FORMULATION AND EVALUATION OF SUSTAIN RELEASE MATRIX TABLETS OF AN ANTI-HYPERTENSIVE DRUG USING VARIOUS CROSS-LINKING AGENT

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ABSTRACT

The main aim of 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 table was prepared by direct compression method using various concentration of chitosan and sodium alginate with combination of various release retardant polymer. The powder mixtures were subjected to various pre-compression and post compression parameters. In-vitro dissolution studies were carried out for 24 hours using 0.1 N HCL for first 2 hours and pH 6.8 phosphate buffer for 24 hours and the result indicates that formulations F₄ and F₇ showed good dissolution profile compared to other formulations. 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 (F₄ and F₇) were physiochemically stable throughout its study period. In conclusion, formulation containing higher concentration of chitosan and sodium alginate along with release retardant polymers sustained the drug release for the period of 24 hours.

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. Nevertheless; it is probable that about 80% of all drugs to produce systemic effect are administered by oral route. The oral route is one of the best convenient routes for the drug administration because this route has several advantages like painless administration of the drug and self-administration of drug. Among the solid dosage forms commonly employed tablets have a number of potential advantages like they are unit dose form, they offer the greatest capabilities of all oral dosage forms for the greatest dose precision, the least content variability, having low cost, they are in general the easiest and cheapest dosage form to package and ship and they possess best-combined properties of chemical, mechanical and microbiological stability.

Matrix tablets are oral drug formulation designed to prolong the duration of action by using release retardant polymers. Matrix tablet offers several advantages relative to other extended release dosage form like easy to manufacture, versatile, effective and low cost and can made to release high molecular weight compounds. Matrix tablets are generally prepared by blending a drug and carrier material followed by compression. Hydrophilic matrix tablets are widely used for controlled delivery of drugs. On contact with water or body fluids the outer surface of these tablets swells by polymer hydration and chain relaxation forming a hydrogel coat around the dry central core. It is generally accepted that the gel layer constitutes a diffusional barrier that retards water uptake and hence, drug release.

High blood pressure is a major independent risk factor for cardiovascular disease and stroke; indeed, 5.8% of all deaths are directly linked with hypertension. All in all, hypertension is one of the five chronic diseases (psychological illnesses, diabetes, heart disease, asthma), which are responsible for half the expenditure of the health system.

Valsartan is an angiotensin II receptor antagonist and is widely used in the management of hypertension to reduce cardiovascular mortality in patients with left ventricular dysfunction following myocardial infarction, and in the management of heart failure. Valsartan is a potent and highly selective type I antagonist that lowers blood pressure in hypertensive patients. The aim of the present investigation was to formulate and evaluate the matrix tablets of an antihypertensive drug containing Valsartan as an active agent.
MATERIALS AND METHODS

Drugs and chemicals

Valsartan was procured from Yerrow Chem Product, Mumbai, India. Carbopol 934P, chitosan and sodium alginate were procured from S.D. fine chemical, Mumbai, India. All other ingredients used were of analytical grade.

Preparation of Valsartan matrix tablets

Sustain release matrix tablets of Valsartan was prepared by direct compression method using various concentrations of chitosan and sodium alginate as cross-linking agents, carbopol 934P as release retardant polymers, magnesium stearate as lubricant, talc as a glidant and microcrystalline cellulose as filler. Each formulation contains 80mg of pure drug. The calculated quantity of drug and excipients were weighed accurately and passed through sieve no. 60 separately. Sieved powder materials were transferred to mortar in geometrical dilution method and mixed well for about 10-15 min and at the end of mixing glidant and lubricant were added and further mixed for 3-5 min. Before compression of powder mixtures, hardness was adjusted and compressed into 250 mg tablets using single punch tablet machine (Lab Press, India) equipped with 8mm flat surface punches under 6-8 kg/cm³ compression force. Compositions of sustain release matrix tablets of Valsartan was dissipated in table 1.

| Table 1: Formulation design of Valsartan matrix tablet. |
|-----------------|---|---|---|---|---|---|---|
| Formula code    | F1 | F2 | F3 | F4 | F5 | F6 | F7 |
| Valsartan       | 80 | 80 | 80 | 80 | 80 | 80 | 80 |
| Carbopol        | 100| 100| 100| 100| 100| 100| 100|
| Chitosan        | -- | 5  | 10 | 15 | -- | -- | -- |
| Sodium alginate | -- | -- | -- | -- | 5  | 10 | 15 |
| PVP K 30        | 5  | 5  | 5  | 5  | 5  | 5  | 5  |
| Magnesium Stearate | 3 | 3  | 3  | 3  | 3  | 3  | 3  |
| Talc            | 2  | 2  | 2  | 2  | 2  | 2  | 2  |
| MCC QS to       | 250| 250| 250| 250| 250| 250| 250|

Evaluation parameters

Pre-formulation studies

In order to formulate safe, acceptable, efficacious, stable and bio-available dosage forms, pre-formulation studies were required. In this view, powder mixtures were subjected to various evaluation parameters such as angle of repose (θ), bulk density, true density, compressibility index (CI), Hausner’s ratio (H). Pre-compression studies were helpfull in determination of flow properties and compressibility properties of powder mixtures. Angle of repose was
determined by funnel method. Bulk density and Tapped density was determined by bulk density apparatus.[5,7, 8]

**Post-compression parameters of prepared tablet**

After compression, prepared tablets were subjected for various official tests such weight variation, thickness, hardness, friability and drug content.[4, 8, 9]

**In-vitro dissolution studies**

The in-vitro dissolution studies were performed using the USP-II (Paddle) dissolution apparatus (Lab India) at 50 rpm. Dissolution media used was 0.1 N HCL for first 2 hours and 6.8 pH phosphate buffer for remaining 22 hours. Temperature of dissolution medium was maintained at 37±0.5°C. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analysed on UV spectrophotometer at 249 nm using pH 6.8 phosphate buffer as a blank. Percentage cumulative drug release was calculated and same data were treated with various kinetics parameters such as zero order, first order kinetics and Higuchi equation. The mechanism of drug releasewas understood by fitting the data to Korsmeyer-peppas equation $M_t / M_a = Kt^n$, where ‘$M_t / M_a$’ is fraction of drug released at time ‘t’, ‘K’ is kinetic constant and ‘n’ is release exponent which characterized the drug release mechanism.[10,11]

**Stability study**

Stability study of two best formulations were carried out at 25ºC/60% and 40ºC/75% RH for a period of three months. The selected formulations were packed in aluminium foil in tightly closed container and preserve in stability chamber. During stability study prepared tablets were analysed for hardness, friability, drug content and in-vitro drug release.[12,13]

**RESULT AND DISCUSSION**

**Compatibility study**

FT-IR spectra of Valsartan, carbopol, chitosan and its physical mixture, showed there was no change in significant peak of Valsartan in mixture, indicating no interaction between drugs and excipients (fig 1 an fig 2).
Figure 1: IR Spectrum of Valsartan.

Figure 2: IR Spectrum of drug and its physical mixture.
Pre-compression evaluation

Evaluation of powder blended characteristics

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/cm³ and the tapped density between 0.4101-0.4880 g/cm³ 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 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.

Post-compression evaluation

The prepared tablets were evaluated for weight variation, hardness, friability and drug content. Results of post-compression studies were shown in table no. 2. The average thickness for all the formulations was found in the range of 3.8-4.2 mm which was within the allowed limit of deviation i.e. 5% of the standard value. Tablet hardness is one of the critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before its administration. Hardness test was performed by “Monsanto hardness tester”. All the formulations have an average hardness in between 6.0 to 8.0 kg/cm². This ensures good handling characteristics of all formulation batches. Friability of prepared tablets was determined by using “Roche friabilator”. The average percentage friability for all the formulations was found in between 0.447% to 0.72%, which was found within the pharmacopoeial limit. As the powder material was free-flowing, tablets obtained were uniform in weight due to uniform die fill with acceptable variation as per IP standards. The weight variation for all formulations was found in the range of 249.92 to 253.88 mg. The percentage of the drug content for formulation F1 to F7 was found in between 98.25% w/w and 101.61% w/w.
Table 2: Post-compression evaluation results.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Diameter (mm)± SD</th>
<th>Thickness (mm)± SD</th>
<th>Weight variation (mg)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Drug content (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>7.82±0.012</td>
<td>3.9±0.09</td>
<td>250.89±0.12</td>
<td>7.3±0.04</td>
<td>0.61±0.007</td>
<td>98.25±0.044</td>
</tr>
<tr>
<td>F2</td>
<td>7.80±0.002</td>
<td>4.0±0.02</td>
<td>253.88±0.60</td>
<td>7.8±0.03</td>
<td>0.52±0.005</td>
<td>100.31±0.037</td>
</tr>
<tr>
<td>F3</td>
<td>7.85±0.007</td>
<td>4.2±0.01</td>
<td>251.12±0.52</td>
<td>8.0±0.07</td>
<td>0.58±0.031</td>
<td>98.54±0.07</td>
</tr>
<tr>
<td>F4</td>
<td>7.84±0.022</td>
<td>3.9±0.07</td>
<td>249.81±0.13</td>
<td>6.5±0.04</td>
<td>0.72±0.016</td>
<td>99.67±0.087</td>
</tr>
<tr>
<td>F5</td>
<td>8.0±0.015</td>
<td>4.0±0.04</td>
<td>250.80±0.32</td>
<td>6.8±0.08</td>
<td>0.665±0.09</td>
<td>99.37±0.058</td>
</tr>
<tr>
<td>F6</td>
<td>7.94±0.010</td>
<td>3.8±0.09</td>
<td>248.92±0.44</td>
<td>7.1±0.03</td>
<td>0.714±0.01</td>
<td>98.97±0.073</td>
</tr>
<tr>
<td>F7</td>
<td>7.97±0.016</td>
<td>4.1±0.01</td>
<td>252.61±0.60</td>
<td>6.0±0.05</td>
<td>0.447±0.00</td>
<td>101.61±0.08</td>
</tr>
</tbody>
</table>

**In-vitro drug release study**

The *in-vitro* release profile for chitosan-carbopol and sodium alginate-carbopol based Valsartan sustain released matrix tablets are illustrated in figure 3. The *in-vitro* release of Valsartan, from 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 study was 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* release of 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-carbopol, 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 F₁ do not contains any crosslinking agent, so almost all drugs was released at the end of 12 hrs. Formulation F₂, F₃, F₅, and F₇ 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 F₄ and F₇ 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.
Release kinetic studies
The in-vitro drug release data of all formulations were analysed for determining kinetics of drug release. The highest correlation coefficient ($r^2$) obtained from kinetic model gives an idea about model best fitted to the release data. From the results of kinetic studies, 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. Further, to understand the drug release mechanism, the data were fitted into Korsmeyer/Peppas exponential model, the release exponent (n) ranges in between 0.483-0.7911, indicating that all the formulations followed non-fickian release mechanism.

Stability studies
Based on the results of in-vitro drug release studies, two best formulations F₄ and F₇ were selected for three month Stability studies at 25°C/60% RH and at 45°C/75% RH. The selected formulations were evaluated for physical appearance, hardness, friability, 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.

CONCLUSIONS
In this present study sustain release matrix tablets of Valsartan, an anti-hypertensive agent were successfully formulated by using chitosan and sodium alginate as crosslinking agents.
and carbopol as release retardant polymer. The results of pre-compression evaluation showed drug and excipients were compatible, powder mixture exhibited good to acceptable flow properties which in turn gives tablets with uniform hardness, thickness and weight. Formulation F4 and F7 containing higher concentration of chitosan and sodium alginate respectively and release retardant polymers showed desire percentage of drug release at the end of 24 hours for the management of the hypertension, this may leads to improve patient compliance by reducing dose and frequency of administration.

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REFERENCES

