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Research Paper

DEVELOPMENT & EVALUATION OF FAST DISINTEGRATING FILMS AND TABLETS OF VALSARTAN

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Orodispersible dosage forms are used for accurate dosing, enhanced bioavailability, rapid action, patient compliance, easy of administration, enhanced palatability. Valsartan is a specific and selective type-1 angiotensin II receptor antagonist which blocks the blood pressure increasing effects angiotensin II via the renin-angiotensin-aldosterone system. Valsaratan orodispersible films are prepared using all polymers HPMC E3,HPMC E15,HPMC 5cps,HPMC 15cps,HPMC 50cps, HPMC 50cps+CP in 39.68 mg., 59.52 mg quantity with different formulations with citric acid as disintegrating agent. Valsartan orodispersible tablets are prepared using different superdisintegrating agents(MCC pH101,MCC pH102, CCS, SSG, L-HPC, Crospovidone, Camphor) with different concentrations. ODF formulation F1, F5 exhibited faster disintegration time (11 sec, 13 sec) than other formulations and a drug release of 102.12%, 98.27% respectively. ODT formulations(CP+CCS), T9(efferevescence), T10(sublimation) showed faster disintegration (17,21,18 sec) and 94.18%, 92.62%, 93.54% drug release at the end of 15 minutes. By comparing the drug release studies found that ODFs drug release more than ODTs.

Keywords: Valsartan, Disintegrating films, Tablets

INTRODUCTION

Definition

Oral film is relatively a new dosage form in which thin film is prepared using hydrophilic polymers which rapidly dissolves on tongue or buccal cavity.

These thin films are also called as oro dissolving films, rapid disintegrating films (RDF), quick dissolving films (QDF), & fast mouth dissolving films (MDF).

- It facilitates Rapid onset of action and improved bioavailability.
- Useful for pediatric, geriatric patients.

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CLASSIFICATION OF ORAL FILMS

There are 3 different subtypes

1) Flash release
2) Mucoadhesive melt away wafer
3) Mucoadhesive sustained-release wafers

AIM AND OBJECTIVE

- The main aim of this study is to formulate Oral Disintegrating Films & Tablets of Valsartan to achieve rapid disintegration.
- Oral disintegrating tablets and Films of Valsartan were designed with a view to enhance the patient compliance and provide quick onset of action.

The *objectives* of ODF & ODT of Valsartan are:

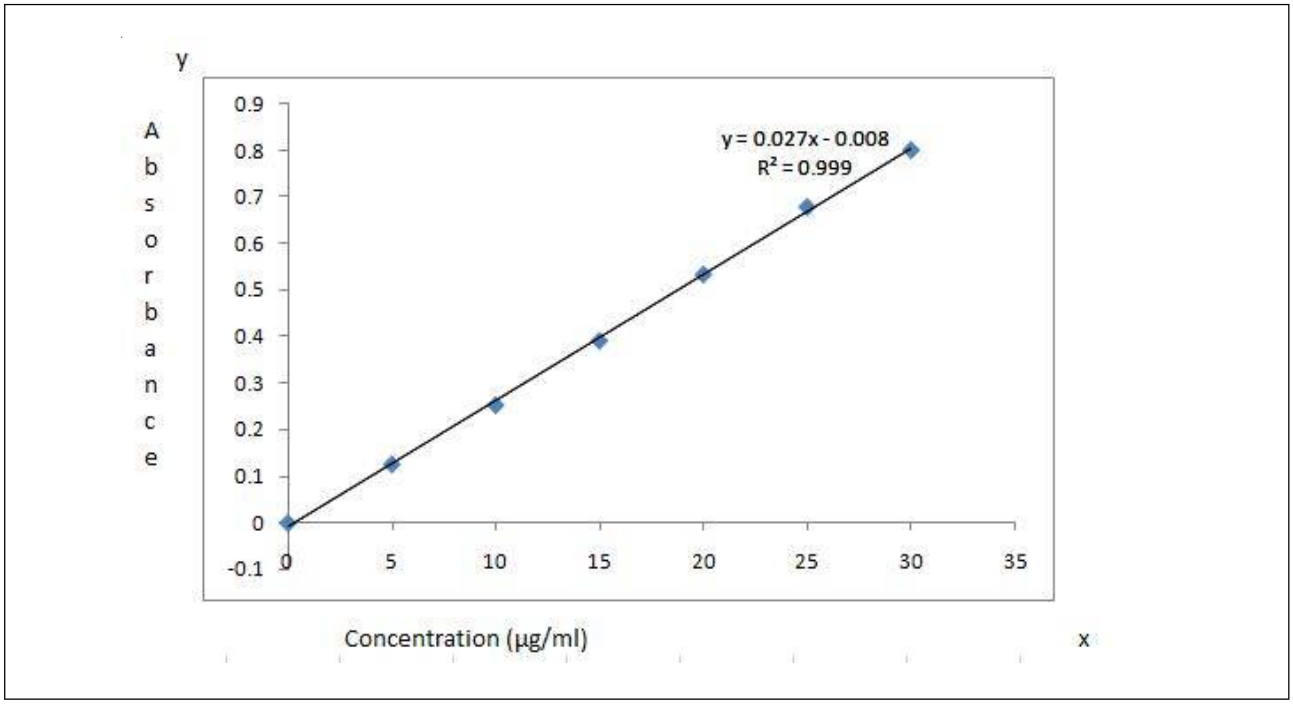
- To prepare oral disintegrating tablets of Valsartan by direct compression technique & oral disintegrating films by solvent casting method in order to achieve rapid disintegration time.
- To evaluate the Valsartan formulations by invitro and invivo taste evaluation methods and select the best formulation among them.

PLAN OF WORK

- Selection and optimization of film forming polymers to formulate Valsartan ODFs by solvent casting method.
- Selection and optimization of superdis-integrants to formulate Valsartan ODTs by direct compression method.
- To evaluate these Valsartan formulations by invitro methods and to select the best formulation among them.
- Invivo evaluation of taste, mouth feel and disintegration time of optimized Valsartan films.
- Comparison of optimized ODT formulation with conventional marketed Valsartan tablets.

RESULTS AND DISCUSSION

Standard Graph of Valsartan



Formulation of Valsartan ODF

Ingredients (mg)	Formulation code										
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Valsartan	20	20	20	20	20	20	20	20	20	20	20
HPMC E3	39.68	59.52	.....	.....	.....	.....	.....	.....	.....	.....	.....
HPMC E15	.....	.....	39.68	59.52	.....	.....	.....	.....	.....	.....	.....
HPMC 5cps	.....	.....	.....	.....	39.68	59.52	.....	.....	.....	.....	.....
HPMC 15cps	.....	.....	.....	.....	.....	.....	39.68	59.52	.....	.....	.....
HPMC 50cps	.....	.....	.....	.....	.....	.....	.....	.....	39.68	59.52	.....
HPMC 50cps+CP	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	39.68+3
Citric acid	1.89	1.89	1.89	1.89	1.89	1.89	1.89	1.89	1.89	1.89	1.89
Sodium lauryl sulphate	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56	0.56
PEG-400	0.007 ml	0.008 ml	0.007 ml	0.008 ml	0.007 ml	0.008 ml	0.007 ml	0.008 ml	0.007 ml	0.008 ml	0.007 ml
Sodium saccharine	0.944	0.944	0.944	0.944	0.944	0.944	0.944	0.944	0.944	0.944	0.944
Menthol	0.472	0.472	0.472	0.472	0.472	0.472	0.472	0.472	0.472	0.472	0.472
Erythrosine	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Dichloromethane	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml
Ethanol	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml	0.708 ml

Strips with dimensions 2×3 cm^2 after drying.

EVALUATION OF FILMS

Formulation	Appearance	Tackiness	Weight variation (mg)	Thickness (mm)	Folding endurance	Disintegration time (sec)	Drug content (%)
F1	Transparent	Non sticky	65.73±0.52	0.05±0.004	78.3±1.69	11.6±1.24	99.8±0.65
F2	Transparent	Non sticky	85.73±0.52	0.06±0.08	83.6±1.69	14±1.41	97.6±0.71
F3	Transparent	Non sticky	64.88±0.59	0.06±0.08	95.6±2.60	17.6±1.24	95.6±0.54
F4	Transparent	Non sticky	84.9±0.37	0.07±0.004	98.6±2.05	19.3±1.24	94.6±0.17
F5	Transparent	Non sticky	64.56±0.38	0.06±0.04	100±1.63	13.3±1.28	98.7±0.18
F6	Transparent	Non sticky	85.03±0.85	0.06±0.04	98.6±2.86	16.3±1.24	95.7±0.12

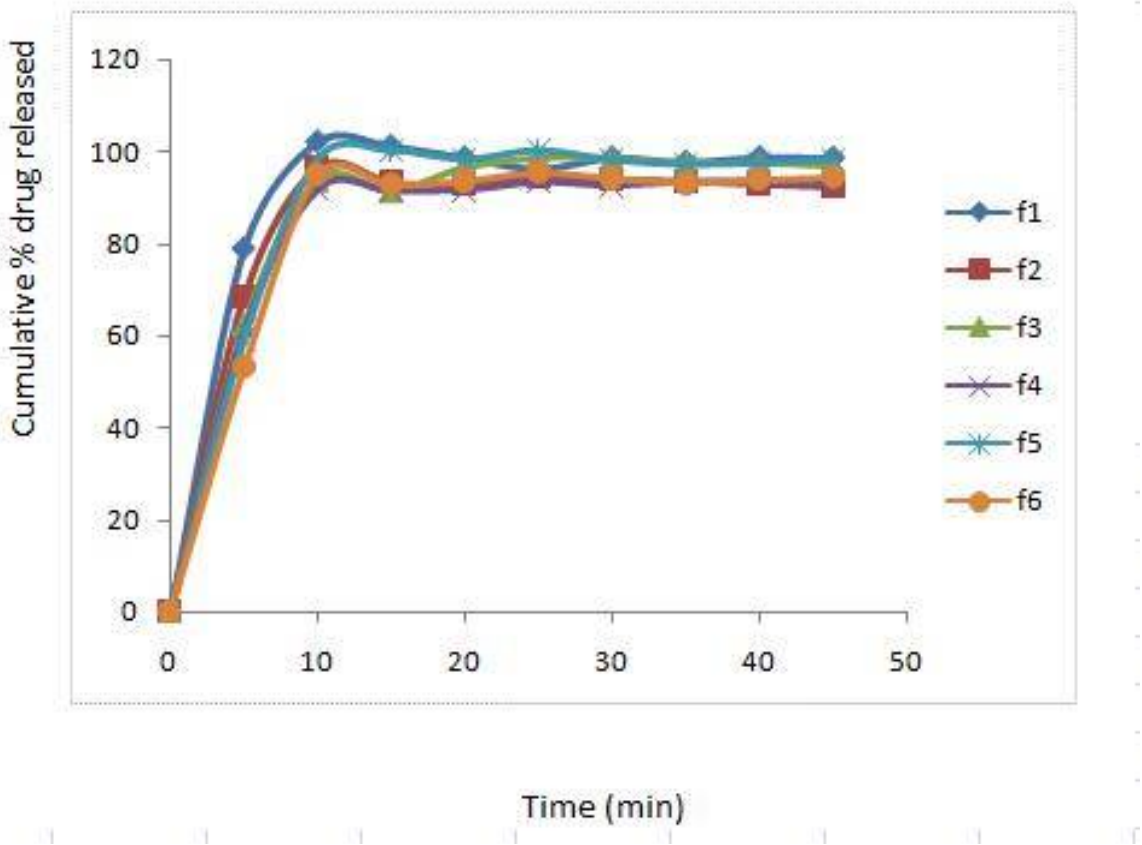
Results are expressed in terms of mean ± SD (n=3)

Formulation	Appearance	Tackiness	Weight variation(mg)	Thickness (mm)	Folding endurance	Disintegration time (sec)	Drug content (%)
F7	Transparent	Non sticky	66.87±0.54	0.06±0.08	98.6±2.49	20.3±0.94	94.1±0.18
F8	Transparent	Non sticky	84.03±0.23	0.07±0.04	103±4.08	21.6±0.94	96.4±0.11
F9	Transparent	Non sticky	66.12±0.39	0.06±0.09	116±4.89	19.1±0.94	91.4±0.12
F10	Transparent	Non sticky	86.26±0.45	0.07±0.09	108±2.44	21.1±1.24	91.2±0.18
F11	Transparent	Non sticky	65.23±0.22	0.07±0.04	98.6±2.86	16.3±0.94	93.3±0.28

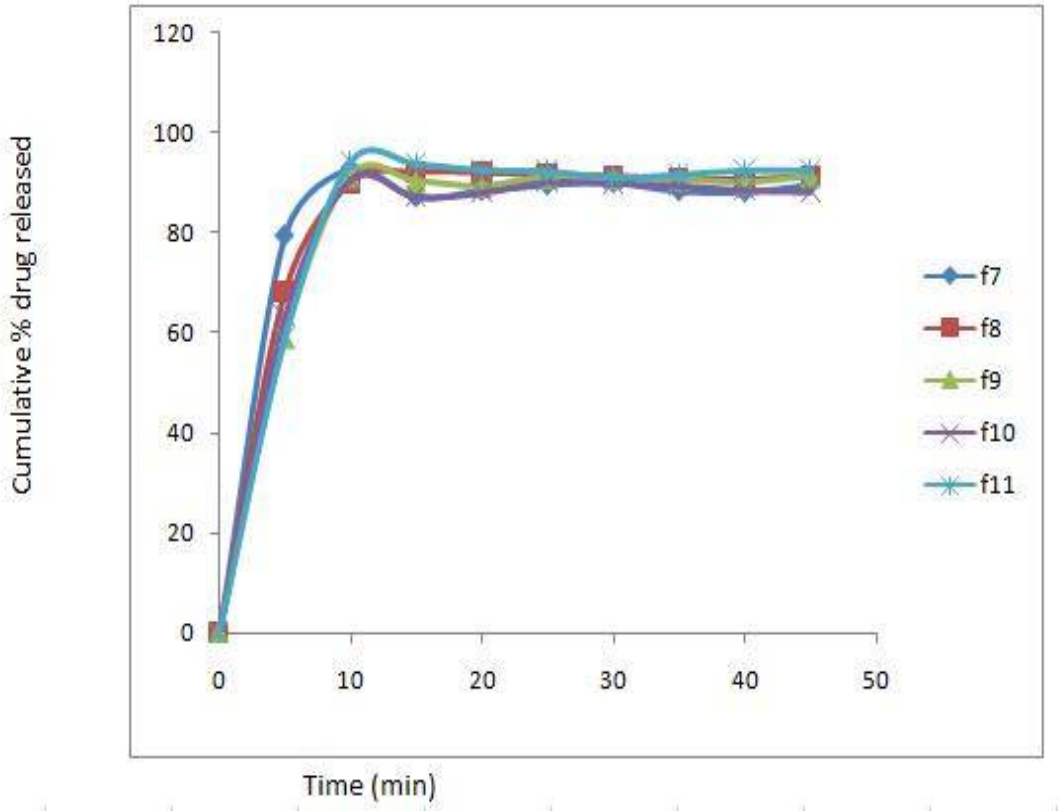
Results are expressed in terms of mean ± SD (n=3)

Dissolution of films

Time	Formulation code					
(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	78.84	68.28	62.12	61.12	59.29	53.12
10	102.12	96.24	93.57	91.82	98.27	94.78
15	101.16	93.12	91.24	91.56	100.18	92.72
20	98.68	92.72	96.24	91.72	98.27	93.55
25	96.24	94.12	98.37	93.43	100.18	95.34
30	98.68	93.78	98.24	92.76	98.16	94.14
35	97.7	93.36	97.18	93.48	97.12	93.16
40	98.72	92.78	97.36	93.48	97.54	93.72
45	98.57	92.19	96.57	92.7	98.19	94.28



Time		Formulation code			
(min)	F7	F8	F9	F10	F11
0	0	0	0	0	0
5	79.39	68.24	59.12	63.31	58.82
10	92.79	90.12	91.38	90.67	94.16
15	87.12	92.28	90.38	87.26	93.78
20	88.39	92.12	89.36	88.12	92.58
25	89.57	91.79	91.26	90.26	92.34
30	90	91.47	91.14	90.02	91.02
35	88.34	90.82	90.78	89.58	91.68
40	88.12	90.69	90.09	88.62	92.45
45	89.56	91.54	91.39	88.32	92.59



Invivo Evaluation of Films

- The optimized Valsartan films were tested for taste, mouth feel & disintegration time in a panel of 10 subjects in *invivo*.
- The films were placed on the tongue and the taste, mouth feel and disintegration time were recorded.
- z- Bitter
- zz- Slightly bitter
- zzz- Acceptable

Formulation F1	Taste	Mouth feel	*In vivo* Disintegration time
Subject 1	+++	+++	+++ (8 sec)
Subject 2	+++	+++	+++ (7 sec)
Subject 3	+++	+++	+++ (8 sec)
Subject 4	+++	+++	+++ (8 sec)
Subject 5	+++	+++	+++ (7 sec)
Subject 6	+++	+++	+++ (7 sec)
Subject 7	+++	+++	+++ (7 sec)
Subject 8	+++	+++	+++ (7 sec)
Subject 9	+++	+++	+++ (8 sec)
Subject 10	+++	+++	+++ (8 sec)

Formulation F5	Taste	Mouth feel	*In vivo* Disintegration time
Subject 1	+++	+++	+++ (10 sec)
Subject 2	+++	+++	+++ (10sec)
Subject 3	+++	+++	+++ (11sec)
Subject 4	+++	+++	+++ (10 sec)
Subject 5	+++	+++	+++ (11 sec)
Subject 6	+++	+++	+++ (11 sec)
Subject 7	+++	+++	+++ (10 sec)
Subject 8	+++	+++	+++ (11 sec)
Subject 9	+++	+++	+++ (10 sec)
Subject 10	+++	+++	+++ (11 sec)

Formulation of Valsartan ODTs

Formulation of Fast dissolving tablets of Valsartan										
Ingredients (mg)	Formulation code									
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
Valsartan	40	40	40	40	40	40	40	40	40	40
Microcrystalline cellulose pH 101	20	20	20	.....	.....	.....	.....	20	20	20
Mannitol	78.5	78.5	78.5	78.5	78.5	78.5	78.5	69.5	64.5	48.5
Sodium starch glycolate	3	3	.....	3	.....	.....	.....	.....	.....	.....
Crosscaramelloe sodium	3	.....	3	.....	3	.....	.....	.....	.....	.....
Cross povidone	.....	3	3	.....	.....	3	.....	.....	.....	.....
L-HPC	.....	.....	.....	.....	.....	.....	3	.....	.....	.....
MCC pH102	.....	.....	.....	23	23	23	23	.....	.....	.....
Camphor	.....	.....	.....	.....	.....	.....	.....	15	20	.....
Sodium bicarbonate	.....	.....	.....	.....	.....	.....	.....	.....	.....	20
Citric acid	.....	.....	.....	.....	.....	.....	.....	.....	.....	16
Sodium saccharine	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	1	1	1	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2	2	2	2
Total weight	150	150	150	150	150	150	150	150	150	150

Preformulation characteristics of Valsartan ODTs

Formulation code	Angle of repose (°)	Bulk density (gm/cm^3)	Tapped density (gm/cm	Carr's index (%)	Hausner's ratio
T1	23.19±0.63	0.55±0.34	0.64±0.13	16.36±0.24	1.16±0.12
T2	24.1±0.75	0.53±0.12	0.6±0.12	13.2±0.12	1.13±0.05
T3	24.77±0.56	0.5±0.17	0.58±0.24	16±0.19	1.16±0.02
T4	25.27±0.34	0.51±0.18	0.58±0.28	13.72±0.13	1.13±0.02
T5	25.97±0.28	0.53±0.28	0.61±0.19	15.09±0.32	1.15±0.05
T6	26.56±0.78	0.51±0.27	0.6±0.11	20±0.19	1.17±0.05
T7	29.19±0.91	0.5±0.24	0.59±0.27	18±0.34	1.18±0.02
T8	27.82±0.56	0.5±0.25	0.6±0.34	20±0.27	1.2±0.08
T9	24.1±0.94	0.52±0.28	0.62±0.22	19.23±0.12	1.19±0.03
T10	29.93±0.32	0.51±0.35	0.63±0.12	19.6±0.24	1.19±0.07

Results are expressed in terms of mean±SD (n=3)

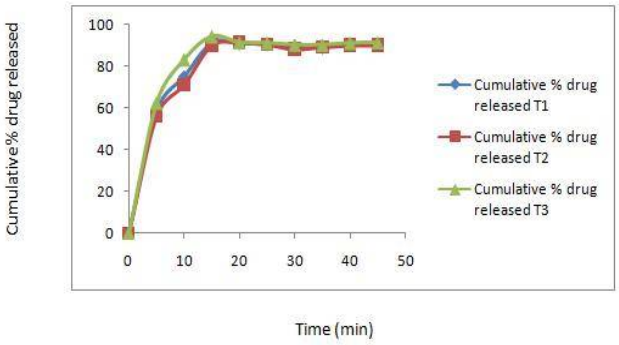
Tabletting characteristics of Valsartan ODTs

Formulation code	Thickness (mm)	Weight variation(mg)	Hardness (kg/cm^3)	Friability (%)	Disintegraton time(sec)	Wetting time(sec)	Water absorption ratio(%)	Drug content (%)
T1	4.02±0.07	150±0.007	2.2±0.02	0.066±0.03	21±2.00	23±1.00	61±1.33	93.67±0.65
T2	4.10±0.15	150±0.101	2.1±0.10	0.51±0.07	20±1.00	22±1.00	62±1.24	98.02±0.42
T3	4.08±0.12	151.20±0.004	2.1±0.09	0.35±0.06	16±1.00	17±1.00	68±0.98	101.34±0.87
T4	4.02±0.04	152.07±0.024	2.0±0.02	0.15±0.06	26±1.00	27±0.00	64±1.03	91.69±0.43
T5	4.06±0.04	149.03±0.003	2.4±0.02	0.05±0.06	24±2.00	26±1.00	62±1.12	94.29±1.11
T6	4.02±0.09	152.08±0.105	2.1±0.02	0.15±0.05	23±1.00	25±1.00	61±1.27	91.02±0.37
T7	4.08±0.08	154.17±0.213	2.2±0.03	0.14±0.04	30±0.00	31±1.00	63±1.51	92.08±0.56
T8	4.02±0.03	152.11±0.101	2.9±0.03	0.75±0.01	22±1.00	24±1.00	59±1.76	92.37±0.73
T9	4.06±0.02	150.45±0.92	2.2±0.02	0.23±0.03	19±2.00	21±2.00	65±1.12	99.72±0.92
T10	4.07±0.07	151.01±0.199	2.1±0.02	0.07±0.02	17±1.00	18±0.00	65±1.02	100.76±0.82

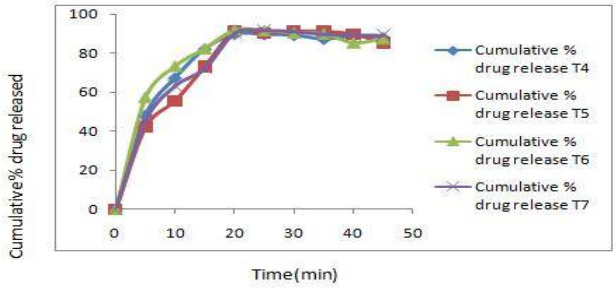
Results are expressed in terms of mean±SD (n=3)

Dissolution of Valsartan ODTs

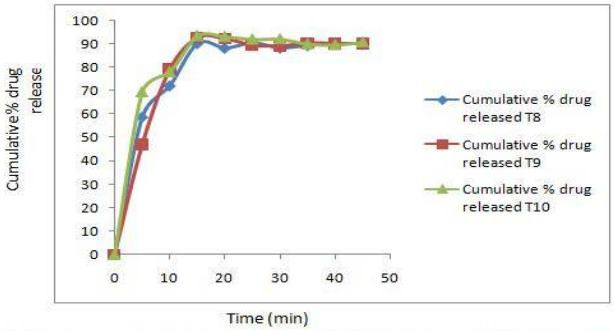
Time (min)	Cumulative % drug released		
	T1	T2	T3
0	0	0	0
5	58.75	56.22	62.28
10	75.12	71.22	83.1
15	91.29	90.15	94.18
20	91.09	91.57	91.29
25	90.57	90.59	91.09
30	89.34	88.28	90.22
35	89.21	89.38	90.17
40	90.19	90.12	91.09
45	90.27	90.16	91.33



Time (min)	Cumulative % drug release			
	T4	T5	T6	T7
0	0	0	0	0
5	48.22	42.03	57.15	45.29
10	67.39	55.67	73.18	63.18
15	82.18	73.3	82.12	72.12
20	89.76	91.27	91.59	90.18
25	89.57	90.29	91.36	91.63
30	89.2	91.35	90.22	91.01
35	87.25	91.27	89.72	89.69
40	88.68	89.79	85.08	89.25
45	88.09	85.43	87.12	89.07

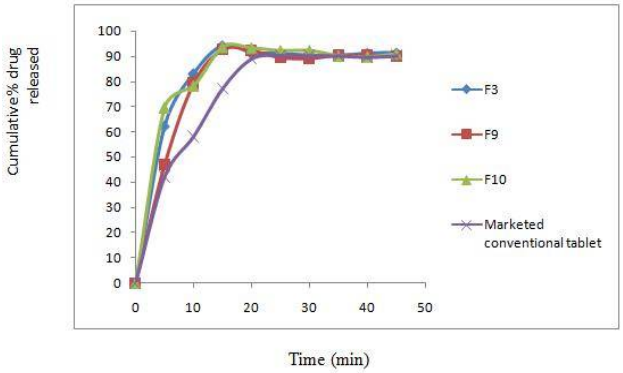


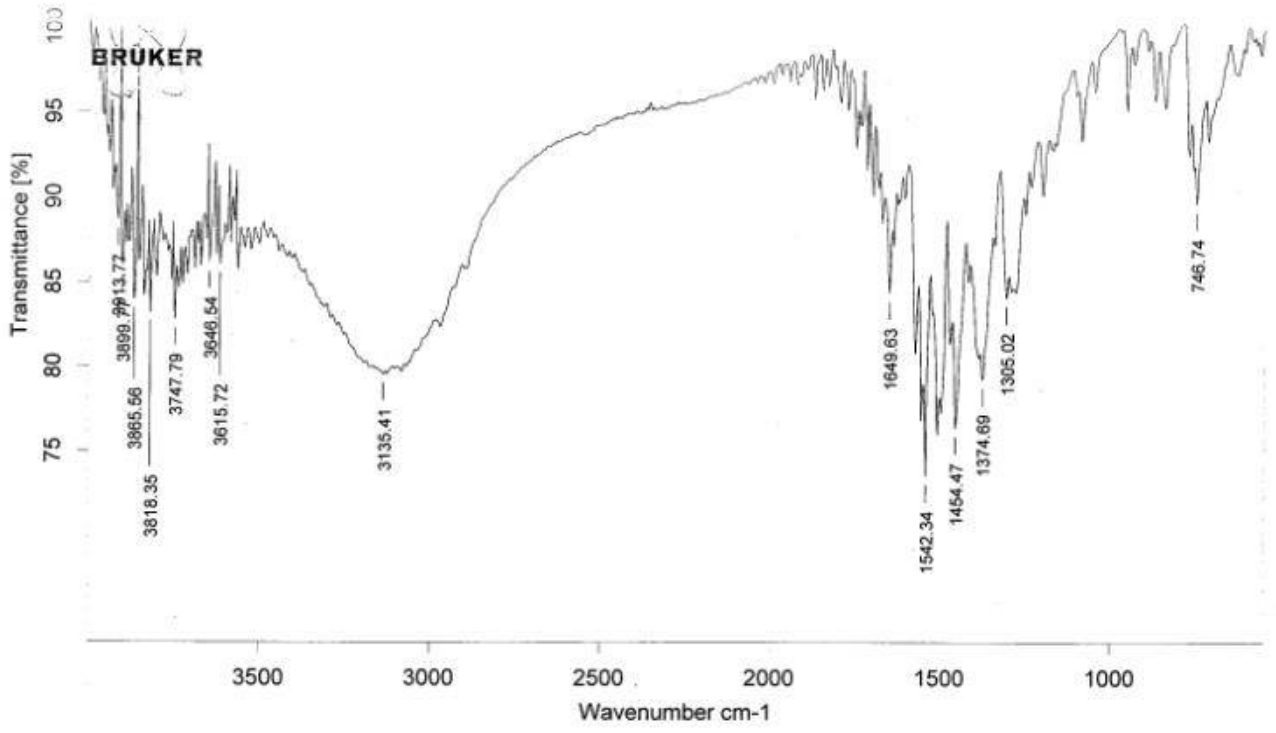
Time (min)	Cumulative % drug released		
	T8	T9	T10
0	0	0	0
5	58.72	47.01	69.59
10	72.14	79.19	78.17
15	90.21	92.62	93.54
20	88.21	92.15	93.22
25	90.38	89.39	92.1
30	88.28	89.12	92.18
35	89.34	90.34	90.09
40	90.11	90.12	89.72
45	90.01	90.07	90.89



Comparison of optimized Valsartan ODTs with conventional marketed Valsartan tablet

Time (min)	Cumulative % drug release			
	T3	T9	T10	marketed conventional tablet
0	0	0	0	0
5	62.28	47.01	69.59	42.18
10	83.1	79.19	78.17	58.22
15	94.18	92.62	93.54	77.29
20	91.29	92.15	93.22	89.02
25	91.09	89.39	92.1	90.34
30	90.22	89.12	92.18	90.22
35	90.17	90.34	90.09	90.12
40	91.09	90.12	89.72	89.57
45	91.33	90.07	90.89	90.12




BRUKER
Transmittance [%]
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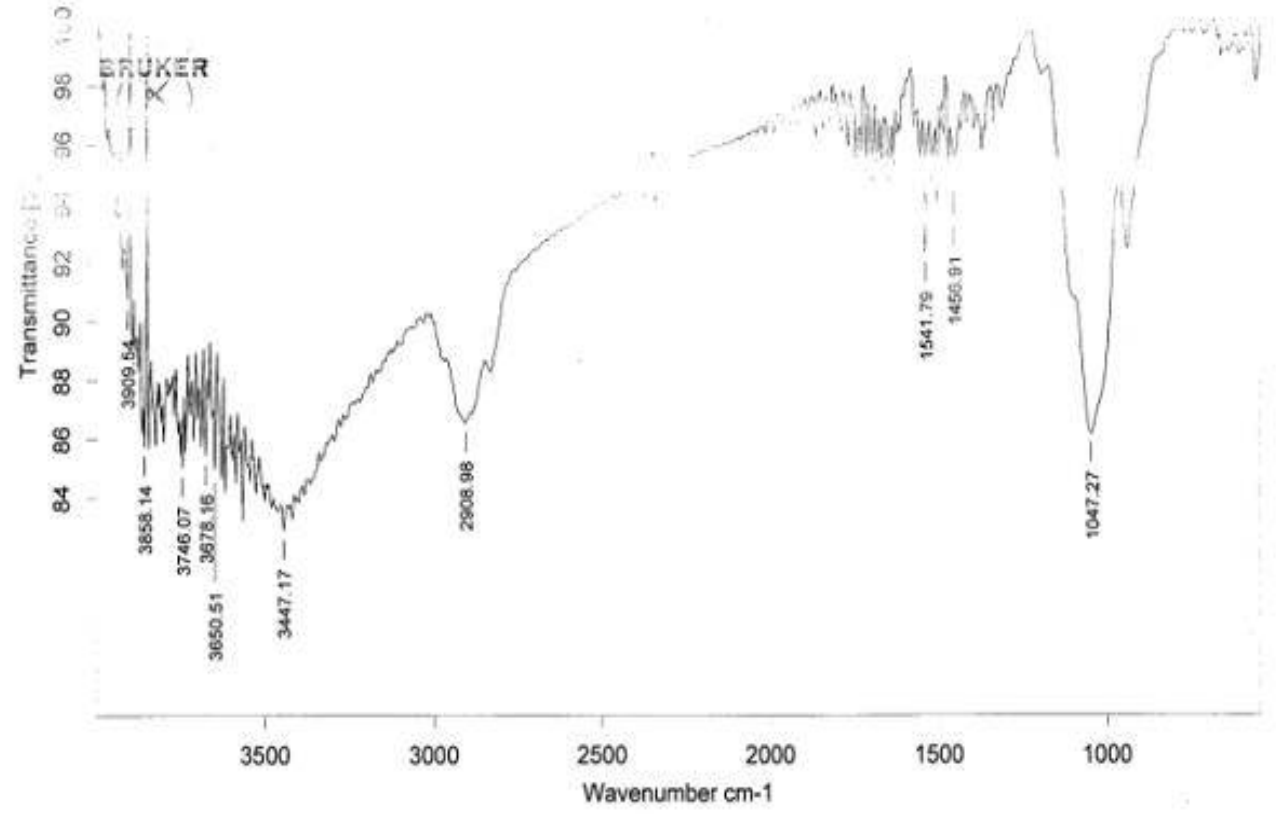
95
90
85
80
75
3899.72
3865.56
3818.35
3747.79
3646.54
3615.72
3135.41
1649.63
1542.34
1454.47
1374.69
1305.02
746.74
3500
3000
2500
2000
1500
1000
Wavenumber cm-1


BRUKER
Transmittance [%]
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96
92
90
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3858.14
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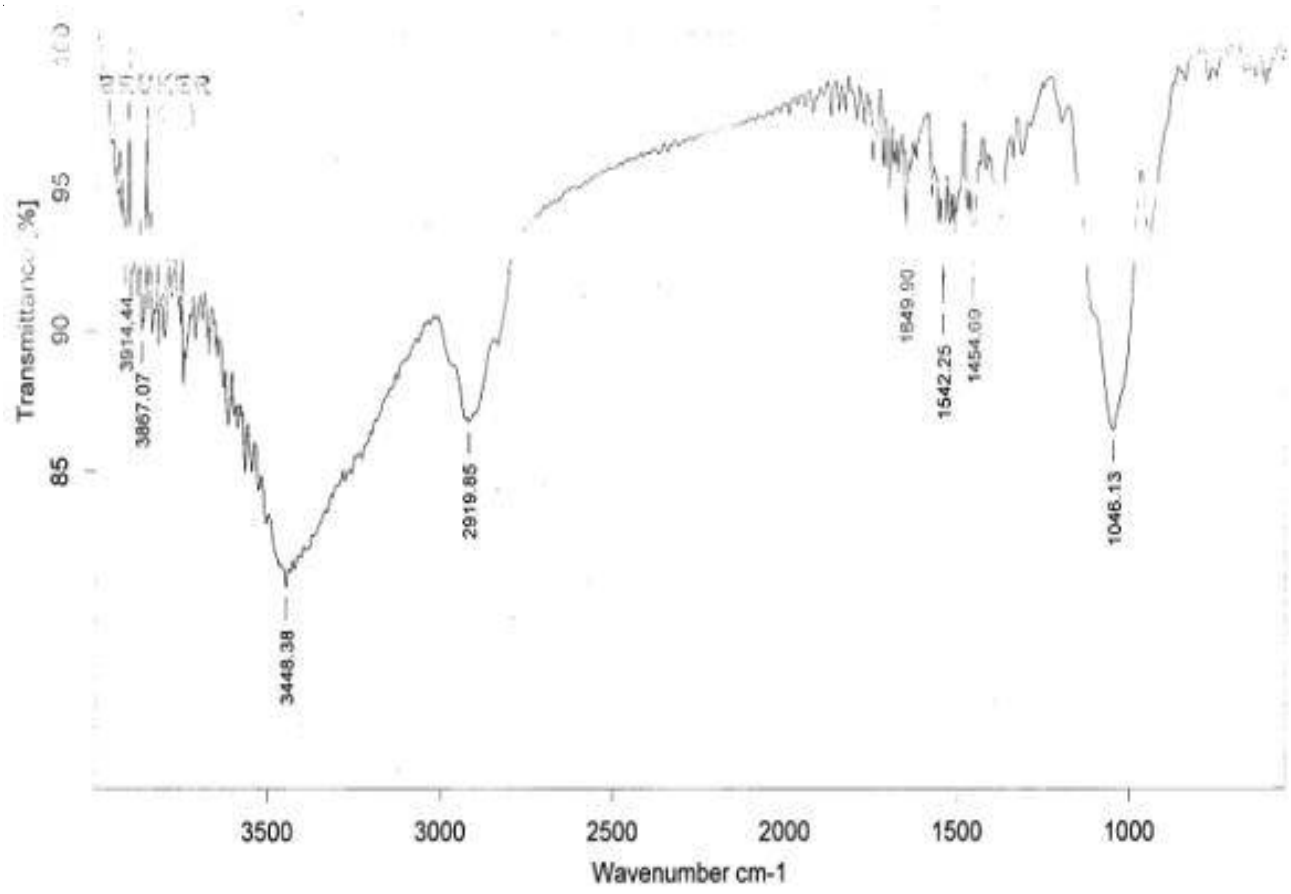
3500
3000
2500
2000
1500
1000
Wavenumber cm-1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2500
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1500
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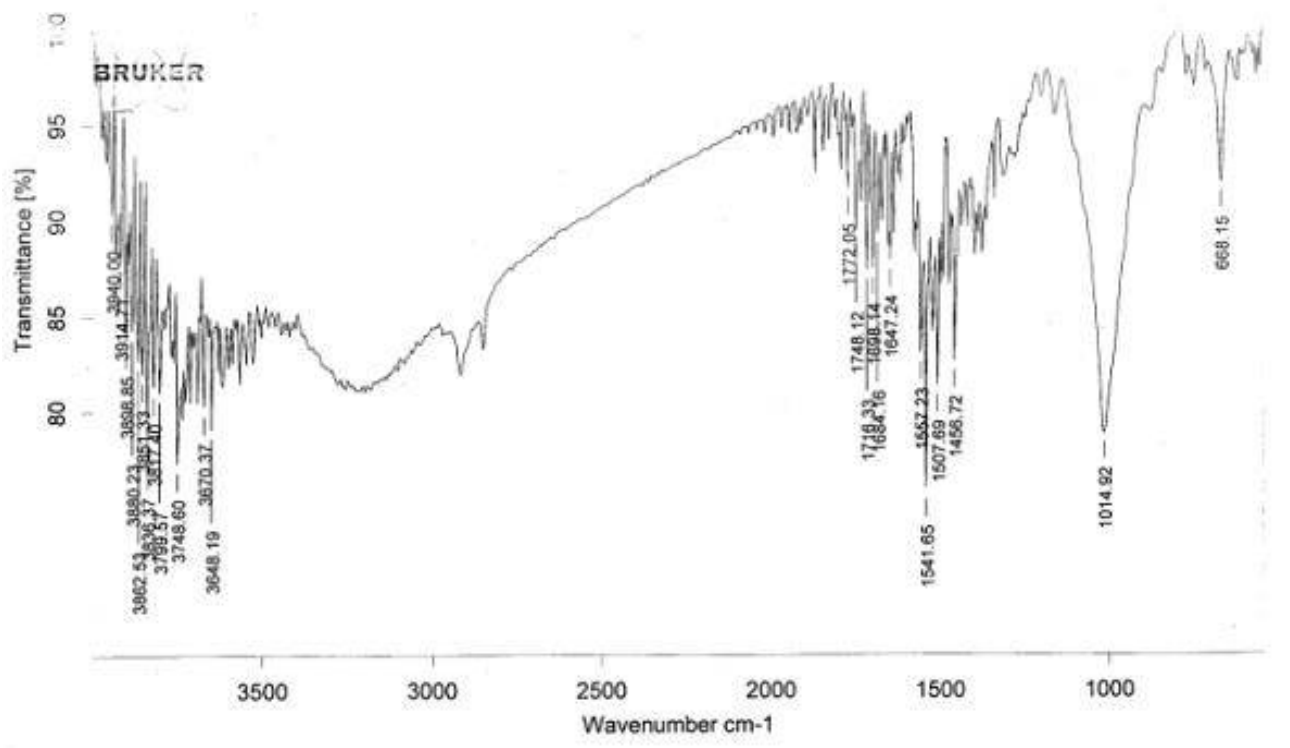
Wavenumber cm-1


BRUKER
Transmittance [%]
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1748.12
1718.33
1684.16
1647.24
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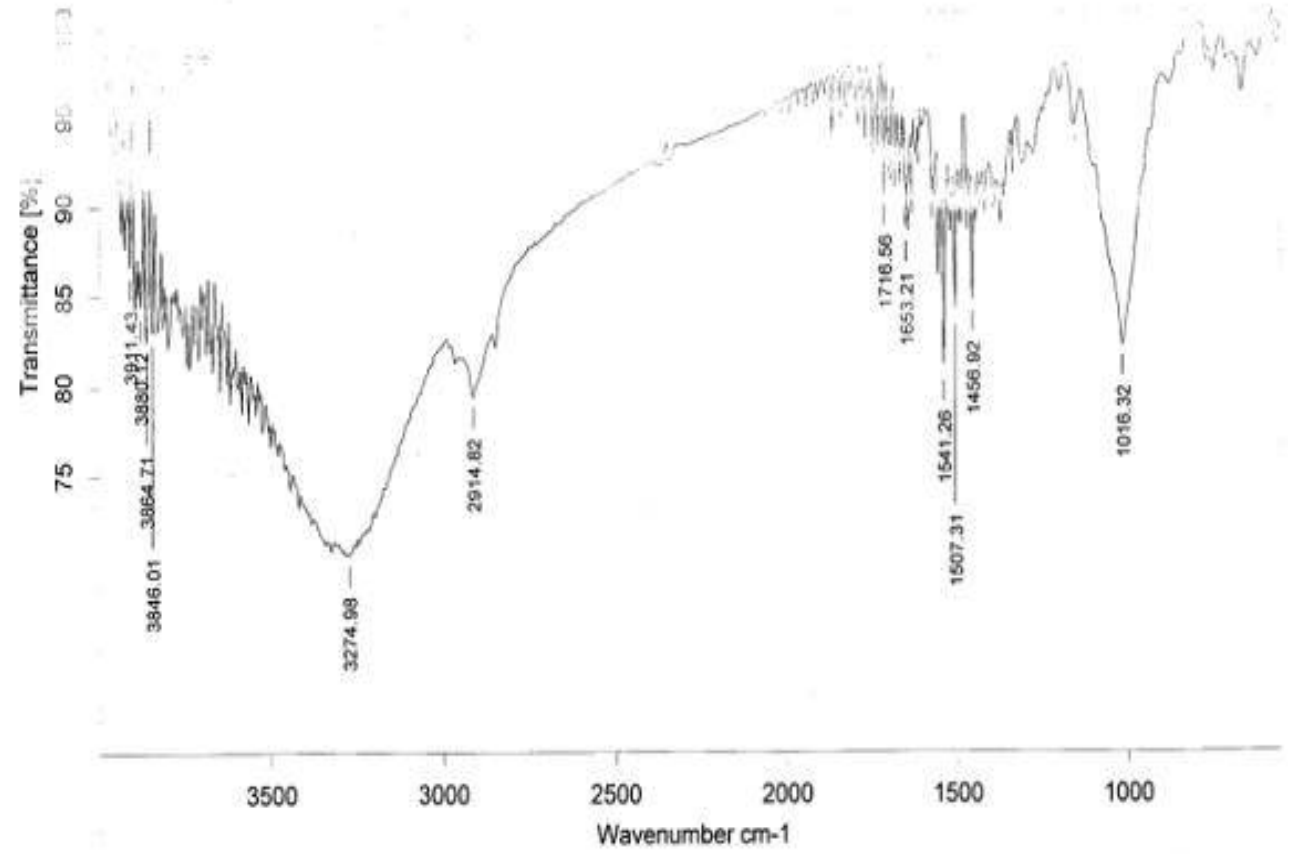
3500
3000
2500
2000
1500
1000
Wavenumber cm-1


Transmittance [%]
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80
85
90
95
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3807.12
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1507.31
1456.92
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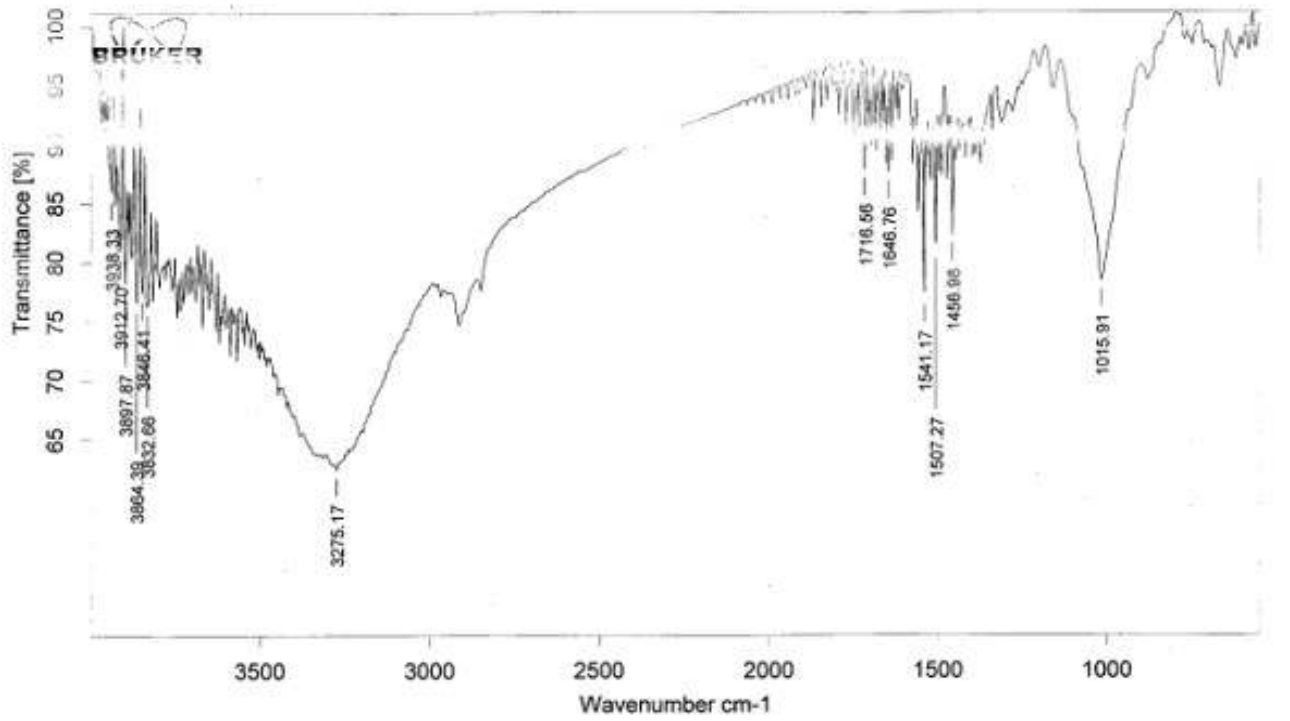
3500
3000
2500
2000
1500
1000
Wavenumber cm-1


BRUKER
Transmittance [%]
65
70
75
80
85
90
95
100
3864.38
3832.66
3897.87
3912.70
3938.33
3846.41
3275.17
1716.56
1646.76
1541.17
1507.27
1456.98
1015.91
3500
3000
2500
2000
1500
1000
Wavenumber cm-1

FTIR STUDIES

Infra-Red band assignments for Valsartan, Optimized formula F1, F3, F5, T3, T9, T10

IR Spectra	Peak of Functional groups [wavelength (cm^{-1})]			
	CH (Aliphatic)	C-O(Carboxylic acid)	C-H (Aliphatic)	C=O (Amide)
VAL	3615.72	1542.34	3135.41	1649.63
F1	3613.90	1541.17	3125.60	1649.90
F3	3610.17	1541.79	3128.19	1636.72
F5	3612.38	1542.25	3132.98	1642.25
T3	3610.37	1541.85	3134.17	1647.24
T9	3615.08	1541.26	3128.22	1641.26
T10	3612.05	1541.17	3133.85	1646.76

FTIR STUDIES

- The above peaks can be considered as characteristic peaks of Valsartan. These peaks were not affected and prominently observed in IR spectra of Valsartan along with polymers. This indicates there is no interaction between Valsartan and polymers. (The formulation F1 contains HPMC E3, F3 contains HPMC E15, F5 contains HPMC 5cps, T3 contains CCS+CP, T9 contains Camphor, and T10 contains Sodium bicarbonate and Citric acid.)

CONCLUSION

- Oral Disintegrating Tablets & Films of Valsartan were formulated with an aim to improve the versatility, patient compliance and rapid onset of action. The formulations were developed with an objective to use by the geriatric and mentally disabled patients.
- Valsartan Oral Disintegrating Films were prepared by solvent casting method using different grades of Hydroxy Propyl Methyl Cellulose like HPMC-E3, HPMC-E15, HPMC 5cps, HPMC 15cps, HPMC 50cps in the ratio of 1:2 (drug: polymer) and 1:3.
- Of the 11 ODF formulations, formulation F1, F5 exhibited faster disintegration time (11 sec, 13 sec) than other formulations and a drug release of 102.12%, 98.27% respectively.
- Valsartan ODTs were prepared by direct compression method using combination of super disintegrants (F1-F3)
- Formulations of F4-F7 were prepared by direct compression method using 2% of different super disintegrants
- Formulations of F8, F9 were formulated by sublimation and F10 by effervescence method.
- Formulations of CP+CCS (T3), effervescence (T10) and sublimation (T9) showed better disintegration.
- Among the ODT formulations T3, T9, T10 showed faster disintegration(17,21,18 sec) and 94.18%, 92.62%, 93.54% drug release at the end of 15 minutes.
- The drug release was found to be fast in ODFs than ODTs.

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