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DEVELOPMENT AND CHARACTERIZATION OF CONTROLLED RELEASE DRUG DELIVERY SYSTEMS OF VALSARTAN MATRIX TABLETS

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ABSTRACT

The objective of the present study was to develop a delayed release matrix tablets of Valsartan,an anti hypertensive drug. The delayed release tablets were prepared by direct compression and formulated using different drug and polymer ratios, formulations such as F1 to F9. Natural polymer like Guargum, Pectin and Cellulose were used.Compatibility of the drug with various excipients was studied. The tablets were evaluated and showed compliance with Pharmacopoeial limits. The optimized formulation(F1) on the basis of acceptable tablet properties and *in vitro* drug release. The resulting formulation produced robust tablets with optimum hardness, consistent weight uniformity, drug content, invitro release studies and friability. All tablets but one exhibited gradual and near completion delayed release for Valsartan, and 98.75% released at the end of 20h. The results of dissolution studies indicated that formulation F1, the most successful of the study, exhibited drug release pattern very close to theoretical release profile.

KEYWORDS: Valsartan, Guargum, Pectin,Cellulose, delayed release, Matrix Tablets.

INTRODUCTION

Oral delivery of drugs is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation, etc. Many of the drug delivery systems, available in the market are oral drug delivery type systems. Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have a ideal drug delivery system

possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action Thus the objective of the pharmacist is to develop systems that can be as ideal system as possible. Attempts to develop a single- dose therapy for the whole duration of treatment have focused attention on controlled or delayed release drug delivery systems. The therapy of many chronic diseases requires a repeated dosing of a drug .drugs having a short half-life have to administered up to several times daily within short intervals. To reduce the application frequently delayed formulations have been developed. The therapy of many chronic diseases requires a repeated dosing of a drug .drugs having a short half-life have to administered up to several times daily within short intervals. To reduce the application frequently delayed formulation have been developed.

Delayed Release Dosage Forms

Delayed release, delayed action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Basically there are three basic modes of drug delivery i.e. targeted delivery, controlled release and modulated release. Targeted delivery refers to the systemic administration of a drug carrier with the goal of delivering the drug to specific cell types; tissues or organs. Controlled release refers to the use of a delivery device with the objective of releasing the drug into the patient's body at a predetermined rate, or at specific release profiles. On the other hand modulated release implies use of as drug delivery device that releases the drug at a variable rate controlled by environment conditions, biofeedback, sensor input or an external control device. Many times delayed release and controlled release terms are used interchangeably. However delayed release system deliver the active agent although at slower than a conventional formulation but the release is substantially affected by external environment. Delayed release dosage forms are generally administered by four delivery modes, namely Oral controlled drug delivery, transdermal drug delivery, implantable drug delivery and particulated drug delivery.

Basically there are four delivery modes to achieve delayed release.

Oral controlled drug delivery, transdermal drug delivery, implantable drug delivery, particulate drug delivery. Oral controlled delivery systems can be broadly divided into following categories based on their mechanism of drug release.

- Dissolution controlled release.
- Encapsulation dissolution control.
- Matrix dissolution control.
- Diffusion controlled release.
- Reservoir devices.
- Matrix devices.
- Ion exchange resin.
- Osmotic controlled release.
- Gastro retention system

Therapeutic advantages of the DR forms

Frequency of administration is reduced.

Patient compliance can be improved.

Blood level oscillation characteristic of multiple dosing of conventional dosage form is reduced because a more even blood level is maintained.

Total amount of drug administered can be reduced, thus maximizing availability with minimum dose. Better control of drug absorption can be attained, since the high blood level peaks that may be observed after administration of a dose of a high availability drug can be reduced by formulation in extended action form. The safety margin of high potency drug can be increased and incidences of both local and systemic adverse side effects can be reduced in sensitive patients.

Disadvantages of DR dosage form

Administration of DR dosage form dose not permits the prompt termination of therapy. Physicians have less flexibility in adjusting dosage regimens. This is fixed by the dosage form regimen. DR forms are designed for normal population i.e. on the basis of average drug biologic half-lives. Consequently, disease states that alter drug disposition, significant patient variation are not accommodated. Economy.

MATERIALS AND METHODS

Materials

Valsartan is the gifted sample from Karnataka Antibiotics, Bangalore, Guargum is obtained from the Mother herbs, Delhi, Pectin is obtained from Spectrum reagents and chemicals, Cochin, Celllose and Lactose is obtained from Loba chemie Pvt. ltd, Mumbai, Magnesium stearate and talc is procured from the S.D. Fine Chemicals, Mumbai

Preparation of matrix tablet

Initially, valsartan tablets with different concentration of hydrophilic polymer were prepared by direct compression technique. Required quantities of all ingredients were weighed individually on electronic balance (citizen India). All ingredients were first sieved through sieve #44 and mixed for 5 min by adding lactose then blended with talc and magnesium stearate for lubrication which were then compressed on rotatiry tablet compression machine using circular 6.5mm tooling set was used as dissolution medium for first 2 hrs and (pH 6.8) phosphate buffer for up to 20 hrs the test of the period as dissolution medium.

The paddle was adjusted at 75 rpm and the temperature of 37±0.5ºC was maintained throughout the experiment. Samples of 5 ml were withdrawn at known time intervals and were replaced with same volume of fresh dissolution media after each withdrawal. The samples were analyzed for drug contents by measuring absorbances at 249 nm using UV-VIS double beam spectrophotometer thermo scientific, India.

FORMULATION FOR VALSARTAN

Table-1: formulation chart

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valsartan	40mg	40mg	40mg	40mg	40mg	40mg	40mg	40mg	40mg
Guar gum	40mg	80mg	120mg	-	-	-	-	-	-
Pectin	-	-	-	40mg	80mg	120mg	-	-	-
Cellulose	-	-	-	-	-	-	40mg	80mg	120mg
Lactose	160mg	120mg	80mg	160mg	120mg	80mg	160mg	120mg	80mg
Talc	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Magnesium stearate	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg	5mg
Total weight	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg	250mg

RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Table-2: Preformulation studies of blend of all formulation

Formulation code	Angle of repose(θ)	Bulk density (g/cm3)	Tapped density (g/cm3)	Compressibility index (%)	Hausner's ratio
F1	22.4±0.02	0.49±0.03	0.57±0.05	16.1±0.02	1.12±0.03
F2	21.2±0.04	0.51±0.04	0.56±0.03	15.9±0.04	1.11±0.01
F3	19.7±0.06	0.51±0.05	0.57±0.04	17.6±0.01	1.19±0.04
F4	18.8±0.03	0.54±0.06	0.60±0.06	13.2±0.06	1.15±0.05
F5	17.2±0.04	0.52±0.03	0.56±0.04	14.8±0.06	1.18±0.04
F6	19.2±0.05	0.53±0.05	0.58±0.05	15.4±0.09	1.21±0.07
F7	19.8±0.6	0.51±0.06	0.55±0.02	14.4±0.08	1.16±0.04
F8	17.6±0.04	0.50±0.08	0.54±0.06	16.4±0.09	1.19±0.06
F9	17.2±006	0.49±0.07	0.50±0.03	17.9±0.07	1.21±0.08

Angle of Repose (θ): - The values were found to be in the range from 17^0 - 22^0, tabulated in Table 2. This indicates Excellent flow property of the powder blend.

Bulk Density: The values obtained for bulk density for all (F_1-F_9) formulations are tabulated in Table 2. The values were found to be in range of 0.49-0.54 gm/cm^3.

Tapped Density: The values obtained for bulk density for all (F_1-F_9) formulations are tabulated in Table 2. Tapped density ranges from 0.50 to 0.60 gm/cm^3.

Compressibility Index: Compressibility index value ranges between 13.2-17.9 %, tabulated in Table 2, indicating that the powder blends have the required flow property for direct compression.

Hausner's Ratio: The values were found to be in the range from 1.12– 1.21, tabulated in Table 2.

Evaluation studies of tablets

Table -3: Evaluation of tablets of Valsartan

Formulation code	Weight variation	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content %
F1	250.2±0.5	2.4±0.03	5.14± 0.02	0.39±0.03	98. 75 ±0.027
F2	245.4±0.6	2.3±0.02	5.16±0.12	0.37± 0.07	97.89 ±0.022
F3	246.3±0.4	2.4±0.06	5.27± 0.31	0.33± 0.06	98.23 ±0.024
F4	251.2±0.5	2.35± 0.04	5.15± 0.25	0.41 ±0.02	98.34 ±0.029
F5	253.5±0.6	2.4± 0.02	5.16 ± 0.13	0.28 ±0.06	98.45 ±0.027
F6	247.4±0,4	2.25±0.03	5. 19± 0.23	0.40± 0.04	99.24 ±0.028
F7	254.3±0.7	2.4±0.06	5.24± 0.37	0.36± 0.04	96.92 ±0.024
F8	248.2±0.5	2.38±0.08	5.17± 0.22	0.39±0.02	98.15 ±0.027
F9	252.5±0.6	2.3±0.07	5.21 ± 0.34	0.39±0.06	98.82 ±0.022

***In-vitro* drug dissolution**

Table -4: Drug release study by *in-vitro* drug dissolution

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	30.06±0.75	28.75±0.99	25.48±0.64	23.62±0.73	20.11±1.27	19.44±0.87	24.36±1.02	21.82±1.01	20.12±0.89
4	48.13±0.99	41.2±0.79	29.56±0.59	31.73±0.89	26.34±0.96	22.23±0.95	25.13±1.09	23.01±1.29	21.45±0.91
6	59.75±0.69	45.62±0.79	36.29±0.61	41.19±1.02	35.65±0.91	28.18±0.85	31.01±1.09	29.13±0.05	25.88±0.91
8	71.45±0.97	55.49±0.89	46.71±0.75	46.12±1.59	42.01±1.21	35.62±0.89	37.11±1.31	35.15±0.09	31.29±0.99
10	79.21±1.09	59.32±0.98	51.76±0.06	58.72±1.09	49.92±1.09	46.62±1.25	48.82±1.11	44.52±1.59	41.82±0.96
12	84.16±1.05	71.81±0.85	58.12±0.93	64.28±0.96	56.43±0.96	51.56±1.29	58.08±1.17	56.25±1.14	51.66±1.07
14	87.14±0.86	76.51±1.52	61.46±0.78	69.38±1.26	61.14±0.62	55.91±0.54	61.42±1.91	62.35±1.99	54.19±0.69
16	91.25±0.65	82.11±0.89	77.19±0.96	81.42±0.58	65.23±1.06	62.89±0.52	72.38±0.92	75.41±1.94	61.45±1.09
18	95.52±1.23	89.12±0.89	81.95±0.91	84.18±0.65	75.71±0.52	71.79±1.45	81.11±1.89	81.21±1.25	78.15±1.56
20	98.75±0.61	95.35±0.88	88.24±0.75	87.46±0.41	84.65±1.52	80.29±1.25	89.21±1.79	85.96±0.99	81.96±0.84

Thickness:- The maximum thickness of the formulation was found to be 2.4mm. The minimum thickness of the formulation was found to be 2.25mm. The average thickness of the all formulation was found to be 2.32mm as hown in table 3.

Hardness test: The measured hardness of tablets of each batch ranged between 5-5.8 kg/cm^2 and was tabulated in Table 3. Tablet hardness was increased as increasing the compression force. This ensures good handling characteristics of all batches.

Friability Test: The values of friability test are tabulated in Table 3. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation Test: The percentage weight variation for all formulations was shown in Table 3. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Drug Content Uniformity: The percentage of drug content was found to be between 97.15 and 98.82 of Valsartan, which was within acceptable limits. Table 3 showed the results of drug content uniformity in each batch.

The in-vitro dissolution study of Valsartan tablet is tested in phosphate buffer 6.8(simulated fluid). The in vitro drug release study of valsartan tablets from each batch (F_1 to F_9) was carried out in phosphate buffer 6.8(simulatedfluid) for 20 hrs and the values are shown in Table 4. The plot of % Cumulative drug release V/s time (hrs) were plotted and depicted as shown in Figure 1.

From the in vitro dissolution data, it was found that the drug release study from formulations containing Guargum(F_1-F_3) was 98.75%, 95.35% and 88.24% drug release respectively. Formulations containing pectin (F_4-F_6) showed 87.46%, 84.65% and 80.29 respectively. Formulations containing cellulose (F_7-F_9) showed 89.21%, 85.96% and 81.96% respectively.

It was observed from the results that, guargum formulations showed maximum dissolution rate with more than 98.75% of drug release in 20 hrs, Pectin formulations released more than 87.46% of drug release in 20 hrs, Cellulose formulations released more than 89.21% of drug release in 20 hrs. In all the formulations upto 15% concentration, there was linearly decrease

in dissolution rate. At higher concentration, all the formulations showed decrease in dissolution rate.

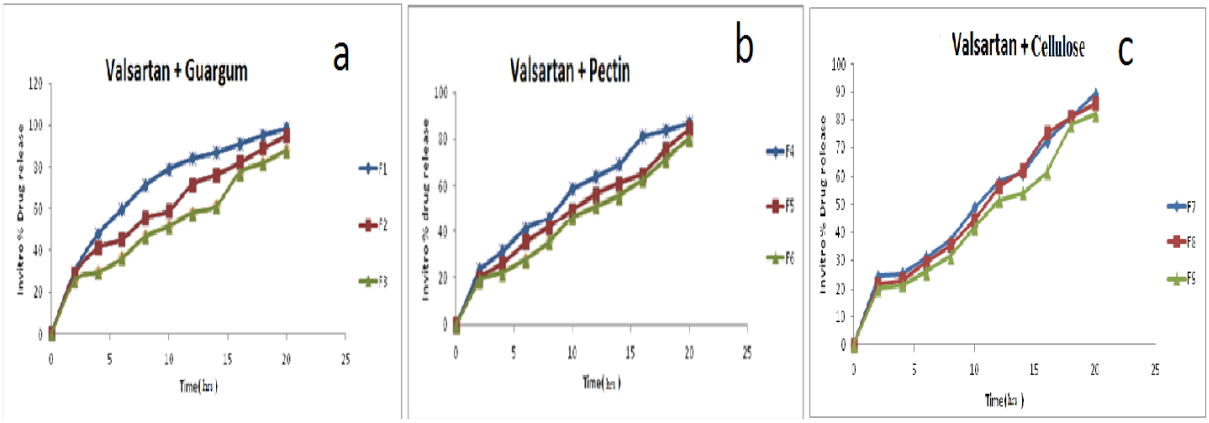

Figure – 1) *in-vitro* drug dissolution of Valsartan with Guargum 2)*in-vitro* drug dissolution of Valsartan with pectin 3) *in-vitro* drug dissolution of Valsartan with Cellulose

DRUG RELEASE KINETICS

Table -5: R^2 values for optimized formulation

Formulation Code	Zero order R^2	First order R^2	Higuchi R^2	Korsmeyar peppas R^2
F1	0.868	0.950	0.986	0.978

The results of dissolution data fitted to various drug release kinetic equations to know the order of release by treating the data according to Zero order and First order, higuchi and korsmeyar peppas equation. The kinetic values obtained for different formulations are tabulated in Table 5. The linearity indicates that the release of drug from the tablets is followed First order.

COMPATIBILITY STUDY

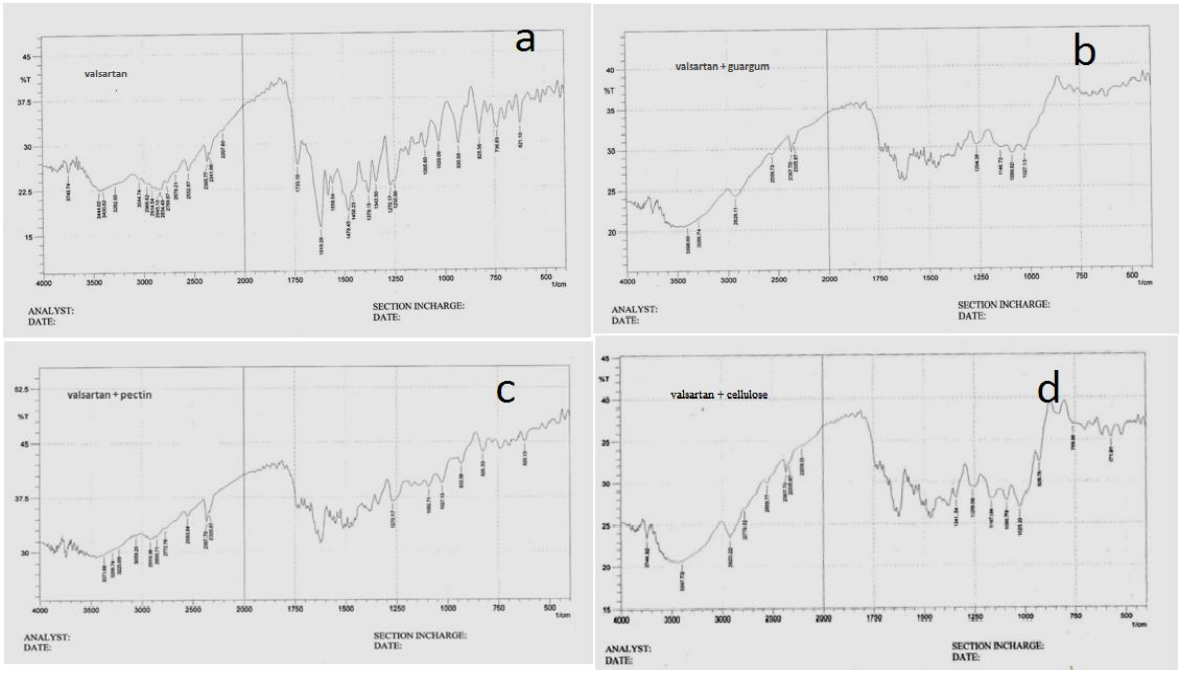

Figure 2: 1) FTIR spectra pure drug of valsartan 2) FTIR spectra of valsartan with guargum 3) FTIR spectra of Valsartan with Pectin 4) FTIR spectra of Valsartan with cellulose

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Valsartan were obtained at different wave numbers in different samples.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components as shown in the figure 2.

Table -6: Stability data of F_1 formulation.

Parameters	Time in months			
	0 (Initial)	1st month	2nd month	3rd month
Hardness (kg/cm^2)	3.14± 0.02	3.14± 0.05	3.14± 0.02	3.14± 0.03
Friability (%)	0.39±0.03	0.39±0.04	0.39±0.04	0.39±0.02
Drug content (%)	98.75±0.027	98.75±0.027	98.75±0.015	98.80±0.011
In-vitro drug release (%)	98.75±0.61	98.75±0.035	98.75±0.025	98.72±0.018

The stability of this formulation table 6 was known by performing stability studies for three months at accelerated conditions of 40^0C $\pm$ 75 % RH on optimized formulation. The

formulation was found to be stable, with no change in the hardness,friability and drug content and in- *vitro* drug release pattern.

CONCLUSION

The conclusions drawn from the present investigation are as follows.

In this project, an attempt is made for Delayed release matrix tablets of valsartan which is used in the treatment of hypertention. This formulation will be evaluated for tablet characteristic, drug content invitro dissolution studies. Delayed release matrix tablets of valsartan were successfully formulated and evaluated. The drug content was uniform in all the formulations of tablets prepared. The low values of standard deviation indicate uniform distribution of drug. Delayed release matrix tablets of valsartan were successfully prepared by direct compression method using guar gum, pectin, cellulose as polymers.

Delayed release tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-1 was identified as better formulation among the developed formulations. F-1 formulation drug release profile was found to be 98.75%. The drug release profile of F1 (guar gum) is higher than rest of the formulations made by using pectin and cellulose. In the formulation-1 having swellable polymer as guar gum showing better drug release profile than other polymer (cellulose and pectin). Hence the natural polymer guar gum is better suitable for delayed release delivery than other polymers.

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