



Review Paper

A REVIEW ON CAPTOPRIL ORAL SUSTAINED/CONTROLLED RELEASE FORMULATIONS

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ABSTRACT

Captopril provides effective treatment for hypertension and congestive heart failure. However clinical use requires the daily dose of 37.5-75mg to be taken at three times. Development of a prolonged action dosage form for captopril will bring many benefits. The development of oral controlled or sustained captopril formulations has been a challenge for a long period of time. The reason being the drug is highly water soluble, unstable in alkaline intestinal pH and decrease in bioavailability in presence of food. Various attempts have been made to regulate the release and increase the bioavailability of the drug. This review focuses the recent progress and attempts made on the oral sustained or controlled release formulation for captopril.

Keywords: *Captopril, Controlled Release Formulations, Bioavailability*

Introduction:

Captopril (1-[(2S)-3-mercapto-2-methyl propionyl]-1-proline), an angiotensin converting enzyme, has been widely used for the treatment of hypertension and congestive heart failure. The drug is considered as a drug of choice in antihypertensive therapy due to its effectiveness and low toxicity. It is mainly prescribed for patients who are chronically ill and require long term therapeutic agents. The dose required is 37.5-75mg to be taken three times a day in divided doses. The drug acts orally and after single oral dose ingestion the antihypertensive action is only effective for 6-8hrs [1].

The drug is freely water soluble and has elimination half life of 1.7hr. The drug is stable at pH1.2 and as the pH increase it becomes unstable and undergoes pseudo first order degradation reaction [2]. Also the drug is susceptible to degradation, especially in

aqueous solution and is considered a drug likely to present stability problems. This fact compromises the therapeutic effect of the drug [3].

Development of a once daily captopril oral formulation would be a significant advantage for patient compliance accompanied by minimization of the drug side effects as a result of reduction in the drug blood concentration fluctuations, especially in long-term therapy [4]. The development of oral controlled release formulations for captopril is somewhat difficult. This difficulty arise from the fact that the drug suffering in vitro and in vivo instability being degraded to different metabolites in vivo and pseudo-first order type degradation reaction with minor changes in pH range in vitro. Besides that the drug shows a mixed type of absorption from the GIT (being passively absorbed in part and through the peptide-carrier mediated in the other part). The drug also suffers from dose phenomenon and burst effect (being freely water soluble) when formulated as sustained or controlled formulation. On the other hand, the drug reflects

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prominent food reactions and its bioavailability decreases in the presence of food [5]. The present study reviews thoroughly about the various approaches made for the controlled or sustained release formulation of captopril.

APPROACHES OF ORAL SUSTAINED/CONTROLLED RELEASE FORMULATIONS:

To achieve the rapid action, Bolourtchian et al developed sublingual tablets of captopril which was effective and safe method of lowering arterial blood pressure in patient with hypertensive emergencies. More rapid attainment of plasma concentration and more rapid onset of pharmacological effect have been observed after sublingual administration of captopril than oral route [6].

Various pharmaceutical approaches have been made to design long acting devices to administer once a day formulation as controlled and sustained release systems to deliver the drug. The different methodologies applied and their limitations are described as follows.

Matrix tablets:

Various methods are available to formulate water soluble drugs into sustained release dosage forms by retarding the dissolution rate. One of the methods used to control the drug release and thereby prolonging therapeutic activity is to use of hydrophilic or lipophilic polymers. In recent years, the considerable attention has been focused on hydrophilic polymers in the design of oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Among the hydrophilic polymers, cellulose derivatives such as methyl cellulose, hydroxyl propyl methyl cellulose, and sodium carboxy methyl cellulose are generally considered to be stable and safe as release retardant excipients in the

development of oral controlled release dosage forms. These semisynthetic polymers are quite expensive when compared with natural polymers such as guar gum, alginates, and so forth. The natural polymers are nontoxic and easily available [7]. The cellulose derivative polymers are suitable for preparing formulations with soluble or insoluble drugs and at high or low dosage levels. Hydration of polymers results in the formation of gel layer that controls the release rate of the drug [8].

Ali Nokhodchi et al described the effects of various polymers such as hydroxy propyl methyl cellulose (HPMC), ethyl cellulose (EC) and sodium carboxy methyl cellulose and surfactants on the release rate of captopril from matrix tablets. This work has showed that surfactants can be used to control the release rate of captopril from HPMC-EC matrices. However, they are not able to produce the zero-order release pattern for captopril matrices. The magnitude of the increase or decrease of release rate remarkably depends on the type of surfactant and on concentration. The results also show that the surfactants are able to change the mechanism of captopril release from the matrices. The principle mechanism by which surfactants retard drug release from HPMC-EC matrices is the drug/surfactant ionic interaction [9].

Coated tablets:

It is a classical technique to control the drug release. The drug has cross the barriers before it reaches the physiological fluids. The type and composition of the barriers is the release determining step. Barriers are mainly composed of hydrophilic or hydrophobic polymers and that is due to the compatibility of these substances beside their in vivo safety even when used in large amounts.

Guittard et al described a coated tablet formulation of captopril capable of showing in vivo sustained release pattern and that was by making use of a semi permeable coat prepared from a mixture of micro

crystalline cellulose acetate, poly vinyl pyrrolidone (PVP) and tri propyl citrate. The core tablet consisted of captopril blended with HPMC, Micro crystalline cellulose, PVP and magnesium stearate and wetted with anhydrous ethanol, dried and compressed [10].

Floating tablets:

These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastro intestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine [11].

Martinez et al studied the in vitro sustained release of captopril from metalose SH 4000 SR/sodium bicarbonate floating tablets. This was studied at two different compaction pressures. Other studied variables include the kinetics of the hydration volume, the matrices floating time and the matrix density. The results show that matrices compacted at 55MPa float in the dissolution medium for more than 8h while those compacted at 165MPa float only when sodium bicarbonate is included in the formulation. The increase of the matrix polymer proportion increases the maximal hydration volume as well as the time to attain this maximum. The matrices hydration volume increases with the inclusion of sodium bicarbonate in the formulation. The matrix density is lower when compacted at 55MPa. The drug release constant (k) decreases and the exponent indicative of the release mechanism (n) increases with increasing polymer contents. The drug released with time is lesser when sodium bicarbonate is included in the formulation. Carbon dioxide bubbles obstruct the diffusion path and decrease the matrix coherence. The effect of

compaction pressure to reduce the drug release rate has to be made clear in further studies [12].

Patel et al worked on sustained release non-effervescent floating matrix tablet of captopril with a view of prolonging gastric residence time as well as avoiding intestinal degradation. The hydrophilic matrix containing HPMC K15MCR and HPMC K100MCR alone and in combination could not control the drug release pattern. Incorporation of hydrophobic polymer ethyl cellulose in granulation fluid showed good release pattern. Invitro drug release, invitro buoyancy and swelling behavior remained unaffected by change in pH and osmolarity [13].

Rahman et al developed a bilayer tablets for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. Final formulation released approximately 95% drug in 24h invitro, while the floating lag time was 10min and the tablet remained floatable throughout all studies [14].

Meka et al was developed a gastro retentive floating drug delivery system with multiple unit minitables based on gas formation technique in order to prolong the gastric residence time and to increase the overall bioavailability of the drug. The system containing the drug containing core units prepared by direct compression process, which were coated with three consecutive layers of an inner seal coat. Effervescent layer (sodium bicarbonate) and an outer gas entrapped polymeric membrane of Eudragit RL30D, Eudragit RS 30D and combination of them. The drug release was controlled and linear with the square root of time [15].

Khatab et al developed and optimized the release of captopril from sustained release matrix floating

tablets and capsules prepared by wet granulation. HPMC 4000 and 15000 were used as the release controlling polymers, Eudragit RS100 and RSPM as granulating agent, sodium bicarbonate as gas forming agent. The tablets and capsules maintained their floating characteristics over the period of 8hrs [16].

Slow release granules and Sustained release oily matrix:

Stulzer et al developed the captopril granules of controlled release with different polymers as ethyl cellulose, ethyl/methyl cellulose and immediate release with polyvinyl pyrrolidone by fluid bed drier technique. The dissolution profile of granules coated with ethyl cellulose showed a median time release of 4hrs whereas for granules coated with ethyl/methyl cellulose was 3.5hrs. The blockage of angiotensin I-induced hypertensive effect lasted 8 hr in granules coated with PVP and of more than 12 hr in the granules coated with ethyl cellulose and ethyl/methylcellulose [17].

To obtain a prolonged action dosage of captopril slow release granules, modified release tablets, enteric coated granules and oily semisolid matrix (OSSM) were formulated by Seta et al. The coated slow release granules and the modified release tablets showed them to be markedly inefficient under fasting conditions. The AUCs of these products were 0.64-1.69 ($\mu\text{g hr/ml}$), which is about 20-40% of the AUC obtained by conventional tablets under fasting conditions. Under non-fasting conditions, the CSR granules and enteric coated granules suffered additional decreases in AUC. The AUC of the enteric coated granules under non-fasting conditions was only 20% of the AUC% with the uncoated granules under fasting conditions. The OSSM maintained higher plasma captopril level for a long time as compared with the CSR granules under the same non-fasting conditions. Although the AUC ($0.83 \mu\text{g.h/ml}$) of

OSSM was only half of the conventional tablets (non-fasting condition), this formulation is expected to offer an effective prolonged-action dosage form of captopril [4].

Further study was made by Seta et al in the semisolid oily matrix systems to improve the bioavailability of captopril in non fasting conditions. These were made using oily semisolid vehicles as the base into which ascorbic acid was added. In the oily semisolid matrix, fine captopril crystals were suspended in an oily semisolid base composed of edible oil (soya bean) and a thickening agent (glyceryl monostearate). Ascorbic acid improved stability of the drug and worked much more effectively. This maintained more than 80% inhibition of ACE activity for over 8.5hrs, while conventional tablets could maintain the same effect only for 2.5hrs [18].

This work was further extended in human treatment of oily semisolid matrix. Pharmacokinetic analysis was performed based on plasma concentrations of captopril in humans (n=8) after a single oral administration of conventional tablets or this system reformulated for humans. Calculated AUC of plasma captopril concentration were 250.5 for conventional tablets and 283.5 (ng.h/ml) for OSSM. The mean residence times obtained by both formulations were 1.75 h and 3.59 h, respectively. The duration time in which plasma captopril concentration stayed above 50% inhibitory concentration of angiotensin converting enzyme activity was calculated. Total duration time (TDT) per day of conventional tablets (12.5 mg) taken 3 times daily was calculated to be 10.95 h. The TDT of OSSM was 17.00 h when the OSSM (18.75 mg of captopril) was administered twice a day at 12-h intervals. Consequently, OSSM dosed twice a day is expected to show a

greater efficiency than conventional tablets taken 3 times daily [19].

Sustained release microparticles:

Microparticles are small solid particulate carriers containing dispersed drug particles either in solution or crystalline form. They are made from natural and synthetic polymers. Dandagi et al worked on microparticles of Captopril using bovine serum albumin as a drug carrier prepared by emulsification-heat stabilization technique. The in vitro study of captopril loaded microparticles showed release of drug up to 24hrs. The in vivo result showed preferential drug targeting towards liver, lungs, spleen and kidneys [20].

Kamel et al studied about the captopril microparticles using cellulose propionate prepared by solvent evaporation method. The antihypertensive effect of these microparticles was compared with the available aqueous oral solution. The release kinetics from the propionate microparticles showed diffusion mechanism. After oral administration of the selected microparticles to hypertensive rats showed reduction in the systolic blood pressure over 24hrs compared to reference drug solution [21].

Mucoadhesive microcapsules:

The adhesive properties of certain types of polymer could be used to increase the residence time of orally administered drugs. A fuller understanding of the molecular processes underpinning such Mucoadhesive phenomena will help in the optimal design of the delivery systems [22]. It has been an interested topic to deliver the drugs at the site of absorption and to facilitate intimate contact of the dosage form with the to the underlying absorption surface to improve and enhance the bioavailability of the drugs [23]. Altaf et al worked on Captopril microcapsules were prepared with a coat consisting of alginate and Mucoadhesive polymers such as HPMC, Carbopol 934p, chitosan and cellulose

acetate phthalate using emulsification ionic gelation process. Drug release pattern in these formulations was diffusion controlled, gradual over 8hrs and followed zero order kinetics [24].

Elementary osmotic pump:

The elementary osmotic pump is a new delivery system that delivers the agent by an osmotic process at a controlled rate. The system is constructed by coating an osmotically active solid agent with the rate controlling and semi permeable membrane with an orifice of critical size through which solubilized agents are delivered or dispensed [25]. When the system happens to be inside the GIT, the fluid enters the core through the membrane and dissolves the active material. The osmotic pressure generated inside the core induces the release of drug in solution at a slow but constant rate [26]. These are mostly available for water soluble drugs [27, 28].

Xu et al designed an elementary osmotic pump using Cellulose acetate in acetone containing a plasticizer and a porogen was used as a coating solution. An orifice was drilled in the center of the coated tablet by a micro drill. NaCl was used as an osmotic pressure accelerant and pregelatinisatum as a loading agent. This system released the drug at a constant rate, independent of the pH of the medium. Pharmacokinetic research indicated that these can prolong the effective drug duration, reduce the frequency of taking the drug and lower the max blood concentration of the drug, which can greatly reduce the side effects of Captopril [29].

DISCUSSION:

As has been described earlier, the matrix tablet of Captopril was not able to produce the zero-order release pattern. The magnitude of the increase or decrease of release rate depends on the type of surfactant on its concentration. They also showed that the surfactants change the mechanism of captopril release from the matrices.

The release profiles of a captopril from Metalose matrices display greater percentages of drug released compared to similar matrices containing sodium bicarbonate. This is attributed to an obstruction effect of the diffusion path by carbon dioxide bubbles. No concluding evidence was found indicating significant greater release profiles of Captopril matrices. The hydrophilic matrix tablets prepared by using HPMC K15MCR and HPMC K100MCR alone and in combination could not control the drug release pattern. Incorporation of hydrophobic polymer like Ethyl cellulose in granulation fluid showed good release pattern. Development of bilayer floating tablets of Captopril using HPMC K-grade polymer as a carrier showed promising results. However further clinical studies are needed to assess the utility of this system for patients suffering from hypotension.

With regard to the slow release granules reviewed, the sustained release was upto 8h which is comparatively short time. Seta et al developed semisolid oily matrix systems in which ascorbic acid was added to improve stability of drug and maintained inhibition of ACE activity for 8.5h. It is not suitable for delivery of captopril in a sustained release dosage form.

Microparticulate system of captopril was formulated using bovine serum albumin as carrier by emulsification-heat stabilizing method to localize drug at the absorption site, enhance its bioavailability, reduce dose thereby improving patient compliance. Captopril sustained release microparticles prepared by emulsion-solvent evaporation method using acetate propionate showed invitro release upto 8h. Furthermore, lack of gastric residence enhancement will add to the problems encountered with these systems to control the in vivo release of captopril.

The mucoadhesive microcapsules of captopril comply with zero order release pattern. This shown

invitro release upto 8h. Prolongation of residence time of the dosage form to produce once or twice a day dose application, in case of these systems faced with different difficulties. It is the same situation with captopril elementary osmotic pump shown comparatively short invitro release.

Prolongation of residence time by floating systems showed sustained release upto 8h which is short. It is difficult to design a floating system to overcome all these factors. Undoubtedly, these systems enhance the gastric residence of the drug to improve its biological activity and furthermore, they are of value when food effects are encountered.

CONCLUSION:

As has been described, all the controlled release dosage forms available for captopril claims to release the drug upto 8h. These need the drug administration for two to three times a day which is not feasible to for once a formulation. In some cases, the optimum release of drug was shown but with *in vitro* data only. The *in vivo* release was studied under animals only. Further clinical studies are needed to assess the utility of these systems for patients suffering from hypotension. Only by considering these factors collectively, it is feasible to formulate a controlled release dosage forms to deliver captopril, however extensive studies are required to examine the factors that play role in development of controlled release formulations of captopril. Surprisingly, despite of all these research work, there are likely to be no well established captopril controlled release formulations reported to be in the market.

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