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FORMULATION AND CHARACTERIZATION OF ORAL DISINTEGRATING TABLETS OF VALSARTAN BY SUBLIMATION AND EFFERVESCENCE METHODS

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ABSTRACT

The purpose of this research is to develop Oral Disintegrating tablets 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 ODTs were prepared by direct compression method using combination of super disintegrants and compare with sublimation and effervescent methods,prepared ODTs showed good physicochemical properties and compile with official pharmacopeial limits ,FTIR & DSC studies indicated that valsartan drug was pure and not show any incomparability with other excipients used for formulation development, Formulations of CP+CCS (T3), effervescence (T10) and sublimation (T9) showed better disintegration. Order of the superdisintegrant activity is as follows: (CP+CCS)> (CP+SSG)> (CCS+SSG), 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.

INTRODUCTION:

Orally disintegrating tablets (ODTs) rapidly disintegrate in the mouth without chewing upon oral administration and without the need for water, unlike other drug delivery systemss and conventional oral solid immediate-release dosage forms. ODT dosage form; also commonly known as fast melt, quick melts, fast disintegrating and orodispersible systems have the unique property of disintegrating the tablet in the mouth in seconds. For acute conditions, this dosage form is easier for patients to take anytime, anywhere those symptoms occur. For chronic conditions, it is assumed to improve compliance. Some important advantages of ODT drug delivery over others are ease of swallowing for patients and convenience of taking the medication anytime without the need of water. Some limitations include difficulty in developing extremely high doses (typically in excess of 500mg) and sometimes-extensive taste masking of bitter tasting actives (Parakh S.R. et.al.2003;William R.P.et.al 2005) Orally

disintegrating dosage forms are often formulated for existing drugs with an intention to extend the patent life of the drug through product differentiation. They are evaluated against the innovator drug in a bioequivalence study in humans to establish comparability of pharmacokinetic parameters. Drug delivery systems are technologies that transport the active drug into the body's circulatory system. Drug can be delivered into the body by various means, depending on its physical and chemical properties. Some may alter the method of taking the drug; others alter the desired therapeutic activity(Suresh Bandari .et.al.2008; Jaccard T.T.et.al.1985)

Valsartan is an ARB(angiotensin II receptor blockers) that selectively inhibits the binding of angiotensin II to AT1, Slightly soluble in water, soluble in alcohol, Valsartan is rapidly absorbed after oral administration. Plasma levels peak 2-4 h after oral administration, the bioavailability is 25%, In healthy volunteers, it is reported that valsartan is well tolerated after single and multiple dosing (5,9,10). No adverse signs or symptoms or changes in the clinical laboratory parameters were observed that could be associated with valsartan. Headache, cough, dizziness, and fatigue were the most common symptoms reported, dosage is 40 to 160 mg twice a day(C.P.Jain .et.al.2009)

In present work the main aim of this study is to formulate Oral Disintegrating Tablets of Valsartan by using of sublimation and effervescence methods to achieve rapid disintegration, Release was compared with that of marketed conventional tablet.

1. MATERIALS & METHODS

2.1. MATERIALS

Valsartan was procured from Aurobindo Laboratories, Hyd, Sodium starch glycolate Cross povidone, Cross carmellose sodium, Sodium bicarbonate, Citric acid, Camphor, Mannitoi, Avicel PH 101 &102, Sodium saccharine Magnesium stearate, talc as a gift sample and other chemicals and solvents were of analytical grade/IP/equivalent grade and procured from laboratory.

2.2. DRUG EXCIPIENTS COMPATIBILITY STUDIES

2.2.1 Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

2.2.2. Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug, individual polymers and optimised formulations were subjected to the study. Five to ten milligrams was taken in the pierced DSC aluminum pan and scanned in the temperature range of 25–220 °C. The heating rate was 10°C/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyzer (DSC 822, Mettler Toledo, Switzerland) was used for this purpose.

2.3. EVALUATION OF TABLETS

2.3.1. Physical evaluation

The flow properties of the prepared granules were determined by the angle of repose, by using fixed funnel method. The bulk and tapped densities for the prepared granules were determined by tapping method and the compressibility index was calculated by using the data. The tablets were evaluated for thickness, diameter, weight variation, hardness, friability using

the reported procedure. The thickness and diameter of the tablets were carried out using vernier calipers. Weight variation was performed according to the U.S.P procedure. Hardness was determined by using A Monsanto hardness tester. Friability was determined using Roche friability testing apparatus

2.3.2. Drug content estimation

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 10 ml of 6.8 buffer was added and then the solution was subjected to sonication for about 20 min. The solution was made up to the mark with 6.8 buffer. The solution was filtered. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 250nm by using UV-Visible spectrophotometer.

2.3.3. Wetting time and Water absorption ratio (R):

The wetting time of the tablet was measured by placing five circular tissue papers (10 cm in diameter) in a Petri dish of 10 cm diameter. Water (10 ml) containing methylene blue (0.1% w/v) was added to the Petri dish. A tablet was carefully placed on the surface of the tissue paper and the time required for the dye to reach the upper surface of the tablet was recorded as wetting time. The measurements were carried out in triplicate. Water absorption ratio can be calculated using:

Water absorption ratio = $100 (W_a - W_b)/ W_b$

Where,

W_b = weight of tablet before absorption of water and

W_a = weight of tablet after absorption of water.

2.3.4 Disintegration Time:

For this purpose, a petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the petridish and the time for the tablet to completely disintegrate into fine particles was noted using a stop watch.

***2.3.5. In-vitro* dissolution studies:**

In-vitro dissolution study of the prepared formulations was carried out in USP rotating paddle method (apparatus 2). 6.8 p^H phosphate buffer was used as dissolution medium (900 ml). 5 ml of aliquot was withdrawn at the specified time intervals (5, 10, 15, 20, 25, 30, 35, 40 and 45 min) filtered through whatmann filter paper and absorbance was measured spectorphotometrically at 250nm.An equal volume of fresh medium, which was pre warmed at 37^0c, was replaced into dissolution media after sampling to maintain the constant volume throughout the test.

2. RESULTS AND DISCUSSION

3.1. Drug excipients compatibility studies

3.1.1 Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra of IR spectrum of pure Valsartan, optimized ODT formulations T3, T9, T10, optimized formulations of ODF F1 & F5 were recorded. The scans were evaluated for presence of principal peaks of drug, shifting and masking of drug peaks due to presence of polymer. Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and excipients, samples were analyzed over the range 400 – 4000 cm−1. The peak functional groups present in Valsartan were given in **Table 3 & Figure 1-4.**

The peaks can be considered as characteristic peaks of Valsartan. These peaks were not affected and prominently observed in IR spectra of Valsartan along

with disintigrants. This indicates there is no interaction between Valsartan and disintegrates. (The formulation T3 contains CCS+CP, T9 contains Camphor, and T10 contains Sodium bicarbonate and Citric acid.)

1.2. Differential Scanning Calorimetry (DSC)

The purity of drug (valsartan) was determined by Differential Scanning Calorimetry (DSC). Its melting thermogram is shown in Fig 5. The reported melting point is in the range of 105-110 °C and the DSC thermogram of valsartan showed a sharp melting endothermic peak at **105.49 °C** indicating the purity of drug.

3.1.3 Physical properties of powdered blends

The granules of eight formulations were evaluated for angle of repose, bulk density, tapped density, Carr' index and Hausner's ratio showed in Table 4. It was found that formulations, the granules have excellent flow property as they showed the angle of repose value less than 30. Carr's index value was found to be less than 20 good flow property. Hausner's ratio also showed good flow property.

3.1.4 Physicochemical properties of Valsartan Orally Disintegrated Tablets

The tablets were prepared by direct compression method and evaluated for thickness, weight variation; hardness, friability, in-vitro disintegration, assay and in-vitro release studies and results were reported in table 5. In all formulations, tablet weight was found to be 149.03±0.3mg to 154.1±0.21mg, which was in pharmacopoeial limits. The thickness varies between 2.02±0.09mm to 2.08± 0.08mm. Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.0± 0.02kg to 2.9±0.03kg for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 91.0 ± 0.32% - 101.3 ± 0.08% of Valsartan, which was within the acceptable limits.

Wetting time was determined for all the formulations. The values lie between17 - 31 sec. The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant affected the wetting of the tablets. On comparing the superdisintegrants the formulations containing crosspovidone+ crosscarmellose sodium and crosspovidone + SSG take less wetting time than the other formulations containing single superdisintegrants. The wetting time of tablets prepared by sublimation and effervescence method was also found to be less. Water absorption ratio ranged from 59±1.76% to 68 ± 0.98%. Crosspovidone and Crosscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling.

Disintegration time is considered to be important criteria in selecting the best ODT formulation. The *in-vitro* disintegration time for all the ten formulations varied from 16 to 30 seconds. The rapid disintegration was seen in the formulations containing combination of superdisintegrants (CP+CCS) and in the formulations prepared by Sublimation and Effervescence methods. This is due to rapid uptake of water from the medium, swelling and burst effect. The disintegration time of formulation (T3) containing 2%CP+ 2%CCS, (T9) tablets prepared by sublimation method, (T10) tablets prepared by effervescence method was found to be 16 sec, 19 sec and 17 sec which were lower than other formulations and was selected as the best ODT formulation among all the 10 formulations.

Table 1: Formula of Valsartan ODTs prepared by direct compression method with various superdisintegrants

Ingredients (mg)	Formulation code						
	F1	F2	F3	F4	F5	F6	F7
Valsartan	40	40	40	40	40	40	40
Avicel pH 102	20	20	20	23	23	23	20
Mannitol	78.5	78.5	78.5	78.5	78.5	78.5	78.5
SSG	3	3	-	3	-	-	-
Crosscaramelloe sodium	3	-	3	-	3	-	6
Cross povidone	-	3	3	-	-	3	-
Sodium saccharine	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	1	1	1	1	1	1	1
Talc	2	2	2	2	2	2	2
Total weight	**150**	**150**	**150**	**150**	**150**	**150**	**150**

Table 2: Formulae of Valsartan ODTs prepared by direct compression method using Sublimation and Effervescence methods

Ingredients (mg)	Formulation code		
	F8	F9	F10
Valsartan	40	40	40
AVICEL pH101	20	20	20
Mannitol	69.5	64.5	48.5
Camphor	15	20	-
Sodiumbicarbonate	-	-	20
Citric acid	-	-	16
Sodium saccharine	2.5	2.5	2.5
Magnesium stearate	1	1	1
Talc	2	2	2
Total weight	**150**	**150**	**150**

Table 3: Infra-Red band assignments for Valsartan, Optimized formula T3, T9, T10

IR Spectra	Peak of Functional groups [wavelength (cm^{-1})]			
	CH (Aliphatic)	C-O(Carboxylic acid)	C-H (Aliphatic)	C=O (Amide)
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

Table 4. Physical properties of powdered blends

Formulation Code	Angle of repose (˚)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	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±0.56	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±0.11	15.09±0.32	1.15±0.05
T6	25.56±0.78	0.51±0.27	0.6±0.19	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	19.6±0.24	1.19±0.03
T10	29.93±0.32	0.51±0.18	0.63±0.32	19.23±0.32	1.19±0.07

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

Table 5: Physicochemical characteristics of Valsartan ODTs

Formulation code	Thickness (mm)	Weight variation (mg)	Hardness $(kg/cm)^2$	Friability (%)	Invito DT (sec)	Wettig time (sec)	Water absorption ratio (sec)	Drug content (%)
T1	2.02±0.07	150±0.00	2.2±0.02	0.26±0.03	21±2.0	23±1.0	61±1.33	93.6±0.65
T2	2.10±0.15	150±0.10	2.1±0.10	0.3±0.07	20±1.0	22±1.0	62±1.24	98.0±0.42
T3	2.08±0.12	151±0.00	2.1±0.09	0.3±0.06	16±1.0	17±1.0	68±0.98	101.3±0.8
T4	2.02±0.04	152.07±04	2.0±0.02	0.1±0.06	26±1.0	27±0.0	64±1.03	91.6±0.43
T5	2.06±0.04	149.03±03	2.4±0.02	0.2±0.06	24±2.0	26±1.0	62±1.12	94.2±1.11
T6	2.02±0.09	152±0.02	2.1±0.02	0.2±0.03	23±1.0	25±1.0	61±1.27	91.0±0.37
T7	2.08±0.08	154.1±0.2	2.2±0.03	0.4±0.07	30±1.0	31±1.0	63±1.51	92.0±0.56
T8	2.02±0.03	152.1±0.0	2.9±0.03	0.3±0.06	22±1.0	24±1.0	59±1.76	92.3±0.73
T9	2.06±0.02	150.4±0.2	2.2±0.02	0.4±0.06	19±1.0	21±1.0	65±1.12	99.7±0.92
T10	2.07±0.07	151±0.19	2.1±0.02	0.2±0.06	17±1.0	18±1.00	65±1.02	100.7±0.8

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

Table 6: Cumulative percent Valsartan released from ODTs: T1, T2 & T3 containing varying concentrations of different superdisintegrants.

Time (min)	Cumulative % drug released		
	T1	T2	T3
0	0	0	0
5	58.75±1.09	56.22±1.08	62.28±2.92
10	75.12±2.12	71.22±2.91	83.11±2.11
15	91.29±1.38	90.15±1.74	94.18±1.08
20	91.09±1.26	91.57±1.11	91.29±1.09
25	90.57±1.09	90.59±1.09	91.09±1.21
30	89.34±3.10	88.28±1.05	90.22±2.09
35	89.21±1.88	89.38±1.28	90.17±2.02
40	90.19±1.62	90.12±1.56	91.09±1.05
45	90.27±2.91	90.16±1.43	91.33±1.51

Table 7: Cumulative % Valsartan released from ODTs: T4, T5, T6 &T7 containing 2% concentration of different superdisintegrants

Time (min)	Cumulative % drug release			
	T4	T5	T6	T7
0	0	0	0	0
5	48.22±0.97	42.03±1.08	57.15±1.55	45.29±0.88
10	67.39±0.86	55.67±0.71	73.18±1.08	63.18±0.73
15	82.18±0.54	73.3±1.32	82.12±2.32	72.12±1.90
20	89.76±1.11	91.27±1.68	91.59±0.87	90.18±2.96
25	89.57±0.51	90.29±1.72	91.36±2.92	91.63±0.75
30	89.20±0.73	91.35±0.91	90.22±1.96	91.01±2.43
35	87.25±0.31	91.27±0.87	89.72±0.88	89.69±0.72
40	88.68±0.45	89.79±0.73	85.08±1.45	89.25±0.94
45	88.09±0.56	85.43±1.03	87.12±1.98	89.07±1.44

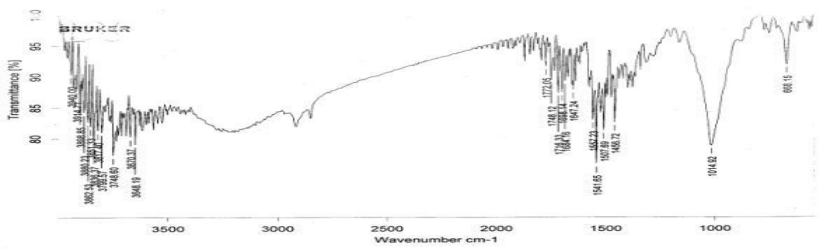

Figure 1: FTIR spectra of T3

Table 8: Cumulative % Valsartan released from ODTs: T8, T9, & T10 prepared by Sublimation method and Effervescence method

Time (min)	Cumulative % drug released		
	T8	T9	T10
0	0	0	0
5	58.72±0.87	47.01±0.83	69.59±0.87
10	72.14±0.92	79.19±1.02	78.17±0.98
15	90.21±1.77	92.62±1.87	93.54±1.88
20	88.21±1.42	92.15±1.93	93.22±1.89
25	90.38±1.80	89.39±1.97	92.1±2.13
30	88.28±1.54	89.12±0.96	92.18±2.45
35	89.34±1.62	90.34±1.84	90.09±2.10
40	90.11±1.64	90.12±1.96	89.72±1.98
45	90.01±1.79	90.07±1.95	90.89±2.04

Table 9: Comparison of cumulative % dug release of best formulations of ODTs with marketed conventional tablet

Time (min)	Cumulative % drug release			
	T3	T9	T10	Marketed tablet
0	**0**	0	0	0
5	62.28±0.92	47.01±0.83	69.59±0.87	42.18
10	83.11±1.99	79.19±1.02	78.17±0.98	58.22
15	94.18±.2.11	92.62±1.87	93.54±1.88	77.29
20	91.29±2.08	92.15±1.93	93.22±1.89	89.02
25	91.09±2.02	89.39±1.97	92.12±2.13	90.34
30	90.22±2.21	89.12±0.96	92.18±2.45	90.22
35	90.17±2.11	90.34±1.84	90.09±2.10	90.12
40	91.09±2.32	90.12±1.96	89.72±1.98	89.57
45	91.33±2.41	90.07±1.95	90.89±2.04	90.12

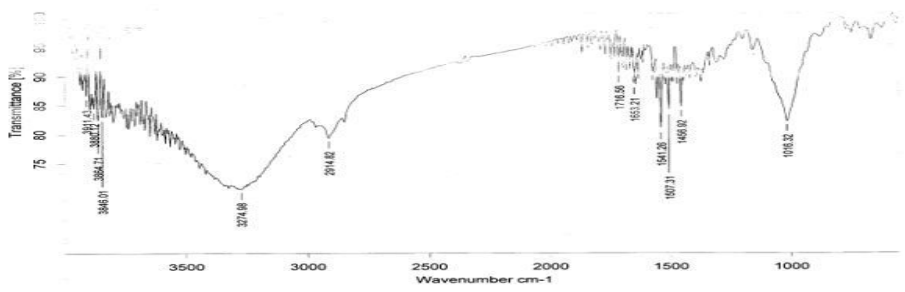

Figure 2: FTIR spectra of T9

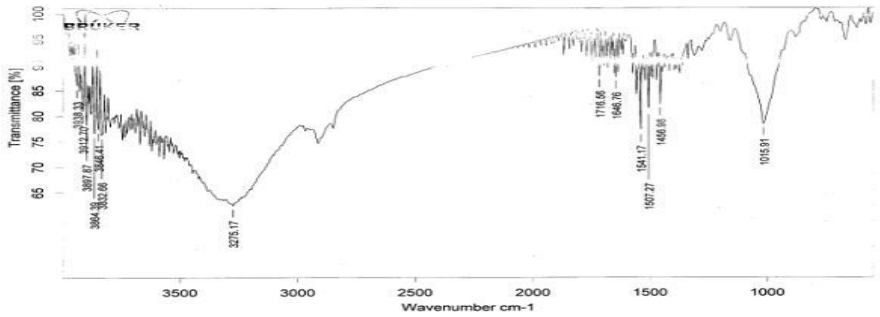

Figure 3: FTIR spectra of T10

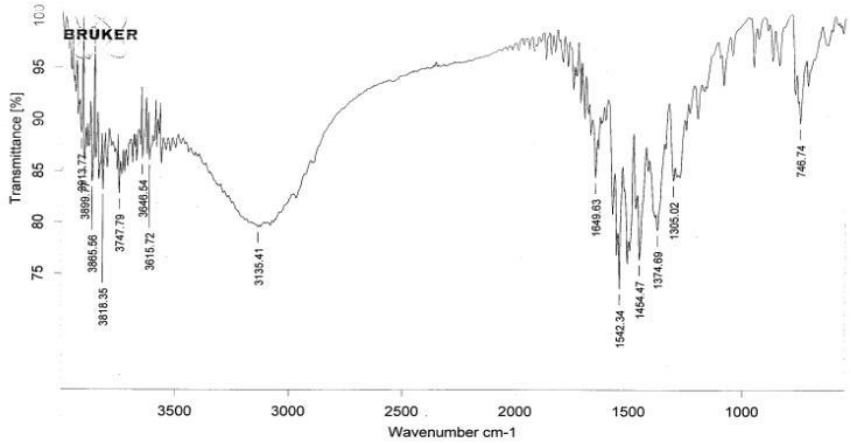

Figure 4.FTIR spectra of Valsartan

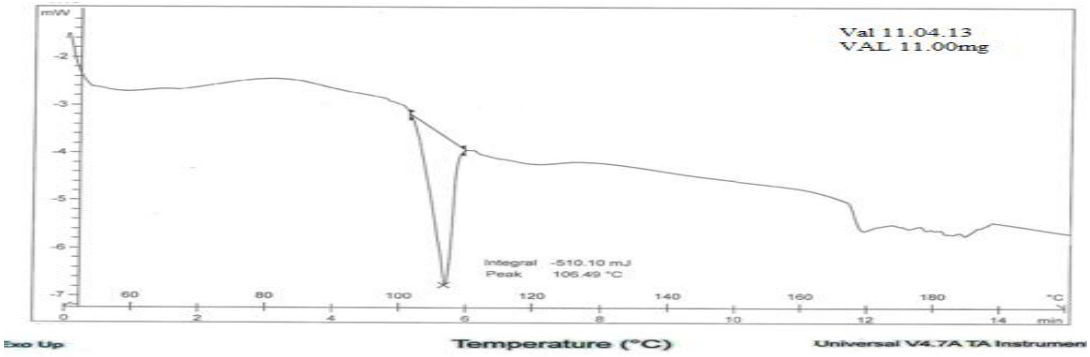

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Fig 4a) DSC thermogram of Valsartan

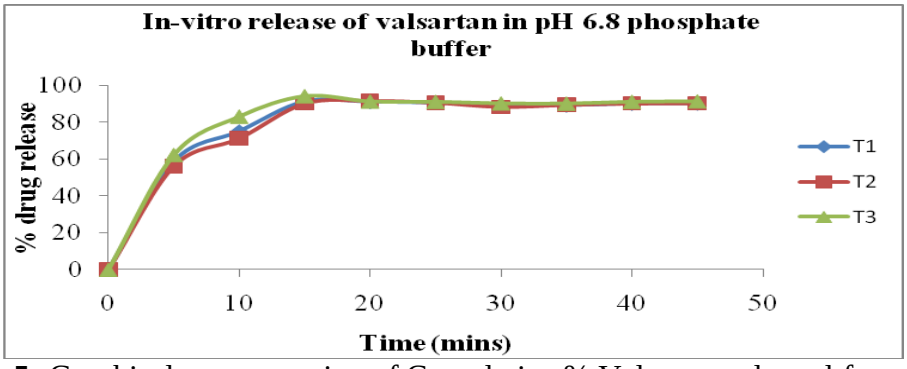

Figure 5: Graphical representation of Cumulative % Valsartan released from ODTs containing 2% concentration of combination of SSG, CCS and CP

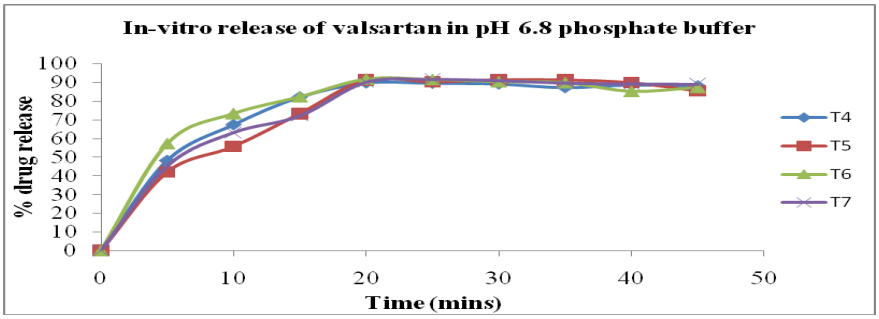

Figure 6: Graphical representation of Cumulative % Valsartan released from ODTs containing 2% concentration of different superdisintegrants

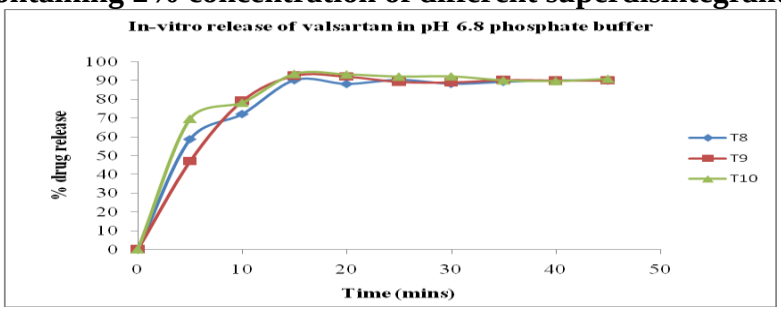

Figure 7: Graphical representation of Cumulative % Valsartan released from ODTs prepared by Sublimation & Effervescent method

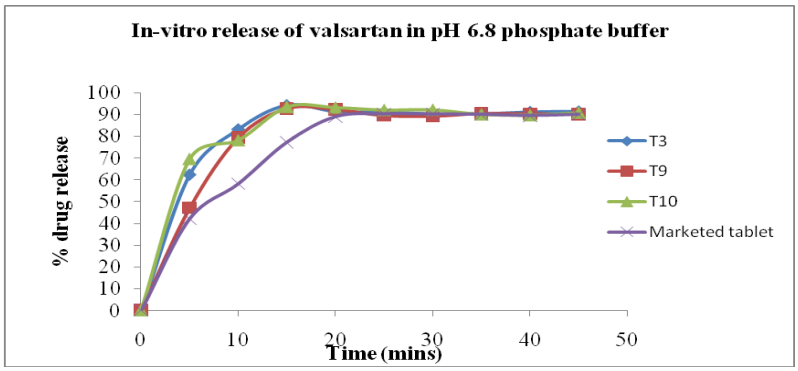

Figure 8: Graphical representation of cumulative % Valsartan released from T3, T9, T10 & Marketed conventional tablet

3.1.5 In-vitro release studies

In vitro dissolution studies of the prepared ODTs was performed in pH 6.8 buffer using dissolution apparatus type 2. Formulation T1 which contained combination of SSG+CCS has recorded drug release of 91.29% within 15 minutes. Formulation T2 which contained combination of SSG+CP has recorded drug release of 91.57% within 15 minutes. Formulation T3 which contained combination of CCS+CP has recorded drug release of 94.18% within 15 minutes. Data was represented in **Table 6 & Figure 5.** Formulation T4 which contained SSG 2% has recorded drug release of 89.76% at the end of 20 minutes **(Table 7 & Figure 6**). Formulation T5 which contained CCS 2% has recorded drug release of 91.27% at the end of 20 minutes. Formulation T6 which contained CP 2% has recorded drug release of 91.59% within 20 minutes. Formulation T7 which contained L-HPC 2% has recorded drug release of 90.18% within 25 minutes.

Formulation T8 which contained tablets prepared by Sublimation method with 1.6% of camphor has recorded drug release of 90.21% within 15 minutes (**Table 8 & Figure 7).** Formulation T9 which contained tablets prepared by Sublimation method with 1.6% of camphor has recorded drug release of 92.62% within 15 minutes. Formulation T10 which contained tablets prepared by Effervescence method has recorded drug release of 93.54% within 15 minutes. From all the formulations, T3, T9 and T10 was selected as optimized formulations based on in-vitro release studies and was compared with marketed product and reported in **Table 9 & Figure 8.**

CONCLUSION

The current research work demonstrates the successful development of an ODT of Valsartan, the formulations were developed with an objective to use by the geriatric and mentally disabled patients. Prepared ODTs showed good physicochemical properties and compile with official pharmacopeial limits.

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