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DESIGN OF CONTROLLED RELEASE NON-ERODIBLE POLYMERIC ATENOLOL MATRIX TABLET USING MICROWAVE OVEN-ASSISTED SINTERING TECHNIQUE

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Keywords:

Atenolol, Controlled release systems, Preformulation, Sintering, Eudragit S-100

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ABSTRACT: The objective of the present study was to evaluate the effect of microwave sintering condition on matrix formation and subsequent drug release from polymer matrix tablet for controlled release. The atenolol floating SR matrix tablets were prepared by using tragacanth, sodium bicarbonate, Eudragit S-100 and citric acid was incorporated as a gas generating agents. Atenolol controlled release tablets were estimated in terms of their physico-chemical parameter like weight variation, friability, hardness, drug content, contact angle, floating lag time *in-vitro* drug release, specific gravity and stability study as per ICH guidelines. The results of *in-vitro* drug release studies showed that the optimized formulation (F6, L2, I2, H4) could extend drug release (99.5%) for 24 hours. The release pattern of atenolol was fitted to different models based on coefficient of correlation (r). The present work also deals with the application of sintering technique to matrix tablets of atenolol to achieve sustained release. The results of the present work stated that sintering caused decrease in drug release as compared to unsintered tablets. It was found that F6, L2, I2 and H$ gave better results compared to other formulations. The stability studies were carried out according to ICH guideline which indicates that the selected formulations were stable. Hence we finally conclude that microwave oven sintering is better than conventional hot air oven sintering process in preparation of controlled release tablets.

INTRODUCTION: Controlled release drug delivery has become the norm in dosage form design and intensive research has been undertaken in achieving better drug product effectiveness reliability and safety. The objective of the design and manufacture of the compressed CR tablet is to deliver orally the correct amount of drug in the desired location and to have its chemical integrity protected to the point.

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Recent advances in Novel Drug Delivery System (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance [1 - 3]. Atenolol is β - 1 cardio selective adrenergic receptor blocker, widely used in the treatment of hypertension. The drug is soluble in water (BCS Class III) and has half-life of 6 - 8 h with oral bioavailability of 50% due to smaller dose of drug (less than 50 mg).

In this study, an attempt was made to design and formulate the floating matrix tablets of atenolol so as to increase its gastric retention thereby ensuring slower and complete release of atenolol. The sustained drug delivery can be achieved by matrix tablet where a solid drug is dispersed in an

insoluble matrix. The rate of release of drug is dependent on the rate of drug diffusion and not on the rate of solid diffusion. The matrix tablets can be prepared by wet granulation method. Wet granulation has several advantages over dry granulation method like better flow properties of granules and less generation of dust while mixing [4 - 5, 18]. Microwave sintering involves the heating of compact at a temperature below the melting point of the solid constituents in a controlled environment. It is simple, effective and economical process to obtain sustained release of drug from the tablet with comparatively less quantity of polymer [6 - 7].

Present research work has been undertaken to evaluate the effect of sintering condition on matrix formation and subsequent drug release from polymer matrix tablet for controlled release. The present study highlights the use of a microwave oven for the sintering process in order to achieve more uniform heat distribution with reduction in time required for sintering. Administration of conventional tablets of atenolol has been reported to exhibit fluctuations in plasma drug levels, resulting either in manifestation of side effects or reduction in drug concentration at the receptor sites [8, 10].

MATERIALS AND METHODS: Materials: Atenolol (Yarrow Chem product, Mumbai), All other excipients was obtained from Eisen Pharmaceuticals, Pune.

Methods:

Preliminary Studies: Matrix granules of atenolol were prepared by wet granulation method. Various polymers such as ES - 100, tragacanth, ethyl cellulose, lactose, were investigated as singly and in combination in different ratios. Tragacanth was used as a binder to prepare granules, which were passed through sieve no. 16. The granules were dried at 45 ºC for 30 min. The dried granules were screened through sieve no 16 and stored at ambient temperature for further studies. The granules were mixed with magnesium stearate and talc in require quantity and compressed using rotary tablet compression machine (Rimek) using 13 mm diameter flat punches. The tablets were placed in beaker and subjected to microwave irradiation at 450, 560 and 700 watt for 20, 15 and 10 min in microwave oven.

Experimental Design: [8 - 10] A 3^2 full factorial design (Design Expert, Version 7, Stat-Ease Inc, Minneapolis, MN) was used to design the formulation. Dependent variable X1: Eudragit S 100 X2: Tragacanth and Independent Variables Y1. Drug Content Y2: Swelling Index Y3. Buoyancy was taken. Following batches were developed.

RESULTS:

TABLE 1: TABLET COMPOSITION OF ATENOLOL SUSTAINED RELEASE TABLETS (F1 TO F9)

Ingredient weight in mg	F1	F2	F3	F4	F5	F6	F7	F8	F9
Atenolol	111	111	111	111	111	111	111	111	111
Tragacanth	30	30	30	40	40	40	50	50	50
Eudragit S100	30	40	50	30	40	50	30	40	50
Lactose	10	10	10	10	10	10	10	10	10
$NaHCO_3$	11	11	11	11	11	11	11	11	11
Citric acid	11	11	11	11	11	11	11	11	11
Magnesium Stearate	22	22	22	22	22	22	22	22	22
MCC	10	30	20	30	20	10	20	10	30
Talc	5	5	5	5	5	5	5	5	5
Final weight	270	270	270	270	270	270	270	270	270

TABLE 2: TABLET COMPOSITION OF ATENOLOL SUSTAINED RELEASE TABLETS (L1 TO L9)

Ingredients weight in mg	L1	L2	L3	L4	L5	L6	L7	L8	L9
Atenolol	111	111	111	111	111	111	111	111	111
Tragaecanth	30	30	30	30	30	30	30	30	30
Eudragit L100	30	30	30	30	30	30	30	30	30
Lactose	10	10	10	10	10	10	10	10	10
$NaHCO_3$	11	11	11	11	11	11	11	11	11
Citric acid	11	11	11	11	11	11	11	11	11
Magnesium Stearate	22	22	22	22	22	22	22	22	22
MCC	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Final weight	270	270	270	270	270	270	270	270	270
Sintering temp (^{0}C)	60	60	60	70	70	70	80	80	80
Sintering time (mins)	10	15	20	10	215	20	10	15	20

TABLE 3: TABLET COMPOSITION OF ATENOLOL SUSTAINED RELEASE TABLETS (I1 TO I9)

Ingredients weight in mg	I1	I2	I3	I4	I5	I6	I7	I8	I9
Atenolol	111	111	111	111	111	111	111	111	111
Tragacanth	40	40	40	40	40	40	40	40	40
Eudragit S100	40	40	40	40	40	40	40	40	40
Lactose	10	10	10	10	10	10	10	10	10
$NaHCO_3$	11	11	11	11	11	11	11	11	11
Citric acid	11	11	11	11	11	11	11	11	11
Magnesium stearate	22	22	22	22	22	22	22	22	22
MCC	20	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5	5
Final weight	270	270	270	270	270	270	270	270	270
Sintering temp (ºC)	60 ^{0}C	60 ^{0}C	60 ^{0}C	70 ^{0}C	70 ^{0}C	70 ^{0}C	80 ^{0}C	80 ^{0}C	80 ^{0}C
Sintering time (h)	10	15	20	10	15	20	10	15	20

TABLE 4: TABLET COMPOSITION OF ATENOLOL SUSTAINED RELEASE TABLETS (H1 TO H9)

Ingredients weight in mg	H1	H2	H3	H4	H5	H6	H7	H8	H9
Atenolol	111	111	111	111	111	111	111	111	111
Tragaecanth	50	50	50	50	50	50	50	50	50
Eudragit L100	50	50	50	50	50	50	50	50	50
Lactose	10	10	10	10	10	10	10	10	10
$NaHCO_3$	11	11	11	11	11	11	11	11	11
Citric acid	11	11	11	11	11	11	11	11	11
Magnesium stearate	22	22	22	22	22	22	22	22	22
MCC	30	30	30	30	30	30	30	30	30
Talc	5	5	5	5	5	5	5	5	5
Final weight	270	270	270	270	270	270	270	270	270
Sintering temp (ºC)	60 ^{0}C	60 ^{0}C	60 ^{0}C	70 ^{0}C	70 ^{0}C	70 ^{0}C	80 ^{0}C	80 ^{0}C	80 ^{0}C
Sintering time (min)	10	15	20	10	15	20	10	15	20

TABLE 5: DATA FOR BLEND EVALUATION OF FORMULATION (F1 TO F9)

Formulation no.	Angle of repose (^{0})	LBD (g/cm^2)	TBD (g/cm^2)	Compressibility index (%)
F1	29^{0}84’	0.3846	0.4166	7.68
F2	22^{0}39’	0.4545	0.5555	18.18
F3	29^{0}53’	0.4	0.5	20
F4	26^{0}90’	0.3846	0.4545	15.37
F5	27^{0}56’	0.3571	0.4132	13.57
F6	25^{0}93’	0.3125	0.3676	14.98
F7	29^{0}89’	0.3703	0.4504	17.78
F8	28^{0}75’	0.4201	0.5102	17.65
F9	25^{0}07’	0.3496	0.4065	13.99

TABLE 6: DATA FOR BLEND EVALUATION OF FORMULATION (L1 TO L9)

Formulation no.	Angle of repose (^{0})	LBD (g/cm^2)	TBD (g/cm^2)	Compressibility index (%)
L1	20.56	0.4576	0.5642	18.8940
L2	24.58	0.4892	0.5234	6.53419
L3	23.16	0..4615	0.5846	21.0571
L4	26.57	0.5032	0.5948	15.4001
L5	25.34	0.4542	0.5346	15.0392
L6	27.65	0.3987	0.476	18.2321
L7	23.68	0.5542	0.6243	11.2285
L8	24.97	0.4653	0.5612	17.0883
L9	25.67	0.4565	0.5346	14.6090

TABLE 7: DATA FOR BLEND EVALUATION OF FORMULATION (I1 TO I9)

Formulation no.	Angle of repose (^{0})	LBD (g/cm^2)	TBD (g/cm^2)	Compressibility index (%)
I1	24.05	0.4576	0.5678	19.4082
I2	23.48	0.5123	0.6743	24.02449
I3	25.61	0.4861	0.6021	19.2659
I4	27.08	0.5721	0.6431	11.0402
I5	21.	0.5143	0.5976	13.9390
I6	26.	0.4698	0.5124	8.31381
I7	28.	0.4137	0.5064	18.3056
I8	30.	0.5678	0.6542	13.2069
I9	27.	0.5490	0.6341	13.4206

TABLE 8: DATA FOR BLEND EVALUATION OF FORMULATION (H1 TO H9)

Formulation no.	Angle of repose (^{0})	LBD (g/cm^2)	TBD (g/cm^2)	Compressibility index (%)
H1	30.14	0.4865	0.5472	11.09282
H2	21.45	0.4216	0.5684	24.2688
H3	27.08	0.4675	0.5824	19.7287
H4	26.48	0.5032	0.6542	23.0816
H5	28.46	0.5431	0.7102	23.5288
H6	29.46	0.4862	0.5216	6.7861
H7	24.15	0.4675	0.5462	14.4084
H8	27.64	0.4642	0.5231	11.2598
H9	23.08	0.5548	0.6742	17.7098

Post Compression Parameters:

TABLE 9: PHYSICAL PROPERTIES OF TABLET FORMULATIONS (F1 TO F9) OF ATENOLOL SUSTAINED RELEASE MATRIX TABLETS

Parameters	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug content (%)	99.53	97.09	96.51	101.16	98.02	101.86	99.18	102.32	101.86
Hardness (kg/cm^3)	8.6	9.6	8.8	11.2	10.4	8.9	9.8	10.4	9.8
Swelling index (%)	193.24	203.01	178.32	181.39	206.21	221.25	185.67	206.17	222.05
Buoyancy lag time (min)	2.15	2	No float	2	1.30	1	1.30	0.45	0.55

TABLE 10: PHYSICAL PROPERTIES OF TABLET FORMULATIONS (L1 TO L9) OF ATENOLOL SUSTAINED RELEASE MATRIX TABLETS

Parameters	Formulation Codes								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
Drug content (%)	98.37	96.86	97.09	103.48	100.81	99.18	95.11	99.41	100.34
Hardness (kg/cm^3)	10.8	11.0	12.2	11.2	12.4	12.0	12.6	13.2	13.4
Swelling index (%)	83.87	143.64	214.03	194.75	222.82	251.13	194.27	240.44	275.31
Buoyancy lag time (min)	1.30	1.20	2.30	1.35	1.30	1.10	1.00	1.55	2.05

TABLE 11: PHYSICAL PROPERTIES OF TABLET FORMULATIONS (I1 TO I9) OF ATENOLOL SUSTAINED RELEASE MATRIX TABLETS

Parameters	Formulation Codes								
	I1	I2	I3	I4	I5	I6	I7	I8	I9
Drug content (%)	100.46	96.74	95.46	98.83	100.81	99.53	99.18	101.27	95.11
Hardness (kg/cm^3)	8.8	6.6	7.2	6.4	5.8	6.6	5.6	5.2	5.6
Swelling index (%)	84.32	142.43	212.46	196.97	225.25	250.25	196.14	242.14	272.5
Buoyancy lag time (min)	1.45	2	2.05	2.30	2.25	1.30	1.45	3	3.45

TABLE 12: PHYSICAL PROPERTIES OF TABLET FORMULATIONS (H1 TO H9) OF ATENOLOL SUSTAINED RELEASE MATRIX TABLETS

Parameters	Formulation Codes								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
Drug content (%)	96.62	99.18	99.53	96.62	102.44	100.11	98.02	100.23	101.39
Hardness (kg/cm^3)	9.4	9.8	10.2	9.6	8.0	8.4	8.6	7.8	7.6
Swelling index (%)	152.59	175.81	184.04	183.87	200.25	222.16	202.48	225.75	227.82
Buoyancy lag time (min)	0.50	1	1-1.5	1	0.45	1.30	5	1.40	2

TABLE 13: KINETICS OF OPTIMIZED FORMULATIONS FROM ALL THE FACTORIAL BATCHES

S. no.	Model	F6		L6		I2		H4	
		R^2	k	R^2	k	R^2	k	R^2	k
1	Zero order	0.9803	11.4925	0.859	9.4253	0.887	9.4595	0.650	0.0077
2	First order	0.6791	-0.3711	0.962	-0.1391	0.973	-0.1407	0.650	-0.0001
3	Higuchi matrix	0.9184	26.8997	0.994	22,931	0.993	22.932	0.962	-0.0191
4	Hixson and Crowell method	0.9339	18.1338	0.984	25.783	0.979	24.783	0.982	0.0270
5	Korsemeyer and Peppas model	0.8400	-0.0688	0.937	-0.0404	0.954	-0.0407	0.650	0.000

Stability Studies: [11- 12] The optimized formulations were subjected to stability at 25 ^{0}C ± 2 ^{0}C/60% ± 5% RH, 30 ^{0}C ± 2 ^{0}C/65% ± 5% RH and 40 ^{0}C ±2 ^{0}C/ 75% ± 5% RH for period of 90 days. The tablet samples were then analysed for physical characteristics and drug release profile. Following table states the stability study results.

Characterization of Powder Properties: A flow property plays an important role in tablet formulations because in presence of improper flow, it may cause more weight variation. Values of Carr's Index (compressibility) below 25% gives rise to good flow properties but readings above 25% indicate poor flow properties. It was found that the compressibility (Carr's index) of the powder were below 25% and hence they exhibit good flow characteristics. The Carr's index of the powder was in the range of 6.5 to 24.2, which indicate a good flow property of the powders. The parameter of angle of repose of all the powder blends was obtained within the range of 20 - 30 ^{0}C.

Evaluation of Tablets:

Physical parameters: The punches that are used to compress the tablets were 8 mm, spherical shaped. The shape and size of the tablets were found to be within the limit. The hardness of the tablets was found to be in the range of 6.4 to 10.1 kg/cm^2. It was within the range of monograph specification. The thickness of tablets was found to be in the range of 1.90 to1.94 mm. The friability of the tablets was found to be less than 1% and thus, it was within the range of standard specification.

***In-vitro* release studies:** [12-17] *In-vitro* dissolution study (USP Paddle Method) was performed in phosphate buffer pH 7.4 as the dissolution medium. The % drug release of all the tablet formulations was calculated using the PCP disso software and the drug release pattern was carried out. The cumulative % drug release patterns of all the formulations are shown in **Tables 15 - 18**. The concentrations of the solutions are calculated by using the standard regression equation.

TABLE 14: STABILITY STUDY RESULTS

Test	Aluminium foil		
	Initial	3M 25 °C/60 % RH	3M 40 °C/75 % RH
Appearance	Complies	Complies	Complies
White, round uncoated tablets			
Assay	96.9%	99.2%	97.3%
95-105.0% of labeled amount			
Dissolution	92.0%	95.0%	93.0%
NLT 85% (Q)	91.0%	97.0%	98.0%
of labelled amount in	94.0%	98.0%	97.0%
45 minutes	90.0%	98.0%	92.0%
	93.0%	97.0%	96.0%
	92.0%	96.0%	98.0%
Related Substance	0.01	0.023	0.013
(i) Impurity F NMT 0.20%			
(ii)Any other Known Impurity	0.025	0.046	0.034
NMT 0.20%			
(iii) Single Maximum Unknown	0.021	0.057	0.059
Impurity: NMT 0.10%			
(iv) Total Impurities NMT 0.50%	0.12	0.103	0.094

TABLE 15: CUMULATIVE % DRUG RELEASE PATTERN (F1 TO F9)

Time (hrs)	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	21.42	20.07	18.91	16.79	22.58	23.45	21.52	20.07	19.59
2	26.63	25.76	24.12	23.54	23.74	22.29	26.93	24.71	25.67
3	31.85	29.63	29.05	32.62	28.95	32.23	33.59	29.24	30.69
4	41.40	43.72	41.31	38.21	40.34	41.79	37.35	40.34	39.38
5	51.54	49.03	48.06	45.17	50.77	55.79	49.03	51.23	48.84
6	57.52	51.25	55.40	56.75	57.72	60.61	57.72	60.42	53.36
7	98.21	70.84	77.99	86.67	87.16	78.47	84.74	76.06	64.47
8	-	99.00	96.28	97.89	98.07	99.02	100.07	96	98.06
9	-	-	-	-	-	-	-	-	-
10	-	-	-	-	-	-	-	-	-

From **Table 15**, it was observed that, after 10 s of dissolution study of all the formulations shows % drug release in the range of 96 - 100.07 %.The drug release Pattern is graphically represented in **Fig. 1**. From the drug release profile, it was observed that formulations F1 - F3 shows comparatively more drug release as compared to other formulation.

The drug release pattern shows that the % drug release after 12 hrs was found within the range of 76.93 - 91.46 %.The graphical representation of the drug release profile is given in **Fig. 2**. From the drug release pattern, it was observed that the formulation L4 shows good drug release within 12 h. The drug release pattern shows that the % drug release after 12 hrs was found within the range of 89.67 - 108.49 %. The graphical representation of the drug release profile is given in **Fig. 3**. From the drug release pattern, it was observed that the formulation L4 shows good drug release within 10 h.

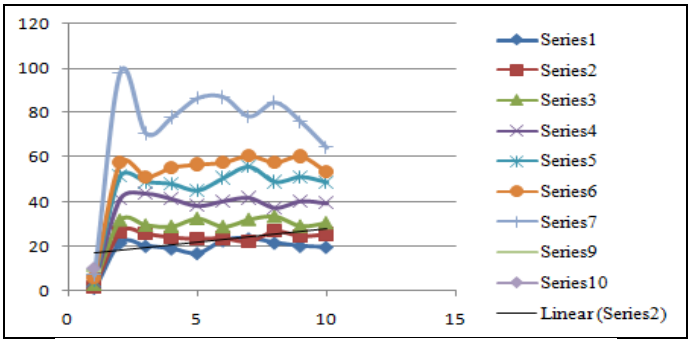

FIG. 1: DISSOLUTION PROFILE OF F1 TO F9

TABLE 16: CUMULATIVE % DRUG RELEASE PATTERN (L1 TO L9)

Time (h)	Formulation Codes								
	L1	L2	L3	L4	L5	L6	L7	L8	L9
1	20.07	22.39	23.55	22.00	21.52	27.02	18.91	19.59	19.40
2	26.64	25.00	24.57	25.67	25.67	36.96	21.13	21.91	21.52
3	32.52	28.95	32.23	28.95	31.17	38.61	38.22	34.55	36.00
4	48.16	44.01	41.11	41.11	35.32	41.79	39.96	40.83	39.96
5	53.18	50.19	48.16	43.14	40.54	50.96	40.92	45.94	47.87
6	58.59	55.59	50.67	48.84	48.26	54.82	49.98	50.48	50.77
7	67.18	57.81	55.59	50.57	51.54	59.74	50.67	52.89	51.73
8	68.91	60.42	57.52	60.42	59.65	63.32	57.91	59.65	57.52
9	84.36	62.54	65.25	64.67	67.18	69.40	66.31	64.47	60.42
10	90.15	69.30	71.81	69.30	70.07	72.58	70.75	68.53	67.47
11	90.15	80.50	79.44	77.22	76.15	76.83	73.93	72.77	71.81
12	91.46	86.87	88.22	80.50	79.44	77.22	78.95	77.50	76.93

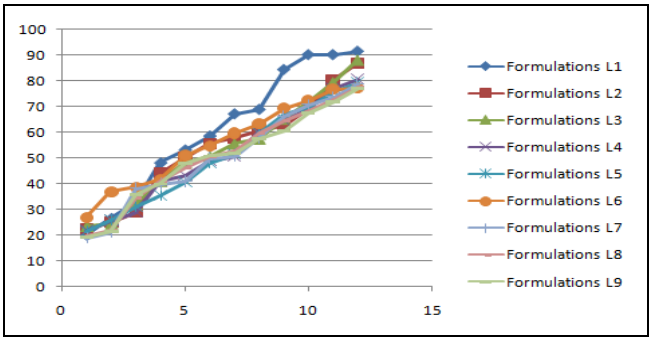

FIG. 2: DISSOLUTION PROFILE OF L1 TO L9

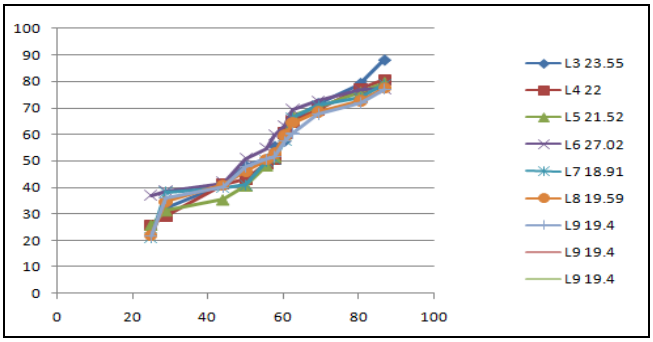

FIG. 3: DISSOLUTION PROFILE OF I1 TO I9

TABLE 17: CUMULATIVE % DRUG RELEASE PATTERN (I1 TO I9)

Time (h)	Formulation Codes								
	I1	I2	I3	I4	I5	I6	I7	I8	I9
1	21.52	23.71	24.51	22.49	21.52	25.09	25.19	21.13	21.62
2	28.76	31.21	26.44	25.38	26.46	36.58	36.38	22.87	22.49
3	34.16	37.35	34.16	31.17	36.00	38.51	39.54	34.65	26.64
4	46.62	40.83	41.21	40.44	40.83	42.37	43.87	40.44	32.72
5	55.50	50.03	53.37	43.72	52.99	50.09	50.99	47.97	41.79
6	60.03	56.08	56.66	50.09	56.37	54.63	55.12	53.08	47.00
7	66.31	59.74	59.74	53.95	65.16	60.13	60.43	57.62	55.59
8	75.77	64.28	64.28	65.57	66.31	66.21	69.31	67.56	55.59
9	86.58	72.77	72.77	66.31	70.75	71.23	74.28	74.90	64.96
10	88.89	80.59	80.59	69.98	76.15	85.61	85.64	85.61	73.06
11	95.17	89.18	85.32	85.52	84.74	95.46	98.41	94.20	79.05
12	99.03	108.39	107.25	96.81	96.13	115.73	110.43	108.49	89.67

TABLE 18: CUMULATIVE % DRUG RELEASE PATTERN (H1 TO H9)

Time (h)	Formulation Codes								
	H1	H2	H3	H4	H5	H6	H7	H8	H9
1	26.64	29.53	30.79	27.70	32.14	21.13	27.60	28.95	32.14
2	30.89	33.49	37.35	31.17	35.42	26.64	31.27	32.72	33.59
3	36.29	38.22	40.34	34.65	37.64	28.36	36.29	35.42	36.58
4	40.92	40.83	44.69	37.35	38.57	31.17	39.18	38.22	41.40
5	48.06	45.94	48.97	40.44	41.98	35.31	41.89	41.79	43.72
6	60.23	50.09	50.48	44.69	44.98	37.16	46.04	45.94	47.00
7	65.25	57.62	57.52	47.00	48.35	40.44	49.03	48.35	50.48
8	71.33	61.35	61.29	48.74	55.59	44.98	51,54	51.83	54.63
9	76.33	67.37	67.56	56.66	58.59	47.97	54.72	56.56	56.66
10	79.05	70.55	69.78	61.29	60.42	50.77	57.52	59.74	60.23
11	85.42	75.86	74.90	65.05	66.11	51.54	60.23	65.25	63.32
12	88.70	79.24	79.3	69.40	70.84	56.66	64.28	68.23	67.08

The drug release pattern shows that the % drug release after 12 hrs was found within the range of 56.66 - 88.70 %. The graphical representation of the drug release profile is given in **Fig. 4**. From the drug release pattern, it was observed that the formulation H4 shows good drug release within 12 h.

Release Experiments: The release pattern of all the formulations was calculated using PCP disso V3 software. All the formulations were fitted for zero order release, first order release, Higuchi matrix model, Hixson and crowell powder dissolution model and korsemeyer-peppas model. The equations for all the models are shown in the **Table 19 - 22**.

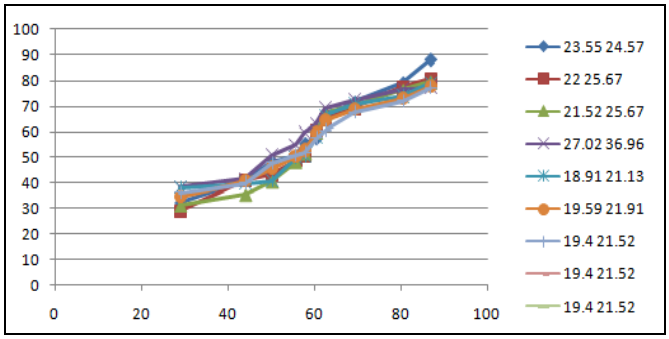

FIG. 4: DISSOLUTION PROFILE OF H1 TO H9

TABLE 19: BEST FITTING MODELS FOR FORMULATIONS F1 TO F9

Formulation	Best fitting model
F1	Zero order
F2	Zero order
F3	Zero order
F4	Zero order
F5	Zero order
F6	Zero order
F7	Zero order
F8	Zero order
F9	Zero order

TABLE 20: BEST FITTING MODELS FOR FORMULATIONS L1 TO L9

Formulation	Best fitting model
L1	1st order
L2	Matrix
L3	Matrix
L4	Matrix
L5	Matrix
L6	Matrix
L7	Matrix
L8	Matrix
L9	Matrix

TABLE 21: BEST FITTING MODELS FOR FORMULATIONS I1 TO I9

Formulation	Best fitting model
I1	Hixon Crowel
I2	Matrix
I3	Matrix
I4	Matrix
I5	1st order
I6	Matrix
I7	Matrix
I8	1st order
I9	Matrix

TABLE 22: BEST FITTING MODELS FOR FORMULATIONS H1 TO H9

Formulation	Best fitting model
H1	Matrix
H2	Matrix
H3	Korsemeyer Peppas
H4	Korsemeyer Peppas
H5	Korsemeyer Peppas
H6	Korsemeyer Peppas
H7	Korsemeyer Peppas
H8	Korsemeyer Peppas
H9	Korsemeyer Peppas

FTIR Study: FTIR spectrums of the drug and excipients were taken and it shows no interaction among each other.

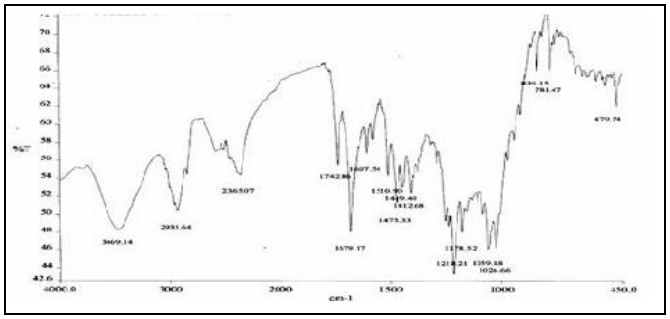

FIG. 5: FTIR SPECTRUM OF ATENOLOL

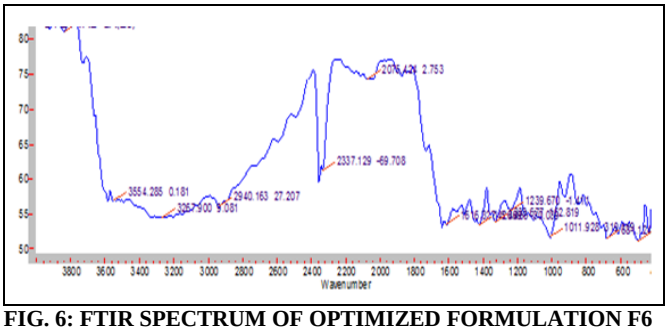

FIG. 6: FTIR SPECTRUM OF OPTIMIZED FORMULATION F6

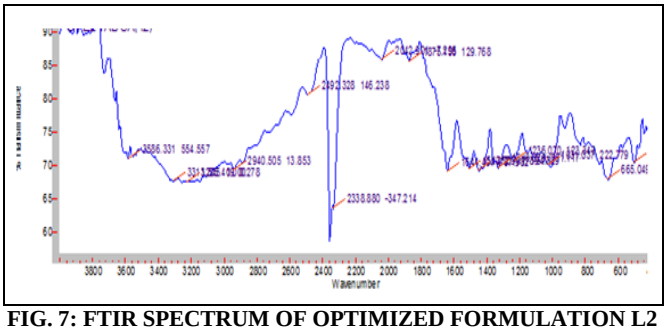

FIG. 7: FTIR SPECTRUM OF OPTIMIZED FORMULATION L2

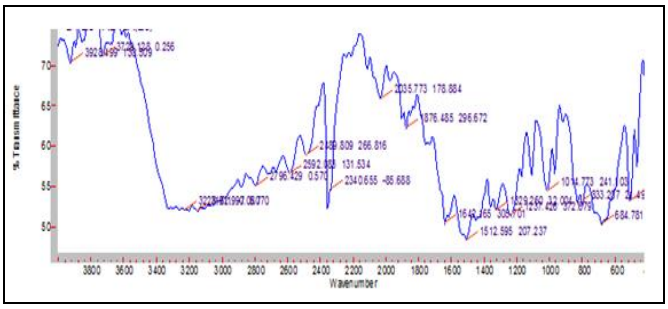

FIG. 8: FTIR SPECTRUM OF OPTIMIZED FORMULATION I2

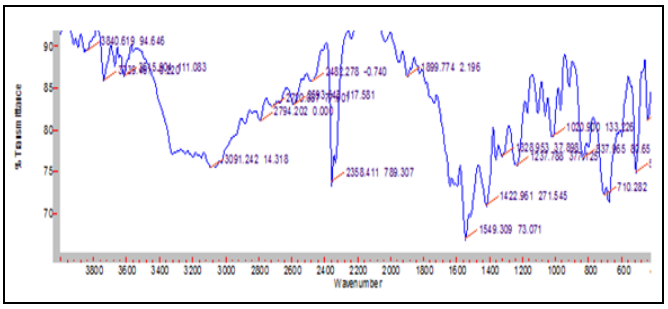

FIG. 9: FTIR SPECTRUM OF OPTIMIZED FORMULATION H4

Contact Angle Measurement: [19] The drop of phenolphthalein was placed on sintered and unsintered tablet. The droplet spreads immediately on the unsintered tablet due to more porosity while the droplet remains intact on the surface of sintered tablet due to less porosity. The effect of sintering on the wettability of the tablet surfaces was established by taking the photographs of the tablet surfaces on which drop of colored water was placed. Contact angle is indicative of the wettability of the tablet surface.

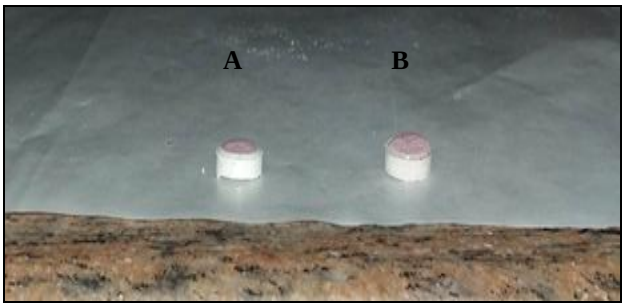

FIG. 10: (A) DROPLET IS SEEN TO BE STILL ON THE SINTERED TABLET (B) DROPLET IS SEEN TO BE IMMERSED IN THE UNSINTERED TABLET

Powder XRD Study: Following figure shows pXRD graph of Atenolol in mixture.

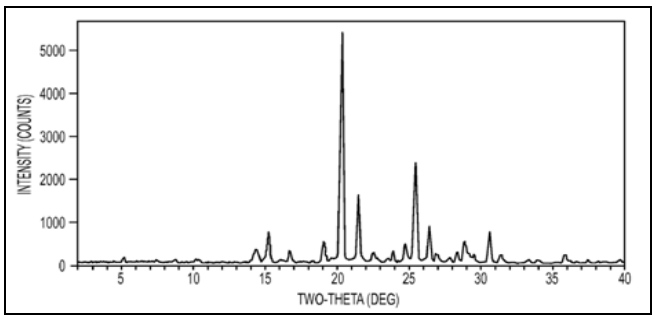

FIG. 11: pXRD GRAPH OF ATENOLOL IN MIXTURE

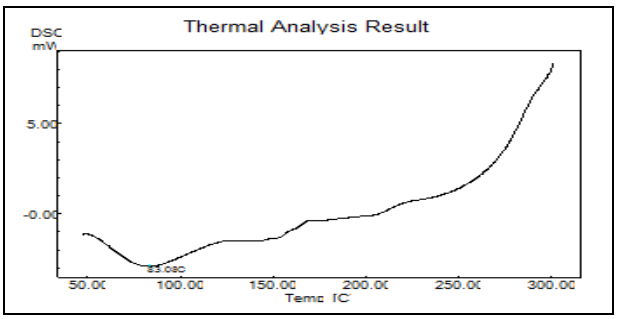

FIG. 12: DSC GRAPH OF ATENOLOL IN MIXTURE

DSC Study: Following graph shows result of differential scanning calorimetry.

Scanning Electron Microscopy (SEM) Study:

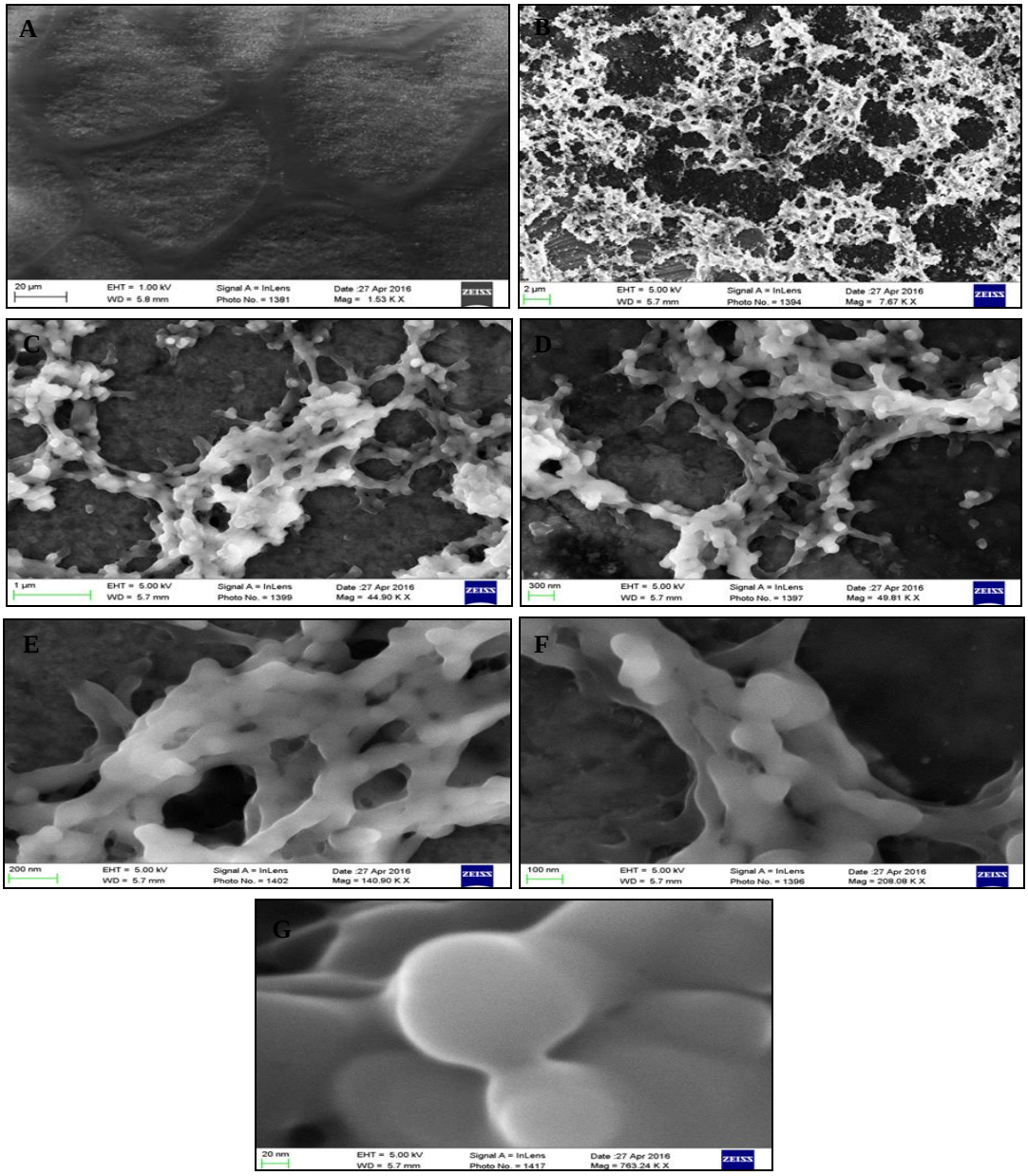

FIG. 13: SEM OF ATENOLOL WITH INCREASING SINTERING TEMPERATURE AND SINTERING TIME SEQUENCING FROM (A) TO (G)

CONCLUSION: The aim of the study was to formulate a stable as well as robust dosage form. The *in-vitro* dissolution of the test formulation is comparable with innovator reference formulation in all media. Matrix tablet of atenolol can be prepared successfully by wet granulation method using tragacanth, Eudragit polymers as retardant and by using lactose as filler. Sintering technique is optimized for the preparation of robust, effective SR tablet of atenolol. This technique describes the mechanism of strengthening the mechanical properties of consolidated pharmaceutical powders at elevated temperatures, for solid bond formation during tablet compression. In present study sintering was carried out at 60 ^{0}C, 70 ^{0}C, 80 ^{0}C for 1.5, 3, 4.5 h. Coalescence of Eudragit particles is influenced by minimum film forming temperature.

Exposure to such kind of temperature makes the structural changes in the tablet compacts that resulted in matrix tablet structure. On sintering it was found that F6, L2, I2 and H4 gave better results compared to other formulations. The aim was to release the loading dose 111 mg in first 2 h

and release the remaining amount in next 22 h and therefore thermal sintering was optimized.

On applying various models on the dissolution study release all the formulations showed matrix diffusion model. As tablets were sintered by thermal exposure, the sustained release of drug may be due to the chemical interaction with polymer. The hydrophobic properties of surfaces after sintering were increased. This correlated well with the SEM micrographs. The lower wettability is responsible for retardation of drug release due to less penetration of dissolution medium in matrix tablet.

FTIR spectrums and DSC graph of the drug and excipients were taken and it shows no interaction among each other.

The XRD study results revels that the powder characteristics were same as that of standard one after stability. The final prepared tablets were charged for stability study, samples were withdrawn and tablet showed no change in physical appearance, related substance, assay and drug release. Thus stability results prove that the formulation was stable at accelerated condition.

The final prepared tablets were charged for stability study, samples were withdrawn and tablet showed no change in physical appearance, related substance, assay and drug release. Thus stability results prove that the formulation was stable at accelerated condition. During sintering of tablets, polymer particles transform from glossy state to rubbery state and redistributed to entangle the drug particles, leading to drug release retardation.

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