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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE VALSARTAN BASED ON MATRIX TABLET BY USING HYDROPHILIC POLYMER

Pawan Jalwal*, Anu, Neetu, Neha, Babita

Department of Pharmaceutical Sciences, Baba Mastnath University, Asthal Bohar, Rohtak

Abstract

Valsartan is an angiotensin II receptor antagonist (more commonly called an "ARB", or angiotensin receptor blocker, with particularly high affinity for the type I (AT_1) angiotensin receptor. By blocking the action of angiotensin, valsartan dilates blood vessels and reduces blood pressure. It is indicated for treatment of high blood pressure either alone or in combination with hydrochlorothiazides. Controlled release drug delivery systems are developed to modulate the apparent absorption or alter the site of release of drugs, in order to achieve specific clinical objectives that cannot be attained with conventional dosage forms. Unlike sustained release preparations, which is used to retard the release of therapeutic agent and its plasma profile is sustained in duration. Matrix systems fall into category of sustained release oral solid products. In a matrix system, the drug substance is homogeneously mixed into the rate controlling materials and other inactive ingredients as a crystalline, amorphous dispersion. Drug release occurs either by drug diffusion or erosion of the matrix system. Matrix system is widely used due to easy to fabricate in a wide range of sizes and shapes, capability of accommodating both low and high drug loading and active ingredients with a wide range of physical and chemical properties and it is suitable for both non-degradable and degradable systems. The solubility of Valsartan was enhanced by making sustained release matrix tablet. Then formulation was characterized and evaluated by FTIR, drug content, swelling index and *in vitro* dissolution studies.The present study involved the preparation of sustained release matrix tablet of Valsartan by hydrophilic polymer. The tablets were prepared with both direct compression and wet granulation methods. It was found that wet granulation method facilitated greater efficiency in controlling valsartan release behavior from the matrices. Hence, all further formulations were prepared with wet granulation technique..

Keywords: Angiotensin, Matrix system, Swelling index, drug content, hydrophilic polymer etc

INTRODUCTION

Valsartan is an Angiotensin Receptor Blockers (ARB) that selectively inhibits the binding of angiotensin II to AT_1 which is found in many tissues such as vascular smooth muscle and the adrenal glands. This effectively inhibits the AT_1 mediated vasoconstrictive and aldosterone-secreting effects of angiotensin II and results in a decrease in vascular resistance and blood pressure. Valsartan is selective for AT_1 and has virtually no affinity for AT_2. Inhibition of aldosterone secretion may inhibit sodium and water reabsorption in the kidneys while decreasing potassium excretion. The primary metabolite of valsartan, valeryl 4-hydroxy valsartan, has no pharmacological activity. Valsartan having melting point 116 to 117 °C. The molecular formula is $C_{24}H_{29}N_5O_3$ and the molecular weight is 435.51. The chemical name of Valsartan is

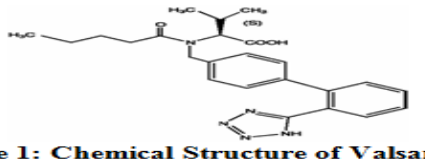


Figure 1: Chemical Structure of Valsartan

According to biopharmaceutical classification system, it is mentioned under the class III. It is an antihypertensive drug practically insoluble in water, soluble in water, ethanol methanol. The prescription doses of valsartan are 40, 80, 160, and 320 mg. Store tablets/capsules at room temperature away from light and moisture. Do not store in the bathroom. Keep all medications away from children and pets. Store the suspension at room temperature for up to 30 days, or in the refrigerator at 36-46 degrees F (2-8 degrees C) for up to 75 days. Do not freeze. Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed. Valsartan is used to treat high blood pressure (hypertension) and heart failure. It is also used to improve the chance of living longer after a heart attack. Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. Valsartan belongs to a class of drugs called angiotensin receptor blockers. It works by relaxing blood vessels so that blood can flow more easily. This drug may also be used to help protect the kidneys from damage due to diabetes.

Table 1: Pharmacokinetic parameters of Valsartan

Absorption	t_{max} C_{max} Mean absorption bioavailability	2-4 hours 50% 23%
Distribution	V_d Albumin protein binding	17 L 94-97%
Biotransformation	Hydroxy metabolites have been identified, Metabolites are inactive	20%
Excretion	Primarily eliminated by biliary excretion Elimination by renal excretion Half life Clearance	83% 13% 6 hours 2 L/hours

Materials and methods

Valsartan was gifted from Dr. Reddy's pharmaceutical, Hyderabad, India. Guar gum and Pectin were purchased from Thomas baker (chemicals) Pvt. Ltd., Mumbai. Isopropyl alcohol and lactose were purchased from S. D. fine chemical limited, Mumbai. Magnesium stearate was purchased from Merck Ltd., Mumbai and talc was purchased from Lob chemie Pvt. Ltd., Mumbai. All other ingredients used were of analytical grade.

Experimental methods

Table 2: Formulation of Valsartan By direct compression

Ingredients	B1(mg/tab)
Drug	160
Guar Gum	40
Pectin	-
Magnesium stearate	2
Talc	2
Lactose	196
Total	**400**

Preparation of tablets containing Valsartan by wet granulation method:

Table 3: Formulation of Valsartan using low amount of various polymers by Wet Granulation:

Ingredients	B02 (mg/tab)	B03 (mg/tab)	B04 (mg/tab)
Drug	160	160	160
Guar Gum	40	-	40
Pectin	-	40	40
Magnesium stearate	2	2	2
Talc	2	2	2
Lactose	196	196	156
Total	**400**	**400**	**400**

Table 4: Formulation of Valsartan using intermediate amount of various polymer with wet granulation:

Ingredients	B05 (mg/tab)	B06 (mg/tab)	B07 (mg/tab)
Drug	160	160	160
Guar Gum	60	-	40
Pectin	-	60	60
Magnesium stearate	2	2	2
Talc	2	2	2
Lactose	176	176	136
Total	**400**	**400**	**400**

Table 5: Formulation of Valsartan using high amount of various polymers with Wet granulation:

Ingredients	B08 (mg/tab)	B09 (mg/tab)	B10 (mg/tab)
Drug	160	160	160
Guar Gum	80	-	40
Pectin	-	80	80
Magnesium Stearate	2	2	2
Talc	2	2	2
Lactose	156	156	116
Total	**400**	**400**	**400**

In-vitro evaluation

Evaluation of granule

Table 6: Tapped density, Bulk density, Angle of repose, Carr's index, Hausner's Ratio values of different batches blend of Valsartan.

Batch No.	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's ratio	Carr's index (%)	Angle of repose
B 01	0.354	0.577	1.57(very poor)	36.44(V. Poor)	57.29(v.poor)
B 02	0.533	0.720	1.35(poor)	25.97(poor)	38.18(fair)
B 03	0.603	0.736	1.22(fair)	18.07(fair)	28.63(excellent)
B 04	0.545	0.681	1.24(fair)	19.97(fair)	40.91(passable)
B 05	0.539	0.725	1.34(passable)	25.65(passable)	40.91(passable)
B 06	0.609	0.753	1.23(fair)	19.12(fair)	28.63(excellent)
B 07	0.645	0.762	1.19(fair)	15.35(fair)	40.91(passable)
B 08	0.482	0.633	1.31(passable)	23.85(passable)	31.82(good)
B 09	0.547	0.661	1.20(fair)	17.24(fair)	33.69(good)
B 10	0.634	0.736	1.16(good)	13.85(good)	28.63(excellent)

From the result it was concluded that the powder blend had good flow properties and these can be used for tablet manufacture.

Evaluation of sustained release matrix tablet of Valsartan:

Table 7: Evaluation of sustained release matrix tablet of Valsartan

Formulation	Thickness (mm)	Weight (mg)	Hardness (kg/cm^3)	Friability (%)
B 01	2.32	302.5	1.2	-
B 02	3.04	403.4	3.6	0.432
B 03	3.03	401.2	3.4	0.217
B 04	3.05	401.2	3.2	0.732
B 05	3.06	402.2	3.2	0.212
B 06	3.08	402.3	3.3	0.191
B 07	3.03	401.5	3.4	0.462
B 08	3.04	400.3	4.3	0.617
B 09	3.05	401.3	3.5	0.174
B 10	3.02	399.6	3.6	0.503

The result showed that thickness, weight and hardness were within Pharmacopoeial limits. So they pass the above tests.

Drug Content Uniformity

Table 8: Drug Content in the sustained release matrix tablets of Valsartan

Formulation Code	Drug Content (%)
B01	-
B02	96
B03	92.4
B04	90
B05	97.5
B06	94
B07	92
B08	98
B09	96.3
B10	93.5

The drug content uniformity of all the formulation was found to be in the range of 90 % to 98% which showed that there was uniform distribution of the drug throughout the batch.

Effects of different of polymers on formulation:

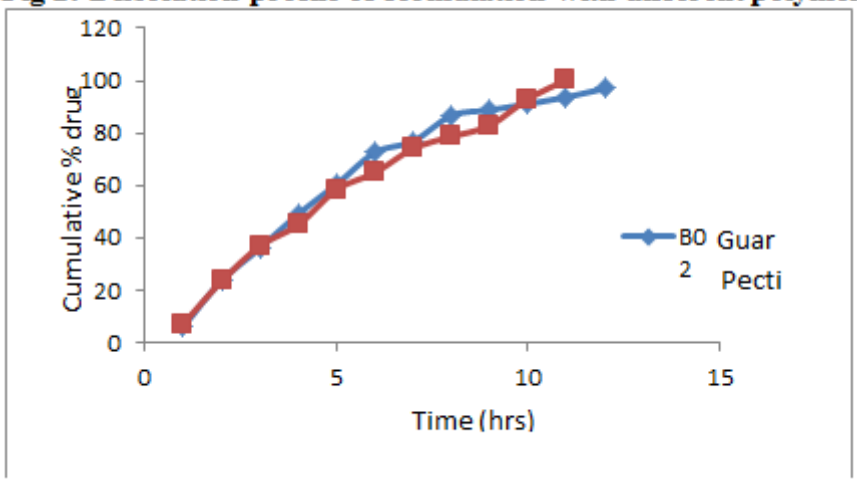
Formulation batches were prepared using different polymers alone and lactose as diluents and release profile was given in table 9.

Table 9: Release profiles of formulation using different polymers

Time (hrs.)	Cumulative % Drug Release	
	B02	B03
1	6.255	7.222
2	23.743	23.546
3	36.129	36.961
4	49.173	45.045
5	60.401	58.460
6	72.686	64.929
7	76.888	74.143
8	86.748	78.648
9	88.846	82.923
10	91.130	93.138
11	93.763	100.282
12	97.003	

Formulations with different polymers resulted in different release profiles. Guar Gum show slower release profile as compared to pectin because guar gum act as a binder.

Fig 2: Dissolution profile of formulation with different polymers.



Result and discussion

(B01) was prepared by direct compression but it was failed because it was not compressed so this batch failed. Then we prepared batches (B02-B10) by wet granulation and studied their release kinetic. Batch (B02) followed Hixon-crowell kinetic having (R^2- 0.9935). Batch (B03) followed zero order kinetic having (R^2- 0.9734). Batch (B04) followed zero order kinetic having (R^2-0.9936). Batch (B05) followed Hixon-crowell kinetic having (R^2-0.9638). Batch (B06) followed Higuchi kinetic having a (R^2-0.9765). Batch (B07) followed Higuchi kinetic having (R^2-0.9932). Batch (B08) followed Hixon-crowell kinetic having (R^2-0.9935). Batch (B-09) followed zero order kinetic having (R^2-0.9746). Batch (B10) followed zero order kinetic having (R^2-0.9911). Lubricated blends were characterized for physical properties like loose bulk density, tapped density, angle of repose, Carr's index, Hausner´s ratio; all blends showed satisfactory properties. All lubricated blends were compressed into tablets using round shaped punches. Tablets were evaluated for uniformity

of weight, thickness, hardness, percentage (%) friability and in vitro release studies. The release kinetics of the final batch (B04) was carried out and it was found batch followed zero order kinetic models. The optimized formulation has drug release profile up to 12 hours

Conclusion

The conclusions of the present research work are as follows:

- The absorbance maxima of Valsartan were found to be 249 nm which was selected for UV analysis.
- The physical compatibility study at 40^{o} C/ 75% RH showed that Valsartan and excipients used found to be physically compatible.
- FTIR spectra data showed that Valsartan and excipients used found to be compatible.
- Melting point of Valsartan was found to be 116^{o}C.
- Formulation was prepared with two processes i.e. direct compression and wet granulation,Wet granulation method facilitated greater efficiency in controlling Valsartan release behavior from the matrices as compared to direct compression.
- Characterization of granules prepared by selected manufacturing processes like bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose was done and found to have good flow and compressibility.
- The tablets prepared were found to be within the limits with respect to hardness, average weight, %friability, thickness, swelling index and in vitro dissolution study.
- *In vitro* dissolution studies of the best formulation (B04) showed complete release of drug in 12 hrs.
- The fine particle grades are more compressible than the standard premium grades, resulting in harder tablets.
- Increasing tablet hardness provided a much great control over dissolution rate.
- Guar gum is the best polymer as compared to pectin because when we increase the concentration of guar gum the release was decrease and there was an increase in time of release of drug but when we increase the concentration of pectin the release was increase.
- The concentration of polymer is the determining factor in controlling the release of valsartan.
- Under the study of kinetic models, five models have been studied namely Zero Order, First Order, Higuchi, Hixon-Crowell, Korsmeyer's-Peppas model. It was found that the drug release followed zero order kinetic (having maximum R^2 value of 0.9936.

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Corresponding Author:

Pawan Jalwal
Department of Pharmaceutical Sciences,
Baba Mastnath University,
Asthal Bohar, Rohtak-124001
E-mail- pawan_jalwal@rediffmail.com
Mobile No. 09812875605