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Dissolution enhancement of valsartan using sublimating agent for the formulation of porous tablet

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ABSTRACT

Valsartan belongs to a class of antihypertensive agents called angiotensin II receptor blockers (ARB's). The drug has low bioavailability, it can be increased by enhancing solubility in gastric fluids using rapid disintegration. By that mechanism, the porous compacts of valsartan having improved solubility were prepared and the dissolution profile is noted. The valsartan loaded porous compacts are prepared using micro crystalline cellulose as carrier material, lactose as diluent, ammonium carbonate as subliming agent & talc as glidant. FT-IR was used to evaluate the drug-polymer interaction. The dry granules of valsartan were prepared in different concentrations of sublimating agent and compressed. The resultant compacts are evaluated for their actual drug content (assay), morphology, flow properties, disintegration &dissolution rate. The valsartan porous tablets shows better disintegration, and the best dissolution rates compared to normal tablets. The formulations (F_4, F_5, and F_6) dried at 75ºC for 8hr has shown better drug release than air dried formulations (F_1, F_2, F_3). The pre compression & post compression studies of prepared compacts is under limits. The average pore size distribution is found as 736nm.The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good result.

Key words: Porous tablets, Subliming agent, Disintegration, Pore size distribution.

INTRODUCTION

Oral route has been the most popular and successful route for drugs because of convenience and ease of application, greater compliance in dosage form design and ease of production and low cost of such a system. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery system[1].In recent days one of the major challenges in the drug development is poor aqueous solubility of drug[2]. Therapeutic response of a drug depends upon the solubility and dissolution rate of drug. Solubility is one of the parameters to get the desired concentration of drug into the systemic circulation in order to get the desired pharmacological response[3].If the rate of dissolution of a drug is slower than the rate of absorption then it is said to be dissolution limited[4]. The tablet formulation of lot of potential hydrophobic and/or lipophilic drug molecules can be very problematic due to their poor pharmacokinetics/ADME parameters[5]. These include a low solubility in the stability range of temperature and/or a low dissolution rate of the drug in the intestinal lumen, low permeation properties through the gastrointestinal (GI) wall and rapid intestinal wall metabolism or high hepatic first pass effect[6] .There are several methods available to enhance the solubility of poorly aqueous soluble drugs. However, surrounding them, the technique of porous tablet is one of the most promising techniques[7].

Porous tablet is "A solid dosage form containing medicinal substances or active ingredients which disintegrates rapidly within a few seconds when placed up on tongue/administered". Porosity is a characteristic that influences many of the critical quality attributes of finished pharmaceutical products. The more porous a product, the more water or gastric fluid should be able to infiltrate the tablet and dissolve the tablet, allowing the active pharmaceutical ingredient (API) to be released. Dissolution rate is a key attribute for immediate-release drugs.[8]

The performance of porous tablets depends on the technology used in their manufacture. The disintegrating equity of these tablets is attributable to the quick ingress of water into the tablet matrix, which creates pores and results in rapid disintegration. Hence, the basic approaches to develop porous tablets include maximizing the porous structure of the tablet matrix, assimilating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation. The mechanism of drug release in porous tablets is by quick entry of water into the tablet matrix to cause rapid disintegration and instantaneous dissolution of the tablet / by incorporation of an apt disintegrating agent or highly water soluble excipients in the tablet formulation etc.

Many methods of preparing PTs have been described to date,[9] including lyophilisation,[10,11]moulding,[12] and the compression of wet powders to construct highly porous structures.[13]freeze drying method, , and compression method. The compression method is the most widely used method for making tablets. Some are focused on unique granulation methods, such as the spray-drying method and flash-heat processing to create shear form; some are focused on selecting specific excipients such as water-insoluble calcium salts, specific disintegrant combination, and specific sugar combination; and some are focused on special treatment after compression, such as sublimation, sintering, and humidity treatment[14].These methods, while effective, are time consuming and technically difficult, often requiring special processing equipment.

As a result, these methods are not easily adopted by pharmaceutical companies. Additionally, the tablets produced by these methods disintegrate instantly, they are usually very weak and fragile. The mechanical strength of the tablets may not be enough to withstand packaging, transportation, and patient handling. the tablet components are mixed and pressed into predetermined shape, the improvement which comprises incorporating into the mix at least one inert readily volatilizable solid adjuvant, pressing the mix into shape, and thereafter volatilizing the adjuvant, whereby the resulting tablets are porous, strong, shape retaining and readily disintegratable. Volatilization can be effected by sublimation or application of vacuum. The adjuvant preferably comprises urethane, urea, ammonium carbonate, ammonium bicarbonate, hexamethylene-tetramine, benzoic acid, phathalic anhydride, naphthalene or camphor present in about 5 to 50 percent, especially about 10 to 30 percent, by weight of the total tablet mix[15].In future, development of porous tablet dosage form is also beneficial for optimal therapy in terms of efficacy safety and patience compliance.

Valsartan is an angiotensin II receptor antagonist and is prescribed widely in cardiovascular diseases like hypertension, angina pectoris, arrhythmias and myocardial infractions. It has been reported that valsartan absorption in the duodenum and jejunum is directly proportional to dose availability.In the present study, porous tablets of valsartan were prepared using a pore forming agent ammonium carbonate. Influence of pore forming agent on properties of tablets (disintegration, hardness and drug release) were investigated.

MATERIALS AND METHODS

Materials

Valsartan (API) was obtained from AurabindoPharma Pvt ltd, Visakhapatnam, Microcrystalline Cellulose (Carrier material), Lactose (Diluent), Ammonium Carbonate (Subliming agent), Talc (Glidant) are obtained from.

Methods

Pre-formulation studies are the first step in the rational development of dosage form of a drug substance. Studies for physical properties, melting point and solubility studies were performed. Calibration curve of valsartan was plotted by spectrophotometric method in the range10µg/ml-50µg/ml.

Preparation of porous compacts

In the process of optimization to prepare desirable porous compacts following batches were designed.

Table1: Formulae of ingredients used indifferent batches

Formula	F_1	F_2	F_3	F_7
	Master formula (gm)	Master formula (gm)	Master formula (gm)	Master formula (gm)
Valsartan	40	40	40	40
Microcrystalline Cellulose	50	50	50	50
Lactose	140	140	140	140
Talc	8	8	8	8
Ammonium Carbonate	12.5	25	37.5	-
Total Weight	250.5	263	275.5	238

First batch of the porous compacts prepared using different carrier material & porous material percentages like 5%, 10%, 15%.The required & fixed amount of valsartan, microcrystalline cellulose were triturated in a mortar & pestle to form a freely flowing powder. To above powder blend, ammonium carbonate (subliming agent agent) was added. To this blend lactose was added to conquer required weight. Finally talc was added. Then, this powder blend passed through sieve no.22 and evaluated for flow properties and compressed using 10mm and 12mm punches using 10-station tablet compression machine. Similarly, three other batches of tablets were prepared using ammonium carbonate at different concentrations as 5%, 10%, 15%.

Post-compression studies of the prepared tablet:
Post compression tests for Hardness, Thickness, Weight variation, Uniformity of Drug content, Assay, Friability, and Disintegration were performed

In-vitro drug release studies:
The release rate of drug from tablets can be determined using USP dissolution testing apparatus 2 (paddle method). The study was carried out in 900 ml of pH 7 ammonium phosphate buffer maintained at 37 ºC. The formulation was added to the dissolution medium and the paddle was fixed to the shaft. The top assembly was brought down into solution and the shaft was set to rotate at 75 rpm. Samples equivalent to 5 ml were withdrawn at different time intervals for a period of 5 min. After each sampling, an equal quantity of the dissolution media was replaced into the dissolution jar. The UV absorbances of filtered samples were measured at 250nm and the cumulative release in percentage at various time intervals were calculated using the respective formulas.

Pore size Distribution:
The pore size distribution of the prepared tablet was analysed by SEM (Scanning Electronic Microscopy) analysis.

RESULTS AND DISCUSSION

Melting point
Melting point of drug was found to be 116^0C-117^0C.

Solubility studies
Valsartan showed maximum solubility in PEG 600 (83.91mg/ml) hence the same was selected as non-volatile solvent.

Table 2: Solubility of Valsartan in various non-volatile solvents

S.No.	Solvent	Solubility (mg/ml)
1	Water	0.0234
2	Tween 20	69.73
3	Tween 80	76.57
4	PEG 200	65.41
5	PEG 600	83.91
6	0.1N HCl	0.07
7	0.01N HCl	0.10
8	Acetate buffer	4.5

Flow properties of granules
Compressibility index, Hausner's ratio, Bulk density and tapped density values were found to be within limits. Compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area and

cohesiveness of material. The powdered blend has required flow property and compressbility. So, these batches are suitable for tablet compression.

Table 3: Pre-compression parameters for formulated batches

Formulation	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (º)	Flow Property
F1	0.44	0.50	12.58	1.13	28.44	Very Good
F2	0.45	0.52	15.19	1.15	28.36	Very Good
F3	0.44	0.52	15.48	1.18	28.52	Very Good
F7	0.45	0.51	13.48	1.13	29.32	Very Good

Post Compression Studies

After compression, all the tablets were dried at 75°C for 8hrs and were evaluated for various parameters like weight variation, hardness, thickness, friability, disintegration and in vitro drug release. All formulations were found to have good hardness so they were taken for further studies. The measured hardness of tablets of each batches are in the range of 2 to 2.5kg/cm^2.Tablets mean thickness were almost uniform in all formulations and were found to be in the range of 2.40 mm to 2.6mm.Friability values are found to be less than 1% in all the cases and considered to be satisfactory. The total weight of each formulation was maintained constant and the weight variation of the tablets was within limits of 5%. All the tablets passed the pharmacopoeia specifications for disintegration and for valsartan porous tablets disintegration time was reduced to 30 sec. this may be due to the formation of pores on the surface of tablet. The in-vitro drug release was not satisfactory as they showed only 22-25% drug release in 30mins for formulations F1 to F3. The next trials (F4, F5, and F6) were planned by heating them at 75ºC for 8 hr and the results showed disintegration time around 30-45sec. formulations F4 , F5 and F6 exhibited in-vitro drug release of 90 % in 30mins whereas formulation F7 which was deficient in Ammonium carbonate has shown only 25% drug release in 30mins. Form these result we can emphasise that pore formation may be highly responsible for the lower disintegration time and higher dissolution rate. Quick entry of water into the tablet matrix due pore formation led to rapid disintegration and instantaneous dissolution of the tablet.

Table 4: Evaluation parameters of formulated porous tablets before drying (F1-F4)

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Drug Content (%)	Disintegration (sec)
F1	2.57	2.5	0.31	245	100	30
F2	2.54	2.5	0.25	249	98	42
F3	2.56	2.5	0.29	247	101	47
F7	2.52	2.5	0.31	249	102	15

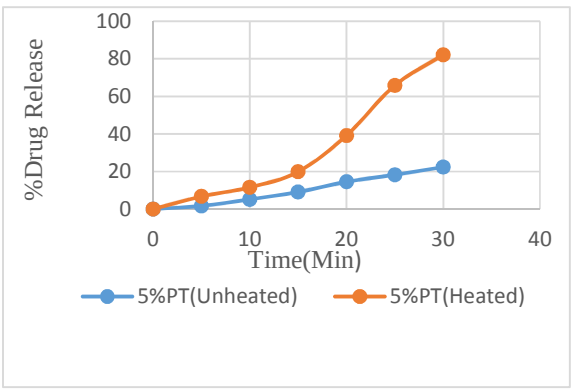
Table 5: Evaluation parameters of formulated porous tablets after drying (F4-F6)

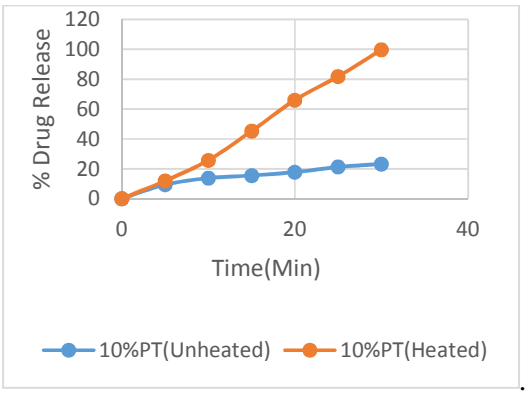
Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Weight Variation (mg)	Drug Content (%)	Disintegration (sec)
F4	2.57	2	212	100.5	30
F5	2.54	2	216	98.8	40
F6	2.56	2	214	102.3	45

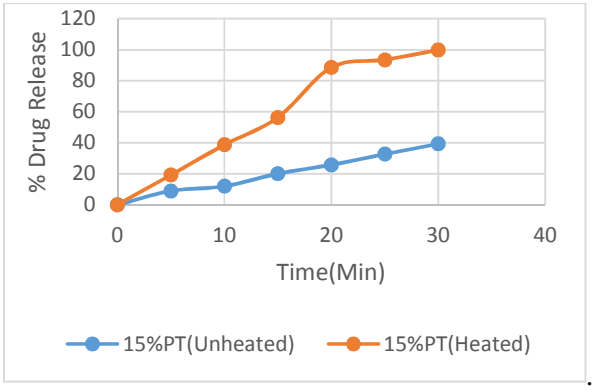
Table 6: In vitro Release Profile of Valsartan from formulations (F1-F7)& Marketed formulation

Time	Cumulative % drug release							
	F1	F2	F3	F4	F5	F6	F7	Marketed formulation
0	0	0	0	0	0	0	0	0
5	1.69	9.36	8.84	6.75	11.96	19.17	2.86	19.24
10	5.20	13.78	11.96	11.57	25.75	38.62	6.89	20.00
15	9.10	15.53	20.02	19.89	45.26	56.31	9.87	20.28
20	14.56	17.76	25.75	39.20	65.93	88.56	12.87	20.54
25	18.33	21.23	32.64	65.93	81.80	93.47	19.89	20.56
30	22.36	23.28	39.27	82.19	99.6	99.8	24.97	20.77

Fig1: graphs showing data of various formulations



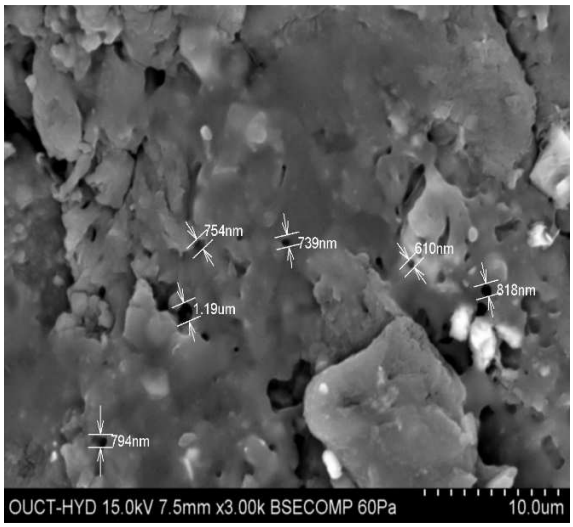


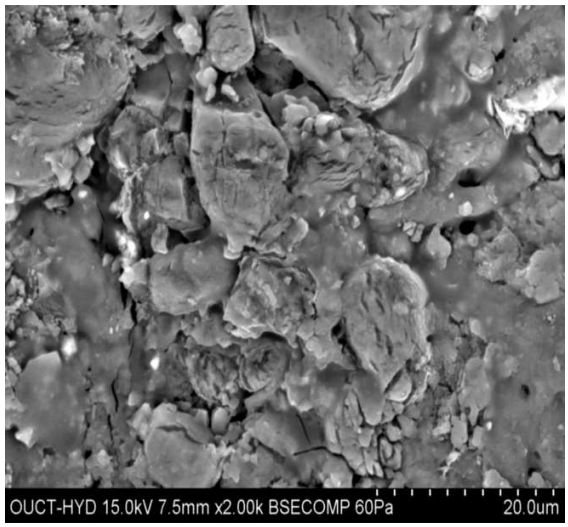


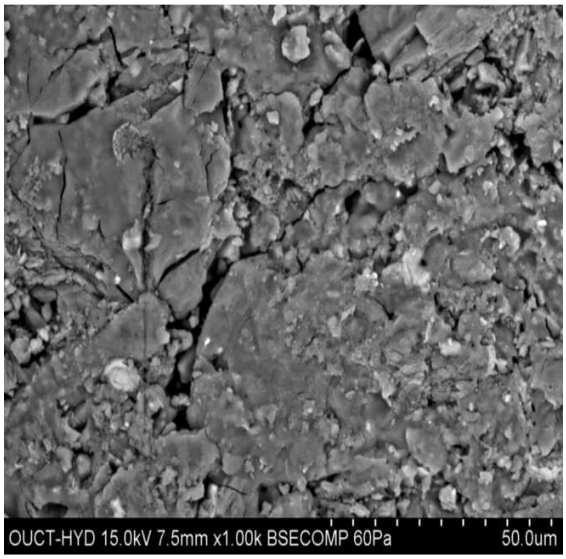
Scanning Electron Microscopy

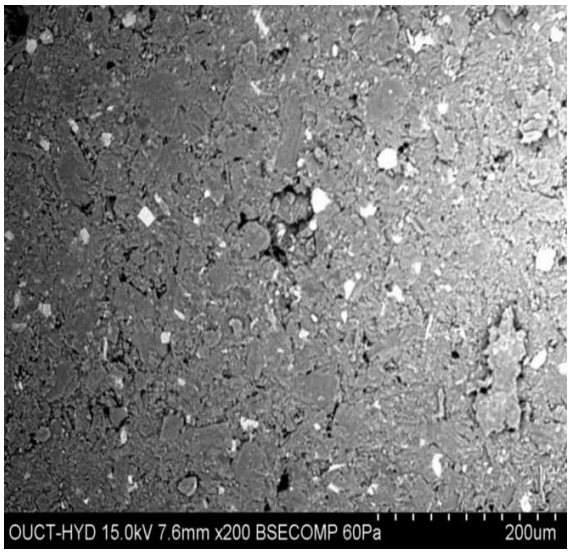
The prepared formulations of the porous tablets are examined for the pore size distribution by SEM analysis. The F6 of having high capacity of drug release was taken into consideration for pore size distribution. It was examined under 10µm, 20µm 50µm & 200µm magnifications. The resultant pictures are shown above. At 10 µm, it shows the pore sizes as 754nm, 739nm, 794nm, 610nm & 818nm respectively. The average pore size distribution was found as 743nm.

Fig2: Scanning electron microscopy images









CONCLUSION

This dissertation work was done with an aim to design an immediate release oral dosage of valsartan and evaluation of the tablets for various parameters including in vitro drug release studies. Valsartan tablets were formulated by using microcrystalline cellulose as carrier material, ammonium carbonate as subliming agents, lactose as diluent, and talc as lubricant. The powdered blend is compressed into tablets and were analysed for the parameters such as average weight, disintegration time, friability, thickness, weight variation, hardness, moisture content and drug content. The formulation F6 is formulated by using subliming agent where it can ensure burst release of the drugs so that there release cannot be interlinked. The formulation F6 containing 15% of ammonium carbonate showed disintegration time of less than 45seconds after drying. Ammonium Carbonate as subliming agent was found to be most effective of all other subliming agents as it had showed drastic effect on the drug release. All other parameters such as Hardness, Thickness, Weight variation and drug content were also found to be within limits. The dissolution profiles and drug content of the tablets were found to be satisfactory even after subjecting the tablets to stability studies. The formulation F6 and process can be easily scaled up and can be easily employed in large scale production because the process is simple, cost effective and precise and also yields reproducible good result that involves complex process for manufacturing the tablets.

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