Journal of Pharmacreations

PharmaCreations

ISSN: 2348-6295

Pharmacreations \ Vol 9 \ Issue 2 \ Apr - Jun - 20222

Jouranl Home page: www. pharmareations.com

Research article Open Access

Formulation and evaluation of sustainedrelease matrix tablets of a selective antihypertensive drug

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ABSTRACT

The present work was to formulate and evaluate sustain release matrix tablets of Valsartan, an angiotensin II Receptor type 1 antagonist. Sustain release formulation are those which delivers the drug locally or systemically at a predetermined rate for a fixed period of time. The matrix tablet was prepared by direct compression method using by various concentration of chitosan and sodium alginate with combination of various release retardant polymer. The powder mixtures were subjected to various pre-compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post-compression parameters such as weight variation, thickness, hardness, friability,drug content, *in-vitro* dissolution and stability studies. *In-vitro* dissolution studies were carriedout for 24 hours using 0.1 N HCL for first 2 hours and pH 6.8 phosphate buffer for 24 hours and the result showed that formulations F_4 and F_7 showed good dissolution profile to control the drug release respectively. Formulation containing higher concentration of chitosan and sodium alginate along with polymers sustained the drug release for the period of 24 hours. The compatibility of the drug, polymers and other excipients were determined by FT-IR Spectroscopy. Results showed that the drug was compatible with polymers and other excipients. The release data was fitted to various mathematical models such as Zero-order, First-order, Higuchi equation and Korsmeyer- Peppas model to evaluate the kinetics and the drug release. The drug release followed first order and the mechanism was found to be non-Fickian. The stability studies were carried out for 3 months and result indicates that the selected formulations (F_4 and F_7) were stable.

Keywords: Carbopol 934P, Chitosan, sodium alginate, sustain release matrix tablet, Valsartan.

INTRODUCTION

Oral delivery of drugs is 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.[1] Approximately 50% of the drug delivery systems available in the market are oral drug delivery systems and historically too, oral drug administration has beenthe predominant route for drug delivery. It does not pose the sterility problem and minimal risk of damage at the site of administration.[2]

Pharmaceutical products designed for oral delivery are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption. These immediate release dosage forms have some limitations such as:

1. Drugs with short half-life require frequent administration, which increases chancesof missing dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makesattainment of steady state condition difficult.
3. The fluctuating drug levels may lead to precipitation of adverse effects especiallyof a drug with small therapeutic index, whenever overmedication occurs.

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.[3]

Design and formulation of oral sustained release drug delivery system[4,5]

The oral route of administration is the most preferred route due to flexibility in dosage form, design and patient compliance. But here one has to take into consideration, the various pH that the dosage form would encounter during itstransit, the gastrointestinal motility, the enzyme system and its influence on the drug and the dosage form. The majority of oral sustained release systems rely on dissolution, diffusion or a combination of both mechanisms, to generate slow release of drug to the gastrointestinal tract. Theoretically and desirably a sustained release delivery device, should release the drug by a zero-order process which would result in a blood-level time profile similar to that after intravenous constant rate infusion. Plasma drug concentration-profiles for conventional tablet or capsule formulation, a sustained release formulation, and a zero order sustained release formulation.

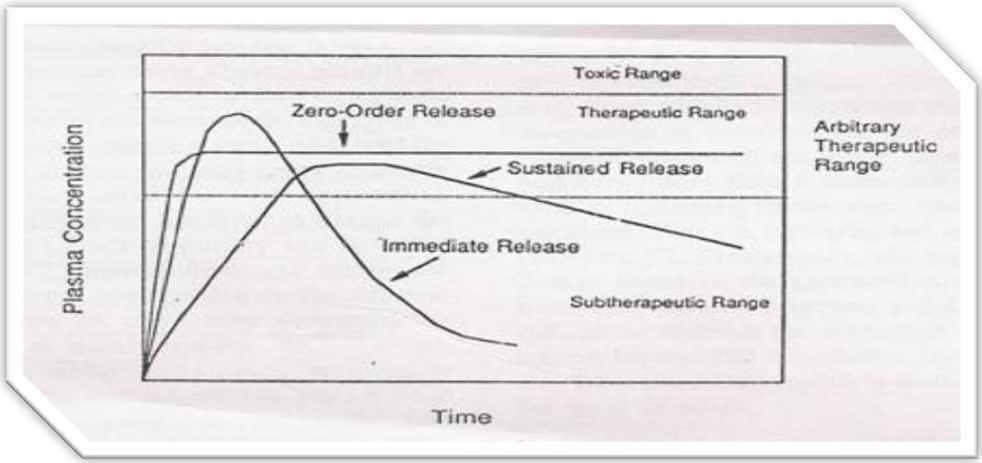

Fig 1: Plasma Concentration-profiles Vs Time (sustained release formulationand zero order formulation)

Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both.Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval.

Delayed release system, in contrast, may not be sustaining, since often the function of these dosage forms is to maintain the drug in the dosage for some time before release, for example. Enteric coated tablet. A sustained release dosage form will provide a therapeutic concentration of the drug in the blood that is maintained throughout the dosing interval with a reduction in a peak concentration ratio.[6-8]

Matrix Tablets

Matrix tablets are the type of controlled drug delivery systems, which releasethe drug in continuous manner by dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug release, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the release retardant. Alternatively drug and release retardant blend may be granulated prior to compression.[9]

The main aim of the present work was to formulate sustain release matrix tablets of Valsartan using various concentration of cross linking agents like chitosan and sodium alginate and release retardant polymers.

Valsartan is an angiotensin II receptor antagonist, which acts by constricting blood vessels and activating aldosterone, which in turn results in reduced blood pressure. It is also used to treat congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack. Due to its shorter half- life (5-6.5hrs) and frequent administration, Valsartan was selected as candidate for developing sustain released matrix tablets.

Tablets are considered as safe, cheap and stable dosage form with better patient compliance and convenience. Due to its shorter half-life, this drug is best candidate for formulation of sustain released dosage form tablets.

Pre-Formulation Studies

Preformulation testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as an investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of pre-formulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms which can be mass produced.

RESULTS AND DISCUSSION

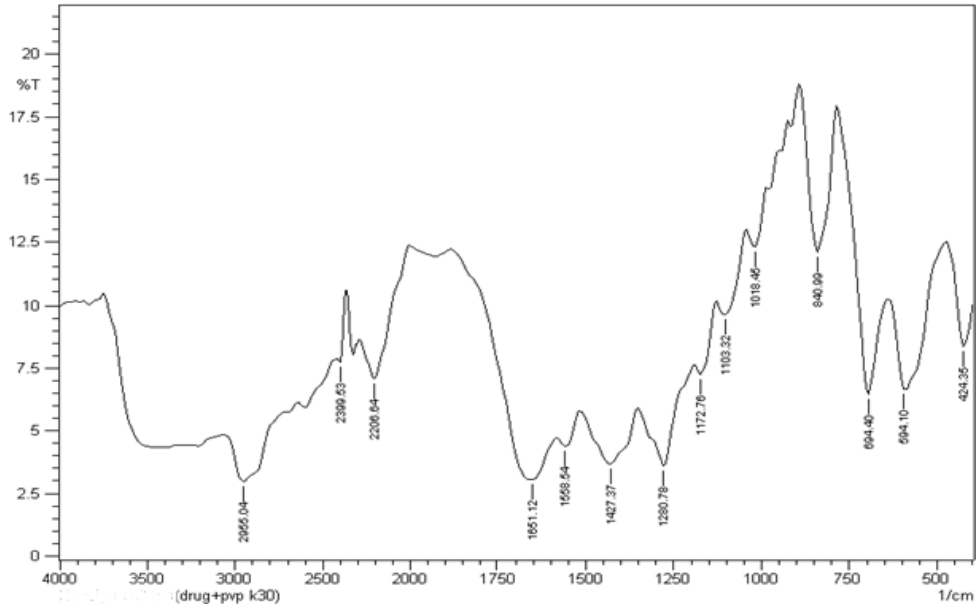

Fig 2: IR Spectrum of Pure Drug Valsartan

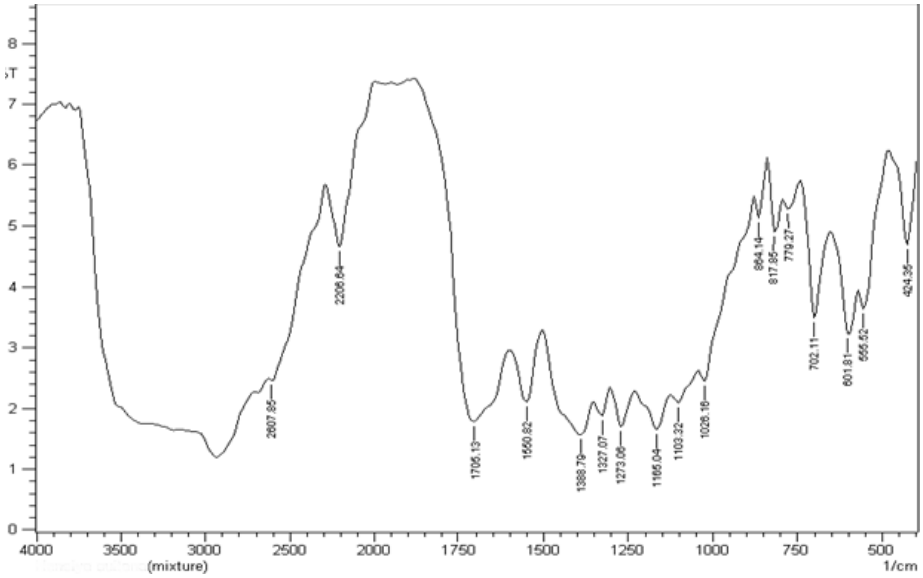

Fig 3: IR Spectrum of Drug + Physical mixturesFORMULATION

Design

The main aim of present study was to formulate sustain release matrix tablets of Valsartan using chitosan in order to improve its therapeutic efficacy and decrease the adverse effects by minimizing the dosing frequency.
In this case nine formulations of sustain released matrix tablets were prepared by using different polymers such as Chitosan, Sodium alginate, Carbapol, MCC and PVP K_{30} in different ratios. The detailed composition of each formulation is given in the table no 5.
The powder mixture was subjected to pre-compression and post-compression evaluation before and after compression.

Evaluation Parameters

Evaluation of powder blended characteristics of matrix tablet formulation

For each type of formulation, blends of Valsartan and other excipients were prepared and evaluated for various parameters such as bulk density, tapped density, Carr‟s compressibility index, Hausner‟s ratio and angle of repose. Bulk density was found in the range of 0.355-0.3850 g/cm^3 and the tapped density between 0.4101-0.4880g/cm^3 indicating both parameters were found to be within the limits. Using the above two density data, Carr‟s compressibility index were calculated. The compressibility index and Hausner‟s ratio was found in the range of 7.27-18.42% and 1.053-1.24 respectively indicating that all powder blends showed excellent to acceptable flow properties. The flow property of all powder blends was better explained from angle of repose. The angle of repose was found in the range of 25.33-31.43°. The results of angle of repose showed all powder blends exhibited good to acceptable flow property. The results of pre-compression parameters are shown in table 1.

Table 1: Evaluation parameters of pre-formulation characteristics of powder blend

Formulations Number	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Carr's Index (%)	Hausner's Ratio	Angle of Repose (θ)
F1	0.3716±0.0011	0.4101±0.0025	7.27±0.659	1.177±0.0076	29.73±0.41
F2	0.3803±0.0005	0.4120±0.0026	7.58±0.514	1.053± 0.0060	25.33±0.63
F3	0.3843±0.0015	0.4120±0.005	7.43±0.760	1.059±0.0088	28.44±0.35
F4	0.376±0.0020	0.4270±0.0037	13.78±0.386	1.073±0.0053	27.48±0.52
F5	0.355±0.0017	0.4600±0.0024	17.31±0.794	1.224±0.011	31.34±0.13
F6	0.3810±0.0045	0.4880±0.0065	18.42±0.120	1.24±0.0020	28.26±0.43
F7	0.3850±0.0081	0.4384±0.133	10.88±0.030	1.123±0.0021	27.27±0.42

Table 2: Post-compression parameters results

Formulation	Diameter (mm)± SD	Thickness (mm)± SD	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	7.92±0.012	3.4±0.09	250.59±0.12	7.4±0.04	0.66±0.007	98.22±0.044
F2	7.90±0.002	4.1±0.02	253.88±0.60	7.9±0.03	0.53±0.005	100.35±0.037
F3	7.95±0.007	4.4±0.01	250.22±0.52	8.1±0.07	0.54±0.031	98.55±0.07
F4	7.95±0.022	3.7±0.07	249.71±0.13	6.4±0.04	0.76±0.016	99.69±0.087
F5	8.0±0.015	4.1±0.04	250.40±0.32	6.7±0.08	0.665±0.09	99.34±0.058
F6	7.74±0.010	3.7±0.09	248.82±0.44	7.2±0.03	0.711±0.01	98.91±0.073
F7	7.47±0.016	4.2±0.01	252.61±0.60	6.1±0.05	0.448±0.00	101.63±0.08

In-vitro drug release study

In this study carbopol was chosen as polymer and it was combined with chitosan and sodium alginate to explore their sustain release capability. The *in-vitro* release data for chitosan-carbopol and sodium alginate-carbopol based Valsartan sustain released matrix tablets are represented in table 17 and illustrated in figure 4. The *in-vitro* release of Valsartan, from prepared matrix tablets formulations was mainly affected by dissolution medium, concentration of chitosan, concentration of sodium alginate and concentration of polymers. *The in-vitro* release of Valsartan form prepared matrix tablets also depends on swelling behaviour of the tablets, higher the tablet swells comparative the lesser amount of drug release. The *in-vitro* release studywas performed in 0.1 N HCl for initial first 2 hrs, and then the medium was replaced by phosphate buffer pH 6.8) and study was continued for 24 hour. The *in-vitro* releaseof Valsartan was higher in first 6-7 hours in all formulations. After 1 hour, approximately 10.29%-18.34% of Valsartan from chitosan-carbapol tablets, 16.90%- 21.91% from sodium alginate-carbapol, 25.12% from tablets containing only release retardant polymer has been released. Initially amount of drug release was higher but after 6-7 hrs drug release was retarded. Formulation F_1 do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation F_2, F_3, F_5, and F_7 containing lower concentration of chitosan and sodium alginate showed almost all drug release within 16 hrs, 20 hrs, 16 hrs and 18 hrs respectively.

Thus these formulations were not considered as good formulation as the maximum amount of drug was released before desire period of time i.e. 24 hrs. The ionic interaction between crosslinking agents and negatively charged polymers was greatly reduced at this pH 6.8 and forms a loose network with increase porous surface which allows great part of dissolution media. Formulation F_4 and F_7 containing highest concentration of chitosan and sodium alginate respectively along with carbopol gum respectively prolong the release of Valsartan to 24 hrs which might be due to the fact that the self-assembled poly electrolyte complexes film was formed on the surface of

cross linking agent-polymer based system. Swelling study also showed that formulation which contains higher concentration of cross linking agent showed higher swelling capacity and prolonged the drug release to 24 hrs.

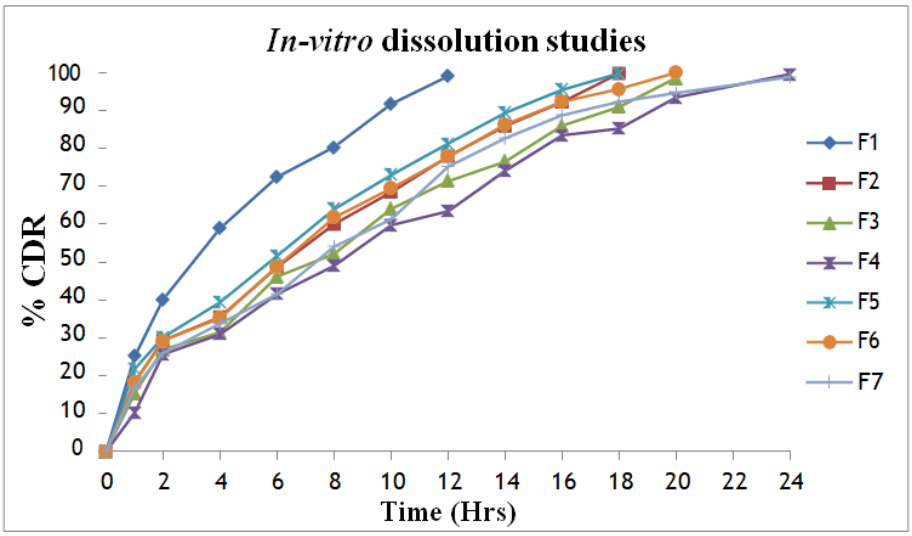

Fig 4: Comparative dissolution profile of the formulations F_1 to F_7

Table 3: *In-vitro* drug release profile of Valsartan sustain release matrix tablets

Time (Hrs)	Cumulative Percentage Drug Release						
	F_1	F_2	F_3	F_4	F_5	F_6	F_7
0	0	0	0	0	0	0	0
1	25.12±0.09	18.34±0.43	15.386±0.33	10.29±0.55	21.91±0.54	18.25±0.32	16.90±0.85
2	40.02±0.12	29.24±0.21	26.905±0.45	25.64±0.62	30.92±0.43	29.25±0.22	25.99±0.42
4	58.82±0.14	35.45±0.33	31.465±0.21	30.94±0.53	39.33±0.54	35.20±0.64	33.71±0.79
6	72.41±0.14	48.71±0.2	46.137±0.13	41.54±0.45	51.64±0.51	48.82±0.73	41.55±0.54
8	80.03±0.28	59.99±0.54	52.186±0.43	48.96±0.38	63.93±0.65	61.73±0.85	54.08±0.64
10	91.61±0.34	68.41±0.55	63.97±0.42	59.68±0.42	72.96±0.72	69.40±0.88	61.27±0.53
12	99.07±0.12	77.09±0.22	71.33±0.54	63.38±0.38	81.23±0.42	77.73±0.95	75.14±0.43
14	--	85.86±0.26	76.50±0.65	74.11±0.43	89.37±0.45	86.24±0.76	82.67±0.48
16	--	92.15±0.33	85.96±0.66	83.39±0.14	95.39±0.62	92.28±0.87	88.75±0.48
18	--	99.71±0.42	90.88±0.59	85.21±0.11	99.77±0.11	95.62±0.73	92.23±0.48
20	--	--	98.54±0.43	93.39±0.14	--	99.99±0.61	94.54±0.48
24	--	--	--	99.54±0.11	--	--	98.78±0.48

Release kinetic studies

The *in-vitro* drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics and Higuchi model. The highest correlation coefficient(r^2) obtained from these method gives an idea about model best fitted to the release data. From the results of kinetic studies, the examination of correlation coefficient „r" indicated that the drug release followed first order release kinetics. It was found that the value of „r" for first order ranged from 0.981-0.992, which is near to 1 when compared to Higuchi square root ranged from 0.892-0.958 and zero order ranged from 0.895-0.969. So, it was understood to be following first order release pattern followed by all formulations. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer Peppas exponential model $M_t / M_a = Kt^n$. Where M_t/ M_a is the fraction of drug released after time 't' and 'k' is kinetic constant and 'n' release exponent which characterizes the drug transport mechanism. The release exponent (n) ranges in between 0.483-0.7911. For all the formulations F_1 to F_9 the values for 'n' ranged above 0.89 which indicates that all the formulations followed non-fickian release mechanism. The relative complexity of the prepared formulationsmay indicate that the drug release mechanism was possibly controlled by the combination of diffusion and erosion.

Table 4: Release exponent values and release rate constantvalues for different formulations

	Zeroorder	Firstorder	Higuchi'splots	Korsmeyer-Peppas plots		Best fitModel	Drug releasemechanism
Batch	R^2	R^2	R^2	R^2	N		
F_1	0.927	0.981	0.9115	0.913	0.591	First order	Non-Fickian
F_2	0.964	0.972	0.8942	0.911	0.592	First order	Non-Fickian
F_3	0.914	0.985	0.9215	0.894	0.6054	First order	Non-Fickian
F_4	0.945	0.976	0.8924	0.894	0.574	First order	Non-Fickian
F_5	0.941	0.997	0.9582	0.902	0.486	First order	Non-Fickian
F_6	0.896	0.958	0.9023	0.924	0.7947	First order	Non-Fickian
F_7	0.892	0.982	0.9254	0.939	0.4847	First order	Non-Fickian

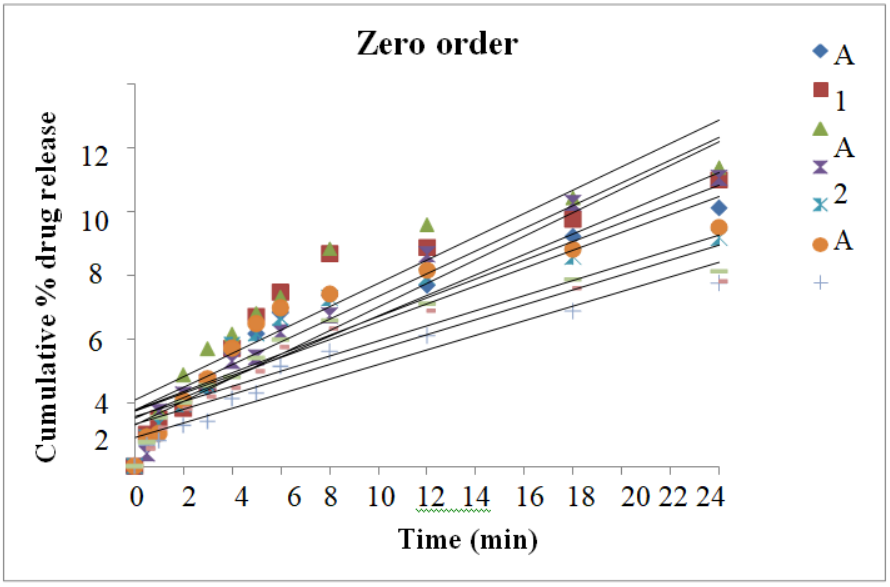

Fig 5: Comparative Zero Order release profile of formulations $F_1$to F_7

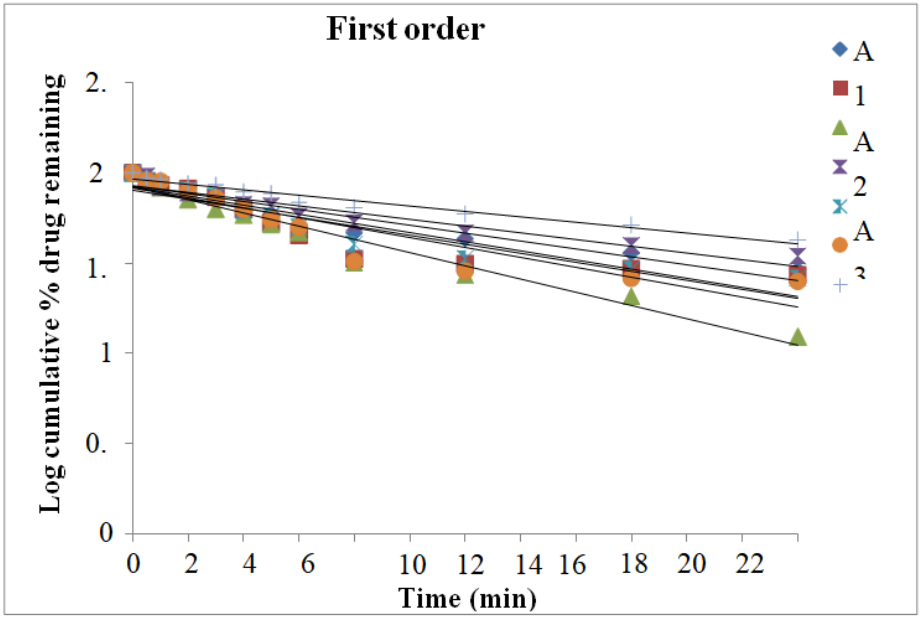

Fig 6: Comparative First Order release profile of formulations F_1 to F_7

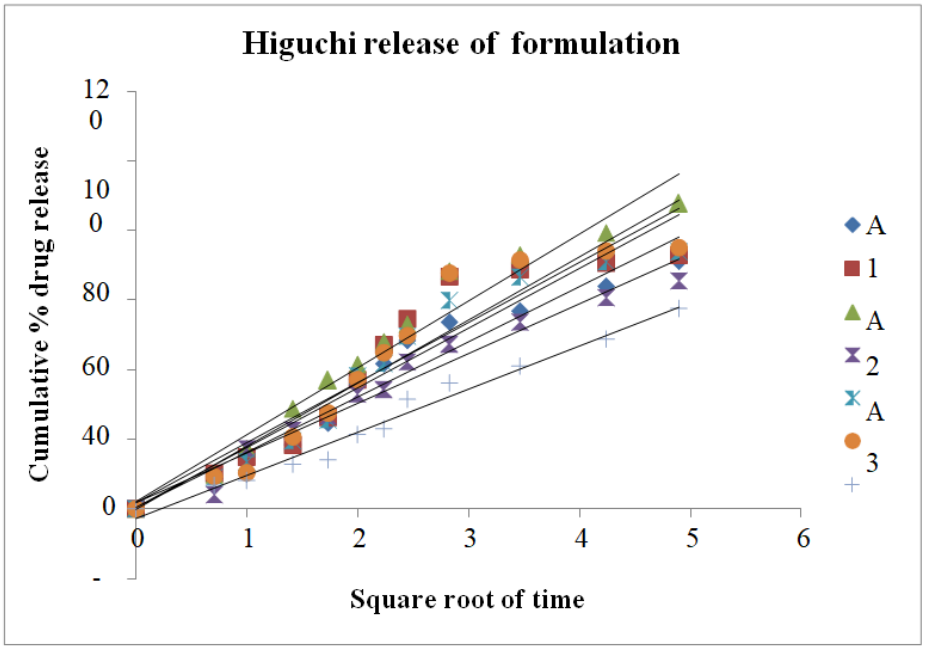

Fig 7: Comparative Higuchi release profile of formulations F_1 toF_7

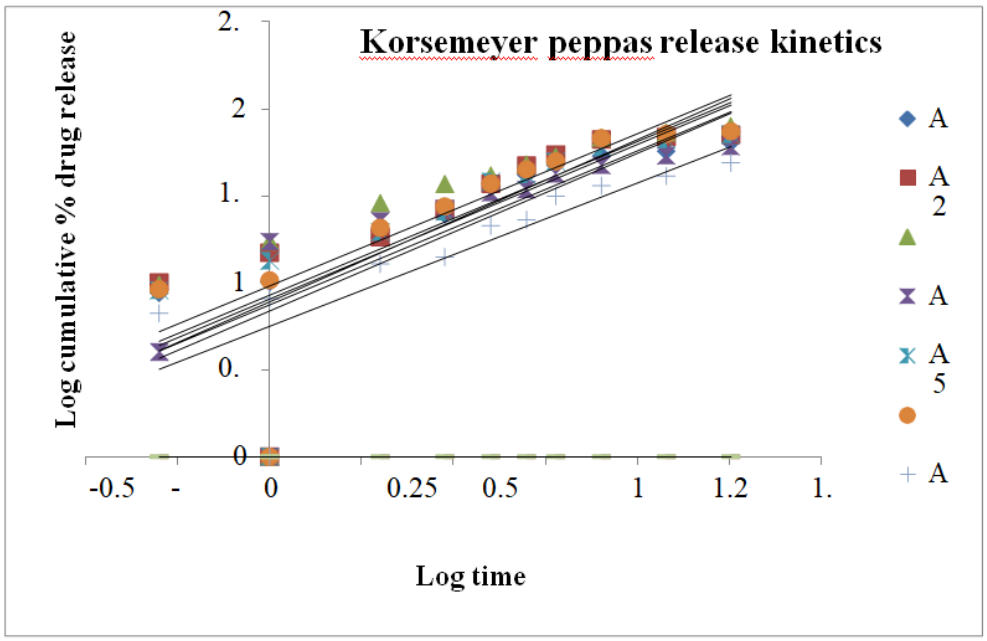

Fig 8: Comparative Korsemeyer peppas release profile of formulations F_1 toF_7

Stability studies

Based on the results of *in-vitro* drug release two best formulations F_4 and F_7 were selected for three month stability studies at 25ºC/60% RH and at 45ºC/75% RH. The stability studies were conducted according to the method described in section four. The selected formulations were evaluated for physical appearance, hardness, friability, and drug content and *in-vitro* drug release. The results showed that there was no significant change in physical appearance, hardness, friability, drug content and drug release profile throughout the study period. Three months of stability studies revealed that; there was no any significant degradation of the drug. Thus prepared formulations were physically and chemically stable. The result of stability studies were tabulated in table 5.

Table 5: Results of stability studies for formulation F_4 stored at25ºC/60% and 45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_4				Formulation F_4			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	% Drug content	% CDR
Initial	8.1±0.07	0.55±0.1	99.66±0.3	99.2±0.4	8.1±0.07	0.51±0.2	99.2±0.3	99.2±0.2
After1 month	7.8±0.12	0.61±0.3	98.83±0.1	99.7±0.4	7.8±0.098	0.65±0.1	98.4±0.2	99.1±0.3
After 2 month	7.6±0.46	0.64±0.2	97.97±0.2	98.5±0.4	7.4±0.07	0.67±0.3	97.6±0.3	98.5±0.2
After 3 month	7.7±0.13	0.64±0.1	97.75±0.3	98.1±0.4	7.5±0.07	0.63±0.1	97.9±0.3	97.6±0.2

Table 6: Results of stability studies for formulation F_7 stored at 25ºC/60% and45ºC/75% RH

Storage period	Stored at 25ºC/60% RH				Stored at 40ºC/75% RH			
	Formulation F_7				Formulation F_7			
	Hardness Kg/cm^2	% friability	% Drug content	% CDR	Hardness Kg/cm^2	% friability	Drug content	% CDR
Initial	6.5±0.06	0.54±0.2	103.6±0.3	98.4±0.5	6.6±0.09	0.55±0.3	96.9±0.3	98.8±0.5
After 1 month	6.6±0.16	0.56±0.3	98.6±0.1	98.6±0.5	6.4±0.21	0.56±0.1	96.4±0.3	98.4±0.5
After 2 month	6.9±0.21	0.62±0.4	99.2±0.2	98.2±0.5	6.2±0.11	0.58±0.1	96.3±0.3	97.7±0.2
After 3 month	6.4±0.15	0.63±0.3	98.2±0.6	97.7±0.5	6.1±0.23	0.63±0.3	96.1±0.3	97.8±0.3

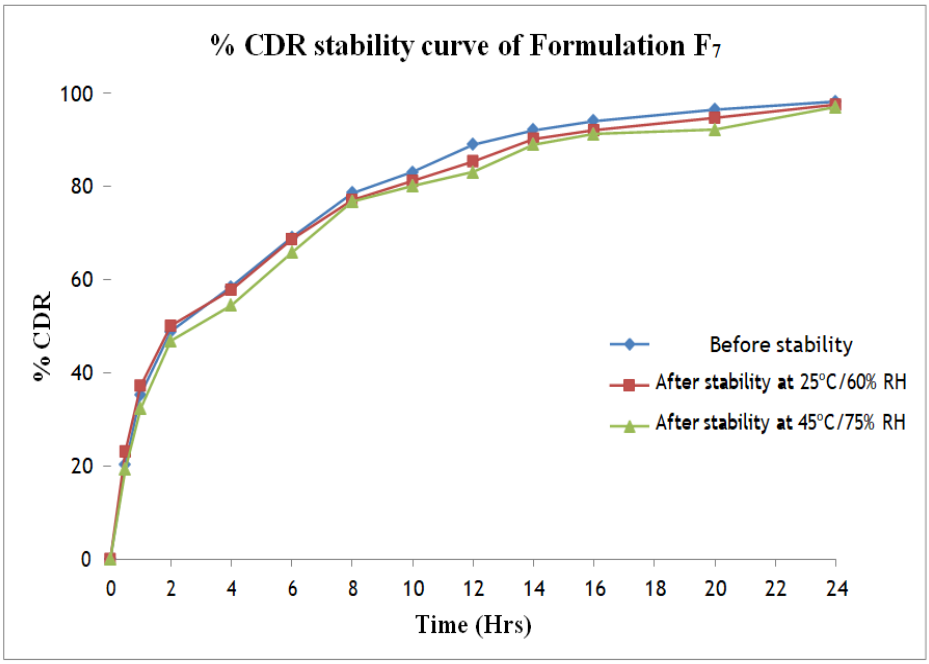

Fig 9: Dissolution rate profile of formulation F_4 before and afterstability.

Summary

Valsartan is an angiotensin II receptor antagonist, which acts by constricting blood vessels and activating aldosterone, which in turn results in reduced blood pressure. It is also used to treat congestive heart failure, and to reduce death for people with left ventricular dysfunction after having had a heart attack. Due to its shorter half- life (5-6.5hrs) and frequent administration, Valsartan was selected as candidate for developing sustain released matrix tablets.

The oral route is the route most often used for administration of drugs.Tablets are the most popular oral formulations available in the market and arepreferred by

patients and physicians alike. Sustain release dosage forms have been demonstrated to improve therapeutic efficiency by maintenance of a steady drug plasma concentration 2-3 times.

The use of polymers in sustaining the release of drugs has become an important tool in the formulation of pharmaceutical dosage forms. Sustain release can be achieved by using carbopol 934P along with cross-linking agents and other excipients used were PVP K30 as binding agent, MCC as a direct compressible agent, talc and magnesium stearate as a glidant and lubricating agent respectively.

- Drug and excipients were subjected for compatibility study using FT-IR, which suggested that there was no interaction between drug and excipients.
- All the formulations were subjected for various pre-compression studies such as angle of repose, bulk density, tapped density, Carr's index, Haunser's ratio and results revealed that the powder mixtures showed good to acceptable flow and compressibility properties.
- All the formulations were subjected for various post-compression studies such as weight variation, hardness, thickness, friability, drug content and *in-vitro* dissolution studies. The hardness and thickness of prepared tablets were found in the range of 6.0 to8.0 kg/cm^2 and 7.8.0-8.0 mm and all other parameters were within the standard official specifications.
- The results of *in-vitro* dissolution study indicated that the drug release from formulation F_4 and F_7 showed 99.54% and 98.78% respectively at the end of 24 hours in sustain manner.
- To analyze the mechanism of drug release from the matrices, the *in-vitro* drug release data were fitted to Zero order, First order, Higuchi and Korsmeyer's-Peppas model.
- It was observed that the release of drug followed first order and the mechanism was found to be non-Fickian.
- The best formulations F_4 and F_7 were subjected to 3 months stability studies andresults showed there was no significant change in the hardness, friability, drug content and *in- vitro* drug release. Thus it was found that prepared tablets were physico-chemically stable throughout stability period.

Thus it can be summarised that the stable matrix tablet dosage form of Valsartan has been developed for sustain release in the treatment of hypertension.

CONCLUSION

Valsartan is a potent, orally active non peptide tetrazole derivative and selectively inhibits Angiotensin II Receptor type 1 which causes reduction in blood pressure and is used in treatment of hypertension. The objective of the present study was to investigate the possibility of sustaining the valsartan release from matrix tablet prepared by using different concentration of cross linking agents and polymers. The following conclusions can be drawn from the result obtained. The pre-formulation studies like angle of repose, bulk density, tapped density Haunser's ratio and Carr's index of all formulations were found to be within the standard limits. FTIR studies revealed that there was no chemical interaction between drug and other excipients. The powder mixtures were compressed into tablet and evaluated for post-compression parameters like weight variation, thickness, hardness, friability and drug content. All the formulation batches showed acceptable results. The *in-vitro* drug release was studied with USP Type-II dissolution apparatusin both simulated gastric fluid and intestine fluid for a period of 24 hours. Results showed that formulations containing higher concentration of chitosan. i.e. F_4 (99.54%) and sodium alginate i.e. F_7 (98.78%) sustained the drug release over a period of 24hours. The *in-vitro* drug release follows first order and indicated that non-Fickian could be the mechanism of drug release. Stability studies showed that the tablets formulations were stable throughout the stability period. It was concluded that the polymer and cross linking agents plays a major role inthe formulation of sustain release matrix tablets of Valsartan. Finally, the study revealed that the release of drug was low when the matrix tablet contained higher concentration of cross linking agents and polymers also showed similar diffusion and erosion kinetics.

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