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Research Article

DESIGN AND EVALUATION OF HYDRALAZINE HYDROCHLORIDE MOUTH DISSOLVING TABLET FOR THE MANAGEMENT OF HYPERTENSION

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ABSTRACT

Eclampsia and preeclampsia is an acute and life threatening complication during pregnancy. Hydralazine hydrochloride is one of the drugs of choice in treating this condition. The purpose of the present research work was to formulate the orodispersible tablets by using different methods and provide a suitable patient convenience dosage form to enhance the bioavailability and provide quick onset of action. Formulation of orodispersible tablets of Hydralazine hydrochloride were prepared by using various superdisintegrants like crosspovidone, crosscarmellose sodium and sodium starch glycolate by direct compression method and camphor as an excipient by sublimation technique. The formulas were evaluated for compatibility and Precompressional studies. The formulations were evaluated for weight variation, thickness, hardness, friability, content uniformity, disintegration time, wetting time, water absorption ratio and release profile. Among all the formulations F9 and SF9 showed effective percentage of drug release at 12 minutes indicating faster and maximum absorption at the site of administration.

INTRODUCTION

Oral administration is the most acceptable and preferred route for drug delivery. Recent research on formulation is on the basis of advancement of oral formulation overcoming its limitation related to difficulty in swallowing or chewing of solid dosage form. The problem of swallowing tablet was more evident in geriatric and paediatric patients as well as travelling patients as they need water to swallow. This draw back has paved attention in developing fast dissolving drug delivery system[1].

Mouth dissolving tablet (MDTs) formulations has better stability, accurate dosing, easy to manufacture, easy to handle by patients. It's a novel dosage form which is placed in the mouth and disintegrates rapidly with in a seconds. MDTs are also called as Oro dispersible tablets, quick dissolving tablets, fast melt tablets, rapid disintegrating tablets, freeze dried wafers. It's an elegant route for systemic drug delivery.

Hydralazine Hydrochloride drugs are suitable and effective for the treatment of hypertension because it's having a phthalazinone hydrazone hydrochloride chemical group. It has a bioavailability of 30% to 60%, Tmax 1 to 2 hours. Maximum dosing of Hydralazine Hydrochloride is 300mg/day. It enhances the bioavailability resulting from bypassing the first pass effect [2].

MATERIALS AND METHODS

The drug Hydralazine Hydrochloride was obtained from Octopus pharmaceuticals, Chennai. Croscarmalose sodium, Crospovidone, Sodium starch glycolate, Aspartame, Mannitol, Magnesium stearate, Micro crystalline cellulose, Talc, Camphor were procured from Himedia Ltd, Goa and all other excipient used were analytical grade.

Preformulation Studies

Preformulation studies such as physical appearance, solubility, melting point, hygroscopicity and drug excipient compatibility were performed to confirm the suitability and stability of drug and excipient for the formulation of mouth dissolving tablets [3].

Formulation and Development

Precompressional studies

Precompressional parameters like Angle of Repose, bulk density, tapped density, compressibility index and hausner ratio was performed as per the standard procedures.

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Method-A

Formulation of Mouth Dissolving Tablet by Direct Compression Method

Tablets were prepared by direct compression method using super disintegrants such as, crospovidone, croscarmellose sodium and sodium starch glycolate in varying ratios. All the materials were passed through #60 mesh prior to mixing for uniformity in particle size. The drug and microcrystalline cellouse were mixed using glass mortar and pestle in a small portion of both at each time and blended to get a uniform mixture and kept a side. Then the other ingredients were weighed and mixed in a geometrical order and the tablets were compressed using 8mm size punch to get 200 mg weight using ten stations Rimek tablet punching machine. Compositions of different formulations were prepared by direct compression method [4].

Method-B

Formulation of Mouth Dissolving Tablet by Sublimation method

Tablets were prepared by using camphor in different ratios. All the ingredients were passed through #60 mesh separately. Then the ingredients were weighted and mixed in geometrical order and the tablets were compressed using 8mm size punch to get 200 mg weight using ten stations Rimek tablet punching machine. The compressed tablets were than subjected to sublimation at 60˚C for 1 hour. Compositions of different formulations were prepared by sublimation technique [5].

Evaluation of Hydralazine hydrochloride mouth dissolving tablets

The compressed tablets were evaluated for the tests such as weight variation, thickness hardness, friability, *in vitro* disintegration and *in vitro* dissolution rate as per the pharmacopoeia standards and also specific tests for the evaluation of mouth dissolving tablets like wetting time and water absorption ratio were performed.

In vitro drug release profile were fitted with various kinetic equations like Higuchi, Hixson and Crowell model and Korsmeyer and Peppas equation to understand the drug release kinetics from the dosage form [6].

RESULTS

Hydralazine hydrochloride appeared white, odourless, amorphous, and soluble in water with a melting point of 172 ± 0.1º C

The FTIR spectra of the drug, polymer and physical mixtures of various formulations were compared with the spectra of pure drug and individual excipient in which there was no significant change in the spectrum was found, (Table 1) indicates the compatibility of the drug and excipients. There are no extra peaks observed other than normal peaks in the spectra of the mouth dissolving tablets indicate stability of the formulations.

Table 1

Functional Groups	FTIR spectral assignments for Hydralazine Hcl	FTIR Spectral assignments for MDT prepared by Direct compression	FTIR Spectral assignments for MDT prepared by Sublimation method
	Wave number (cm-1)	Wave number cm-1	Wave number cm-1
C-H streching	3941.77, 3778.11, 3018.19, 2799.88	3916.03, 3782.62, 3024.94, 2912.43	3772.62, 3022.92, 2912.43
O-H Stretching	3698.04	3408.90, 3216.43	3406.80, 3210.49
C=O Stretching	1668.75	1590.16, 1554.01	1580.18, 1564.01
O-H Bending	1363.12	1366.91	1384.04
C-O Stretching	1177.36, 1072.25	1283.45	1289.46
C-H Bending	786.07	995.46	996.64

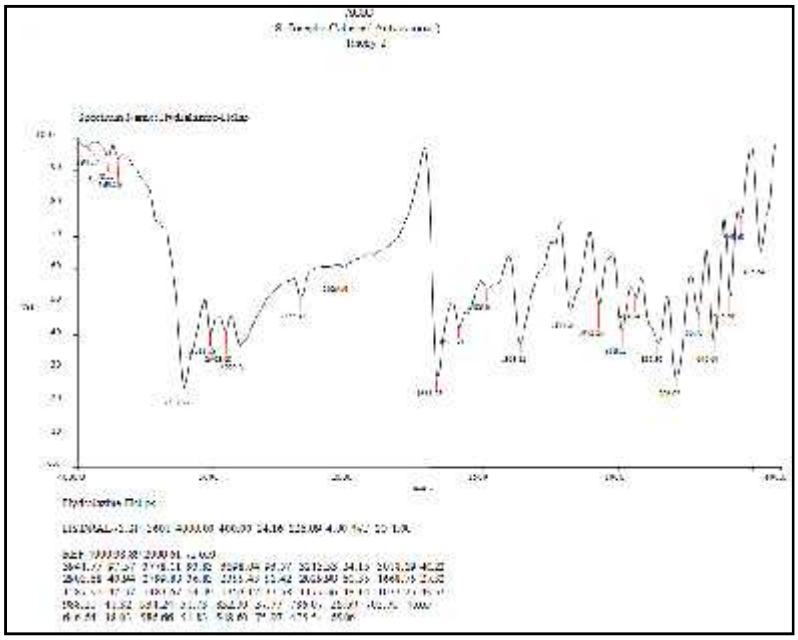

Fig 1 FTIR Spectrum of Hyralazine Hydrochloride

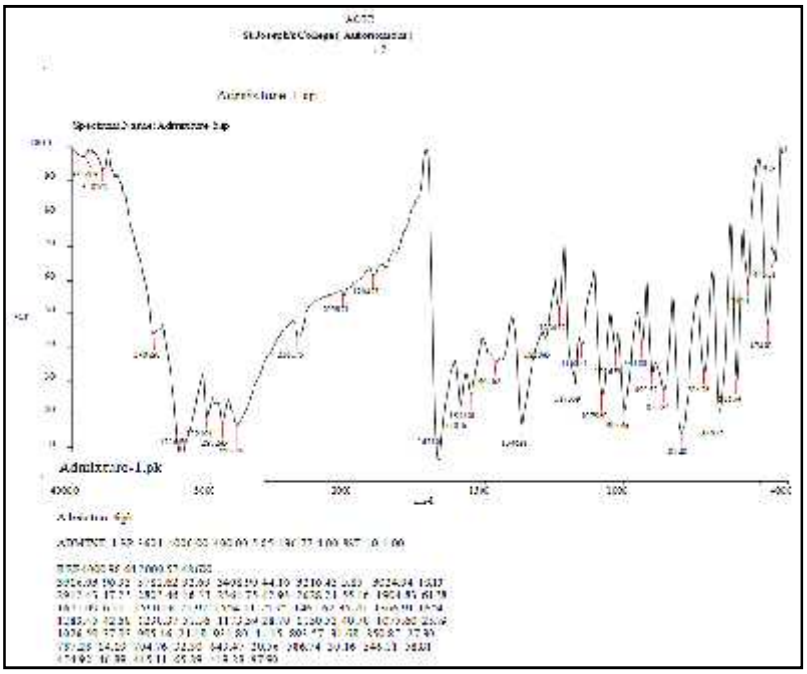

Fig 2 FTIR spectrum of MDT prepared by Direct compression method

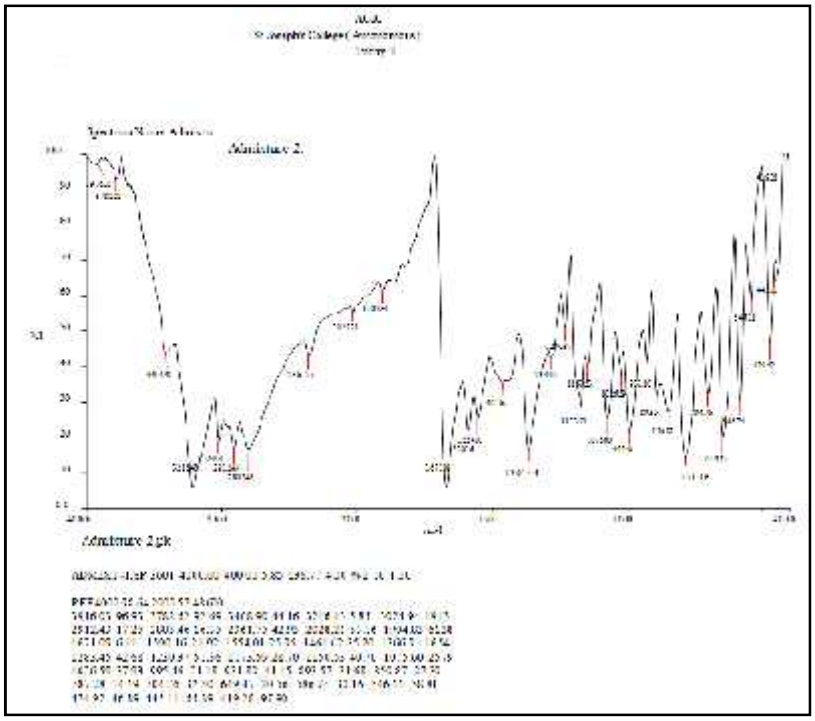

Fig 3 FTIR Spectrum of MDT prepared by Sublimation method

Pre Compressional studies

Table 2 Direct Compression Method

Batch code	Angle of repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index(%)	Hausner's Ratio
API	24.76±0.18	0.31±0.06	0.34±0.08	08.82±0.07	1.09±0.02
F1	37.97±0.16	0.33±0.10	0.39±0.10	15.38±0.06	1.18±0.03
F2	36.02±0.26	0.31±0.10	0.42±0.08	26.19±0.09	1.19±0.02
F3	35.06±0.11	0.36±0.05	0.40±0.03	10.00±0.17	1.35±0.01
F4	34.09±0.13	0.34±0.06	0.43±0.01	21.95±0.68	1.18±0.02
F5	34.64±0.28	0.33±0.03	0.41±0.03	19.51±0.66	1.26±0.03
F6	26.06±0.26	0.32±0.05	0.39±0.03	17.94±0.42	1.17±0.01
F7	34.24±0.33	0.32±0.11	0.34±0.10	05.88±0.08	1.21±0.01
F8	36.96±0.31	0.34±0.10	0.38±0.11	10.52±0.04	1.11±0.02
F9	38.08±0.23	0.35±0.10	0.41±0.05	14.63±0.07	1.17±0.03

Table 3 Sublimation Method

Batch code	Angleof repose (θ)	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Carr's Index(%)	Hausner's Ratio
API	26.27±0.13	0.31±0.03	0.36±0.01	13.88±0.33	1.16±0.04
SF1	31.21±0.16	0.29±0.01	0.34±0.01	14.70±0.23	1.17±0.02
SF2	28.48±0.24	0.31±0.10	0.37±0.04	16.21±0.27	1.19±0.09
SF3	33.16±0.17	0.29±0.02	0.33±0.02	12.12±0.06	1.13±0.03
SF4	30.79±0.14	0.33±0.03	0.39±0.01	15.38±0.85	1.18±0.05
SF5	30.27±0.19	0.31±0.11	0.36±0.03	13.88±0.67	1.16±0.02
SF6	29.13±0.14	0.34±0.01	0.40±0.03	15.00±0.31	1.17±0.04
SF7	31.08±0.13	0.33±0.04	0.37±0.02	10.81±0.13	1.12±0.06
SF8	32.26±0.21	0.31±0.03	0.35±0.01	11.42±0.26	1.12±0.01
SF9	33.41±0.22	0.34±0.02	0.38±0.04	10.52±0.09	1.11±0.03

Table 4 Formula for mouth dissolving tablets of Hydralazine hydrochloride by direct compression method

S.No	Ingredients	Formulation code (amount per tablet in mg)								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
01.	Hydralazine Hcl	50	50	50	50	50	50	50	50	50
02.	Croscarmellose sodium	8	10	12	-	-	-	-	-	-
03.	Crospovidone	-	-	-	8	10	12	-	-	-
04.	Sod. Starch glycolate	-	-	-	-	-	-	8	10	12
05.	Aspartame	5	5	5	5	5	5	5	5	5
06.	Mannitol	50	50	50	50	50	50	50	50	50
07.	Magnesium Stearate	2	2	2	2	2	2	2	2	2
08.	Mcc	83	81	79	83	81	79	83	81	79
09.	Talc	2	2	2	2	2	2	2	2	2

Total weight of tablet = 200mg

Table 5 Formula for mouth dissolving tablet of Hydralazine hydrochloride by Sublimation method

S.No	Ingredients	Formulation code (amount per tablet in mg)								
		SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9
01.	Hydralazine HCL	50	50	50	50	50	50	50	50	50
02.	Crospovidone	6	8	10	-	-	-	-	-	-
03.	Croscarmellose sodium	-	-	-	6	8	10	-	-	-
04.	Sod. Starch glycolate	-	-	-	-	-	-	6	8	10
05.	Aspartame	5	5	5	5	5	5	5	5	5
06.	Mannitol	50	50	50	50	50	50	50	50	50
07.	Magnesium state	2	2	2	2	2	2	2	2	2
08.	Camphor	2	4	6	2	4	6	2	4	6
09.	MCC	83	80	77	83	80	77	83	80	77
10.	Talc	2	2	2	2	2	2	2	2	2

Total weight of tablet = 200mg

Evaluation of Hydralazine hydrochloride mouth dissolving tablets

Table 6 Direction Method

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation test (mg)	200±0.98	201±0.76	199±0.63	197±0.73	201±0.66	199±0.84	200±0.65	201±0.94	201±0.84
Thickness (mm)	2.9±0.02	2.8±0.01	3.0±0.02	3.1±0.04	3.5±0.03	3.7±0.02	2.4±0.08	2.5±0.02	2.8±0.09
Hardness test (kg/cm^3)	2.7±0.33	2.8±0.12	3.0±0.24	3.1±0.2 2	3.5±0.31	3.7±0.42	2.4±0.17	2.5±0.19	2.8±0.27
Friability (%)	0.56±0.17	0.42±0.22	0.51±0.25	0.29±0.17	0.53±0.23	0.56±0.27	0.72±0.19	0.77±0.14	0.79±0.21
Disintegration time (sec)	48±0.84	42±0.64	40±0.68	32±0.92	30±0.87	26±0.68	55±0.83	53±0.84	50±0.73
Wetting time (sec)	46±0.36	40±0.91	39±0.44	30±0.64	28±0.92	22±0.54	51±0.43	50±0.56	48±0.82
Water absorption (%)	71.41±0.73	70.43±0.61	74.98±0.47	84.32±0.65	88.32±0.94	92.87±0.91	64.32±0.43	65.42±0.74	68.50±0.53
Drug content (%)	92.16±0.36	94.68±0.24	97.14±0.42	97.01±0.44	98.42±0.67	99.98±0.56	88.48±0.37	90.50±0.25	91.87±0.52

Table 7 Sublimation Method

	Formulation Code (Sublimation Method)								
Parameters	**SF1**	**SF2**	**SF3**	**SF4**	**SF5**	**SF6**	**SF7**	**SF8**	**SF9**
Weight variation test (mg)	199±0.34	200±1.34	199±0.67	198±0.47	201±0.34	200±0.34	198±1.45	200±0.57	201±0.34
Thickness (mm)	2.81±0.12	2.72±0.34	3.28±0.41	2.94±0.23	3.25±0.34	2.90±0.98	3.16±0.99	2.68±0.34	3.02±0.45
Hardness test (kg/cm^3)	2.68±0.35	3.41±0.87	2.78±1.34	3.45±1.58	2.90±0.46	2.78±0.47	3.07±0.33	2.99±1.23	3.34±0.47
Friability (%)	0.56±0.11	0.63±0.24	0.51±0.45	0.87±0.34	0.70±1.57	0.56±0.34	0.75±0.11	0.66±2.34	0.74±0.87
Disintegration time (sec)	25±0.34	31±0.34	27±1.34	30±0.89	28±0.33	30±0.47	29±0.48	32±0.34	34±0.93
Wetting time (sec)	37±0.23	41±0.36	28±0.45	38±0.35	34±0.33	37±0.78	41±0.78	35±0.35	40±0.37
Water absorption (%)	70±0.67	69±1.34	82±1.40	79±1.20	76±0.61	85±0.99	81±0.56	74±0.36	70±0.46
Drug content (%)	89±0.55	96±0.89	87±0.16	94±0.56	96±0.45	89±0.41	96±0.48	91±0.11	87±0.38

Table 8 Comparative *In-vitro* Dissolution study of MDTs Prepared By Direct Compression Method

Formulation code	TIME(MIN)						
	0	2	4	6	8	10	12
F1	2.27±0.65	11.29±0.59	30.13±0.64	51.27±0.82	60.13±0.84	76.52±0.58	91.80±0.45
F2	3.00±0.46	16.69±0.62	34.41±0.38	45.95±0.59	54.68±0.67	65.70±0.43	87.43±0.58
F3	5.61±0.54	18.40±0.36	31.66±0.45	45.68±0.78	54.90±0.58	76.85±0.63	92.86±0.39
F4	5.34±0.55	15.40±0.53	25.00±0.64	46.93±0.39	60.13±0.55	71.53±0.57	88.88±0.64
F5	7.80±0.37	17.91±0.71	37.50±0.59	49.71±0.52	64.99±0.73	76.52±0.80	94.30±0.61
F6	5.20±0.64	20.80±0.83	38.20±0.55	51.57±0.68	62.80±0.63	76.82±0.43	95.34±0.55
F7	5.75±0.81	18.57±0.45	32.61±0.58	45.68±0.85	64.82±0.52	72.98±0.55	85.25±0.43
F8	5.26±0.58	22.17±0.51	33.81±0.39	49.55±0.78	62.72±0.64	78.43±0.76	89.75±0.57
F9	4.39±0.57	21.98±0.67	36.84±0.54	49.55±0.66	72.68±0.63	79.30±0.82	95.59±0.64

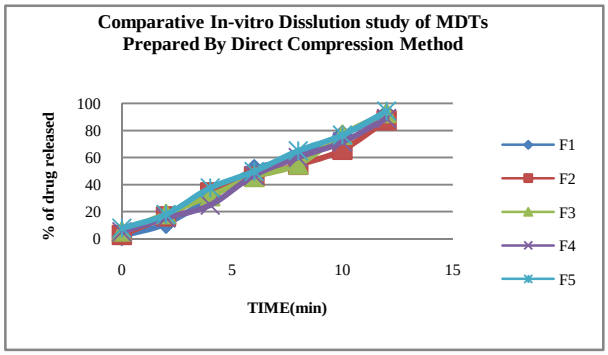

Fig 4 Comparative *In-vitro* Disslution study of MDTs Prepared By Direct Compression Method

Precompressional studies

The data obtained for precompressional parameters such as bulk density, tapped density, Hausner ratio, Carr's index and angle of repose are shown in table The data obtained for precompressional parameters such as bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose are shown in (Table 2,3) and found within acceptable Pharmacopoeia standards [8].

Post compression studies

Evaluations like weight variation, thickness, hardness, friability, wetting time, water absorption ratio assay, wetting time, *in vitro* disintegration time, in vitro drug dissolution study are mentioned in (Table 6,7,8) and figure 4,5.

Table 9 Comparative *In-vitro* Dissolution study of MDTs Prepared By Sublimation Method

Formulation code	TIME(min)						
	0	2	4	6	8	10	12
SF1	5.34±0.3	23.34±14	38.64±0.34	51.43±0.12	72.95±0.246	87.13±0.84	98.31±0.58
SF2	6.16±0.12	20.67±12	41.40±0.24	46.80±0.05	68.80±0.435	86.89±0.77	96.00±0.42
SF3	6.16±0.71	20.67±45	41.40±0.67	46.80±0.71	68.80±0.81	86.89±0.43	96.00±0.54
SF4	9.46±1.5	24.16±0.58	40.22±0.23	59.34±0.23	76.50±0.36	83.90±0.38	96.08±0.43
SF5	7.25±21	23.89±0.76	39.73±0.58	47.89±0.24	64.80±0.58	78.33±0.86	95.29±0.62
SF6	8.34±0.9	23.34±0.45	33.16±16	51.43±0.47	66.19±0.34	79.24±0.51	79.24±0.34
SF7	7.83±0.58	23.610.47	37.82±0.74	46.80±0.61	72.70±0.71	85.11±0.72	98.04±0.71
SF8	8.01±0.12	19.74±0.87	45.46±0.57	60.18±0.12	79.52±0.34	87.45±0.28	100.74±0.52
SF9	7.83±0.23	22.39±0.98	41.34±0.34	52.55±0.58	71.37±14	87.76±0.66	99.98±0.77

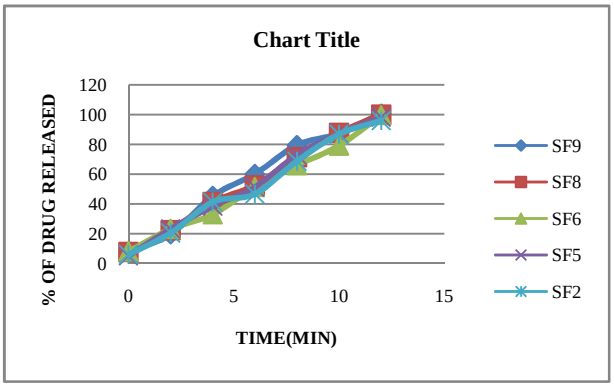

Fig 5 Comparative in-vitro Dissolution Study of MDT Prepared by Sublimation Method

DISCUSSION

Formulation and development

Mouth dissolving tablets of Hydralazine Hydrochloride were prepared by direct compression method and sublimation method and the formula are presented in (Table 4,5)[7].

The tablets weight variation for the optimised formulation F9 and SF9 of mouth dissolving tablets prepared by method A and B was measured in the range of 201±0.94 mg and 201±0.34 mg, Thickness was in the range of 2.8±0.09 and3.02±0.45, hardness in the range of 2.8±0.27 kg/cm2 and 3.34±0.47 kg/cm2. The percentage friability was less than 1% for all formulations ensuring mechanical stability of the formulated tablets [9]. All formulations were evaluated for percentage drug content and found in the range of 92.16 ± 0.36 to 99.98 indicating the compliance with the Pharmacopoeia limits. According to the Pharmacopoeia standards the dispersible tablet must disintegrate within 3 min, but all formulated batches have shown very low disintegration time i.e. 30.047 to 55.083 seconds indicating suitability of formulation for fast dissolving tablet. Wetting time found in the range of46±0.36 and 50±0.56 seconds, water absorption ratio was 65.42±0.74 and 71.41 ±0.73 percentages. *In vitro* study was found to be optimum for the formulation F9 and SF9in the range of 95.59±0.64 percentage and 99.98±0.77 percentage at 12 minutes [10].

CONCLUSION

From this study F9 and SF9 were concluded as optimized formulations from the results of post compression parameters with an effective percentage of drug release at 12 minutes indicating faster and maximum absorption at the site of administration.

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