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Formulation and evaluation of bilayered tablets of sumatriptan succinate by using hydrophilic polymers

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ABSTRACT

Bi-layered [1] tablet refers to tablet which contain subunits. In bi-layer [2] tablets, one layer tablet provides immediate release and the other layer acts as sustained release. Sumatriptan is a new class of anti-migraine [3] drugs that selectively activate 5-HT1B/1D receptors and are called triptans. Our objective is to formulate and evaluate the bi-layer tablets of sumatriptan succinate of dose 250mg an anti-migraine drug. In the present case 50 mg of Sumatriptan succinate has to be released immediately and the remaining 200 mg of Sumatriptan succinate has to be released in a sustained manner. The formulations is optimized [4] by incorporating varying composition of polymers such as Sodium alginate, Hydroxy propyl methyl cellulose E15 and Hydroxy propyl methyl cellulose K15.All the excipients are tested for compatibility with model drug. The pre-formulation parameters such as Tapped density, Bulk density, Compressibility index, Hausner's ratio and Angle of repose were analyzed. The Thickness, Hardness, Friability, Disintegration time, Weight variation and Content uniformity was evaluated for core tablets. The In-vitro drug release was performed by using dissolution apparatus-II (USP paddle type) by maintaining temperature of 37oC ± 5°C. Based on the dissolution result F2 trial formulation (containing HPMC E15 and Sodium alginate) was selected as best formulation. The drug release of F2 follows zero-order. The total amount of drug released from the Formulation 2 is the maximum and it reached to about 99.89%.

Key words: 5-HT1B/1D receptors, Bi-layered tablet, API, HPMC K15, HPMC E15.

INTRODUCTION

Migraine [5] is considered as a neurological disease or disorder that is characterized by recurrent moderate to severe headaches along with symptoms of autonomic nervous system. Bi-layered tablet is an alternative to the oral [6] drug administration. This system is mainly used to administer fixed dose combinations of different APIs are prolong the drug product life cycle and fabricate novel drug delivery systems such as Chewing device, Buccal [7] Mucoadhesive delivery systems [8, 9] and Floating [10] tablets for gastro-retentive drug delivery. They help to control the delivery rate of single or different active pharmaceutical ingredients.

Sumatriptan succinate an anti-migraine drug belonging to triptan class, act as agonist for 5-HT1B and 5-HT1D receptors. Its molecular mass is 413.49 mg/ml. Its half-life is about 2.5 hrs. The drug is soluble in 6.8 phosphate buffer, 1.2 HCl buffer, water and methanol. . Its shows its actions by binding to receptors and then adenylate cyclase activity is stopped which results in vasoconstriction and inhibition of sensory (trigeminal) nerve firing and also stops vasoactive neuropeptide release.

The rationale of the work is to develop a bi-layered tablet of Sumatriptan succinate which is used to treat chronic migraine [11, 12] patients as they experience the headache (migraine) for a long time i.e. about 2 hrs. The sustained layer is formulated by using hydrophilic polymers so that it maintains the bio-availability and also therapeutic concentration of drug in blood and for quick relief immediate layer is formulated.

MATERIALS AND METHODS

a)Materials:
Sumatriptan was obtained as a gift samples from CADILA HEALTH CARE Ltd. Sodium alginate, Hydroxy propyl methyl cellulose (HPMC K15 &HPMC E15), pvpk-30, Starch, Povidone, CCS, SSG, Talc, Magnesium stearate, was purchased from S.D. Fine Chem. Ltd. Mumbai. Analytical chemicals and solvents were used.

b)Methods:
Preparation of calibration curve of sumatriptan succinate (1.2 pH HCl buffer and 6.8 pH phosphate buffer [13] :
100mg of Sumatriptan succinate was accurately weighed and transferred into a 100ml volumetric flask which contains 50ml buffer solution (1.2 PH HCl buffer or 6.8 PH phosphate buffer). It was dissolved and the volume was made up to the mark by using buffer solution (1.2 PH HCl buffer or 6.8 PH phosphate buffer). This gives stock solution-A.

From the stock solution-A to take 1ml and transferred into a 100ml volumetric flask containing 50ml of buffer solution (1.2 PH HCl buffer or 6.8 PH phosphate buffer) and mixed well and the volume was made up to the mark by using buffer solution (1.2 PH HCl buffer or 6.8 PH phosphate buffer). This gives stock solution-B.

From the stock solution-B take 2ml, 4ml, 6ml, 8ml and 10ml of solution was transferred into 10ml volumetric flasks which give concentrations of 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml and 10µg/ml respectively of respective buffer.

I. Pre-formulation studies:
Pre-formulation is considered as important phase where researcher characterizes the physical, mechanical and chemical properties of new drug substance which helps to develop stable, effective and safe dosage forms. Not only for drug, but also they check possible interaction with various excipients. The following data must be considered for the pre-formulation studies.

A. Organoleptic properties:
i. Colour: A small quantity of Sumatriptan succinate was taken in a butter paper and viewed in well-illuminated place.
ii. Taste and odour: Very less quantity of Sumatriptan succinate was used to get the taste with the help of tongue as well as smelled to get the odour.
iii. Physical characteristics:

1. Solubility studies of Sumatriptan succinate:
An excess quantity of Sumatriptan succinate was taken separately and added in 10ml of different solutions (methanol, alcohol, phosphate buffer and water). These solutions were shaken well for few minutes. Then the solubility was observed.

2. Micromeritic properties evaluation:
The loose bulk density (LBD) and tapped bulk density (TBD) of Sumatriptan succinate were determined using a Bulk density testing apparatus. Angle of repose of Sumatriptan succinate was assessed by the fixed funnel method. Carr's index and Hausner's ratio were calculated using TBD and LBD values. Then again the micromeritic properties of these two drugs were checked with the addition of various fillers.

2.1. Bulk density:
It is considered as the ratio of total mass of powder to the bulk volume of powder. It was measured by using the weighed powder (passed through standard sieve #20) pouring into a measuring cylinder and then its volume was measured by dropping the cylinder onto a wooden surface 3 times from a particular height. This volume is called the bulk volume. From this, the bulk density is calculated. It is expressed in g/cc and is given by:

$$\rho_b = \frac{w}{V_b}$$

Where,
w = mass of the powder
Vb = bulk volume of powder

2.2. Tapped density:
It is considered as the ratio of total mass of powder to the tapped volume of powder. It was measured by using the weighed powder (passed through standard sieve #20) pouring into a measuring cylinder and then it is tapped for about 200 times or more until constant volume was achieved. From this, the tapped density is calculated using the formula mentioned below. It is expressed in g/cc.

$$\rho_t = \frac{w}{V_t}$$

Where,
w = mass of the powder
Vt = tapped volume of powder

2.3. Flow properties (Angle of Repose (θ):
Angle of repose is considered as the maximum angle that is possible between the surface of a pile of powder and the horizontal plane. It was determined by using funnel method. Take 10gm of powder and transfer it into the funnel keeping the orifice of the funnel blocked by using the thumb. The lab jack was adjusted in such a way that the lower plate will maintain about a 6.4mm gap from the bottom of the funnel stem and from top of the pile. When the powder is emptied from the funnel, the height of pile (h) and the radius of base (r) were measured by using the ruler. The procedure was repeated for about 3 times and then the average value was noted down. The angle of repose was calculated by using equation.

$$\theta = \tan^{-1}\left(h/r\right)$$

Where,
θ = angle of repose
h = height of the heap
r = radius of the heap

Table-1: Relationship between angle of repose (θ) and powder flow

S. No	Angle of repose(θ)	Type of flow
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Very poor

2.4. Measurement of Powder Compressibility:
i. Compressibility Index:
Compressibility index is used to measure potential strength of a powder which could build up in its arch in a hopper and also the ease with which such an arch could be broken. Compressibility index was determined by Carr's consolidation index:

$$CI(\%) = \frac{tappeddensity - poureddensity}{tappeddensity} * 100$$

Table-2: Carr's index as an indication of granule flow properties

S. No	% CI	Flow Property
1	5-12	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-25	Poor
5	33-38	Very poor
6	>40	Very very poor

ii. Hausner's Ratio:

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5 and it was determined by the following formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured density}}$$

Table-3: Hausner's ratio as an indication of granule flow properties

S. No	Hausner's ratio	Properties
1	1.00 - 1.11	Excellent
2	1.12 - 1.18	Good
3	1.19 – 1.25	Fair
4	1.26 – 1.34	Passable
5	1.35 – 1.45	Poor
6	1.46 – 1.59	Very poor
7	>1.60	Extremely poor

II. Formulation:

A. Blend preparation of immediate release [14] layer:

1. Sifting: Sumatriptan succinate, sodium starch glycolate, Mannitol, microcrystalline cellulose was sifted through 40 mesh sieve.

2. Dry mixing: Sumatriptan succinate was mixed with sodium starch glycolate and then the materials of step 1 were added and mixed for 15 min.

3. Pre-lubrication: Talc was sifted through 40 # sieve and added to the above mixture and mixed.

4. Lubrication: Magnesium stearate was sifted through 60 # sieve and added to the above mixture and mixed well.

Table-4: Composition of Sumatriptan succinate Immediate Release [15] Layer

Ingredients	Amount in mg/tablet
Sumatriptan succinate	50 mg
Sodium starch glycolate	10 mg
Microcrystalline cellulose	15 mg
Mannitol	20 mg
Magnesium stearate	3 mg
Talc	2 mg
Total	100mg

B. GRANULES PREPARATION OF SUSTAINED RELEASE [16] LAYER:

1. Sifting: Sumatriptan succinate, Sodium alginate, Hydroxyl propyl methyl cellulose K4M, Hydroxyl propyl methyl cellulose K100M, starch, Mannitol, Povidone (K-30) were sifted through 40 mesh sieve (stage 1).

2. Granulation:

a. Dry mixing: First the drug, polymer and Povidone (K-30) were taken in a mortar and mixed well. Then starch was added to the above mixture and mixed and to it Mannitol was added and mixed well.

b. Granulation: Granules were prepared by adding isopropyl alcohol.

c. Drying: The produced Sumatriptan succinate granules were dried in air Oven at 50°c.

3. Sieving: Dried granules were passed through 20 mesh sieve.

4. Lubrication: Sifted granules were transferred to a blender. Magnesium stearate and talc which were sifted through 60 mesh sieve were added to the granules and mixed gently for 2 min.

Tablet-5: Composition of Sumatriptan succinate Sustained Release [17] Layer

S.No	Ingredients(mg)	F1	F2	F3	F4	F5
1.	Sumatriptan succinate	200	200	200	200	200
2.	Sodium alginate	-	25	25	50	-
3.	HPMC K 15	25	-	25	-	-
4.	HPMC E 15	25	25	-	-	50
5.	Starch	40	40	40	40	40
6.	Magnesium stearate	5	5	5	5	5
7.	Talc	3	3	3	3	3
8.	Mannitol	94	94	94	94	94
9.	PVP	8	8	8	8	8
10.	Total	400	400	400	400	400

III. Drug-Excipient Compatibility Studies by FTIR:

Infrared spectroscopy is considered as one of the most powerful analytical techniques to identify functional groups of a drug.

Method:

Compatibility study was performed by the preparation of compatibility blends at different ratios of different excipients with the drug, based on their tentative average weight. These blends that are prepared were stored at the accelerated condition of 400C and 75% RH and control samples will be stored at 400C. The ratio of drug to excipient will be varied from 1:1 to 1:10 depending on the purpose of their use and so the samples were kept in double lined poly bags. Then samples were evaluated for the change in their physical characteristics with reference to its control sample which are stored at 400C for about period of 15 days. In the present study, the potassium bromide disc (pellet) method was employed. Chemical stability was confirmed by FTIR spectrometry.

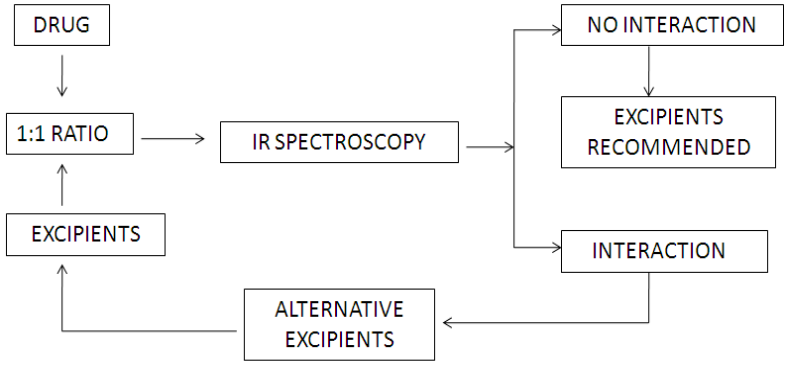

Fig-1: Drug-Excipient Compatibility Studies by FTIR

IV. POST-COMPRESSION PARAMETERS:

1. Hardness:

Hardness indicates the ability to withstand mechanical shocks while handing. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. About five tablets will be randomly selected and then hardness of the tablets was determined.

2. Friability test:

The friability of tablets will be generally determined by using Roche friabilator. It is expressed in percentage (%). About twenty tablets were initially weighed (Wi) and transferred into friabilator. The friabilator was operated at 25rpm for 4min or run up to 100 revolutions. The tablets were weighed again (Wf). The % friability was then calculated by:

$$\%\mathbf{Friability} = \frac{\mathbf{Wt(initial)} - \mathbf{Wt(final)}}{\mathbf{Wt(initial)}} * \mathbf{100}$$

3. Uniformity of weight (Weight variation test):

20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±3%). The percentage deviation was calculated using the following formula:

$$\%\ \mathbf{Deviation} = \frac{\mathbf{Individual\ Weight} - \mathbf{Average\ weight}}{\mathbf{Average\ Weight}} * \mathbf{100}$$

Table-6: Weight variation of tablet

Average weight of a tablet	Percentage deviation
130 mg or less	±10
>130 mg and <324 mg	±7.5
324 mg or more	±5

4. Disintegration [18] test:
The disintegration time for immediate release layer was determined using the disintegration test [19] apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000ml of purified water maintained at 37±20C and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

5. Drug content:
Twenty tablets were weighed and transferred into a mortar, crushed them into fine powder and mixed well. The sample powder equivalent to 250 mg of drug was accurately weighed and transferred to a 100 ml volumetric flask. About 50 ml of phosphate buffer of p^H 6.8 was added and sonicated to dissolve. The volume was made up to the mark with diluent and mixed well. 1 ml of this solution was diluted to 100ml with the same diluent and mixed. Then the amount of drug was determined by measuring the absorbance of the solution using UV-Visible spectrophotometer.

6. In-vitro drug release study:

Apparatus	**:**	Dissolution Apparatus USP Type II (Paddle)
Medium	**:**	pH 1.2 HCl Buffer for 2hours and then Phosphate buffer of pH 6.8
Volume	**:**	900ml
Speed	**:**	50 rpm
Time intervals	**:**	5, 10, 15, 30min, 1, 2, 4, 6, 8, 10, 12hr.
Temperature	**:**	37±20C
Equipment	**:**	UV-Visible spectrophotometer
Wavelength	**:**	226nm

Procedure:
The dissolution test apparatus was kept as per the above conditions. One tablet was placed in each dissolution bowl and the apparatus was run. After specified time interval, 5ml of liquid was withdrawn from the zone midway between the top of rotating paddle and surface of dissolution medium and 1cm away from the wall of jar. The solution was filtered through 0.45µ membrane filter, rejecting the first few ml of the filtrate into a separate test tube. Further 1ml was diluted to 10ml with the dissolution medium. Again 1ml of resulting solution was diluted to 10ml with dissolution medium and mixed well. The instrument was switched on and stabilized. The instrument was made up to zero and then the absorbance of blank and sample was measured at 226nm using the dissolution medium as blank.

7. Calculation:
The % drug release of Sumatriptan succinate present in the tablet was calculated by using the formula:

$$Amount\ dissolved = \frac{Obsorbance\ obtained * Amount\ of\ dissolution * Dilution\ factor * Standard\ concentration}{Standard\ obaorbance * 1000}$$

$$Percentage\ dissolved = \frac{Amount\ dissolved}{Total\ drug} * 100$$

8. DATA ANALYSIS (CURVE FITTING ANALYSIS)
To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as:
1. Cumulative percentage drug released Vs time (*In – Vitro* drug release plots).
2. Cumulative percentage drug released Vs Square root of time (Higuchi's plots).
3. Log cumulative percentage drug remaining Vs time (First order plots).
4. Log percentage drug released Vs log time (Peppas plots).

i. Higuchi release model:
To study the Higuchi release kinetics, the release rate data were fitted to the following equation,

$$\mathbf{Q_t = K.t^{1/2}}$$

Where,
Q_t-The amount of drug release
K- Release rate constant and

t - Release time

When the data is plotted as a cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

ii. Korsmeyer and Peppas release model:

The drug release data was fitted to the following equation,

$$M_t/M_\infty = K.t^n$$

Where,

M_t/M_∞ - The fraction of drug release,
K - The release rate constant,
t - The release time,
n - The diffusion exponent for the drug release.

When the data is plotted as log % of drug released vs log time,

The 'n' value is used to characterize different release mechanisms as given in the following table:

Table-7: Different release mechanisms.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anamolous (non – Fickian) diffusion
0.89	Case – II transport
n > 0.89	Super case – II transport

iii. Zero order release kinetics:

To study the zero – order release kinetics, the release data was fitted to the following equation:

$$Q_t = Q_0 + K_0 t$$

Where,
Qt- The amount of drug released
Q0- The initial amount of drug in solution, it is usually zero
K0- The release rate constant and
t - Release time

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the data obeys zero – order release kinetics, with a slope equal to Ko.

iv. First order release kinetics:

To study the first – order release kinetics, the release data was fitted to the following equation:

$$\log Q_t = \log Q_0 + \frac{Kt}{2.303}$$

When the data is plotted as log cumulative % drug release versus time, it yields a line with slope K.

RESULTS AND DISCUSSION

A. Pre-formulation studies of sumatriptan succinate:

1. Calibration curve for pH-1.2 HCl buffer

Table-8: Standard curve of pH-1.2 HCl buffer limits

Data	Result
Medium	HCl Buffer
λmax	226 nm
R2	0.9992

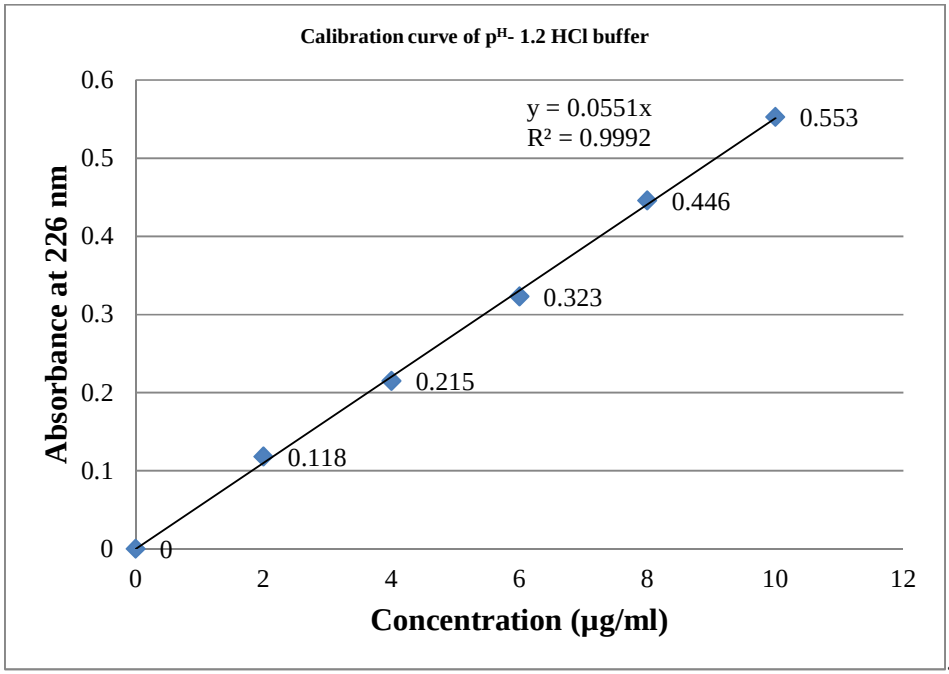

Fig-2: Calibration curve of pH- 1.2 HCl buffer

Table-9: Absorbance of pH-1.2 HCl buffer

S. No	Concentration (µg/ml)	Absorbance at 226 nm
1	2	0.118
2	4	0.215
3	6	0.323
4	8	0.446
5	10	0.553

2. Calibration curve for pH -6.8 Phosphate Buffer:

Table-10: Standard curve of pH-6.8 phosphate buffer limits

Data	Result
Medium	Phosphate Buffer
λmax	226 nm
R2	0.9995

Table-11: Absorbance of pH - 6.8 phosphate buffer

S. No	Concentration (µg/ml)	Absorbance at 226 nm
1	2	0.246
2	4	0.456
3	6	0.695
4	8	0.929

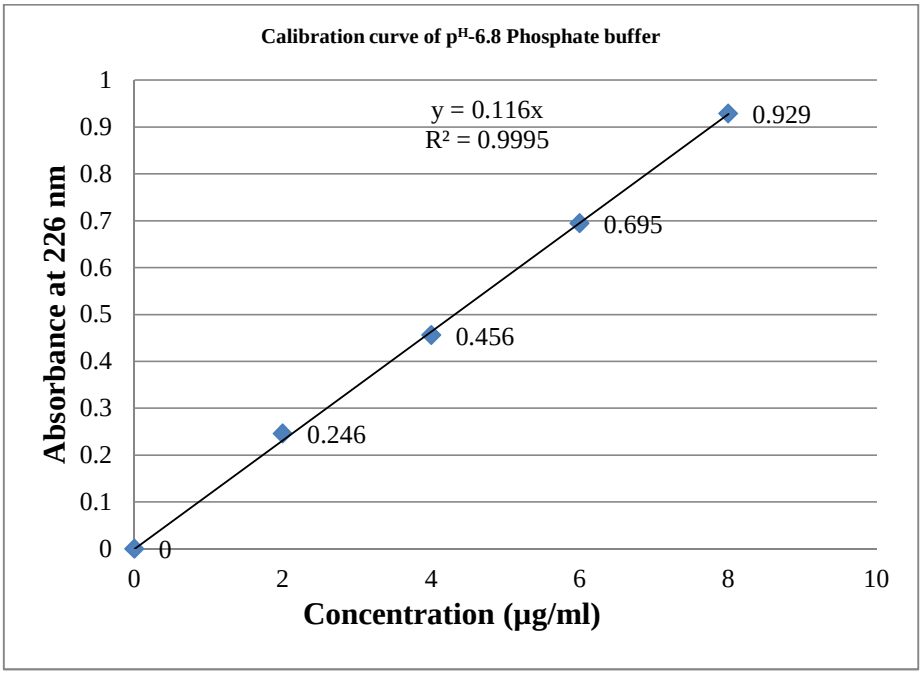

Fig-3: Calibration curve of pH - 6.8 phosphate buffer

B. Pre-formulation evaluations [20]:

1. Organoleptic properties:

i. **Colour:** The colour was found to be white to off-white.

ii. **Taste & odour:** Sumatriptan succinate was found to be bitter in taste and odourless.

2. Physical characteristics:

i. **Solubility:** Sumatriptan succinate was found to be soluble in water

Table-12: Different solvents and their concentrations

Solvent	Concentration
Water	0.388
Phosphate buffer	0.176
Ethanol/Methanol	0.122

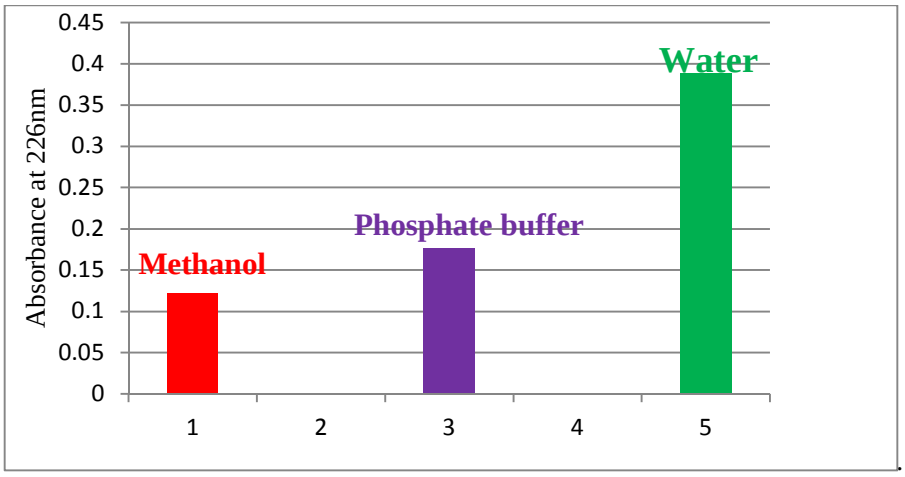

Fig-4: Solubility of sumatriptan succinate in different solvents

ii. Loss on drying:

Table-13: Loss on drying of Sumatriptan succinate

Sl. No	Test	Specification	Observations
1	Loss on drying	Not more than 0.5%	0.3%

iii. Micromeritic properties:

Table-14: Evaluation [21] of micromeritic properties of Sumatriptan succinate

S.No	Material	Bulk density (g/cc)	Tapped density(g/cc)	%Carr's index	Hausner's ratio	Angle of repose
1	Sumatriptan succinate	0.625 g/cc	0.833 g/cc	24.96	1.3328	38.6

Table-15: Evaluation of granules of Sumatriptan succinate sustained release layer

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(θ)	Carr's index (%)	Hausner's ratio
F1	0.29±0.00	0.35±0.01	26.71±2.07	21.54±1.03	1.27±0.01
F2	0.30±0.00	0.37±0.01	25.27±1.53	21.43±1.05	1.27±0.01
F3	0.30±0.00	0.34±0.00	17.90±0.48	15.65±0.44	1.18±0.006
F4	0.33±0.01	0.37±0.00	23.74±2.45	15.41±1.21	1.18±0.01
F5	0.30±0.01	0.37±0.02	23.81±4.83	19.37±2.53	1.24±0.03

Table-16: Evaluation of Sumatriptan succinate immediate release layer

Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio
0.534±0.01	0.948±0.04	43.84±1.783	44.2±3.83	1.794±0.12

iv. pH of solution:

The pH of Sumatriptan succinate solution was found to be 9.63, 4.21 to 5.67 and 12.

C. Drug - excipient compatibility studies by FTIR:

Table-17: Interpretation of sumatriptan by FTIR

Group	Type of stretching	Range cm-1	Observed range cm-1
N-H	bending	1500-1650	1562.48
C-N	vibration	1000-1400	1294.92
S=O	stretching	1050-1400	1135.60

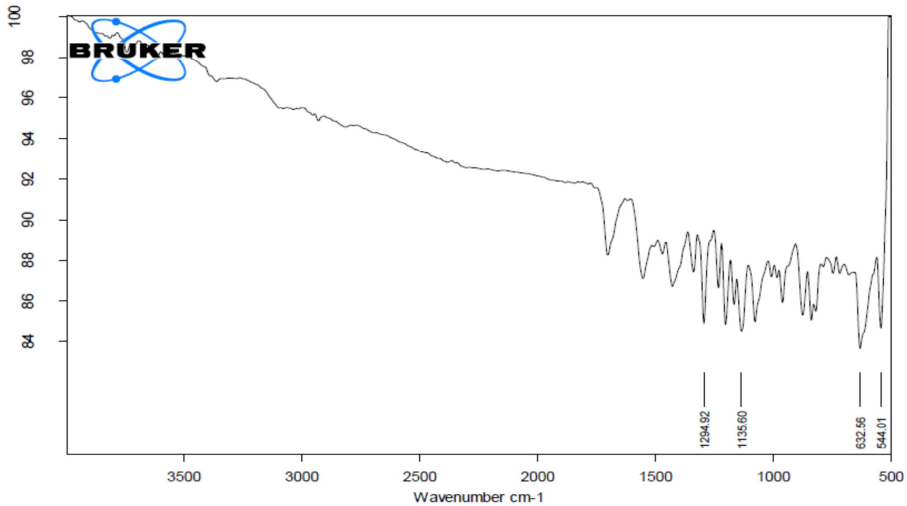

Fig-5: The compatibility study of pure drug of Sumatriptan Succinate

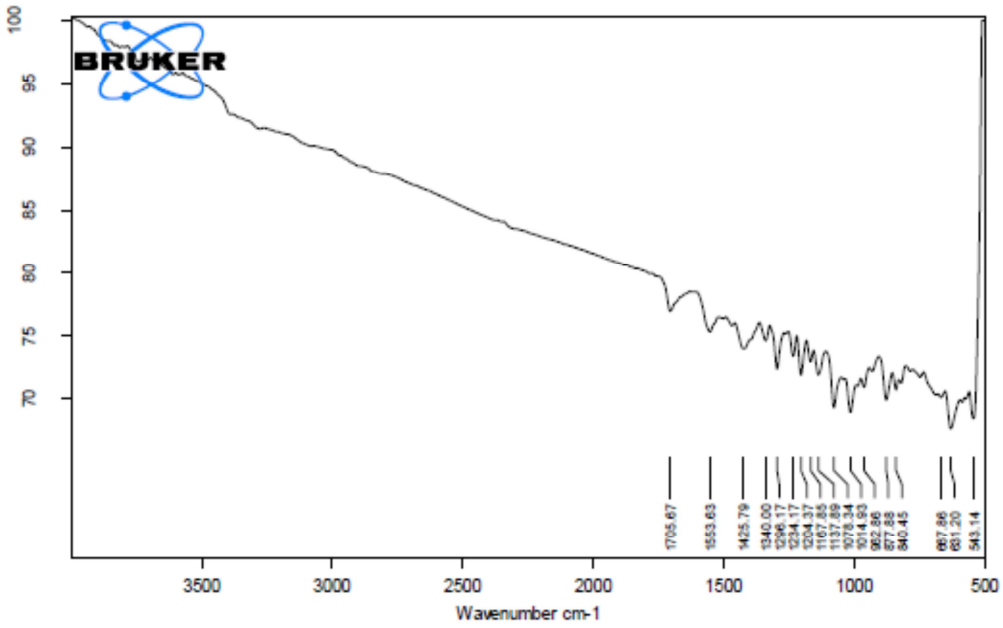

Fig-6: The compatibility study of Formulation 2

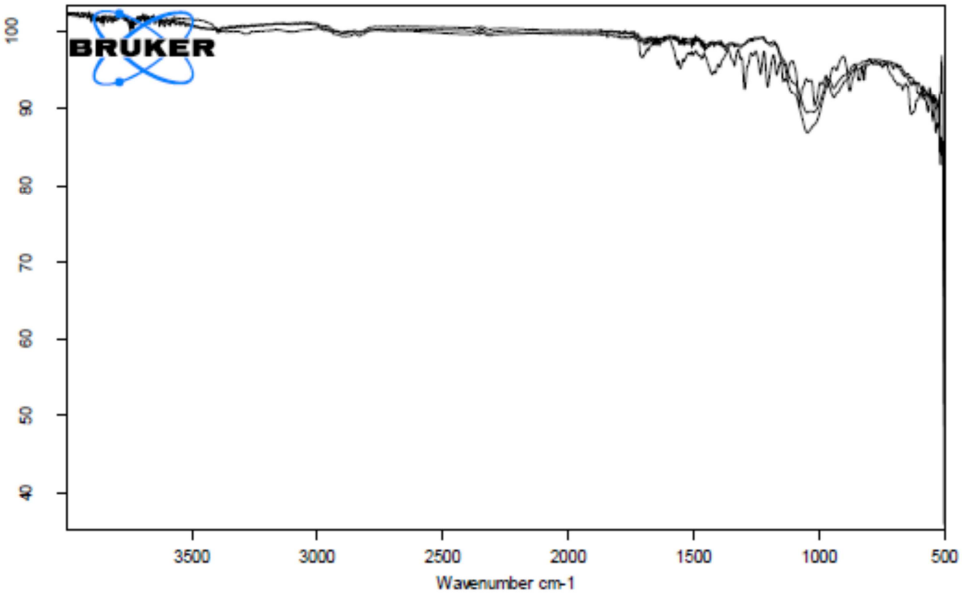

Fig-7: The compatibility study of HPMC E15, HPMC K15 and Formulation 2

D. Post-compression parameters:

i. Physical parameters:

The tablets were evaluated for hardness, friability and weight variation and the results were given in the table.

Table-18: Evaluation [22] of bi-layer tablets of Sumatriptan succinate: F1 to F5

Formulations	Hardness (kg/cm2)	Friability (%)	Weight variation (mg)	Disintegration time (sec)	Drug content (%)
F1	7.8±0.21	0.19	499.85±0.97	71±0.65	98.79±0.38
F2	8±0.36	0.24	501.45±1.15	67±0.69	99.68±0.46
F3	7.2±0.21	0.22	500.75±0.87	71±0.58	97.65±0.51
F4	6.8±0.38	0.18	498.25±1.24	68±0.61	99.95±0.43
F5	7.5±0.25	0.16	500.85±0.96	82±0.84	98.65±0.05

ii. In vitro drug release studies:

The dissolution studies were carried out in pH - 1.2 HCl for 2 hours and then in Phosphate buffer of pH - 6.8.

Apparatus : Dissolution Apparatus USP Type II (Paddle)
Medium : pH - 1.2 HCl for 2 hours and then Phosphate buffer of PH - 6.8.
Volume : 900ml
Speed : 50 rpm
Time intervals : 5min, 10min, 15min, 30min, 1, 2, 4, 6, 8, 10hr and 12hr.
Temperature : 37±0.50C.

Table-19: % dissolved of sumatriptan succinate tablets of F1 to F5

Time (hrs)	% drug released				
	F1	**F2**	**F3**	**F4**	**F5**
5min	28.12	34.84	22.11	24.78	29.43
10min	58.26	61.63	70.30	63.62	67.65
15min	73.61	83.70	75.09	81.04	78.32
30min	87.06	93.04	89.07	86.41	94.40
1	98.45	99.71	95.73	97.11	97.70
2	22.42	17.42	19.28	19.77	21.41
4	37.64	33.57	34.75	32.64	37.49
6	51.12	53.56	59.38	56.73	57.40
8	61.15	69.82	76.91	67.46	69.52
10	87.18	86.15	85.90	74.30	88.74
12	97.12	99.89	96.55	94.51	95.93

Table-20: % pure drug dissolved of sumatriptan succinate tablet

S. No	Time (min)	% pure drug released
1.	5	91.2
2.	10	93.7
3.	15	96.2
4.	30	98.7
5.	60	99.6
6.	90	99.6
7.	120	99.6

Table-21: The cumulative percentage drug release of F1-F5

S. No.	Time (hrs)	Cumulative percentage (%) drug release for 200mg				
		F1	**F2**	**F3**	**F4**	**F5**
1	0	0	0	0	0	0
2	2	44.944	34.944	39.368	40.361	43.726
3	4	75.522	68.521	70.921	66.624	76.512
4	6	102.312	109.312	121.201	115.784	117.152
5	8	122.525	142.525	156.943	137.681	141.888
6	10	174.584	175.829	175.321	151.652	181.112
7	12	194.523	199.784	197.042	192.888	195.784
8	**R2**	0.985	0.9964	0.9782	0.9794	0.9837

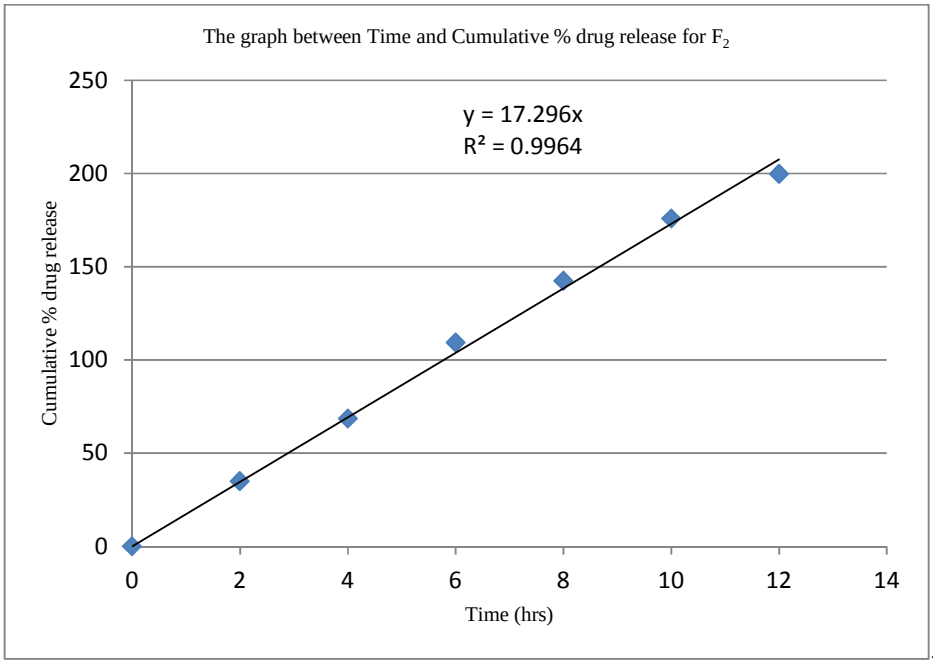

Fig-8: The zero order of Formulation 2 (F2)

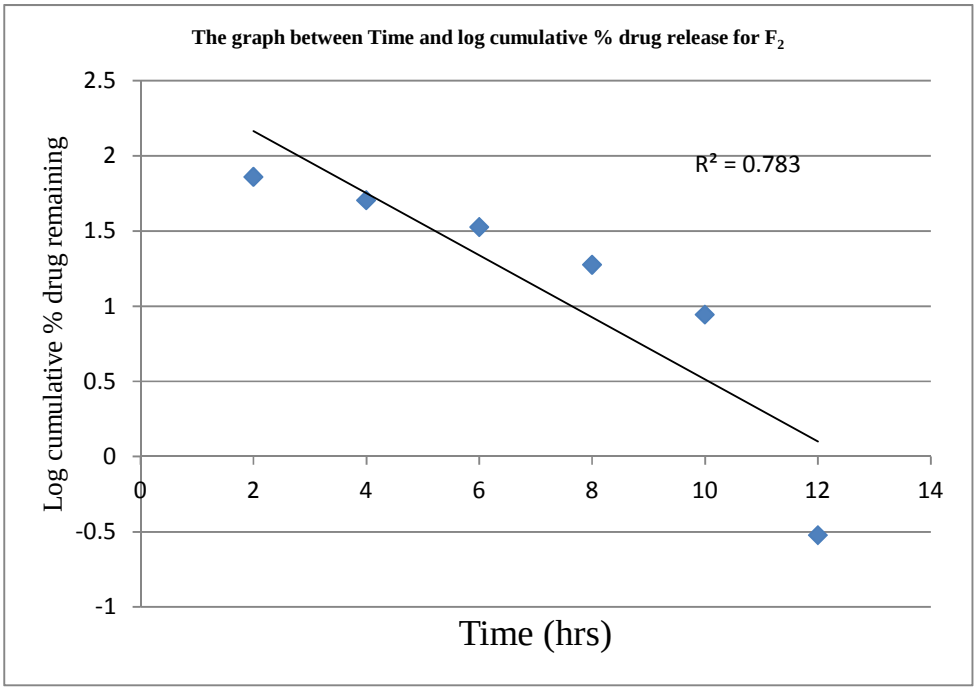

Fig-9: The first order of Formulation 2 (F2)

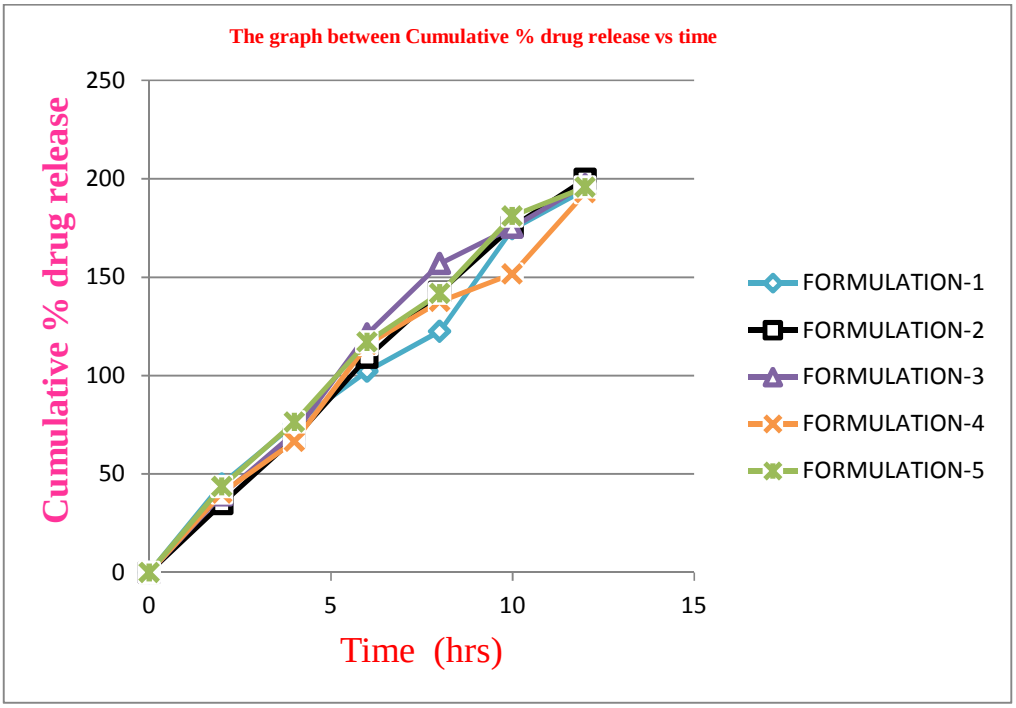

Fig-10: The zero order of Formulation 1 to Formulation 5 (F1 – F5)

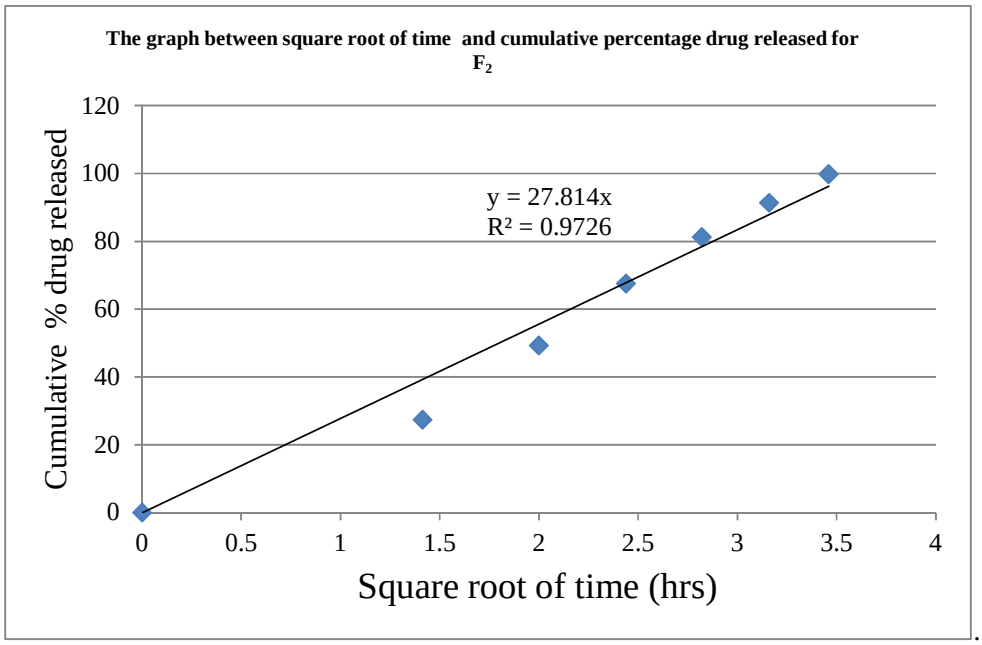

Fig-11: The graph of Higuchi model of Formulation 2 (F2)

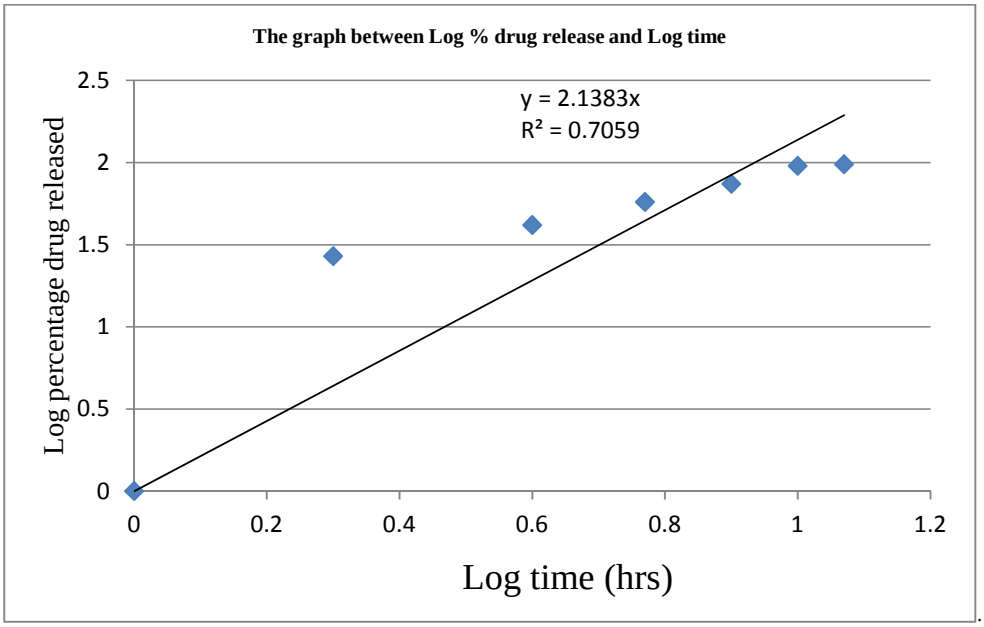

Fig-12: The graph of Peppas model of Formulation 2 (F2)

Table-22: The Regression (R2) time of Formulation 2 (F2)

Formulation	Zero order	First order	Higuchi	Peppas
F2	R2	R2	R2	R2
	0.9964	0.783	0.9726	0.7059

DISCUSSION

In the present work we prepared bi-layered tablet of sumatriptan succinate which contains sustained layer (layer-1) and immediate layer (layer-2). We prepared five formulations with varying concentrations of polymers such as sodium alginate, HPMC K15 and HPMC E15 in sustained layer and sodium starch glycolate was used in an immediate layer as super disintegrant. Sustained layer is prepared by using wet granulation method and immediate layer is prepared by using direct compression method.

The calibration curve of Sumatriptan succinate is carried out in both 1.2 pH HCl buffer and 6.8 pH Phosphate buffer. The absorbance is measured at the λmax of about 226nm. The regression value of pH 1.2 HCl buffer is 0.9992, where as the regression value of pH 6.8 Phosphate buffer was found by 0.9995.

The solubility studies were carried out in various solvents such as water, ethanol and phosphate buffer. The solubility sumatriptan succinate (mg/ml) in water, phosphate buffer and ethanol are found to be 0.338, 0.176 and 0.122 respectively.

The micromeritic properties of sustained and immediate layer of all the five formulations are:
1. The bulk density of the sustained layer found to be in the range between 0.29-0.33 and for immediate layer is 0.54.
2. The tapped density values for all the formulations sustained layer ranges between 0.34-0.37 and for immediate layer is 0.94.
3. The angle of repose values for all the formulations sustained layer ranges between 17.9-26.7. According to standard values 25 to 30 indicates the flow is good and less than 25 indicates the flow is excellent. For immediate layer the value is 43.8 and according to standard, the value is greater than 40, so it indicates poor flow.
4. The Carr's index values for all the formulations sustained layer ranges between 15.4-21.5. According to standard values 12 to 16 the flow is good and 18 to 22 indicate the flow is passable. For immediate layer the value is 44.2 and according to standard greater than 40 indicates very poor flow.

5. The Hausner's ratio values for all the formulations of sustained layer ranges between 1.18-1.27. According to standard values 1.18 to 1.25 the flow is fair it indicates flow is fair. For immediate layer the value is 1.74 and according to standard greater than 1.6 is very poor flow. With this the granules of SR layer were found to be free flowing materials by the addition of small amounts of glidants to improve the flow if necessary and showed suitability to be compressed as tablets of expected weight.

The drug – excipient compatibility studies were conducted by using FTIR. There is a no appearance or disappearance of any characteristic peaks. So there is no interaction between drug and excipients were found. The compatibility of formulations was satisfactory.

Evaluation of bilayered tablets:
Then all the formulations of bi-layered tablets fulfil the official requirements of uniformity of dosage units. The average percentage of deviation of 20 tablets of each formula was less than +5 to -5%.

1. The Hardness values for all the formulations range between to 6.8-8.0 kg respectively.
2. The Friability values for all five formulations of bi-layered tablets are found to be between 0.16-0.24percent respectively.
3. The Weight variation values for all five formulations of bi-layered tablets are found to be between 498-501mg respectively.
4. The disintegration time for all five formulations of bi-layered tablets is found to be between 67-82 seconds respectively.
5. The drug content (%) for all five formulations of bi-layered tablets are found to be between 97.6-99.9 respectively.
6. The formulation 1 contains Drug, HPMC K15and HPMC E15 in the ratio of 1:0.125:0.125 and its result of the invitro drug release (dissolution studies) were found to be 97.12.
7. The Formulation 2 contains Drug, sodium alginate and HPMC E15 in the ratio of 1:0.125:0.125 and its result of the invitro drug release (dissolution studies) were found to be 99.89.
8. The Formulation 3 contains Drug, sodium alginate and HPMC K15 in the ratio of 1:0.125:0.125 and its result of the invitro drug release (dissolution studies) were found to be 96.55.
9. The Formulation 4 contains Drug and sodium alginate in the ratio of 1:0.25 and its result of the invitro drug release (dissolution studies) was found to be 94.51.
10. The Formulation 5 contains Drug and HPMC E15 in the ratio of 1:0.25 and its result of the invitro drug release (dissolution studies) was found to be 95.93.
11. The zero-order regression values of the fives formulations F1, F2, F3, F4 and F5 were found to be 0.985, 0.996, 0.978, 0.979 and 0.983. Due to the above results the formulation 2 is considered as the best formulation. The remaining results of the formulation 2 such as regression values of Peppas and Higuchi plot were found to be 0.973 and 0.983 respectively.
12. The in-vitro drug release for sustained release (layer-1) was about 99.87% in 12 hrs for F2 formulation and for immediate layer (layer-2) it is 99.71% in one hour. Hence of its satisfactory values F2 is considered as the optimized formulation.

CONCLUSION

1. In vitro drug release studies recommended the product for further in vivo [23] studies and stability studies and which may improve patient compliance.
2. From the literature it was known that sumatriptan is used as conventional [24] dosage form in the treatment of migraine. Combination of immediate release layer and sustained release layer improve the patient compliance.
3. From the result F2 has been selected as best formulation among all the other formulation. F2 provide better in vitro release from layer one and two (1 & 2).
4. The data obtained from in vitro release study was fitted to various mathematical models like Zero order, First order, Higuchi model and Peppas model.

The result of mathematical fitting of data obtained indicated that, the best fit model in all the cases was found to be diffusion for optimize formulation F2. Thus the release of the drug from the dosage form was found to be Zero order kinetics.

CONCLUSION

1. This work involves the formulation development, optimization and invitro evaluation [25] of bi-layer tablet containing sumatriptan succinate as immediate release and sustained release layers. In which sodium starch glycolate used as super disintegrant and the hydrophilic matrix formers such as sodium glycolate, hydroxy propyl methyl cellulose (HPMC K15) and hydroxy propyl methyl cellulose (HPMC E15) for immediate release layer.
2. Bi-layered tablet showed the initial burst effect in order to release dose of immediate release layer and then followed by sustained layer release of Sumatriptan for nearly 12hrs indicating the promising potential of bi-layer tablet of Sumatriptan succinate to consider as an alternative to the conventional dosage form for treatment of migraine.
3. To minimize the critical process parameter, direct compression method was selected for the formulation of sumatriptan succinate immediate layer.
4. Under the pre-formulation studies API characterization and drug – excipient compatibility studies were carried out.
5. The polymer and other excipients are selected based on the satisfactory results produced during drug-excipient compatibility studies to develop new formulation.
6. The invitro study showed that the formulation F2 was ideally suited to be sustained release formulation.
7. The final suitable formulation was achieved fruitfully by wet granulation technique for layer-1 and direct compression for layer-2.
8. HPMC E15, sodium alginate and drug in the ratio of 25:25:200 produced desired release profile for Sumatriptan succinate sustained release layer as per in hours specification.

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