Formulation and evaluation of matrix tablets of acarbose
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ABSTRACT
Monolithic matrix tablet of Acarbose were formulated as controlled release tablets employing Hydroxypropyl methylcellulose and Eudragit in different concentration and combination, and sustained release behavior of the fabricated tablets were investigated. controlled released matrix tablets containing 350 mg Acarbose were developed using different drug : polymers combination. Tablet prepared by direct compression method were subjected to physical characterization. Formulation was optimized on the basis of acceptable properties and in-vitro drug release. In-vitro drug release was carried out using USP Type II at 50 rpm in 900 ml of acidic dissolution medium (pH 1.2) for 1hr, followed by 900 ml alkaline dissolution medium (pH 7.4) upto 12 hr. Standard curve and withdrawal samples were analyzed in UV-Visible spectrophotometry 625nm with alkaline potassium permagnate as coloring agent. formulations F1, F2, F3 wherein hydroxypropyl methylcellulose K 100 M was employed, it was found that increasing the concentration of the polymer resulted in linearization of drug release curve and formulation F3 gave satisfactory drug release pattern. Formulations F4, F5, F6 containing Eudragit S-100 showed quite non-linearity in drug release. The drug release rate was strongly influenced by the type of polymer and concentration of polymer. To analyze the release mechanism zero order, Higuchi model and Kosmeyer -Peppa’s model were used. The use of simplified methodology is demonstrated to evolve unified mathematical model.

Keywords: Matrix tablet, Acarbose, Hydroxypropyl methylcellulose K 100 M, Eudragit S-100.

INTRODUCTION
During the last two decades there has been remarkable increase in interest in controlled and sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of controlled release is also being applied to veterinary products also. [1]

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery system or by modifying the molecular structure and/or physiological parameters inherent in a selected route of administration.

Carboxymethylcellulose sodium, hydroxypropylmethyl cellulose, polyethylene oxide, eudragit, carbapoly, polyvinyl-107, and natural gums can be used as matrix materials. The matrix may be tableted by direct compression of the blend of active ingredient and certain hydrophilic carriers or from a wet granulation containing the drug and hydrophilic matrix material. [2]

Diabetes mellitus is a chronic disease that is characterized by disorders in carbohydrate, protein and lipid metabolism. Its central disturbance appears to involve an abnormality either in the secretion of or effects produced by insulin although other factors also may be involved. Diabetes mellitus is a metabolic disorder in which carbohydrate metabolism is reduced while the metabolism of proteins and lipids is increased. [3]

Acarbose(O-4,6-dideoxy-4-[(1S,4R,5S,6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1->4)-O-α-α-D-glucopyranosyl-(1->4)-D-glucose) is an oral alpha-glucosidase inhibitor, especially surcease. It is given by mouth in the treatment of type 2 diabetes mellitus. It has also been studied for the treatment of reactive hypoglycemia, the dumping syndrome and certain types of hyperlipoproteinaemia. Because of its higher water solubility and shorter half life (2 hr), drug requires frequent dosing by oral route. Off various recent techniques for controlling drug release, matrix system offer various advantages of ease of formulation, better control on release profile of drug and better patient compliance. [4]
Material and Methods:

Acarbose was obtained as gift sample from Windlass biotech Ltd (Batch no.B 0880532 02982), Dehadran, Uttrakhand. Hydroxypropyl methyl cellulose (HPMC K 100 M) procured from Suleb Lab, Baroda, Gujarat. Eudragit (S100) was obtained as gift sample from S.D.Fine chemical Ltd, Mumbai, Maharastra. Other materials used were of analytical grade, and procured from commercial sources.

Preparation of Sustained Release matrix Tablets of Acarbose:

Controlled release tablets were prepared by direct compression method using 8% microcrystalline cellulose as directly compressible vehicle. Hydroxypropyl methylcellulose (HPMC K 100 M) and Eudragit (S100) were used as retardant material for preparation of tablets. Other excipients were lactose as a diluent, magnesium stearate as a lubricant and talc as a glidant. For preparation of Controlled release tablets of Acarbose, drug and polymer were weighed accurately, all the ingredients were sieved through 40 mesh screen and mixed with other ingredients and the powder mixture was compressed using single punch machine (Royal artist, Mumbai), 12 mm die and punches were used 350mg is adjusted as a weight of each tablet and hardness between 5-6 kg/cm². In total, 6 formulations containing different amounts of HPMC (F1,F2,F3), and Eudragit (F4,F5,F6) were prepared. [5-7]

The formula for various formulations attempted have been given in table-I

Physical characterization of fabricated tablets:

The crushing strength of ten randomly selected tablets per batch were determined using Monsanto hardness tester. Twenty tablets were rotated in a friabilator (Model EF2,Electrolab, India) at 25 rpm for 4 min. The tablets were then dedusted, and the loss in weight due to fracture or abrasion was recorded as percentage weight loss or % friability (Table I).

Estimation of drug content:

An UV/Vis spectrophotometric method based on the measurement of absorbance at 625 nm in phosphate buffer of pH 7.4 and 0.1 N alkaline potassium permagnate was used as coloring agent for estimation of acarbose. From each batch of prepared tablets, 10 tablets were collected randomly and powdered. A quantity of powder equivalent to 150 mg was transferred into a 100 ml volumetric flask, 100 ml phosphate buffer pH 7.4 was added and the solution was sonication for about 30 min. The solution was made up to 100 ml with alkaline potassium permagnate and phosphate buffer pH 7.4. Same concentration of the standard solution was also prepared by taking 100 mg of drug in a 100 ml volumetric flask made up to volume with coloring agent and phosphate buffer pH 7.4. The drug content was estimated by measuring the absorbance of both standard and sample solutions at 625 nm using UV/Vis spectrophotometer (Syrnonic 2201).[8]

In vitro release studies:

The in vitro dissolution studies were performed using USP type 2 dissolution apparatus (paddle) at 50 rpm. The dissolution medium consisted of 1.2 pH medium for first 1 h and for subsequent 11 h in phosphate buffer pH 7.4 (900 ml), maintained at 37±0.50. The release studies were conducted in triplicate. Aliquot of samples (5ml) were withdrawn at specific time intervals and drug content was determined spectrophotometrically at 625 nm. In vitro release data obtained was treated to zero order rate equation, Higuchi’s equation (Q= Kt½) and Korsmeyer- Peppas Equation to know precisely the mechanism of drug release from matrix tablet.

Results of in-vitro dissolution studies obtained were tabulated and shown graphically according to following modes of data treatment.

- Cumulative Percentage Drug Released Vs. Time in Hours.
- Higuchi’s Classical Diffusion Equation - Cumulative Percentage Drug Released Vs. Square Root T. [9-11]
- Korsmeyer- Peppas Equation - Log cumulative percentage of drug released Vs. Log time

RESULT AND DISCUSSION:

In present work an attempt has been made to formulate controlled release matrix tablets of Acarbose using two retardants namely hydroxypropyl methylcellulose and Eudragit in different concentrations and combinations. The formulation of tablets was done by using direct compression technique which was found acceptable.

The results of evaluation studies can be summarized as follows:

### Table I: Composition of sustained release tablets of acarbose

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acarbose</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Hydroxypropyl methylcellulose</td>
<td>50</td>
<td>100</td>
<td>150</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Eudragit</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50</td>
<td>100</td>
<td>150</td>
</tr>
<tr>
<td>Lactose</td>
<td>111.5</td>
<td>61.5</td>
<td>11.5</td>
<td>111.5</td>
<td>61.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Microcrystalline Cellulose</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>Talc</td>
<td>7.7</td>
<td>7.7</td>
<td>7.7</td>
<td>7.7</td>
<td>7.7</td>
<td>7.7</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>% of polymer to the total tablet weight</td>
<td>14.3</td>
<td>28.6</td>
<td>42.9</td>
<td>14.3</td>
<td>28.6</td>
<td>42.9</td>
</tr>
<tr>
<td>Crushing strength (kg/cm²)</td>
<td>5.2±0.11</td>
<td>5.9±0.09**</td>
<td>5.3±0.32</td>
<td>5.4±0.10</td>
<td>5.6±0.81</td>
<td>5.4±0.71</td>
</tr>
<tr>
<td>% Friability</td>
<td>0.45±0.02**</td>
<td>0.32±0.02</td>
<td>0.25±0.01</td>
<td>0.22±0.02*</td>
<td>0.27±0.01</td>
<td>0.36±0.02</td>
</tr>
<tr>
<td>Uniformity of weight (mg)</td>
<td>346±2.08**</td>
<td>349±1.78</td>
<td>348±4.88</td>
<td>349±3.08</td>
<td>353±2.18**</td>
<td>352±2.11</td>
</tr>
</tbody>
</table>

Weight of each tablet = 350 mg, Quantities in mgs, *Minimum value. **Maximum value.
Table II: Applied mathematical models for kinetic study of acarbose tablet

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Function</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Zero-Order</td>
<td>( % \text{diss} = kt )</td>
</tr>
<tr>
<td>2.</td>
<td>First-Order</td>
<td>( % \text{diss} = 100[1-e^{-kt}] )</td>
</tr>
<tr>
<td>3.</td>
<td>Higuchi</td>
<td>( % \text{diss} = kt^{0.5} )</td>
</tr>
<tr>
<td>4.</td>
<td>Korysmyer - Peppas</td>
<td>( % \text{diss} = kt^n )</td>
</tr>
</tbody>
</table>

\( \% \text{diss} \) = percent dissolved at time \( t \), \( k \) = dissolution rate constant, \( n \) = release component which is indicative of drug release mechanism.

The crushing strength of all the tablets was in the range of 5 to 6 kg/cm². The loss in total weight of the tablets due to friability was less than 0.5%. The high value of crushing strength and low friability indicated that the compressibility of acarbose and adjuvant was good. There are various applied mathematical models for dissolution data of acarbose controlled release tablet (Table II). Figure no.I shows plots of cumulative percentage of Acarbose released V/s. time for promising formulations.

Formulations F1, F2, and F3 contains Hydroxypropyl methylcellulose as release retarding polymer in 14.3%, 28.6%, 42.9% of concentration respectively. Formulations F1 and F2 gave 89.14% and 86.38% of drug release respectively in 12 hours of dissolution study performed. The drug release profile were characterized by an initial burst effect (more than 20% drug release in first hour and slow release thereafter). The biphasic release is often observed from hydrophilic matrix systems. As the release-rate limiting polymer changes from glassy state to a rubbery state, a gel structure is formed around the tablet matrix, which considerably decreases the release of the drug since the drug has to diffuse through this gel barrier into the bulk phase. The strength of the gel depends on the chemical structure and molecular size of the polymer. It was found that drug release was not prolonged to desired level; this may be due to inadequate concentration of retardant polymer and also due to lactose, present in relatively large amount which alter drug release rate mainly by altering the gelation of retardant polymer. The formulation F3 gave 83.95% of drug release in 12 hours of study. This may be due to high concentration of retardant polymer level employed. The mechanism of release may be based on hydration and gelation due to cellulosic nature of retardant polymer at tablet liquid interface. The existence of gel barrier could be expected to retard drug release by limiting exposure of solid drug to dissolution liquid. The drug release may be due to diffusion controlled and swelling controlled mechanism because of inherent swelling characteristic of hydroxylpropyl methylcellulose. The tablets were found swollen at the end of 12 hours indicating a hydrophilic matrix system.

Eudragit (S 100), a retardant polymer was used in formulations F4, F5, F6 in 14.3%, 28.6%, and 42.9% of concentrations, respectively. Formulations F4, F5, and F6 gave 96.85%, 92.14%, and 89.55% of drug release in 12 hours of dissolution study, respectively. It was found that the drug release was not prolonged to desired level this may be due to inadequate hydration of retardant as compared to hydroxypropyl methylcellulose. The tablets were found swollen at the end of 12 hours dissolution study this may be due to inherent swelling property of polymer. In all the above formulations, it was observed that drug release rate was inversely proportional to the concentration of retardant polymer i.e., increase in concentration of retardant polymer resulted in a reduction in the drug release rate.

Figure No. II shows the graphical representation of cumula-
tive percentage of Acarbose release as a function of square root of time. These Higuchi’s plots were found to be nearly linear with correlation coefficient (r) values which are 0.9975 and 0.9967 for F3 & F6 respectively. This linearity suggests that the drug release may be by diffusion controlled mechanism.

Figure No.III shows the graphical representation of log cumulative percentage drug released as a function of log time for Formulations F3 & F6 (the best selected formulations). These plots were found to be nearly linear with correlation coefficient (r) values which are –0.9935, and 0.9974 for F3 and F6 respectively and the slope values were n = 0.467 & 0.487 respectively. This slope values indicates that the release of drug from the matrix tablets might have followed fick’s law of diffusion.

CONCLUSION:

From the findings obtained so far, it can be concluded that,

- Hydroxypropyl methylcellulose in the concentration of 42.9% to the total tablet weight is promising concentration for oral sustained release tablets of Acarbose.
- In all the formulations, drug release rate is inversely proportional to the concentration of polymer and directly proportional to concentration of lactose.
- Formulated tablets exhibited nearly zero order kinetics and the release profile was of matrix diffusion type.
- From this study, it is possible to design promising oral controlled release matrix tablets containing Acarbose for the treatment of diabetes with more efficacy and better patient compliance.

In in-vitro dissolution study, formulations F1, F2, F3 wherein hydroxypropyl methylcellulose was employed, it was found that increasing the concentration of the polymer resulted in linearization of drug release curve and formulation F3 gave satisfactory drug release pattern. The drug release mechanism may be of diffusion and swelling controlled, implies hydrophilic matrix system. Formulations F4, F5, F6 containing Eudragit S 100 showed quite non-linearity in drug release, may be because of inadequate polymer hydration and higher diffusion of drug. In all the formulations drug release rate is inversely proportional to the concentration of the polymer and directly proportional to concentration of lactose.

REFERENCES:


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