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Design and Development of Acetriptan Fast Dissolving Tablets by Different Techniques

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ABSTRACT

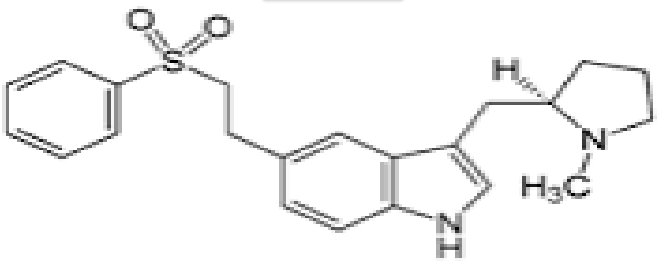
A common complaint about the difficulty in swallowing of the tablet is the taste of tablets. Geriatric, Pediatric, traveling patients who may not have ready access to water are need of easy swallowing dosage forms. The demand for fast dissolving tablets (FDT) has enormously increased during the last decade, particularly for geriatric and Pediatric patients who experience difficulty in swallowing conventional oral dosage forms. In the present work, fast dissolving tablets of Acetriptan were prepared by direct compression method, sublimation method and effervescent methods. The tablets prepared by direct compression method possess a weight variation in the range 97 to 103 mg which is below 7.5%, hardness of 7.4 to 10.1Kg/cm², Percentage friability of 0.37 to 0.78%, disintegration time of 1.4 to 1.6, drug content uniformity was in between 98.60 to 101.10 %. From FTIR and DSC studies results reveals is no interaction between drug and any other formulation excipients. Stability study results reveal that no change in Disintegration, Wetting time, the content of tablets prepared by direct compression and effervescent method. There is a decrease in Disintegration, and Wetting time of tablets prepared by the sublimation method. It may be due to the formation of more pores on tablets after stability. The results concluded that fast dissolving tablets of Acetriptan showing enhanced dissolution will improve bioavailability and by using the sublimation method by using the sublimation method.

INTRODUCTION:

Many patients find difficult to swallow a tablet and hard gelatin capsule, consequently, they do not take medication as prescribed. It is estimated that 50% of the population is affected by this problem which results from a high incident of in compliance and ineffective therapy[5]. The difficulty is experienced in particular by Pediatric and geriatric patients, but it also applied to People who are ill in bed and those actively working patients who are busy or traveling, especially those who have no access to water[6].

Acetriptan is well absorbed after oral administration. The terminal elimination half-life of acetriptan is approximately 4 hours. The means bioavailability of Acetriptan is approximately40%. Drug release usually the rate limiting process for absorption of a Biopharmaceutics. Acetriptan is a BCS class compound displaying poor solubility. Acetriptan reduces the hyperglycemia, hyperinsulinemia, and hypertriglyceridemia characteristic. The metabolic changes produced by Acetriptan result in increased responsiveness of insulin-dependent tissues and are observed in numerous animal models of insulin resistance.

Acetriptan:



IUPAC Name: 3-[2-(dimethyl amino) ethyl]-n-methyl-1H-indol-

-5 -methane sulphonamide butane-1, 4dioate

Empirical Formula: $C_{12}H_{19}Cl_3O_8$

Molecular Weight: 382.52 g/mol

The faster the drug into solution, the quicker the absorption and onset of clinical effect. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than those observed from conventional tablets dosage form.

Patil BS. Et al[81] Formulated mouth dissolving tablets of Atenolol by direct compression method. The two super disintegrants used in this study were croscarmellose sodium and sodium starch glycolate. The prepared batches of the tablet were evaluated for uniformity of weight, thickness, hardness, friability, wetting time, water absorption ratio, and disintegration time and dissolution study. Using the same excipients, the tablets were also prepared, without disintegrants and were evaluated in a similar way. From the results obtained, it can be concluded that the tablet formulation (A4) showed a promising formulation.

The present research investigation is planned with the following objectives:

- To formulate fast dissolving tablets of Acetriptan.
- To evaluate the formulations with respect to various physical parameters.
- To evaluate the formulations with respect to content uniformity, in-vitro release studies, etc.
- Drug crystalline nature was checked by XRD studies.
- To characterize the formulation by instrumental methods like FTIR and DSC.
- To perform the pre and post stability studies on promising formulations.

MATERIALS AND METHODS:

Table No. 1: Material used

Sr. No.	Material	Source
1.	Acetriptan	Gift sample from Astra Zeneca Pharmaceuticals, Bangalore.
2.	Croscarmellose sodium	Gift sample from Lobo chemicals, Mumbai.
3.	Crospovidone	Gift sample from Merck Limited, Mumbai.
4.	Sodium starch glycolate	Gift sample from Merck Limited, Mumbai.
5.	Mannitol	SD Fine ChemiLtd, Mumbai.
6.	Camphor	SD Fine Chemi. Ltd., Mumbai.
7.	Aspartame	Gift sample from Cipla, Kurkhumb.
8.	Magnesium stearate	SD Fine Chemi Ltd., Mumbai.
9.	Talc	SD Fine Chemi Ltd, Mumbai.
10.	Potassium Dihydrogen Pthalate	SD Fine Chemi Ltd, Mumbai.
11.	Sodium hydroxide	SD Fine Chemi Ltd, Mumbai.

METHODS:

Analytical methods for estimation of Acetriptan:

Identification of drug was carried out by FTIR (JASCO FT/IR-5300). Standardization of the drug was carried out by using UV visible spectrophotometer (T_{80}UV/VIS-Spectrophotometer).

Determination of λ_{max} for Acetriptan:

A 5mcg/ml of Acetriptan in phosphate buffer pH 6.8was scanned in UV range between 200-400 nm. Acetriptan showed maximum absorbance at 282 nm (Fig.1) in phosphate buffer pH 6.8. Thus 282 nm was used as wavelength (λmax) for further analysis.

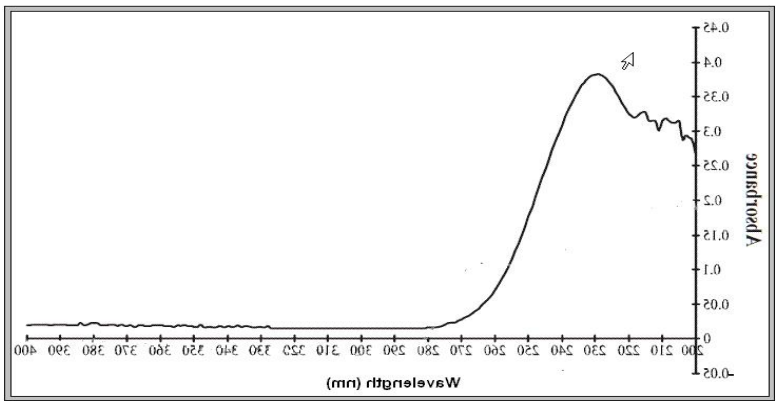


Figure No. 1: UV Spectrum of Acetriptan in pH 6.8-phosphate buffer

Procedures:

100mg of pure drug transferred into 100ml of distill water in a volumetric flask. Withdrawn 10ml from this solution and diluted to 100ml it makes 100mcg/ml (stock solution) then concentration made by withdrawing from stock solution and diluted to 10ml it makes solution of concentration 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml. From the standard curve of Acetriptan (table no.2, Fig.2), it was observed that the drug obeys Beer's law in the concentration range of 10–50µg/ml in phosphate buffer pH 6.8. The linear regression equation generated was used for the calculation of the amount of drug.

Table No. 2: Standard calibration curve of Acetriptan in 6.8 pH

Buffer solution at λ_{max} 282 nm

Sr. No.	Concentration(mcg/ml)	Absorbance(nm)
1.	00	0.000
2.	10	0.192
3.	20	0.390
4.	30	0.591
5.	40	0.791
6.	50	0.933

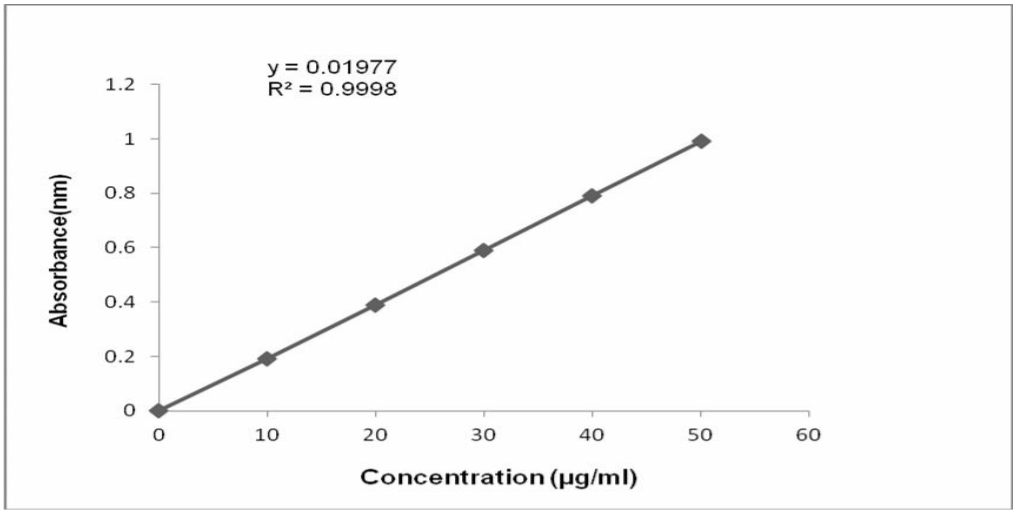


Figure No. 2: Standard calibration curve of Acetriptan in 6.8 pH buffer solutions at λ_{max} 282nm.

Pre-formulation Study:

I) Pre-compression parameters:

a) The angle of repose.

b) Bulk density.

c) Tapped density.

d) Hausner's ratio.

e) Compressibility index (%)

II) Drug-polymer interaction study:

a) FTIR studies.

b) DSC studies.

Methods of Preparation Fast Dissolving tablets:

1. Direct compression method.
2. Sublimation method.
3. Effervescent method.

Preparation of fast dissolving tablets by direct compression technique:

Method: Fast dissolving tablets of Acetriptan were prepared by direct compression method according to the formula given in table no.3

All the ingredients were passed through 40 mesh sieve separately. The drug and microcrystalline cellulose were mixed by a small portion of both each time and blending it to get a uniform mixture kept aside. Then the ingredients were weighed and mixed in geometrical order and tablets were compressed of 6mm sizes flat round punch to get tablet using Rimek Compression Machine.

Table No. 3: Formula of Acetriptan fast dissolving tablets prepared by direct compression method (1-tablet)

Ingredients(mg)	Formulations code											
	ADP_1	**ADP2**	**ADP_3**	**ADP_4**	**ADC_1**	**ADC_2**	**ADC_3**	**ADC_4**	**ADS_1**	**ADS_2**	**ADS_3**	**ADS_4**
Acetriptan	20	20	20	20	20	20	20	20	20	20	20	20
Crosprovidone	3	6	9	12	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	-	3	6	9	12	-	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	3	6	9	12
MCC(AvicelPH-102)	10	10	10	10	10	10	10	10	10	10	10	10
D-Mannitol	64	61	58	55	64	61	58	55	64	61	58	55
Aspartame	1	1	1	1	1	1	1	1	1	1	1	1
Mgstearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total Weight	100	100	100	100	100	100	100	100	100	100	100	100

Sublimation method:

Method: Fast dissolving tablets of Acetriptan tablets were prepared by the sublimation method, according to the formula given in table no 4. The basic principle involved in preparing fast dissolving tablets by sublimation technique is inert solid ingredients (E.g. urea, sodium bicarbonate, ammonium carbonate, camphor, menthol) were added to other tablet excipients and the blend was compressed into a tablet.

Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. The tablets dissolve within 10-20 seconds and exhibit sufficient mechanical strength for practical use. Twelve formulations were developed by varying concentration of subliming agent i.e. camphor. Accurately weighed ingredients were sifted through sieve no. 44 and thoroughly mixed for 10 min and magnesium stearate and other ingredients were added to the blend and thoroughly mixed. The tablets were compressed using Rimek tablet punching machine. The compressed tablets were then subjected to sublimation at 80°C for 30 min. The tablets were evaluated for disintegration time and mean tablet weight.

Schematics figure of sublimation method for the design of mouth dissolving tablets

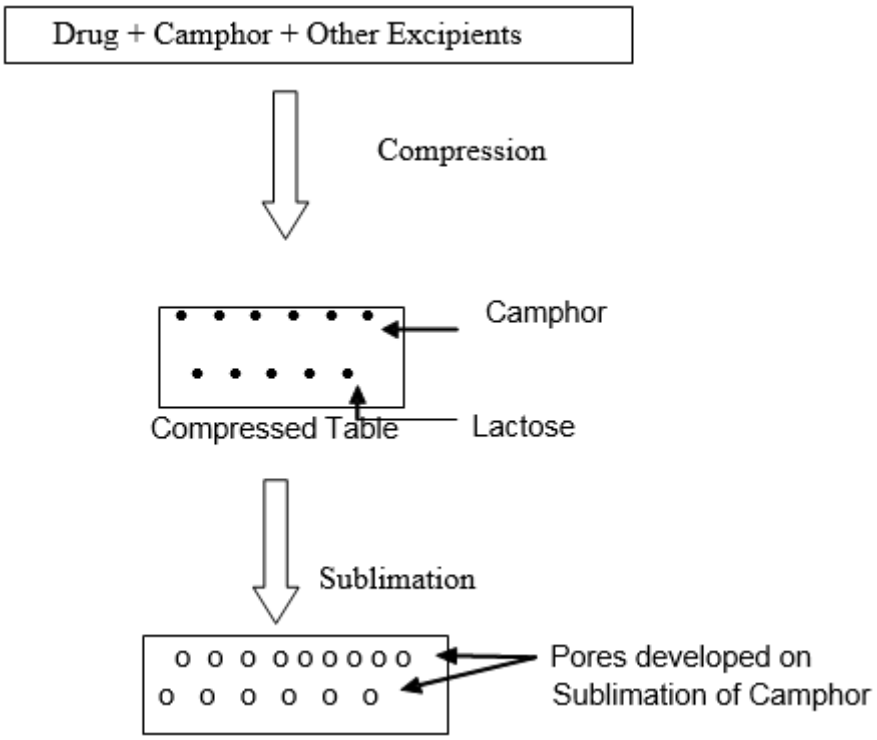


Table No. 4: Formula of Acetriptan fast dissolving tablets prepared by sublimation Method (1 tablet)

Ingredients(mg)	Formulation code				
	AS_1	**AS_2**	**AS_3**	**AS_4**	**AS_5**
Acetriptan	20	20	20	20	20
Croscarmellose sodium	6	6	6	6	6
Mannitol	57	55	53	51	49
Microcrystalline cellulose	10	10	10	10	10
Camphor	2	4	6	8	10
Aerosil	1	1	1	1	1
Aspartame	2	2	2	2	2
Mgstearate	1	1	1	1	1
Talc	1	1	1	1	1
Total Weight	100	100	100	100	100

Effervescent method:

Method: Fast dissolving tablets prepared by the effervescent method according to the formulae given in the tables-5.

All the ingredients were passed through #60 sieves separately. The drug and directly compressible excipient were mixed by adding a small portion of each at a time and blending it to get a uniform mixture and kept aside. Sodium bicarbonate and tartaric acid were pre-heated at temperature of $80^{O}C$ for 2 hrs to remove absorbed/residual moisture and thoroughly mixed in a mortar to get uniform powder and then added to the above blend. Then the other ingredients were mixed in geometrical order in an inflated polyethylene pouch, but magnesium stearate and talc were added at the last and mixed for further two minutes.

Table No. 5: Formula of Acetriptan fast dissolving tablets prepared by Effervescent Method (1 tablet)

Ingredients(mg)	Formulation code							
	AE_1	**AE_2**	**AE_3**	**AE_4**	**AE_5**	**AE_6**	**AE_7**	**AE_8**
Acetriptan	20	20	20	20	20	20	20	20
Croscarmellose sodium	6	6	6	6	6	6	6	6
Sodium bicarbonate	3	6	9	12	3	6	9	12
Citric acid	3	6	9	12	-	--	--	--
Tartaric acid	--	--	--	--	3	6	9	12
Aspartame	2	2	2	2	2	2	2	2
Mannitol	54	48	42	36	54	48	42	36
Microcrystalline cellulose	10	10	10	10	10	10	10	10
Talc	1	1	1	1	1	1	1	1
Magnesium stearate	1	1	1	1	1	1	1	1
Total weight	100	100	100	100	100	100	100	100

RESULTS AND DISCUSSION:

The pre-compression by direct compression, sublimation, and Effervescent methods.

Table No. 6: Pre-compression parameters of direct compression method

Formulation code	Bulk density* (g/cc) ±SD, n=3	Tapped density* (g/cc) ±SD, n=3	Angle of repose* (degree)±SD, n=3	Carr's index* (%)±SD, n=3	Hausner's ratio*±SD, n=3
ADP_1	0.53 ± 0.15	0.62 ± 0.03	28.56 ± 1.55	15.10 ± 0.75	1.17 ± 0.04
ADP2	0.53 ± 0.13	0.64 ± 0.01	26.38 ± 1.35	16.63 ± 0.67	1.18 ± 0.07
ADP_3	0.50 ± 0.01	0.59 ± 0.02	24.19 ± 0.09	15.00 ± 0.58	1.17 ± 0.01
ADP_4	0.49 ± 0.06	0.60 ± 0.02	28.59 ± 1.56	17.13 ± 1.29	1.20 ± 0.03
ADC_1	0.51 ± 0.07	0.62 ± 0.02	26.09 ± 1.23	16.83 ± 1.57	1.20 ± 0.02
ADC_2	0.54 ± 0.09	0.64 ± 0.02	26.41 ± 1.20	15.04 ± 0.60	1.17 ± 0.04
ADC_3	0.51 ± 0.02	0.62 ± 0.03	25.71 ± 1.42	17.53 ± 1.23	1.21 ± 0.01
ADC_4	0.50 ± 0.01	0.59 ± 0.01	26.01 ± 0.13	14.35 ± 1.51	1.16 ± 0.01
ADS_1	0.51 ± 0.06	0.59 ± 0.01	27.41 ± 1.49	14.45 ± 1.36	1.16 ± 0.03
ADS_2	0.52 ± 0.06	0.62 ± 0.02	29.21 ± 1.01	16.05 ± 1.56	1.19 ± 0.03
ADS_3	0.50 ± 0.05	0.60 ± 0.02	26.61 ± 1.25	16.22 ± 1.29	1.19 ± 0.03
ADS_4	0.51 ± 0.02	0.61 ± 0.01	27.50 ± 1.10	16.45 ± 1.89	1.19 ± 0.03

* Average of three determinations

Table No.7: Pre-compression parameters of sublimation method

Formulation code	Bulk density* (g/cc)±SD, n=3	Tapped Density* (g/cc) SD, n=3	Angle of repose* (degree)±SD, n=3	Carr's Index* (%) SD, n=3	Hausner's Ratio* SD, n=3
AS_1	0.49 ± 0.06	0.58 ± 0.01	29.31 ± 1.30	15.96 ± 1.03	1.18 ± 0.03
AS_2	0.50 ± 0.06	0.61 ± 0.01	27.29 ± 1.27	17.95 ± 1.23	1.21 ± 0.03
AS_3	0.52 ± 0.06	0.63 ± 0.01	25.42 ± 1.20	16.56 ± 1.89	1.19 ± 0.03
AS_4	0.51 ± 0.06	0.59 ± 0.01	26.51 ± 1.45	14.47 ± 1.36	1.16 ± 0.03
AS_5	0.52 ± 0.06	0.62 ± 0.02	29.17 ± 1.01	16.05 ± 1.56	1.19 ± 0.03

* Average of three determinations

Table No. 8: Pre-compression parameters of the effervescent method

Formulation code	Bulk density* (g/cc)±SD, n=3	Tapped Density* (g/cc) SD, n=3	Angle of repose* (degree)±SD, n=3	Carr's Index* (%) SD, n=3	Hausner's Ratio* SD, n=3
AE_1	0.53 ± 0.13	0.64 ± 0.01	26.38 ± 1.35	16.63 ± 0.67	1.19 ± 0.07
AE_2	0.51 ± 0.07	0.60 ± 0.01	25.14 ± 0.57	15.75 ± 0.63	1.18 ± 0.05
AE_3	0.50 ± 0.06	0.60 ± 0.02	26.61 ± 1.25	16.22 ± 1.29	1.19 ± 0.03
AE_4	0.51 ± 0.06	0.61 ± 0.01	28.11 ± 1.58	16.31 ± 1.02	1.18 ± 0.02
AE_5	0.49 ± 0.06	0.58 ± 0.01	27.21 ± 1.60	14.59 ± 1.75	1.17 ± 0.03
AE_6	0.51 ± 0.06	0.62 ± 0.02	29.21 ± 1.15	18.85 ± 1.56	1.20 ± 0.03
AE_7	0.53 ± 0.06	0.63 ± 0.02	24.09 ± 1.01	14.82 ± 1.25	1.17 ± 0.03
AE_8	0.50 ± 0.06	0.61 ± 0.01	27.29 ± 1.27	14.95 ± 1.23	1.21 ± 0.03

* Average of three determinations

Figure No. 3: Tablets prepared by Direct compression, Sublimation & Effervescent Method.

Results for Drug Polymer Interaction Studies:

FTIR Studies:

The IR spectrum of pure Acetriptan revealed the presence of a peak at

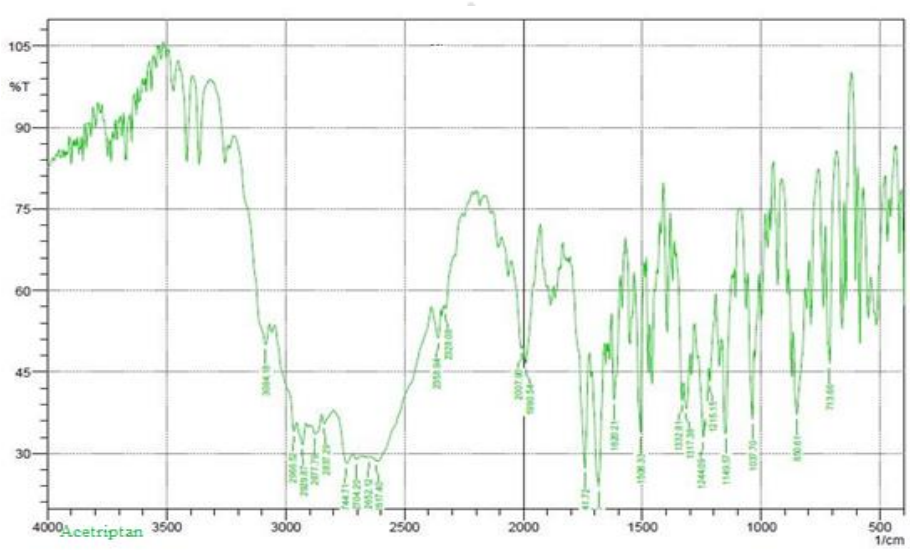


Figure No. 4: IR Spectra Acetriptan

3084/cm due to N-H stretching while Peaks at 2927 and 2740/cm corresponds to CH stretching. Strong absorption peaks were observed in 1742 and 1691/cm that are assigned to drug sulphonyl stretching vibration (S=O). A Peak at 1614/cm indicates the aromatic ring and a Peak at 1244/cm is due to C-O-Ar group.

Results of Post-Compressional Parameters

Hardness:

All methods were maintained within the 2.40 kg/cm^{2}to 4.00 kg/cm^2. The mean hardness test results are tabulated in table no. 9.

Friability test:

The friability was found in all designed formulations in the range 0.12 to 0.81% to be well within the approved range (<1%). The friability study results were tabulated in table no 9.

Weight variation test:

The weight variations were found in all designed formulations in the range 97 to 103mg. The mean weight variation test results are tabulated in table no 9. All the tablets passed weight variation test as the average percentage weight variation was within± 7.5%i.e. in the pharmacopoeial limits.

Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 2.12±0.12 mm to 3.38±0.21 mm. The standard deviation values indicated that all the formulations were within the range. The results of thickness for tablets were shown in table no. 9.

Table No. 9: Post-compressional parameters of tablets prepared by Direct compression, Sublimation & Effervescence method

Formulation Code	Hardness * (Kg/cm²)±SD	Friability (%)	Thickness* (mm)±SD	Weight variation * (mg)±SD
ADP_1	3.0 ± 0.17	0.45	3.05 ± 0.19	100 ± 1.57
ADP2	3.5 ± 0.25	0.37	3.10 ± 0.25	099 ± 1.29
ADP_3	3.3 ± 0.27	0.60	3.15 ± 0.05	099 ± 1.30
ADP_4	3.0 ± 0.05	0.63	3.25 ± 0.10	097 ± 0.78
ADC_1	2.7 ± 0.12	0.51	3.24 ± 0.30	102 ± 0.93
ADC_2	2.6 ± 0.17	0.59	3.10 ± 0.09	102 ± 0.08
ADC_3	2.4 ± 0.20	0.65	2.86 ± 0.08	098 ± 0.08
ADC_4	2.5 ± 0.21	0.67	2.65 ± 0.07	103 ± 0.06
ADS_1	2.7 ± 0.11	0.53	3.11 ± 0.03	098 ± 0.08
ADS_2	2.9 ± 0.25	0.78	2.81 ± 0.03	100 ± 0.06
ADS_3	2.6 ± 0.10	0.65	3.25 ± 0.08	099 ± 0.07
ADS_4	3.0 ± 0.10	0.56	3.38 ± 0.10	098 ± 0.13
Post -compressional parameters of tablets Prepared by sublimation method				
AS_1	3.9 ± 0.07	0.12	2.17 ± 0.06	099 ± 0.06
AS_2	3.8 ± 0.09	0.45	2.34 ± 0.09	099 ± 0.03
AS_3	3.8 ± 0.09	0.59	3.18 ± 0.15	098 ± 0.64
AS_4	3.6 ± 0.06	0.81	2.45 ± 0.07	101 ± 0.06
AS_5	3.4 ± 0.04	0.54	2.12 ± 0.04	100 ± 0.05
Post - compressional parameters of tablets Prepared by the effervescent method				
AE_1	3.9 ± 0.02	023	2.49 ± 0.04	099 ± 0.52
AE_2	3.2 ± 0.32	0.29	3.25 ± 0.09	100 ± 1.49
AE_3	3.6 ± 0.12	0.62	2.62 ± 0.01	102 ± 1.22
AE_4	3.6 ± 0.21	0.15	2.65 ± 0.05	100 ± 0.70
AE_5	4.0 ± 0.21	0.52	3.29 ± 0.12	100 ± 0.61
AE_6	3.5 ± 0.10	0.73	3.25 ± 0.20	102 ± 0.43
AE_7	3.2 ± 0.04	0.43	2.51 ± 0.03	100 ± 0.52
AE_8	3.9 ± 0.34	0.52	2.52 ± 0.04	101 ± 1.20

* Average of three determinations

CONCLUSION

In the present work, fast dissolving tablets of Acetriptan were prepared by direct compression, sublimation, and effervescent methods. Based on the above studies following conclusions can be drawn:

- Tablets prepared by direct compression and sublimation and effervescent methods were found to be good and were free from chipping and capping.

- The hardness of the prepared tablets were found to be in the range of 2.4 to 4 Kg/cm².

- The friability values of the prepared tablets were found to be less than 1%.

- FTIR study indicated that the drug is compatible with all the excipients.

- Compressed tablets containing mannitol and camphor have been prepared by sublimation technique. Removal of volatile material by sublimation generated a porous structure. The tablets dissolve within 10-20 sec. and exhibit sufficient mechanical strength for practical use, which is effective than the direct compression and effervescent methods.

ACKNOWLEDGMENT

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