive properties. The films of sumatriptan succinate were carried out using different grades of HPMC E3, E6, and E15, maltodextrin DE6, xanthan gum and other polymers by solvent casting method. The prepared films were evaluated for film thickness, folding Endurance, Surface pH, morphological properties, %drug content and content uniformity, tensile strength, percent elongation, in vitro disintegration time and in vitro dissolution studies. The optimized formulation F24 prepared using HPMC E15 showed minimum disintegration time (9 sec), highest dissolution rate i.e. 99.6% of drug within 8 min and satisfactory physicochemical properties. The optimized film was evaluated for its bioavailability compared with pure drug as reference standard. Statistical analysis declare that no significant difference between the bioavailability parameters Cmax, Tmax, AUC0–∞ and AUC0–t of the test film (F24) and the reference product (Pure drug) indicated that they exhibited comparable plasma level-time profiles. These results revealed that the oral dissolving film containing sumatriptan succinate is considered to be effectively useful for the treatment of migraine where quick onset of action is expected.

Key words: Sumatriptan succinate, oral dissolving films, *in vivo* studies, solvent casting method.
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INTRODUCTION

Oral drug delivery is the largest and oldest segment of the total drug delivery market. It is the fastest growing and most preferred route for drug administration [1]. The peroral application is an effective and inexpensive way for drugs that can be absorbed in the gastrointestinal tract. The conventional dosage forms given by this route including tablets and capsules suffers from patient non-compliance due to difficulty in swallowing associated with their use. Moreover, the delay in onset of action by this route also calls for a delivery system which could provide a rapid onset and a quick relief [2]. For the last two decades there has been an enhanced demand for more patient-compliant dosage forms. The demand for their technology also increased drastically. A film or strip can be defined as a dosage form that employs a water-dissolving polymer, which allows the dosage form to quickly hydrate, adhere, and dissolve when placed on the tongue to provide rapid local or systemic drug delivery. Drug release may be either quick i.e. within seconds or slower to take few minutes by varying the rate of dissolution of the films [3].

Oral dissolving films offer an attractive route for systemic drug delivery. The improved systemic bioavailability results from bypassing first pass effect and better permeability due to a well supplied vascular and lymphatic drainage, also large surface area of absorption, easy ingestion & swallowing, pain avoidance make the oral mucosa a very attractive and feasible site for systemic drug delivery [4]. The delivery system consist of a very thin oral strip,

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which is simply based on the patient's tongue or any oral mucosal tissue, instantly wet by saliva the film rapidly hydrates and adheres onto site of application. It then disintegrates and dissolves to release the medication [5]. Rapidly dissolving dosage forms are also called as quick dissolving delivery systems, quick disintegrating, oral dissolve dosage forms or melt-in-mouth dosage forms. A fast dissolving film is a novel approach to get quick onset of action and to get immediate relief of the symptoms. Hence, fast dissolving films are the best formulations as they are soluble in saliva, with in 1 minute releasing the drug and inactive ingredients [6]. Bioavailability of drug in film dosage form is greater than the convectional dosage form [7].

Migraine is a chronic, episodic, neurological disorder, which usually begins in childhood, adolescence or early adult life, characterized by unilateral headache often accompanied by nausea and vomiting [8], gastrointestinal disturbance and extreme sensitivity to light and sound [9].

Sumatriptan is a 5-HT1D (5-hydroxy tryptamine 1D)-receptor agonist, used in the treatment of migraine and cluster headache [10]. Sumatriptan succinate is the first member of a new class of antimigraine compounds that act as a specific and selective 5-hydroxytryptamine-1 receptor agonist [11]. The lower bioavailability of sumatriptan succinate is primarily because of presystemic first-pass metabolism and partly because of incomplete absorption [12].

In the present study an attempt was made to prepare oral dissolving films of sumatriptan succinate with the dose of 8 mg inorder to improve the bioavailability, quick on set of action and patient compliance with hydroxy propyl methyl cellulose, maltodextrin DE6, propylene glycol, xanthan gum, citric acid, aspartame and vanillin. The *In vivo* performance of the optimized formulation was also demonstrated using rabbits as an animal model.

MATERIALS AND METHODS

2.1 Materials:
Sumatriptan succinate was generous gift from Matrix laboratories, Hyderabad, India. Hydroxy propyl methyl cellulose of E3, E6 & E15 was obtained from Nectar life sciences, Hyderabad. Maltodextrin DE6, xanthan gum and aspartame was obtained from MSN labs, Hyderabad. Propylene glycol, vanillin, citric acid and amaranth were obtained from SD FINE CHEM LTD, Mumbai. Methanol, acetonitrile and milliQ water are of HPLC grade. All other chemicals used were of analytical grade.

2.2 Animals:
 Male rabbits were (weighing 2-3 kg) selected for this study, all the animals were healthy during the period of the experiment. All efforts were made to maintain the animals under controlled environmental conditions (Temperature 25^0C, Relative Humidity 45% and 12 h alternate light and dark cycle) with 100 % fresh air exchange in animal rooms, uninterrupted power and water supply and rabbits were fed with standard diet and water ad libitum. The protocol of animal study was approved by the institutional animal ethics committee.

2.3 Methods:
2.3.1 Preparation 0f Sumatriptan Succinate Oral Dissolving Films
The oral dissolving films of sumatriptan succinate using polymers were prepared by solvent casting method. Hydroxypropylmethyl cellulose (HPMC) with different grades like HPMC E3, E6, and E15 is known for its good film forming properties and has excellent acceptability. Maltodextrin DE6 as film modifier, it acts as film-forming agent, solubilizer and imparts sweetness to the formulation. Propylene glycol as plasticizer, xanthan gum as stabilizing agent, citric acid as saliva stimulating agent, aspartame as sweetening agent and vanilla was used as a flavouring agent. The aqueous dispersion was prepared by dissolving HPMC, maltodextrin in distilled water maintained at 70°C. The suspension was used after 24 h to remove all the air bubbles entrapped. The active ingredient was added in the required quantity. Then remaining ingredients were added in the proportions given in Table 1 using HPMC E3, Table 2 using HPMC E6, Table 3 using HPMC E15. The solution was poured on petri plate and then kept for drying at 75°C for first 30 min and then it was decreased to 45°C for next 24 h. The resultant film was cut into the dimension of 2 cm X 2 cm in size, in which 8 mg of sumatriptan succinate was included [13].

The formulation was carried out using three different grades of HPMC E3, E6 and E15 and other polymers. The resulting films were evaluated for physicochemical properties.

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Composition of Sumatriptan Succinate Oral Dissolving Films Using Various Grades of HPMC (E3, E6 & E15)

Table 1: Formulation trials using HPMC E3

CODE & INGREDIENTS	F1	F2	F3	F4	F5	F6
SUMATRIPTAN (mg)	80	80	80	80	80	80
HPMC E3 (mg)	300	300	240	240	210	210
MALTODEXTRIN	180	160	120	100	120	140
PROPLYLENE GLYCOL	80	80	100	100	120	140
XANTHAN GUM (mg)	10	9	8	7	5	5
ASPARTAME (mg)	20	20	20	20	20	20
CITRIC ACID (mg)	10	10	10	10	10	10
WATER (mL)	5	5	5	5	5	5
VANILLA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
AMARANTH	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 2: Formulation trials using HPMC E6

CODE & INGREDIENTS	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17
SUMATRIPTAN (mg)	80	80	80	80	80	80	80	80	80	80	80
HPMC E6 (mg)	120	150	150	180	180	240	240	270	180	180	210
MALTODEXTRIN (mg)	120	180	120	120	120	120	120	180	120	120	120
XANTHAN GUM (mg)	10	10	9	8	7	10	10	7	6	5	5
PROPYLENE GLYCOL (mg)	80	80	100	100	120	140	160	140	120	120	140
ASPARTAME (mg)	20	20	20	20	20	20	20	20	20	20	20
CITRIC ACID (mg)	10	10	10	10	10	10	10	10	10	10	10
WATER (mL)	5	5	7	7	7	7	7	7	7	7	7
VANILLA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
AMARANTH	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Table 3: Formulation trials using HPMC E15

CODE & INGREDIENTS	F18	F19	F20	F21	F22	F23	F24	F25
SUMATRIPTAN (mg)	80	80	80	80	80	80	80	80
HPMC E15(mg)	90	90	110	110	130	140	150	160
MALTODEXTRIN (mg)	60	90	100	110	120	110	110	110
XANTHAN GUM (mg)	10	10	8	8	7	6	5	5
PROPYLENE GLYCOL (mg)	100	120	120	120	140	140	140	160
ASPARTAME (mg)	20	20	20	20	20	20	20	20
CITRIC ACID (mg)	10	10	10	10	10	10	10	10
WATER (mL)	5	5	7	7	7	7	7	7
VANILLA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
AMARANTH	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

2.3.2 Evaluation of oral dissolving films:
i) Physical characterization of ODFs:
Physical characterization of MDFs can be carried out by visual inspection for characteristics such as colour, thickness, brittleness, peeling ability, transparency, surface smoothness, tack property and film forming capacity.

The prepared films were subjected for *in vitro* evaluation parameters like film thickness, weight variation, folding endurance, surface pH, tensile strength, percent elongation, disintegration time, dissolution time and % drug content. The film surface pH was measured by placing the film on petri dish was moistened with small qty of distilled water and place the electrode of the pH meter in contact with the surface of the film.

For evaluation of film weight and thickness, films were taken and weighed individually on a digital balance and the film thickness was measured using Digital Vernier caliper (Mitutoyo) at six different places and the average value was calculated. Folding endurance of patch was determined by repeatedly folding a small strip of film (2cm X 2cm) at the same place till number of times the film could be folded at the same place without breaking was recorded as the folding endurance value. Tensile strength is the maximum stress applied to a point at which the strip specimen breaks. During measurement, the strips were pulled at the bottom clamp by adding weights in pan till the film breaks. The force was measured when the films broke. The percent elongation was evaluated using the Instron universal testing instrument (Model F. 4026, Instron Ltd., Japan) with a 5 kg load cell. The percentage increase in the length of a film, when it is pulled under standard conditions of stress just before the point of break is known as percent elongation. %Drug content was estimated by dissolving a sample strip of film (2cm X 2cm) in 100 ml of phosphate buffer pH 6.8 and the absorbance of solutions was noted using spectrophotometer at 283 nm. The

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disintegration test was carried out by taking six 2cm X 2cm films, these films were placed in the disintegration apparatus maintaining the temperature at 37 ± 2^0C and the time taken for disintegration of the films was noted. The *n vitro* dissolution studies were carried out for the films using dissolution apparatus. The values of all the evaluation parameters are given in table.

2.3.3 Drug Excipient Interaction Studies

Drug excipient interaction studies were studied by using Shimadzu - IR Affinity 1 Spectrophotometer to confirm possible interaction between the polymer and drug. The IR spectrum of the samples was prepared using KBr (spectroscopic grade) disks by means of hydraulic pellet press at pressure of seven to ten tons. Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan.

The analysis was performed by heating the 2-3mg samples on aluminium crimp pans at a rate of 10^oC/min in a nitrogen atmosphere.

2.3.4 Stability studies

The stability study of the sumatriptan succinate formulated fast-dissolving films was carried out under different conditions according to ICH guidelines. The film was packed in the aluminium foil and stored in a stability chamber for stability studies. Accelerated Stability studies were carried out at $40\ ^0$C / 75 % RH for the best formulations for 2 months. The patches were characterized for the drug content and other parameters during the stability study period **[14].**

2.3.5 *In vivo* study design

The rabbits were fasted overnight before administration of the formulation (ODF contain sumatriptan 0.75mg) and pure drug (sumatriptan 0.75mg). The rabbits were randomly divided into two groups each group contains three animals. The group A rabbits were anaesthetized with intravenous injection of pentobarbital in a dose of 25mg/kg then positioned on table with the lower jaw supported in a horizontal position and the ODF was carefully placed on the rabbit tongue. The pure drug was administered orally (Dissolved in distilled water) to group B via gastric gavage.

Blood samples for pharmacokinetic analysis were obtained at different time intervals 0, 15, 30, 60, 120,240, 360min and 24hrs after doing. Blood samples were collected in heparinized tubes and were centrifuged for 10min at 3,000 rpm at room temperature.

2.3.6 Preparation of Plasma Samples for HPLC Analysis

Rabbit plasma (0.5 ml) samples were prepared for chromatography by precipitating proteins with 2.5 ml of ice-cold absolute ethanol for each 0.5 ml of plasma. After centrifugation the ethanol was transferred into a clean tube. The precipitate was re suspended with 1 ml of acetonitrile by vortexing for 1 min. After centrifugation (5000 – 6000 rpm for 10 min), the acetonitrile was added to the ethanol and the organic mixture was taken to near dryness by a steam of nitrogen at room temperature. Samples were reconstituted in 200 µl of 70 % of acetonitrile and 30% water was injected for HPLC analysis. The chromatographic conditions were depicted in Table 4 and standard chromatogram was shown in Figure 1.

Table 4: Chromatographic conditions

Column	C18
Mobile Phase	Acetonitrile: sodium Phosphate Buffer PH3.5(30:70)
Flow rate	1.0ml/min
Injection volume	20µl
Retention time	8.490
Temperature	Ambient

2.3.7 Pharmacokinetic analysis

The pharmacokinetic parameters, peak plasma concentrations (C_{max}) and time to reach peak concentration (t_{max}) were directly obtained from concentration time data. In the present study, AUC_{0-t} refers to the AUC from 0 to 24 hrs, which was determined by linear trapezoidal rule and $AUC_{0-\alpha}$ refers to the AUC from time at zero hours to infinity.

The $AUC_{0-\alpha}$ was calculated using the formula $AUC_{0-t} + [C_{last}/K]$ where C_{last} is the concentration in µg/ml at the last time point and K is the elimination rate constant.

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Various pharmacokinetic parameters like area under the curve [AUC], elimination half life (t½). Volume of distribution (V_d), total clearance (Cl_T) and mean residence time for each subject using a non compartmental pharmacokinetic programme RAMKIN.
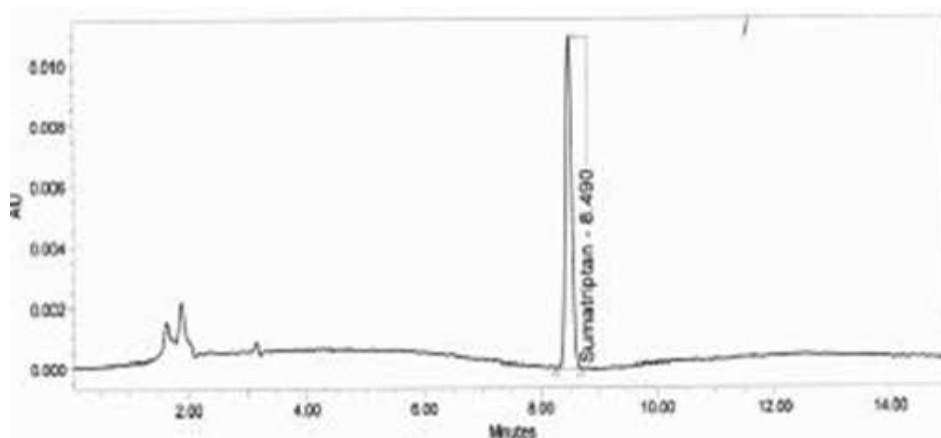

Figure 1: Standard chromatogram of sumatriptan

RESULTS AND DISCUSSION

3.1 Physical characterization of ODFs

Formulations (F1-F5) prepared using HPMC E3 were not evaluated for physical parameters and other tests as they fail to satisfy the preliminary characteristics of films due to their poor film forming ability, tack property and ease of handling/peeling.

Physical characterization of ODFs was carried out by visual inspection and the following observations were made. All the prepared films were evenly coloured and no migration of colour was observed. The increased thickness of film is attributed to the increase in the amount of HPMC. Formulation F7, F8, F9, F10 and F18 were found to be brittle in nature. Formulation F6, F12, F14 and F19 films were tacky and difficult to handle.

Table 5: Evaluation parameters of prepared oral dissolving films

CODE	Thickness (µm)	Weight Variation (mg)	Folding Endurance (count)	Tensile Strength (g/cm^2)	*In vitro* disintegration time(sec)	% Elongation	%Drug content	Surface pH
F6	55±2	69±0.2	100±2	6.8	30±2	3	100.2±0.4	6.67±0.02
F9	62±1	64.3±0.1	105±3	4.5	20±3	4	97.4±0.2	6.76±0.01
F10	54±4	58.3±0.2	107±1	4.4	29±2	5	98.3±0.3	6.28±0.01
F11	67±3	62.2±0.2	109±1	3.2	27±3	8	99.5±0.1	6.09±0.02
F15	64±2	65.1±0.4	104±1	5.1	20±2	5	96.6±1.1	6.68±0.03
F16	68±2	66.9±0.1	108±0	7.2	18±2	5	101.2±0.9	6.72±0.05
F17	70±1	62.1±0.2	105±2	7.5	19±3	9	96.4±1.4	6.78±0.01
F20	96±2	60.5±0.5	111±1	8.2	15±2	8	99.7±1.0	6.75±0.00
F21	92±3	68.5±0.4	112±0	8.8	13±2	7	97.5±1.6	6.67±0.01
F22	90±5	69.2±0.5	106±0	8.5	12±2	5	96.4±0.5	6.92±0.02
F23	92±4	71.2±0.5	108±1	9.1	12±2	6	100.5±0.5	6.64±0.02
F24	90±2	68.1±0.4	112±1	9.5	09±2	8	100.1±0.2	6.81±0.01
F25	96±1	72.0±0.3	110±2	9.8	10±3	10	99.7±1.3	6.77±0.1

3.2 The prepared films were evaluated for the following parameters:

Surface pH of all oral dissolving films prepared by using different polymers was found to be in the range of 6.09 to 6.81 pH (Table 5), which was close to the neutral pH, which indicated that films may have less potential to irritate the sublingual mucosa, and hence, more acceptable by the patients. The weight variation of the formulations was in the range of 60.5±0.5 to 71.2±0.5 mm, which was acceptable. The results showed that as the concentration of polymer increases weight of film also increases. Thickness of oral dissolving film depends on the concentration of polymer. All the oral dissolving formulations of different polymers are show thickness value in the range of 0.04±0.01 to 0.15 ± 0.02 mm (Table 5). The optimized film (F24) has thickness of 90±2 µm. A result of thickness measurement showed that as the concentration of polymer increases, thickness of oral dissolving film also increases. Folding endurance gives an indication of brittleness of the film. It was shown that as the concentration of polymer and plasticizer increases, folding endurance of oral dissolving film increases. The folding endurance value

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of the prepared films ranged from 100±2 to 112±1 (Table 5). The optimized film (F24) has folding endurance value of 112±1, which was desirable. The % drug content and content uniformity was performed for all the fast dissolving oral films and found to contain almost uniform quantity of the drug, as per content uniformity studies indicating reproducibility of the technique. Drug content in the films was evaluated and the values were found to be between 96.4±0.5 to 101.2±0.9 % (Table 5) for three different cuts from each film. The optimized formulation (F24) %drug content was found to be 100.1±0.2. As per the USP requirements, the films found to meet the criteria for content uniformity. No significant difference in the drug content among the films indicated good content uniformity. The tensile testing gives an indication of the strength and elasticity of the film, reflected by the parameters, tensile strength and percent elongation at break. Tensile strength and percent elongation of all prepared formulation is shown in Table 5. Results revealed that optimized formulation (F24) showed better tensile strength (9.5 g/cm^2) and moderate % elongation.

3.3 *In vitro* disintegration studies

The disintegrating time of all the formulations using sumatriptan succinate ranges from 9 to 31 sec. *In vitro* disintegrating time for oral dissolving film using HPMC E6 was ranges from 18 to 31 sec, the results were depicted in figure 2 and the disintegrating time for the films made by the polymer HPMC E15 was ranges from 9 to 18 shown in figure 3. The disintegration time of optimized formulation (F24) was found to be 9 sec, when compared with innovator product (Table 6) IMITREX (30 sec) which was very less and desirable for quick onset of action.

Table 6: **Disintegration time of Innovator product:**

S. No	Name of the product	Disintegration time (Sec)
1	IMITREX (50mg) ODT	30 Sec

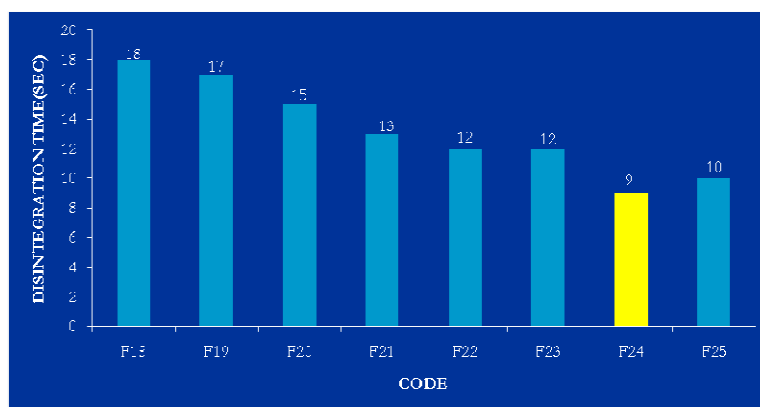**Figure 2: Disintegration profile of oral dissolving films prepared by using HPMC E6**

**Figure 3: Disintegration profile of oral dissolving films prepared by using HPMC E15**

3.4 *In vitro* drug dissolution study of oral dissolving films

Cumulative % drug release was calculated on the basis of drug content of sumatriptan succinate present in the respective film. The results obtained in the *in vitro* drug release for the formulations were tabulated in table. The graphs from F5 to F17 are depicted in Figure 4 and the graphs of formulation F20 to F25 are shown in Figure 5. The formulations F5, F9, F10, F11, F20, F21 & F22 show drug release up to 89% at the end of 8 min. Rapid drug

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dissolutions were observed in F15, F16 and F17 which release 98.6 and 96.1 respectively. The optimized formulation (F24) shows highest percent of drug release 99.45 by the end of 8 min, results are shown in Table 7. The initial release of the optimized formulation was more when compared with innovator product, therefore the onset of action was very quick compare with the innovator product Figure 6.

Table 7: Cumulative % drug release of oral dissolving films

TIME (MIN)	F5	F9	F10	F11	F15	F16	F17	F20	F21	F22	F23	F24	F25	IMITREX (50mg)
1	34.26	31.2	40.25	41.6	45.36	50.45	43.12	32.98	34.76	40.5	45.2	48.12	45	40.21
2	54.1	55.3	50.5	63.5	68.5	69.34	66.2	51.2	54.87	56.78	59.34	69.6	64	69.45
4	63.23	65.3	73.1	78.9	87.1	89.9	81.6	70.65	65.8	68.5	69.2	93.2	91.67	93.88
6	70.12	75.7	83.4	85.35	94.5	95.34	90.65	78	71.45	77.5	92	96.78	95.4	99.67
8	82.37	80.2	85.2	89.1	97.2	98.6	96.1	81.2	75.5	88.6	96.7	99.60	97.65	99.81
10	94.36	83	90.67	91.2	96.12	98.9	96.66	83.12	85.32	90.45	96.34	99.45	98.9	99.81
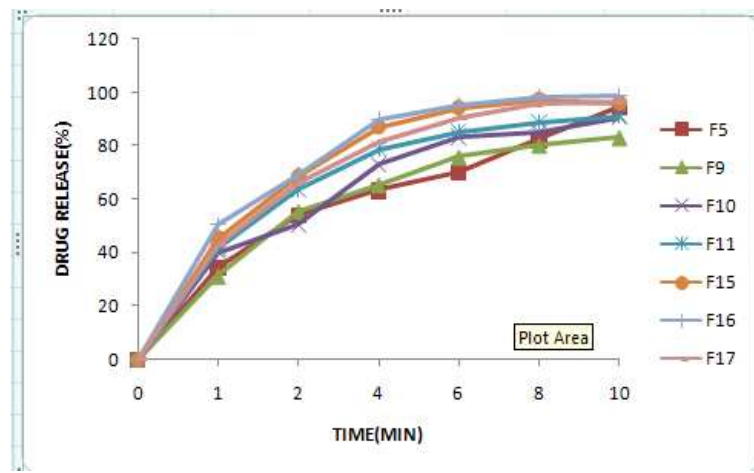
Figure 4: *In vitro* **drug release profiles of sumatriptan succinate ODF formulations (F5-F17)**
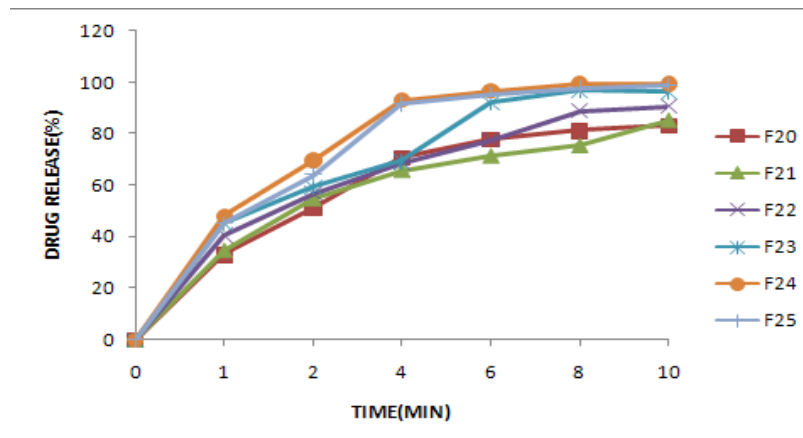
Figure 5: *In vitro* **drug release profiles of sumatriptan succinate ODF formulations (F20- F25)**
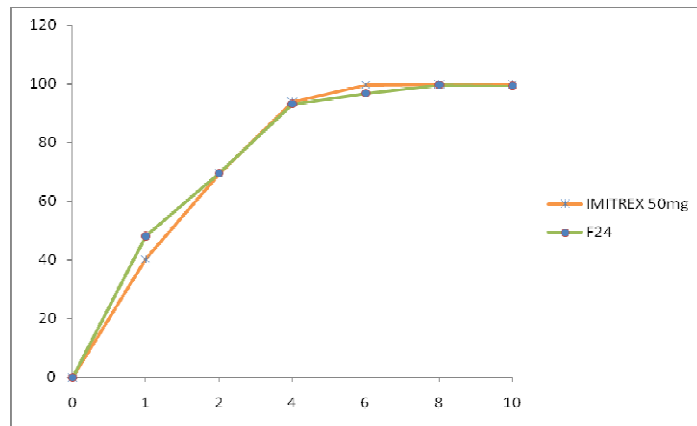
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Figure 6: *In vitro* **drug release profile of optimized formulation (F24) and IMITREX**
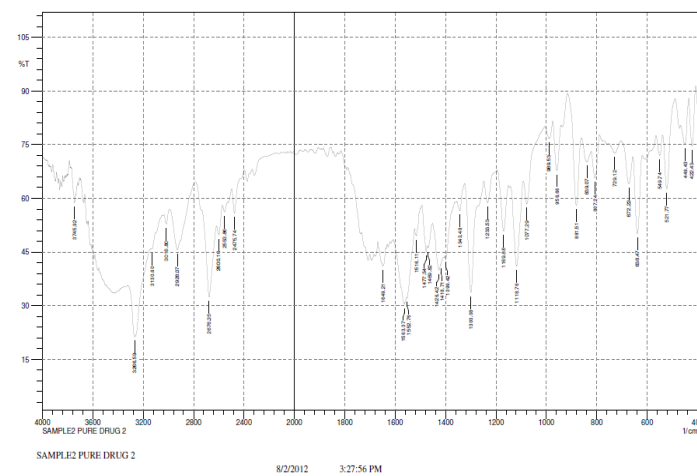
3.5 Drug excipients interaction studies

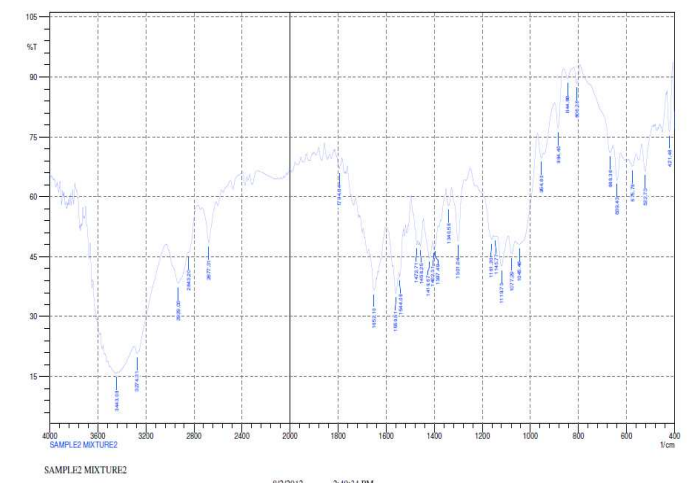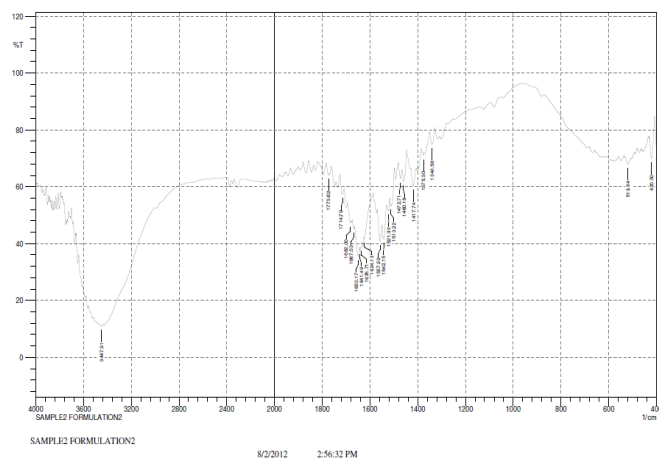**Figure 7: (Pure drug) Sumatriptan succinate**
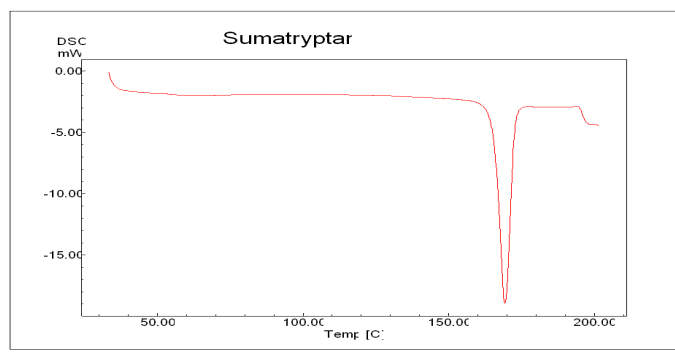

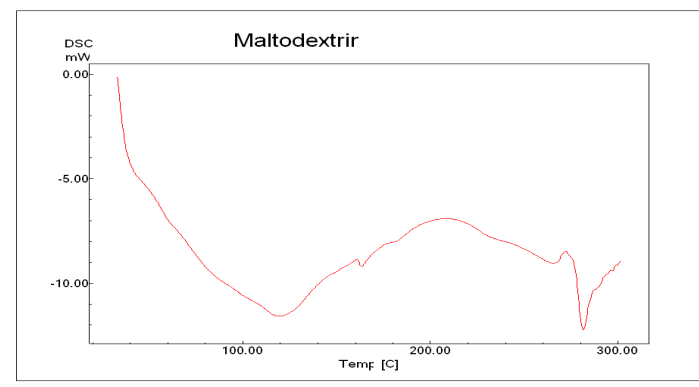**Figure 8: Drug+HPMCE15+Maltodextrin**

Figure 9: Optimized formulation (f24)

3.6 Interpretation of FTIR Data

The FTIR spectra of pure sumatriptan succinate (Figure 8) displayed band at 2928 cm^{-1} due to C-H stretch, at 1710 cm^{-1} due to C=O stretching, at 1649 cm^{-1} due to heterocyclic C=C stretching. The spectra also showed bands at 1563 cm^{-1} due to C=N bending, at 1552 cm^{-1} due to N-H stretching, at 1300 cm^{-1} due to C-OH stretching. The FTIR spectra of pure sumatriptan succinate, HPMC E 15 and Maltodextrin showed in Figure 9. The FTIR spectrum of film containing sumatriptan succinate (Figure 10) exhibited characteristic bands consistent with the molecular structure of sumatriptan succinate such as bands at 2921 cm^{-1} due to C-H stretch, at 1773 cm^{-1} due to C=O stretching, at 1650 cm^{-1} due to heterocyclic C=C stretching, at 1557 cm^{-1} due to C-N stretching, at 1542 cm^{-1} due to N-H stretching and at 1295 cm^{-1} due to C-OH. Thus, the presence of characteristic absorption bands of sumatriptan succinate and the film containing sumatriptan succinate suggest that there is no interaction takes place between the drug and excipients used in the formulation.

3.7 Drug Excipient Compatibility Studies by DSC

Figure 11: DSC Thermogram of Sumatriptan Succinate - Pure Drug
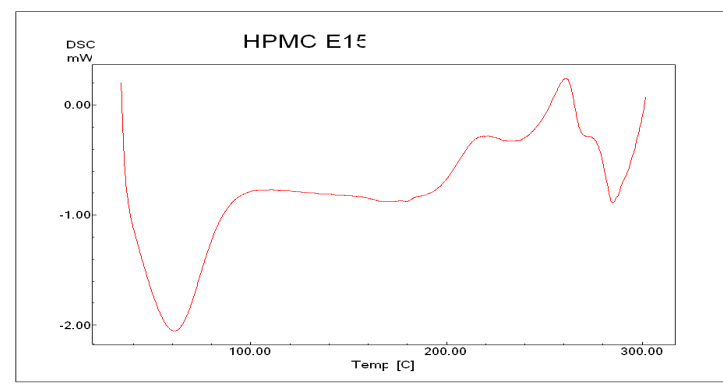

Figure 12: Maltodextrin
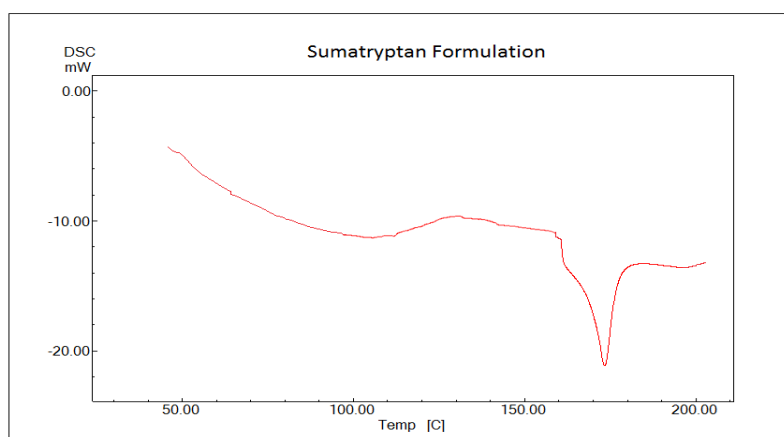
Figure 13: HPMC E15

Figure 14: Sumatriptan Formulation (F24)

DSC thermograms revealed that there is no considerable change observed in melting endotherm of sumatriptan succinate pure drug (165.97) and drug in optimized formulation (168.35). The thermograms of pure drug sumatriptan succinate, maltodextrin, HPMC E15 and optimized film (24) are shown in Figure 11, 12, 13 & 14 respectively. It indicates that there is no interaction takes place between drug and other excipients used in the formulation.

3.8 Stability Studies for (F24) optimized formulation

The optimized film (F24) 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 F24 containing sumatriptan succinate is stable and retained their original properties. The results of disintegration time, drug content and transparency are shown in the Table 8, which indicates no alteration after storage.

Table 8: Accelerated stability testing data of optimized formulation (F24) kept for stability at 40 ºC /75 %RH

Retest Time For F24	Disintegration Time (sec)	Percent Drug Content/ Assay (%)	Transparency
1 Week	9±4	100.1±0.2	Transparent
2 Weeks	10±2	100.2±0.2	Transparent
1 Month	10±2	99.1±0.2	Transparent
2 Months	10±2	99.0±0.2	Transparent

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3.9 Pharmacokinetic Data:

Table 9: Plasma levels of sumatriptan film and pure drug at different time intervals (Mean ± SD, n = 3)

Time (min)	Sumatriptan content (ng/ml)	
	Sumatriptan film	Pure drug (Standard)
0	0	0
15	621	605
30	711	689
60	561	531
120	303	290
240	24	15
360	18	8

Table 10: Comparison of pharmacokinetic parameters of sumatriptan between the film and reference (oral solution of the pure drug) in Rabbits (mean ± SD, n = 3).

Parameters	Film(Sample)	Pure drug (Reference)
AUC_{0-t} (ng. h/ml)	1356.099±43.68	1331.699±46.24
$AUC_{0-\infty}$ (ng. h/ml)	1397.34±48.16	1364.66±46.74
Cmax (ng/ml)	711	689
Tmax (minute)	30	30
Kel (h−1)	0.453 ± 0.519	0.364 ± 0.601
t1/2 (h)	1.536 ± 0.118	1.496 ± 0.293

3.10 Bioavailability Parameters
The mean sumatriptan plasma concentrations - time profiles for the prepared sumatriptan film and the pure drug sumatriptan are shown in Table 9. The bioavailability parameters for the both test film and reference standard are summarized in Table 10. The statistical comparison of C*max*, T*max*, $AUC_{0-\infty}$ and AUC_{0-t} indicated no significant difference between the two treatments, also no significant difference for the period effect was observed in this study. Based on the statistical inferences it was concluded that the two formulations exhibited comparable plasma level-time profiles.

CONCLUSION

In this work, systemic efforts were made to prepare oral dissolving films of Sumatriptan succinate (8 mg/2cm X 2 cm film) by using solvent casting method with different concentrations of HPMC-E3, E6 and E15, maltodextrin and xanthan gum. The bitter taste of the drug was masked by aspartame and vanilla flavour. Among the prepared formulations F24 showed minimum disintegration time 9 sec and the release of drug from F24 was found to be 99.6% within 8 min. Based on the satisfactory physicochemical properties like tensile strength, folding endurance, thickness, disintegration results and dissolution studies of F24, it was concluded that F24 finalized as optimized formulation. The initial release of the optimized formulation (F24) was more when compared with innovator product, therefore the onset of action was very quick compare with the innovator product. DSC and FTIR data revealed that no interactions takes place between the drug and polymers used in the optimized formulation.

In vivo study indicated absence of significance difference between film and pure drug, both exhibited comparable drug -plasma level- time profiles. *In vitro* and *in vivo* evaluation of the films confirmed their potential as an innovative dosage form to improve delivery of sumatriptan succinate. Therefore, the oral dissolving film is considered to be potentially useful for the treatment of migraine where quick on set of action, improved patient compliance and comfort is expected.

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