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FORMULATION AND *IN-VITRO* EVALUATION OF BILAYER TABLETS OF SUMATRIPTAN SUCCINATE

***B. Raja Narender and D. Meghana**

*Associate Professor, Sree Chaitanya Institute of Pharmaceutical Sciences, LMD Colony, Thimmapoor, Karimnagar.

***Corresponding Author: B. Raja Narender**

Associate Professor, Sree Chaitanya Institute of Pharmaceutical Sciences, LMD Colony, Thimmapoor, Karimnagar.

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ABSTRACT

The aim of this work was to design mucoadhesive bilayered buccal tablets of Sumatriptan succinate. Sumatriptan succinate is a serotonin 5-HT1 receptor agonist, used in treatment of migraine. It is absorbed rapidly but incompletely when given orally and undergoes first-pass metabolism, resulting in a low absolute bioavailability. Mucoadhesive polymers like xanthun gum and guar gum along with methyl crystalline cellulose were used for the preparation of mucoadhesive bilayered tablets. The optimized formulation followed Non-Fickian release mechanism. The percentage relative bioavailability of Sumatriptan succinate from selected bilayered buccal tablets was found to be 98.7%. Bilayered buccal tablets of Sumatriptan succinate was successfully prepared and evaluated with improved bioavailability.

KEYWORDS: Sumatriptan succinate, bilayered buccal tablets, mucoadhesive polymers.

INTRODUCTION

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. According to the Indian Pharmacopoeia Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and differ greatly in size and weight, depending on amount of medicinal substances and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of Tablet. All medicaments are available in the tablet form except where it is difficult to formulate or administer.

Advantages and disadvantages of tablets as dosage forms[1]

Tablets are the most popular dosage form used today and therefore there are several advantages associated with their use. However it is also important to highlight the disadvantages associated with their use.

Advantages

- Tablets are convenient to use and are an elegant dosage form.
- A wide range of tablet types is available, offering a range of drug release rates and durations of clinical effect. Tablets may be formulated to offer rapid drug release or controlled drug release, the latter reducing the number of daily doses required (and in so doing increasing patient compliance).
- Tablets may be formulated to release the therapeutic agent at a particular site within the gastrointestinal tract to reduce side effects, promote absorption at that site and provide a local effect (e.g. ulcerative colitis). This may not be easily achieved by other dosage forms that are administered orally.
- Tablets may be formulated to contain more than one therapeutic agent (even if there is a physical or chemical incompatibility between each active agent). Moreover, the release of each therapeutic agent may be effectively controlled by the tablet formulation and design.
- With the exception of proteins, all classes of therapeutic agents may be administered orally in the form of tablets.
- It is easier to mask the taste of bitter drugs using tablets than for other dosage forms, e.g. liquids.
- Tablets are generally an inexpensive dosage form.
- Tablets may be easily manufactured to show product identification, e.g. exhibiting the required markings on the surface.
- The chemical, physical and microbiological stability of tablet dosage forms is superior to other dosage forms.

Disadvantages

- The manufacture of tablets requires a series of unit operations and therefore there is an increased level of product loss at each stage in the manufacturing process.
- The absorption of therapeutic agents from tablets is dependent on physiological factors, e.g. gastric emptying rate.

- ❖ The compression properties of certain therapeutic agents are poor and may present problems in their subsequent formulation and manufacture as tablets.
- ❖ The administration of tablets to certain groups, e.g. children and the elderly may be problematic due to difficulties in swallowing. These problems may be overcome by using effervescent tablet dosage forms.

Bilayer tablets[2,3]

Bilayer tablets are prepared with one layer of drug for immediate release while second layer designed to release drug later, either as second dose or in an extended release manner. Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances, and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose.

Applications

1. Used in combination therapy.
2. Used to deliver the loading dose and sustained dose of the same or different drugs.
3. Used for bilayer floating in which one layer is floating layer another one is release layer of the drug.
4. Used to deliver the two different drugs having different release profiles.

Advantages

1. Bilayer tablet is suitable for preventing direct contact of two drugs and thus two maximize the efficacy of combination of two drugs.
2. Patient compliance is enhanced leading to improve drug regimen efficacy.
3. Patient convenience is improved because fewer daily doses are required compared to traditional delivery system.
4. Bilayer tablets can be designed in such a manner as to modify releases as either of the layers can be kept as extended and the other as immediate release.
5. Fixed low-dose combinations are very useful tools for treatment.

Disadvantages

1. Adds complexity and bilayer rotatary presses are expensive.
2. Insufficient hardness, layer separation, reduced yield.
3. Inaccurate individual layer weight control.
4. Cross-contamination between the layers.

The primary Aim of the study is modified release of drug delivery is to ensure safety and to improve efficacy of drugs as well as patient compliance. If the drug is given in conventional dosage form, it has to be administered several times a day to produce the desired therapeutic effect. Because of the frequent dosing fluctuation in plasma drug level occurs. If the drug dosing interval is not in accordance with biological half-life large peaks and valleys are possible with time-drug concentration in blood curve. The pronounced fluctuations resulting from the conventional drug administration are likely to yield period of no therapeutic effect when drug concentration fall below minimum therapeutic level.

METHODOLOGY[4,5,6]

PREFORMULATION STUDIES

CHARACTERIZATION OF DRUG

Colour and Appearance: The sample was observed visually.

Melting Point: Melting point of drug was determined by Melting point test apparatus.

pH Determination: A 2% saturated solution of Sumatriptan succinate was prepared in distilled water and pH was measured by digital pH meter.

Solubility: Solubility study was carried out as per the I.P. 2007. In this maximum amount of solvent required to dissolve the solute was determined.

Spectral Analysis of Sumatriptan succinate

UV Spectral Analysis of Sumatriptan succinate

UV Spectral Analysis of Sumatriptan succinate in 0.1N HCl

Determination of absorption maximum in 0.1N HCl

The absorption maximum of the standard solution was scanned between 200-40 nm regions on Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum represented.

Preparation of Standard Curve of Sumatriptan succinate in 0.1N HCl[7]

Preparation of 0.1N HCl: 0.1N HCl was prepared by diluting 8.5 ml of hydrochloric acid in 1000 ml of distilled water.

Procedure

Accurately weighed 100mg of Sumatriptan succinate was dissolved in little quantity of 0.1NHydrochloric acid and volume was adjusted to 100ml with the same to prepare a standard solution having concentration of 1000µg/ml. From this above solution 1ml was pipette out and transferred to a 10 ml volumetric flask and the volume was adjusted with 0.1NHydrochloric acid to a concentration of 100µg/ml. From this stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml was pipette out and transferred to 10ml volumetric flasks and final volume was made with 0.1NHydrochloric acid for giving concentrations ranged from 2.0 to 10 µg/ml. The absorbance of these solutions was measured in UV-Visible spectrometer at 227nm using 0.1NHydrochloric acid as blank.

Assay of Sumatriptan succinate

Accurately weighed 25 mg of Sumatriptan succinate was dissolved in little quantity of 0.1N HCl and volume was adjusted to 25 ml with the same to prepare standard solution and the volume was adjusted with 0.1N HCl to

get a concentration of 1000µg/ml. From this stock solution, 0.1ml was pipette out and transferred to 10 ml volumetric flask and final volume was adjusted with 0.1N HCl. Absorbance values of these solutions were measured against blank at 227 nm using UV-Visible spectrophotometer. The percentage purity of drug was calculated by using calibration graph method.

UV Spectral Analysis of Sumatriptan succinate in pH 6.8 phosphate buffer[8]

Determination of absorption maximum in pH 6.8 phosphate buffer

The absorption maximum of the standard solution was scanned between 200-400 nm regions on Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum represented.

Preparation of Standard Curve of Sumatriptan succinate in pH 6.8 phosphate buffer

Preparation of pH 6.8 phosphate buffer

pH 6.8 phosphate buffer

50ml of 0.2M potassium dihydrogen phosphate was taken in 200ml volumetric flask, to which 22.4ml of 0.2M sodium hydroxide solution was added and the volume was made upto the mark with distilled water.

0.2M potassium dihydrogen phosphate

27.218 gm of potassium dihydrogen phosphate was added to 1000ml volumetric flask containing distilled water and the volume was made upto the mark with distilled water.

0.2M Sodium Hydroxide

8gm of Sodium Hydroxide was taken in a 1000ml volumetric flask containing distilled water and volume was made upto the mark with distilled water.

Procedure

Accurately weighed 100mg of Sumatriptan succinate was dissolved in little quantity of pH 6.8 phosphate buffer and volume was adjusted to 100ml with the same to prepare a standard solution having concentration of 1000µg/ml. From this above solution 1ml was pipette out and transferred to a 10 ml volumetric flask and the volume was adjusted with pH 6.8 phosphate buffer to a concentration of 100µg/ml. From this stock solution, aliquots of 0.2, 0.4, 0.6, 0.8 and 1.0 ml was pipette out and transferred to 10 ml volumetric flasks and final volume was made with pH 6.8 phosphate buffer for giving concentrations ranged from 2.0 to 10 µg/ml. The absorbance of these solutions was measured in UV-Visible spectrometer at 227nm using pH 6.8 phosphate buffer as blank.

Infrared Spectrum

The infrared spectrum of Sumatriptan succinate was recorded by using FTIR (Perkin elmer-Pharmaspec-1) instrument. A small quantity of sample was mixed with equal quantity of potassium bromide and placed in sample cell to record its IR spectra.

LOSS ON DRYING

Loss on drying is the loss of weight expressed as percentage w/w resulting from volatile matter of any kind that can be driven off under specified condition. The test can be carried out on the well mixed sample of the substance.

$$\text{Loss on drying} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

DRUG - POLYMERS COMPATABILITY STUDIES

Drug polymers studies holds great importance in designing a formulation In drug formulation it is essential to evaluate the possible interactions between the active principle and the polymers, as the choice of the polymers should be performed in relation to the drug delivery, to their compatibility with the same drug and to the stability of the final product.

Fourier Transform Infra-Red Spectroscopy (FTIR) Study

Sumatriptan succinate powder was mixed with various polymers in the ratio of 1:1. Then, afterwards the samples were scanned with FTIR (Perkin Elmer-Pharmaspec-1) over a wave number range of 4000-400 cm^{-1}.

Differential Scanning Calorimetry Study (DSC)

Sumatriptan succinate powder was mixed with various polymers in the ratio of 1:1. The mixture of drug with polymers to maximize the like hood of obscuring an interaction. Mixture should be examined under Nitrogen to eliminate oxidative and pyrolytic effect at a standard heating rate (2, 5 or 10^0C/minute) on DSC. Over a temperature range, which will encompass any thermal changes due to the mixture of drug with polymers thermograms of pure drug are used as a reference. Appearance or disappearance of one or more peaks in thermograms of drug with polymers is considered as an indication of interaction.

PREPARATION AND EVALUATION OF POWDER BLENDS

PREPARATION OF POWDER BLENDS

All ingredients were weighed and passed through mesh #40 separately. The drug and polymer were blended first in mortar and pestle then the remaining ingredients are added in that and blended for 20 min. Finally the blend is passed through mesh # 20 and used for evaluation of flow characteristics.

EVALUATION OF MICROMERITIC PROPERTIES OF POWDERS

- **Angle of Repose**

The angle of repose was determined by the funnel method. The accurately weighed (10gms) granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of granules. The granules were allowed to flow through the funnel freely onto a clean surface. The diameter of the granules cone was measured and angle of repose was calculated using the following equation:

$\tan \theta = h/r$

Where h is the height of granules cone and r is the radius of the granules cone.

Table 4: Relationship between Angle of Repose (θ) and Flowability.

S. No.	Angle of repose(θ)	Flowability
1	<20	Excellent
2	20 – 30	Good
3	30 – 35	Passable
4	>40	Very poor

- **Bulk Density and Tapped Bulk Density**

An accurately weighed (10 gms) granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The volume occupied by the granules was measured which give bulk volume. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. Both Bulk Density (BD) and Tapped Bulk Density (TBD) of granules were determined using the following formulae.

BD = Weight of the granules/Volume of the granules
TBD = Weight of the granules/Tapped volume of the granules

- **Carr's Compressibility Index**

The compressibility index of the granules was determined using following Carr's compressibility index formula.

Carr's Compressibility Index (%) = [(TBD-LBD)/ TBD] x100

Relationship between % compressibility and flowability is shown in the Table 5.

Table 5: Relationship between % Compressibility and Flowability.

S. No.	% Compressibility	Flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair Passable
4	23-35	Poor
5	33-38	Very poor
6	>40	Very very poor

- **Hausner's ratio**

Hausner's ratio is the ratio between tapped density and bulk density. Hausner's ratio less than 1.25 indicates good flow properties while Hausner's ratio greater than 1.25 shows poor flow of granules.

Table 6: Relationship between Hausner's ratio and Flowability.

S. No.	Hausner's ratio	Flow Property
1	0.0 - 1.25	Free flow
2	1.25 - 1.6	Cohesive flow

FORMULATION OF BILAYER TABLETS

Formulation development of Sumatriptan Succinate IR layer

Table Formulation development of Sumatriptan Succinate IR layer

S.No	Ingredients	Formula (mg)
1	Sumatriptane Succinate	50
2	Crosspovidone	5
3	Methyl crystalline cellulose	20
4	Mannitol	20
5	Magnesium Stearate	3
6	Talc	2

Formulation development of Sumatriptan Succinate SR layer

Table 8: Formulation development of Sumatriptan Succinate SR layer.

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sumatriptane Succinate	200	200	200	200	200	200	200	200	200
Xanthan Gum	50	-	-	100	-	-	25	25	-
Guar gum	-	50	-	-	100	-	25		25
Sodium alginate	-	-	50	-	-	100	-	25	25
Starch	40	40	40	40	40	40	40	40	40
Talc	3	3	3	3	3	3	3	3	3
Mannitol	94	94	94	44	44	44	94	94	94
Megnisium stearate	5	5	5	5	5	5	5	5	5
PVP (2%)	8	8	8	8	8	8	8	8	8

FORMULATION AND CHARACTERIZATION OF BILAYER TABLETS

The bilayer tablets of Sumatriptan succinate were prepared by the direct compression method. The drug and polymers for both IR and SR layer were passed through a # 60 sieve before their use in the formulation.

Formulation of the IR Layer

The IR ingredients (Table 7) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Formulation of the SR Layer

The SR ingredients (Table 8) were accurately weighed and added into the blender in ascending order. The powder mix was blended for 20 min. to obtain uniform distribution of the drug in formulation and subjected for preformulation studies.

Compression of Bilayer Tablet

In the present study bilayer tablet was prepared manually using single station punching machine. Accurately weighed amount of SR powder mix was fed manually into die cavity. SR layer was compressed at mild compression force. After that accurately weighed IR powder mix was manually fed into the die on SR layer and compressed using 8-mm flat punches (Rimek mini press-1 Karnavati Engineering Ltd, Gujarat).

Dose Calculation

For sustained drug release up to 24 hr, the immediate dose of drug was calculated from total dose of Sumatriptan succinate extended release tablet.

$$Dt = Dose\ (1 + 0.693 \times t/t_{1/2})$$

Where,

Dt = Total dose,

Dose = Immediate release dose,

t = Total time period for which sustained release is required,

$t_{1/2}$ = Half-life of drug.

EVALUATION OF BILAYER TABLETS

- **Evaluation of Tablets**
- **Physico-Chemical Properties of Tablets.**
  - Appearance
  - Thickness
  - Hardness
  - Friability
  - Weight variation
  - Drug content
- **In-vitro Drug Release.**
- **Kinetics of in-vitro drug release.**
- **Stability Studies.**

Physico-Chemical Properties of Tablets

Appearance

The tablets were visually observed for any capping, chipping and lamination.

Size and Thickness

The size and thickness of tablet can vary with no change in weight due to difference in density of granulation, the pressure applied to the tablets and speed of the tablet compression machine. The thickness of the tablets was determined using a Vernier caliper. Three tablets from each type of formulation were used and average values were calculated.

Hardness
There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. Hardness tester (Monsanto tester) was used to measure hardness of tablets. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be taken as a zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted in kg/cm^2.

Friability
Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for four minutes, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed tablets was placed in Roche friabilator which was then operated for 100 revolutions. The tablets were then dedusted and reweighed. Percent friability (% F) was calculated as follows,
% Friability = (Initial weight - Final weight / Initial weight) x 100.

Weight Variation
The weight variation test is done by taking 20 tablets randomly and they were weighed individually. The composite weight divided by 20, provides an average weight of tablet. Not more than two of the individual weight deviates from the average weight by % deviation allowed and none should deviate by more than twice its percentage.

Table 9: Specifications of % weight variation allowed in Tablets as per Indian Pharmacopoeia.

Average Weight of Tablet	% Deviation allowed
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
mg or more	5

Drug Content
20 tablets of each formulation taken and amount of drug present in each tablet was determined. Powder equivalent to 25 mg was taken and added in 25 ml of 0.1N HCl followed by stirring for 10 min. This was filtered through a 0.45 µ membrane filter, diluted to get 10 µg/ml concentration and absorbance of resultant solution was measured by UV at 227nm using 0.1N HCl.

In-vitro Dissolution of Tablets
The release rate of sumatriptan succinate from bilayer tablets was determined using USP Dissolution Testing Apparatus type-I (basket method; Veego Scientific VDA-8DR, Mumbai, India). A sample (5 ml) of the solution was withdrawn from the dissolution apparatus and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to a suitable concentration with respected medium. Absorbance of these solutions was measured at 227nm using a Shimadzu-1700 Pharmaspec UV-VISIBLE spectrophotometer. For each formulation, the experiments were carried out in triplicate. The release data were calculated by using PCP disso V3 software.

IN-VITRO DISSOLUTION STUDIES
For Sumatriptan Succinate IR Layer
Medium : 900 ml of 0.1N Hydrochloric acid
RPM : 50
Apparatus : Basket
Time : 15,30,45,60,120 minutes
Wave Length : 227 nm
Temperature : $37^0C \pm 0.5^0C$

For Sumatriptan Succinate SR Layer
Medium : 900 ml of buffer pH 6.8
RPM : 50
Apparatus : Basket
Time : 4^{th}, 6^{th}, 8^{th}, 12^{th}, 24^{th} Hours.
Wave Length : 227 nm
Temperature : $37^0 C \pm 0.5^0C$

Kinetics of In-vitro Drug Release
To study the release kinetics of In-vitro drug release, data was applied to kinetic models such as zero order, first order, Higuchi and Korsmeyer- Peppas.

- **Zero order:** $C = K_0 t$

K_0 - zero-order rate constant expressed in units of concentration/time, t - time in hrs.

- **First order:** $LogC = LogC_0 - Kt / 2.303$

Where C_0 - is the initial concentration of drug, K - first order constant, t - time in hrs.

- **Higuchi:** $Qt = Kt^{1/2}$

Where Q_t - amount of the release drug in time t, K- kinetic constant, t- time in hrs.

- **Korsmeyer Peppas:** $Mt / M\infty = Kt\ n$

Where M_t - represents amount of the released drug at time t,
M_∞- is the overall amount of the drug (whole dose) released after 24 hrs
K- is the diffusional characteristic of drug/ polymer system constant
n- is a diffusional exponent that characterizes the mechanism of release of drug.

STABILITY STUDIES
The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and

light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products" describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

Stability studies were carried out at 40°C / 75% RH for the optimized formulation for 3 months. The tablets were stored at 40°C/75% RH in closed high density polyethylene bottles for 3 months. The samples were withdrawn after periods of 1, 2 and 3 months. The samples were analyzed for its hardness, drug content and In-vitro drug release.

Excipients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sumatriptane Succinate	200	200	200	200	200	200	200	200	200
Xanthan Gum	50			100			25	25	
Guar gum		50			100		25		25
Sodium alginate			50			100		25	25
Starch	40	40	40	40	40	40	40	40	40
Talc	3	3	3	3	3	3	3	3	3
Mannitol	94	94	94	44	44	44	94	94	94
Megnisium stearate	5	5	5	5	5	5	5	5	5
PVP (2%)	8	8	8	8	8	8	8	8	8

RESULTS AND DISCUSSION

CHARACTERIZATION OF DRUG

Colour and Appearance

The drug (Sumatriptan succinate) colour is "White to almost white powder" as same as the reported reference.

Melting Point

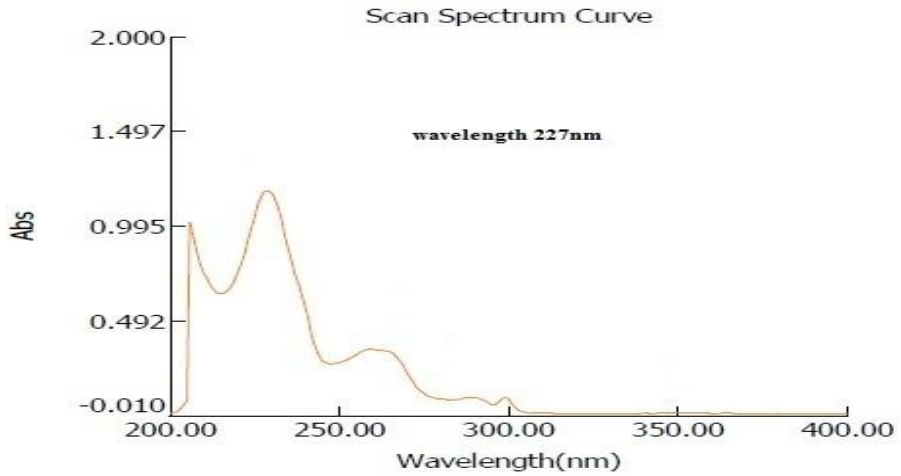
The Melting point of Sumatriptan succinate was found to be 169 ± 1.081. The reported melting point of Sumatriptan succinate is 166-171^{0}C. Hence, observed values are complies with USP.

Solubility study: Freely soluble in water, sparingly soluble in methanol, practically insoluble in methylene chloride.

SPECTROSCOPIC STUDIES

UV Spectroscopy: Determination of λmax and Preparation of Calibration Curve of Sumatriptan succinate by using 0.1NHCL

UV absorption spectrum of Sumatriptan succinate in 0.1N HCl shows λmax at 227nm. Absorbance obtained for various concentrations of Sumatriptan succinate in 0.1N HCl are given in Table 10. The graph of absorbance versus concentration for Sumatriptan succinate was found to be linear in the concentration range of 2-10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-10 µg /ml.



Absorption maximum of Sumatriptan succinate in 0.1N HCl

Concentration and Absorbance data for Calibration Curve of Sumatriptan succinate in 0.1 N HCl

S. No.	Concentrations(µg/ml)	Absorbance at 227nm.
1	0	0
2	2	0.135
3	4	0.251
4	6	0.367
5	8	0.480
6	10	0.594

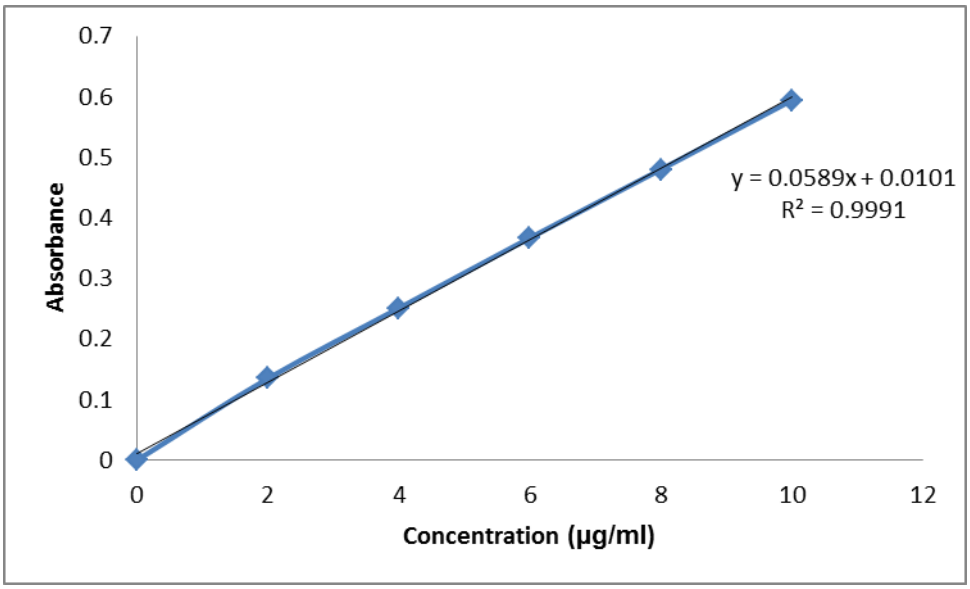


Fig. 2: Calibration Curve of Sumatriptan succinate in 0.1 N HCl.

UV Spectroscopy

Determination of λmax and Preparation of Calibration Curve of Sumatriptan succinate by using pH 6.8 phosphate buffer

UV absorption spectrum of Sumatriptan succinate in pH 6.8 phosphate buffer shows λmax at 227.8nm. Absorbance obtained for various concentrations of Sumatriptan succinate in pH 6.8 phosphate buffer are given in Table 11. The graph of absorbance versus concentration for Sumatriptan succinate was found to be linear in the concentration range of 2-10 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-10 µg /ml.

Table 11: Concentration and Absorbance data for Calibration Curve of Sumatriptan succinate in pH 6.8 Phosphate buffer.

S. No.	Concentrations(µg/ml)	Absorbance at 227.8nm.
1	0	0
2	2	0.145
3	4	0.305
4	6	0.445
5	8	0.604
6	10	0.734

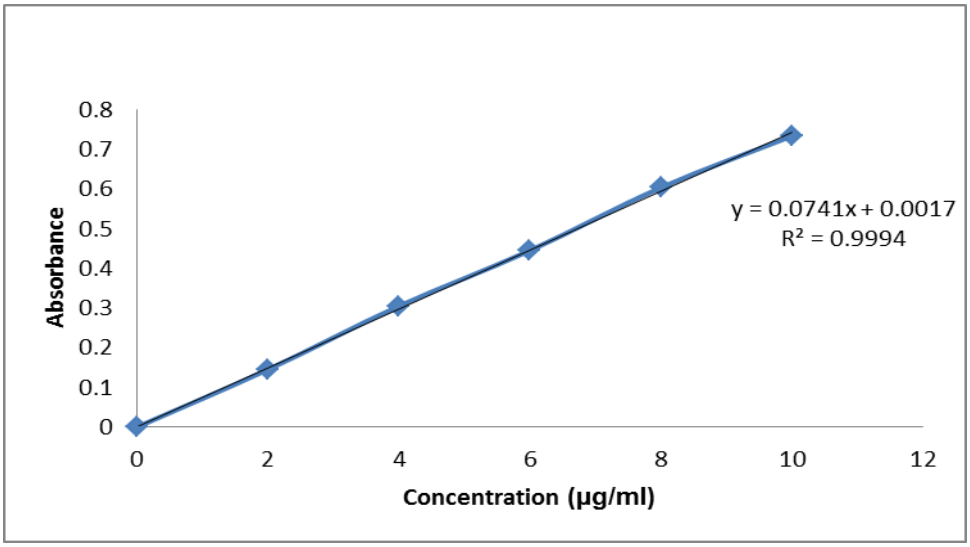


Fig. 4: Calibration Curve of Sumatriptan succinate by using pH 6.8 phosphate buffer.

Fourier Transform Infra-Red Spectroscopy (FTIR)

The IR spectrum of Sumatriptan succinate is shown in figure 5. The interpretation of IR frequencies are shown in table 12.

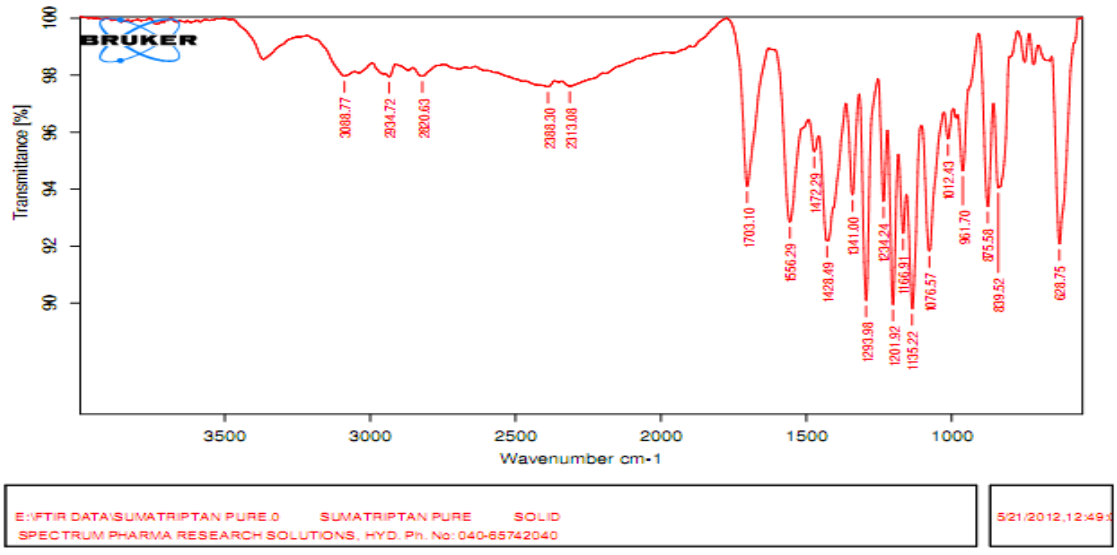


Fig. 5: FTIR spectra of Sumatriptan succinate pure drug.

Interpretation of FTIR Spectrum

Table shows the peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Sumatriptan succinate. Hence, the sample was confirmed as Sumatriptan succinate.

Table 12: Characteristic frequencies in IR Spectrum of Sumatriptan succinate.

Functional groups	Wave No. (cm^{-1})
C-H (Aromatic)	3088.77
C=C (Aromatic)	1556.29
C-C (Loop)	1428.49
N-H (Stretching)	3369.75
C-N	1341.00
S=O	1135.22

From the above figure, it can be seen that, the major functional group peaks observed in spectra of Sumatriptan succinate with guar gum, xanthan gum remains unchanged as compared with spectra of sumatriptan succinate. So from the above IR spectra it can be observed that there is no interaction between Sumatriptan succinate and polymers used in the formulations.

5.2.2 Differential Scanning Calorimetry (DSC)

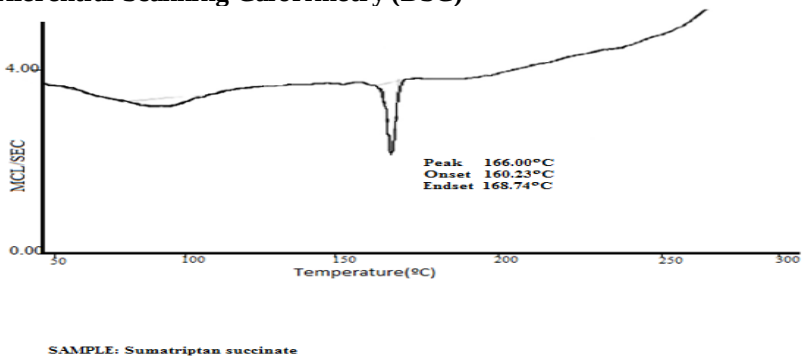


Fig. 10: Thermogram of SUMATRIPTAN SUCCINATE.

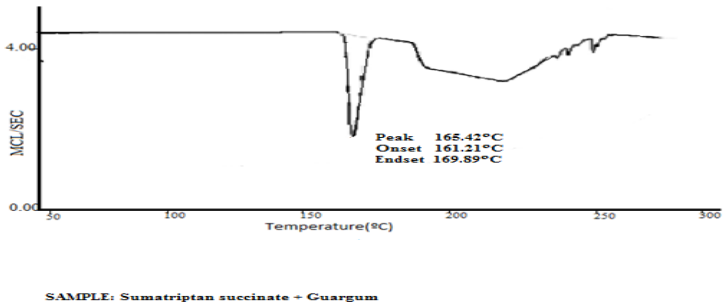


Fig. 11: Thermogram of SUMATRIPTAN SUCCINATE + GUAR GUM.

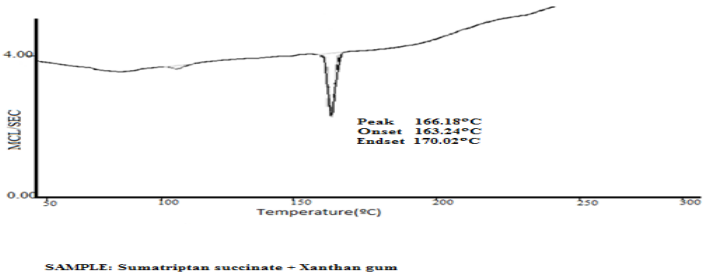


Fig. 12: Thermogram of SUMATRIPTAN SUCCINATE + XANTHAN GUM.

The results of DSC studies are given in above figure. Pure Sumatriptan succinate showed sharp endotherm at 166°C corresponding to its melting point. There was no appreciable change in the melting endotherms of Sumatriptan succinate with Guar gum and Sumatriptan succinate with Xanthan gum as compared to the thermogram of Sumatriptan succinate. So, it could be concluded that there is no interaction between Sumatriptan succinate and Polymers used in the formulations.

5.3 EVALUATION OF MICROMERITIC PROPERTIES OF POWDER BLENDS

Table 14: Preformulation parameters of Sumatriptan Succinate SR granules.

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ) (^{0})	Carr's index (%)	Hausner's ratio
F1	0.43±0.007	0.59±0.006	21.45±1.7	17.34±1.7	1.634±1.2
F2	0.41±0.004	0.62±0.009	27.52±0.4	19.54±0.8	1.382±0.7
F3	0.38±0.009	0.53±0.007	34.62±1.5	23.65±1.1	1.442±1.0
F4	0.53±0.005	0.59±0.004	31.43±0.5	21.45±0.9	1.238±1.3
F5	0.45±0.007	0.54±0.005	24.65±1.3	20.61±1.8	1.327±1.3
F6	0.47±0.005	0.58±0.004	27.95±1.4	25.49±1.3	1.643±0.9
F7	0.52±0.008	0.61±0.006	24.27±1.6	19.62±0.9	1.225±0.7
F8	0.49±0.006	0.54±0.003	31.48±0.9	17.50±1.2	1.505±1.2
F9	0.36±0.009	0.58±0.007	26.65±1.0	22.48±1.7	1.605±0.4

All the values are expressed as a mean ± SD., n = 3.

Table 15: Preformulation parameters of Sumatriptane Succinate IR layer.

Preformulation parameters	Formulation
Bulk density (gm/ml)	0.42±0.008
Tapped density (gm/ml)	0.54±0.005
Angle of repose (θ)^0	24.11±1.4
Carr's index (%)	22.42±1.8
Hausner's ratio	1.7±1.2

All the values are expressed as a mean ± SD., n = 3.

5.3.1 Angle of repose

The results for angle of repose are recorded in Table 14, 15. Angle of repose ranged from 21.45±1.7 to 34.62±1.5. The flow properties of granules in all formulations exhibit good flow.

5.3.2 Bulk density and Tapped bulk density

The results are shown in Table 14, 15. The values of BD and TBD were found to be in the range from 0.36±0.009 to 0.53±0.005 gm/cc and 0.53±0.005 to 0.62±0.009 gm/ml respectively. So, it shows that all formulations having good flow properties and packability.

5.3.3 Carr's Compressibility Index

The results for Carr's Compressibility Index are recorded in Table 14, 15. The Carr's Compressibility Index were in the range from 17.34±1.7 to 25.49±1.3%. This indicates good flow properties of granules.

5.3.4 Hausner's ratio

The results were summarized in Table 14, 15. The Hausner's ratios were found in the range from 1.225±0.7 to 1.643±0.9. So it indicates good flow properties.

5.4 EVALUATION OF TABLETS

5.4.1 Evaluation of Physico-chemical properties of tablets

Table 16: Physico-Chemical Properties of Tablets.

Formulation	Wt.variation (%)	Friability* (%)	Hardness** (kg/cm^2)	Thickness** (mm)	Assay* (%)
F1	0.6012	0.25±0.15	5.5±0.7	6.9±0.9	99.49±0.17
F2	0.5988	0.34±0.19	6.0±0.9	6.8±0.2	100.16±0.16
F3	0.6006	0.26±0.17	6.5±0.2	7.0±0.6	99.88±0.25
F4	0.6018	0.12±0.12	9.3±0.7	7.1±0.4	100.5±0.17
F5	0.6005	0.19±0.15	8.6±0.4	6.9±0.2	98.36±0.25
F6	0.5996	0.32±0.13	6.7±0.8	6.8±0.8	98.98±0.16
F7	0.6005	0.28±0.19	6.8±1.2	7.0±0.5	99.60±0.25
F8	0.6008	0.26±0.12	8.4±1.8	6.9±0.6	99.09±0.25
F9	0.6001	0.15±0.16	9.4±0.9	7.2±0.2	100.72±0.19

All the values are expressed as a mean ± SD., n = 3

All the values are expressed as a mean ± SD., n = 6

5.4.1.1 Appearance
The tablets were observed visually and did not show any defects such as capping, chipping and lamination after punching.

5.4.1.2 Thickness
The thickness of formulations ranged from 6.8±0.2 mm to 7.2±0.2mm. The values are recorded in Table 16.

5.4.1.3 Weight Variation
The percentage deviation from average tablet weight for all the formulations ranged from 499±1.2 to 501±1.5mg. The results are within the specified limits and showed in Table 16. Hence all formulations complied with the test for weight variation as per IP.

5.4.1.4 Hardness
The results of Hardness of tablets were recorded in Table 16. It was found that the values are ranged from 5.5±0.7 to 9.4±0.9 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

5.4.1.5 Friability
The Percentage Friability of all the formulations showed in Table 16. The results are ranged from 0.12±0.12 to 0.34±0.19%. So, the percentage loss of Friability of all the formulations was found to be less than 1%.

5.4.1.6 Drug content
Drug content was found to be uniform among different batches of tablets and ranged from 98.4±0.5 to 100.7±0.9%. These results showed that the all formulations having percentage drug content within the specified limits as per USP.

5.4.2 IN-VITRO DISSOLUTION STUDIES
5.4.2.1 In-vitro dissolution profile
Dissolution profile (% drug release) of formulations F1, F2, F3.
Table 17: In-vitro dissolution data of Formulation F1, F2, F3.

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F1	F2	F3
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	13.1069	10.6103	11.2344
3		0.30	19.2846	19.9724	19.3482
4		0.45	20.7823	21.8448	20.5965
5		1	21.7832	22.3954	22.5879
6		2	23.8459	23.8674	24.7963
7	pH 6.8 phosphate buffer	4	28.8401	29.8935	36.6958
8		6	36.9757	35.7835	43.6383
9		8	43.8476	43.8123	52.5643
10		12	70.4164	66.8263	63.9698
11		24	95.7068	98.6821	96.3459

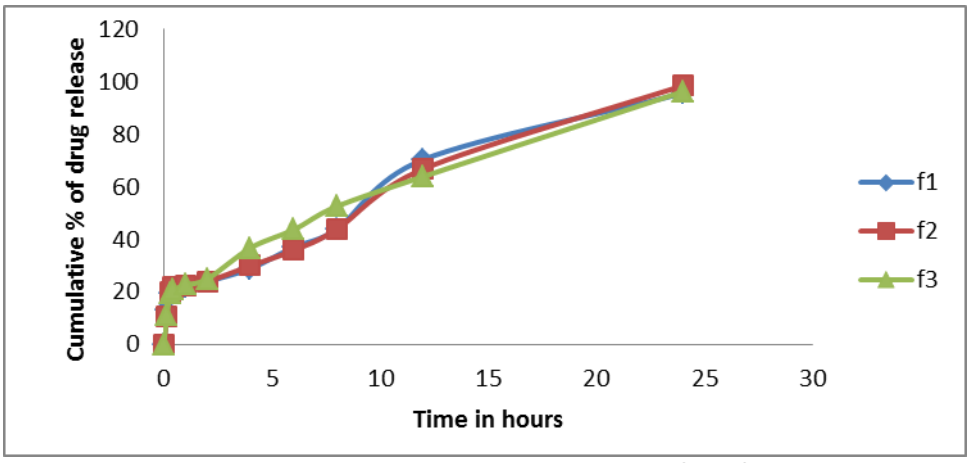


Fig. 13: Cumulative percentage drug release profile of F1,F2,F3.

Dissolution profile (% drug release) of formulations F4, F5, F6.

Table 18: In-vitro dissolution data of Formulation F4, F5, F6.

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F4	F5	F6
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	9.3620	11.8586	11.2344
3		0.30	18.7241	19.3482	19.9724
4		0.45	20.0134	20.5965	20.3498
5		1	20.9986	21.8448	22.3994
6		2	23.5893	23.6735	23.9182
7	pH 6.8 phosphate buffer	4	26.8345	34.2164	29.7834
8		6	33.7256	40.1671	37.8203
9		8	39.8345	45.1260	43.8745
10		12	60.8345	58.5150	57.0274
11		24	88.7643	86.7643	84.7972

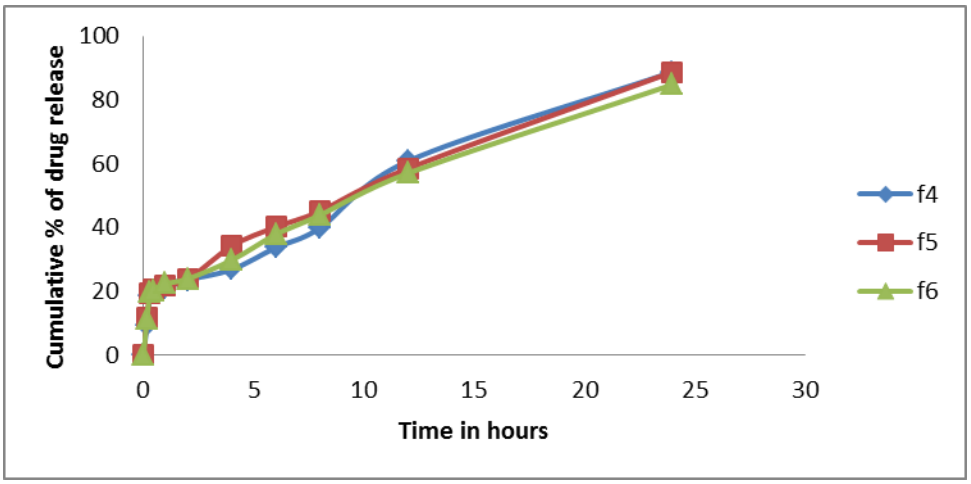


Fig. 14: Cumulative percentage drug release profile of F4, F5, F6.

Dissolution profile (% drug release) of formulations F7, F8, F9.

Table 19: In-vitro dissolution data of Formulation F7, F8, F9.

S.No	MEDIUM	TIME(hrs)	Cumulative % drug release of		
			F7	F8	F9
1	0.1N HCl	0	0.00	0.00	0.00
2		0.15	11.8586	12.4827	11.8586
3		0.30	19.3482	18.1	19.9724
4		0.45	20.7459	20.5965	20.8934
5		1	22.6823	21.8934	21.8347
6		2	23.9823	23.8469	24.7823
7	pH 6.8 phosphate buffer	4	28.8456	27.7823	29.7845
8		6	35.8934	34.8349	36.8934
9		8	42.8934	40.8348	44.8736
10		12	65.8349	65.8934	69.7356
11		24	99.4739	94.2191	96.6986

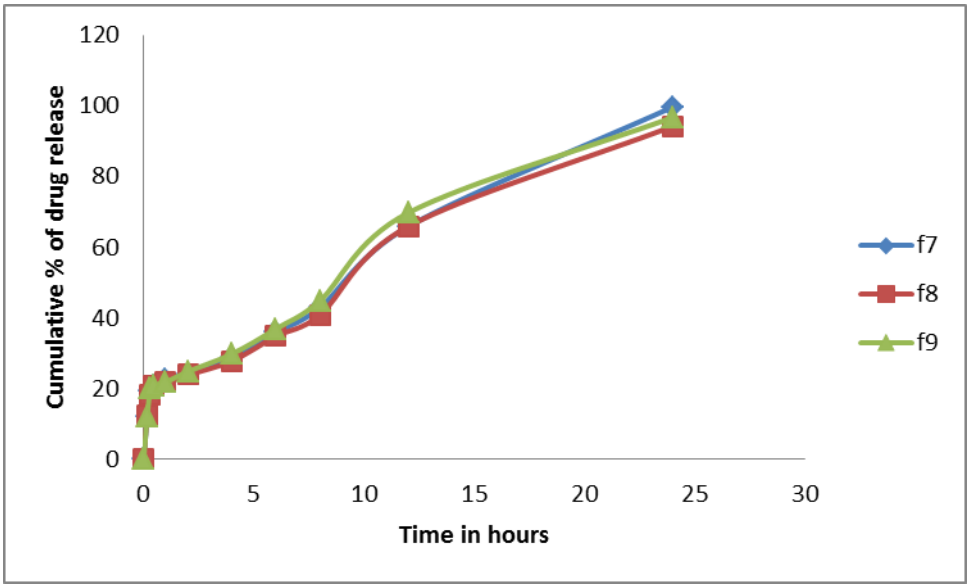


Fig. 15: Cumulative percentage drug release profile of F7, F8, F9.

In-vitro dissolution studies of all the formulation of Sumatriptan succinate bilayer tablets were carried out in 0.1 N HCl for first two hours and in pH6.8 phosphate buffer for next upto 24 hours. The study was performed for 24 hrs and cumulative drug release was calculated at different time interval**.**

The formulation F1, F2 and F3 showed the drug release 95.7068,98.6821, 96.3459 upto 24 hrs but F4, F5 and F6 showed the drug release 88.7643, 86.7643, 84.7972 upto 24 hrs which is having high retarding capacity and due to this the polymer content is decreased in the next three formulations and F7 showed the drug release 99.4739 upto 24hrs and F8,F9 showed the drug release 94.2191, 96.6986% up to 24hours. Hence drug released from F7 formulation shows good retarding capacity and it is considered as the best formulation.

Drug release from all the bilayer tablet formulations followed diffusion control mechanism with R^2 value nearer to one.

5.4.2.2 Kinetics of In-vitro Drug Release

The drug diffusion through most type of polymeric system is often best described by Fickian diffusion (diffusion exponent, n=0.5), but other process in addition to diffusion are important. There is also a relaxation of the polymer chain, which influences the drug release mechanism. This process is described as non- fickian or anomalous diffusion (n=0.5-1.0). Release from initially dry, hydrophilic glassy polymer that swell when added to water and become rubbery, show anomalous diffusion as a result of the rearrangement of macromolecular chain.

The thermodynamics state of the polymer and penetrant concentration are responsible for the different type of the diffusion. A third class of diffusion is case-II diffusion (n=1), which is a special case of non- Fickian diffusion. To obtain kinetic parameter of dissolution profile, data were fitted to different kinetic models.

Table 20: Different Kinetic models for Formulations F1-F9.

Code	Zero order		First order		Higuchi		Korsemayer's-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mgh^{-1/2}$)	R^2	N	
F1	0.9676	0.0166	0.9684	0.0002	0.9742	0.0694	0.9885	0.4032	Peppas
F2	0.9738	0.0164	0.9746	0.0002	0.9778	0.0686	0.9911	0.3970	Peppas
F3	0.9335	0.0162	0.9344	0.0002	0.9745	0.0678	0.9913	0.3775	Peppas
F4	0.9277	0.0136	0.9285	0.0001	0.9681	0.0567	0.9834	0.3596	Peppas
F5	0.9604	0.0137	0.9612	0.0001	0.9719	0.0569	0.9738	0.3475	Peppas
F6	0.9703	0.0138	0.9711	0.0001	0.9722	0.0573	0.9711	0.3482	Matrix
F7	0.9726	0.0169	0.9736	0.0002	0.9602	0.0718	0.9893	0.4051	Peppas
F8	0.9481	0.0293	0.9485	0.0003	0.9911	0.0861	0.9889	0.4462	Matrix
F9	0.8343	0.0296	0.8347	0.0003	0.9882	0.0870	0.9855	0.4476	Matrix

The data obtained from invitro dissolution studies were fitted to zero order, first order, Higuchi, korsmeyers-peppas equation. To confirm the exact mechanism of the drug release korsmeyer and peppas equation superposes

two apparently independent mechanism of drug transport, Fickian diffusion and a case-II transport, for the description of drug release from a swelling polymer.

5.5 STABILITY STUDIES

From the results it was found that formulation F7 is the best formulation amongst the 9 formulations. Thus formulation F7 was selected for stability studies.

5.5.1 Stability studies at the end of First month (30 days)

5.5.1.1 Hardness

The hardness of tablet after one month of stability studies was studied. The results are within the limits. The data is shown in Table 21.

Table 21: Hardness of formulation F1 at the end of 1 month of stability.

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.7±1.6

All the values are expressed as a mean ± SD., n = 6

5.5.1.2 Drug Content

The Percentage drug content of tablet after one month of stability studies was studied. The results are within the official limits. The data is shown in Table 22.

Table 22: Drug content of formulation F7 at the end of 1 month of stability.

S. No.	Formulation	Percentage drug content
1.	F7	99.20 ±1.4

All the values are expressed as a mean ± SD., n = 3.

5.5.1.3 In-vitro dissolution study

The Cumulative percentage drug release from F7 tablet after one month of stability was studied. The data is shown in Table 23.

Table 23: In-vitro dissolution data of formulation F7 at the end of 1 month of stability.

S.No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	11.7210
2	0.30	18.7254
3	0.45	20.26514
4	1	22.3561
5	2	23.0689
6	4	27.1805
7	6	34.0239
8	8	42.1269
9	12	65.0376
10	24	99.0526

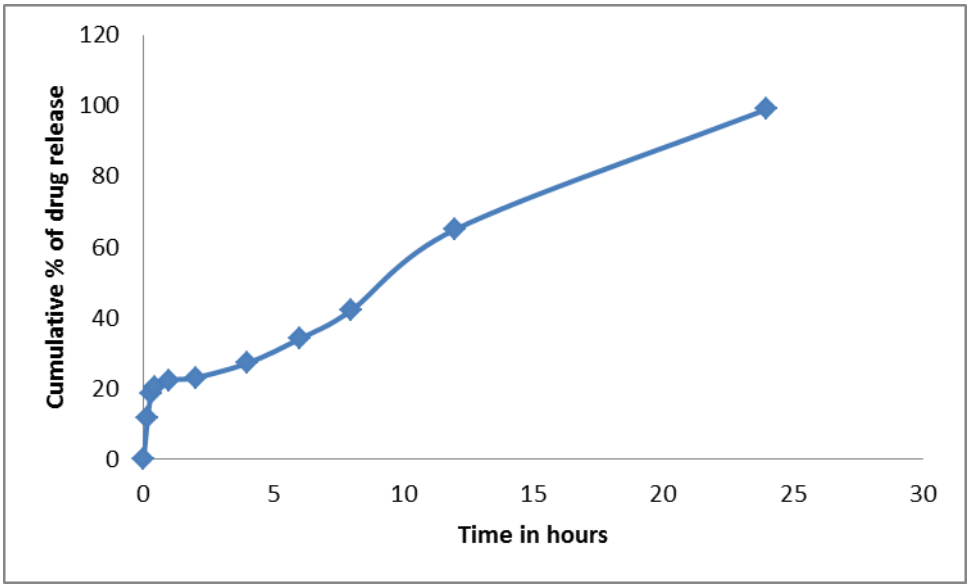


Fig. 25: In-vitro dissolution profile of formulation F7 at the end of 1 month of stability.

5.5.2 Stability studies at the end of Second month (60 days)

5.5.2.1 Hardness

The hardness of tablet after Two months of stability studies was studied. The results are within the limits. The data is shown in Table 24.

Table 24: Hardness of formulation F7 at the end of 2 months of stability.

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.7±0.3

All the values are expressed as a mean ± SD., n = 6.

5.5.2.2 Drug content

The Percentage drug content of tablet after Two months of stability studies was studied. The results are within the official limits. The data is shown in Table 25.

Table 25: Drug content of formulation F7 at the end of 2 months of stability.

S. No.	Formulation	Percentage drug content
1.	F1	99.08 ±0.60

All the values are expressed as a mean ± SD., n = 3.

5.5.2.3 In-vitro dissolution study

The Cumulative Percentage Drug Release from F7 tablet after Two months of stability was studied. The data is shown in Table 26.

Table 26: In-vitro dissolution data of formulation F7 at the end of 2 months of stability.

S.No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	10.8934
2	0.30	18.0657
3	0.45	19.8624
4	1	22.0364
5	2	22.9248
6	4	26.8649
7	6	33.9214
8	8	41.8624
9	12	64.7964
10	24	98.3269

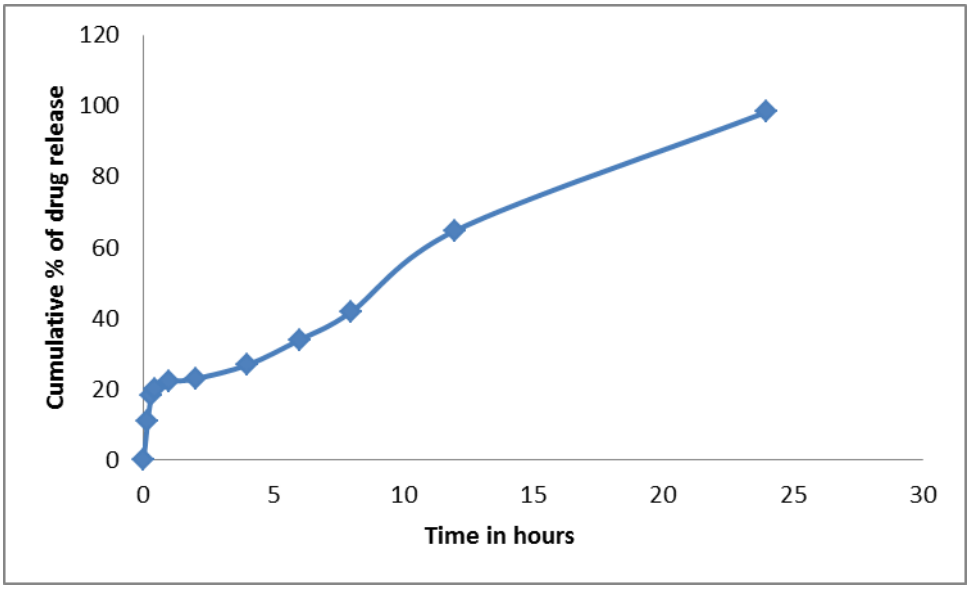


Fig. 26: In-vitro dissolution profile of formulation F7 at the end of 2 months of stability.

5.5.3 Stability studies at the end of Third month (90 days)

5.5.3.1 Hardness

The hardness of tablet after Third months of stability studies was studied. The results are within the limits. The data is shown in Table 27.

Table 27: Hardness of formulation F7 at the end of 3 months of stability.

S. No.	Formulation	Hardness (kg/cm^2)
1.	F7	6.6±1.1

All the values are expressed as a mean ± SD., n = 6.

5.5.3.2 Drug content

The Percentage drug content of tablet after Third month of stability studies was studied. The results are within the official limits. The data is shown in Table 28.

Table 28: Drug content of formulation F7 at the end of 3 months of stability.

S. No.	Formulation	Percentage drug content
1.	F7	98.7±0.8

All the values are expressed as a mean ± SD., n = 3.

5.5.3.3 In-vitro dissolution study

The Cumulative percentage drug release from F7 tablet after Three months of stability was studied. The data is shown in Table 29.

Table 29: In-vitro dissolution data of formulation F7 at the end of 3 months of stability.

S. No	TIME(hrs)	Cumulative % drug release of F7
1	0.15	10.2648
2	0.30	17.9561
3	0.45	19.1359
4	1	21.9624
5	2	22.3219
6	4	26.0364
7	6	33.0934
8	8	40.9632
9	12	64.0329
10	24	98.1298

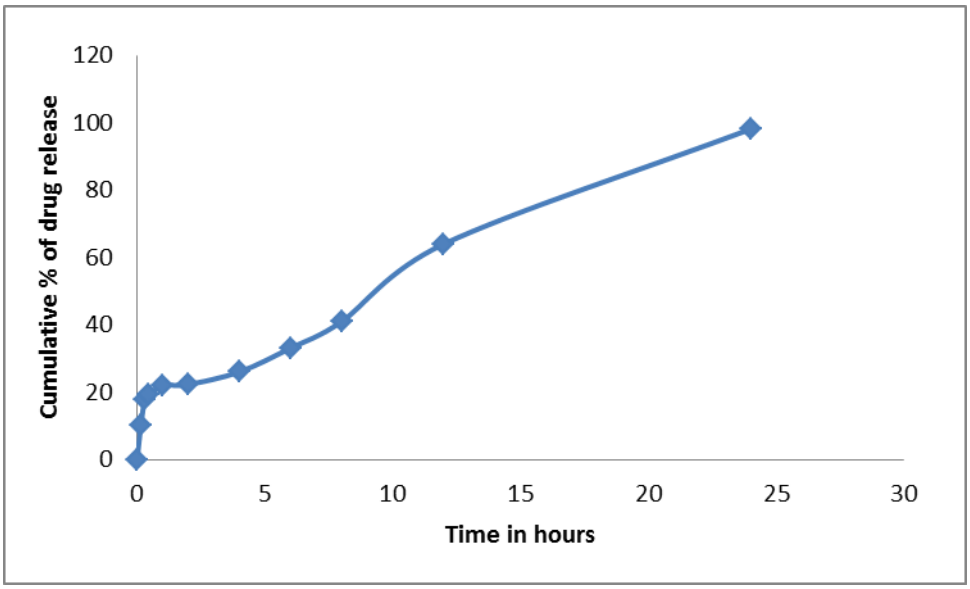


Fig. 27: In-vitro dissolution profile of formulation F7 at the end of 3 months of stability.

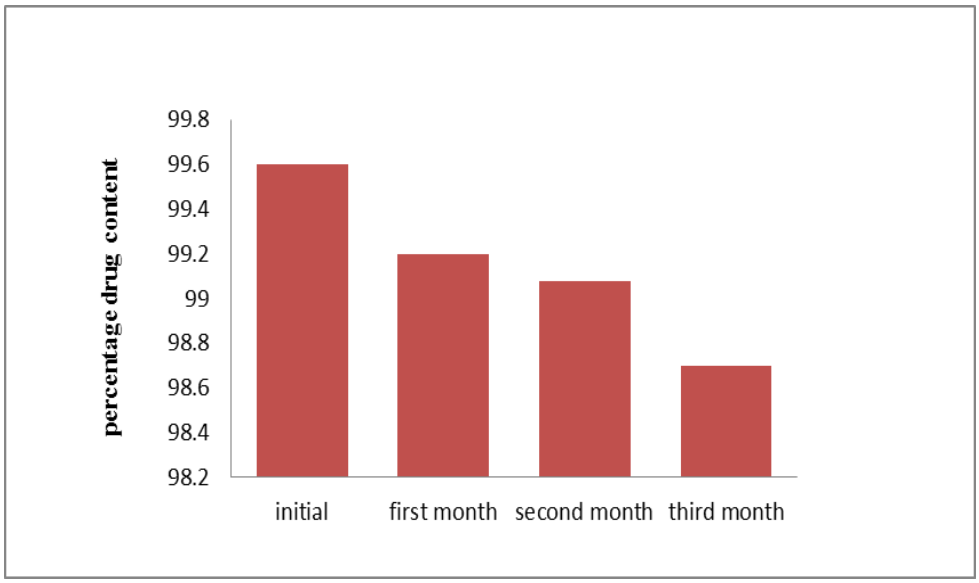


Fig. 28: Comparison of drug content for formulation F7 with initial and different periods of stability.

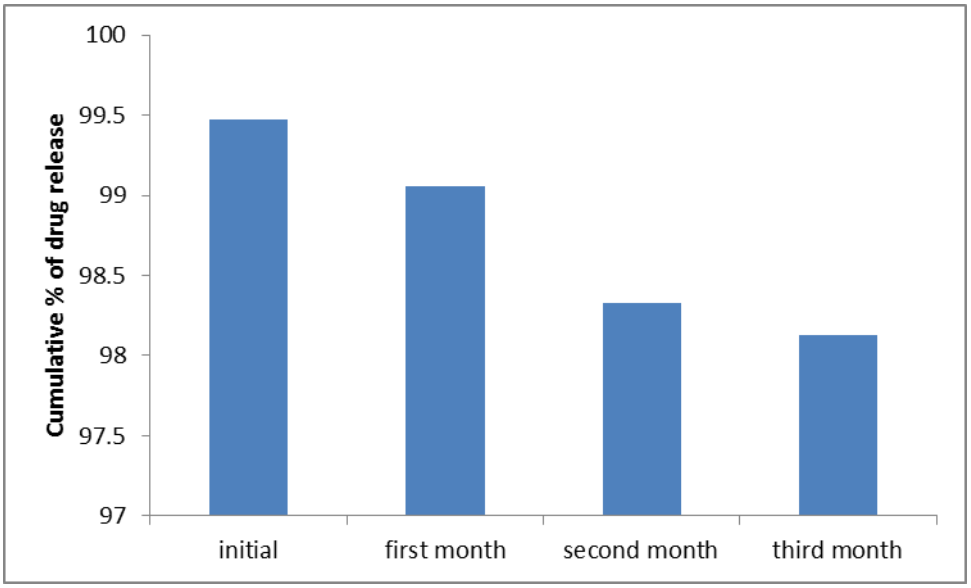


Fig. 29: Comparison of cumulative percentage drug released at the end of 24 hours for formulation F7 with initial and different periods of stability.

No statistically significant differences were observed in Hardness, percentage drug content and cumulative percentage drug release in optimized formulation at the end of three months of stability studies. So it can be concluded that the formulation F7 is stable for short term storage conditions.

SUMMARY

The formulation development and in-vitro evaluation of bilayer drug delivery system of Sumatriptan succinate tablets was performed in the present study.

The bilayer tablets of Sumatriptan succinate were prepared by using polymers like guar gum, xanthan gum, sodium alginate for the treatment of migraine. The dissolution study of F7 bilayer tablets containing guar gum and xanthan gum was concluded the best formulation among other formulations, which showing the most desired drug release. It will be considered as optimized formulation.

The optimized formulation F7 was subjected for stability studies, the formulation was found to be stable in short term stability study.

Preformulation study was carried out for powder blends, it was evaluated to determine the flow characteristics by angle of repose, bulk density, tapped density, carr's index and Hausner's ratio. The data obtained from these studies indicated that the powder blends had good flow properties.

The tablets were prepared with different ratios of polymers by direct compression and wet granulation technique. The formulated tablets were evaluated for physical characterization like thickness, hardness, friability, weight variation and drug content. All the physical parameters of prepared tablets comply with IP specifications.

Evaluation studies of all formulations showed that the drug content, weight variation and friability as per the standards given in IP. The hardness of all formulations was within the limits.

The in-vitro dissolution studies closely indicate that among nine formulations the formulation F7 was found to be the best with good retard of drug release.

The regression correlation co-efficient value was concluded in kinetics modeling of drug dissolution profile for all formulations. The formulation F7 having R^2 value lies between 0.5 to 1.0. Hence it is concluded that formulation F7 following peppas drug release.

From the stability data, it can be concluded that there was no significant changes in any parameters. Hence the formulation F7 is considered to be highly stable formulation.

The overall studies indicate that polymers Xanthan gum, Guar gum showed satisfactory properties. Among the nine formulations the formulation F7 exhibited optimum drugs release profile. Hence, it is concluded that the formulation F7 will be useful for bilayer drug release.

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