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Review

Recent progress in sustained/controlled oral delivery of captopril: an overview

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Abstract

The development of oral sustained or controlled release dosage form of captopril has been an interested topic of research for a long period of time. Difficulties encountered with such topic based on the fact that the drug is freely water soluble and for obvious reasons, such drug is difficult to be delivered orally in a sustained or controlled release manner and, on another hand, the drug is unstable in the alkaline pH of the intestine, which unabled the scientists to localize the developed formulations at the targeted areas of the GIT. Due to its effectiveness and intensive use as a drug of choice in the treatment of hypertension and congestive heart failure, numerous sustained and controlled release formulations of captopril have been made and reported. Despite of these numerous attempts and works, very few have been successful and some of these formulations have been patented. The clinical supportive data regarding the efficacies of these developed formulations are not always available and, furthermore, their claims rely only on in vitro data.

Keywords: Sustained release; Controlled release; Dosage form; Captopril

1. Introduction

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. Beside 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 suffering from dose dumping and burst phenomenon (being freely water soluble) when formulated as sustained or controlled release formulation. On the other hand, the drug reflects prominent food reactions and its bioavailability decreases in the presence of food. Only by considering these pre-mentioned factors collectively, it

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was claimed that the development of such formulations is feasible. Attempts have been made to regulate the release process by incorporating hydrophobic fillers within the system or by using poorly water soluble swellable or not swellable polymers. Other reports showed the usefulness of the so called hydrodynamically balanced systems that float on GIT contents and other authors postulated the use of mucoadhesive systems and for both cases the aim was to increase the residence time of the formulation within GIT. All these formulations will be discussed separately within this article review. The main objective of this review is to discus the different technologies used in recent years to design oral sustained or controlled release delivery systems for captopril and the problems encountered with such formulations.

2. Background

Captopril, (1-[(2S)-3-mercapto-2-methyl propionyl]-$_L$-proline), an orally active inhibitor of angiotensin-converting enzyme (ACE) (Ferguson et al., 1977; Ondetti et al., 1977), has been used widely 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 (Gavras et al., 1978; Bravo and Tarazi, 1979; Brunner et al., 1979; Testa et al., 1993). The drug is freely soluble in water (125–160 mg/ml, at pH 1.9) with pK_a of 3.64 at 25°C and its partition coefficient is pH-dependent. The drug is stable at pH 1.2 and as the pH increases, the drug becomes unstable and undergoes pseudo-first order degradation reaction (Seta et al., 1988a; Anaizi and Swenson, 1993). Enumerated reports in the literature revealed that the drug is absorbed, in part at least, from the stomach and proximal small intestine by an active transport process via the peptide carrier system with a significant passive component to the overall absorption process (Worland et al., 1984; Hu and Amidon, 1988; Wilding et al., 1992).

Approximately 70% of the ingested oral dose is absorbed in healthy fasting human subjects with an absolute bioavailability of 60%, compared to iv dose (Duchin et al., 1982; Brogen et al., 1988). In animals, the bioavailability of captopril is between 47 and 65% in mice and between 35 and 71% in rats (Wong et al., 1980). In a study conducted in human using a single 100 mg tablet of 35S-labeled captopril (Kripalani et al., 1980), the T_{max} for unchanged drug in the blood was found to be 0.93 ± 0.08 h and C_{max} of 800 ± 76 ng/ml. Drug absorption was found to be dose and concentration independent, and the elimination half life of the free drug was in the range of 1–3 h. Another conducted study, using 14C-captopril 10 mg oral and intravenous, showed that the average volume of distribution (V_d) is 0.2 l/kg for the central compartment and 2 l/kg for the elimination (β) phase, 38% (intravenous) and 24% (oral) of the dose was excreted over 24 h as unchanged captopril in the urine (Duchin et al., 1982).

Once absorbed, captopril is extensively metabolized to several forms including a disulfide dimer of captopril, a captopril-cysteine disulfide and mixed disulfides with endogenous thio compounds (Migdalof et al., 1980). Drug absorption was found to be retarded in the presence of food (Singhvi et al., 1982). The drug contains a reactive thiol group postulated to be necessary to its binding to Zn^{2+} of the angiotensin converting enzyme (Antonaccio, 1982) and, furthermore, the drug forms covalent links with plasma protein via disulfide linkages with thiol-containing residues which may explain the extensive tissue binding of the drug (Komai et al., 1981).

The duration of antihypertensive action after single oral dosing of captopril is only 6–8 h, so clinical use requires the daily dose of 37.5–75 mg to be taken at three times (Miazaki et al., 1982). Most recently, it has been reported that the initial recommended dose for the treatment of hypertension is 12.5 mg twice daily by mouth with a maintenance dose being 25–50 mg twice daily and should not exceed 50 mg three times daily. And in the treatment of heart failure, the initial dose is 6.25–12.5 mg taken orally two to three times daily with a maintenance dose of 25 mg two to three times daily (Martindale, 1996). Captopril, which is freely water soluble, is usually prescribed to patients who are chronically ill and require long-term use for its therapeutic benefit. Develop-

ment of once daily captopril oral formulation would be a significant advantage for patient compliance which accompanied by minimization of the drug side effects as a result of reduction of the drug blood concentration fluctuations specially in long-term therapy (Singh and Robinson, 1988; Seta et al., 1988a; Wilding et al., 1992).

Different attempts have been made to design long acting devices in the form of sustained or controlled release preparations to deliver this drug. Formulations reviewed here are categorized in a manner that to ease he discussion purposes of the article review.

2.1. Coated tablets

It is a classical technique to control the drug release. The drug has to cross barrier(s) before it reaches the physiological fluids. The type and composition of the barrier is the release determining step. Barriers are mainly composed of polymers (hydrophobic or hydrophilic) and that is due to the compatibility of these substances beside their in vivo safety even when used in large amounts. Simply, coated tablets composed of a core which contains the drug (alone or with other additives) and coating layer surrounding the former.

Guittard et al. (1993), described a coated tablet formulation of captopril capable of showing in vivo sustained release pattern and that was by making use of a semipermeable coat prepared from a mixture of microcrystalline cellulose acetate, polyvinyl pyrrolidone (PVP) and tri-propyl citrate. The core tablet was composed of captopril blended with hydroxy propyl methylcellulose (HPMC), microcrystalline cellulose, PVP and magnesium stearate, and wetted with anhydrous ethanol, then dried and compressed.

Double coating tablets capable of sustaining the release of captopril have been also described in the literature (Drost et al., 1988). Captopril (14% by weight of the core) blended and mixed with lactose and HPMC (37% w/w, Methocel E4M). The mixture granulated with a solution of polyvinyl pyrrilidone (PVP) and to the dried granules hydroxy propyl cellulose (18.5% w/w, Klucel HF) was added. The blended mixture was lubricated and compressed into tablet cores. Coating solution formed of a mixture of HPMC (27% by weight of the coat, Methocel E-5), ethyl cellulose (Type N-22, 40% w/w) and triethyl citrate (as plasticizer, 5% w/w) was applied onto the tablet cores. The tablet cores further coated with an outer coat composed of HPMC (69% w/w, Methocel E-5), 7% w/w of triethyl cellulose (as plasticizer) and coloring agent. Authors claimed that such formulation is capable to sustain the release of captopril. The in vitro release pattern was not mentioned, however, such device was found to be efficient in controlling the release of procainamide HCl over 12 h period of time with a desired zero order release kinetics when tested in vitro using USP XX method.

Another device having the drug in both outer layer and within the tablet cores have been described by Abramowitz et al., (1992), aiming rapid release of the drug from the outer coat followed by a controlled prolong release from the tablet cores. Authors stabilized the tablet cores by means of a mixture of ascorbic acid (47% w/w), sodium ascorbate (9% w/w) and disodium edetate (8% w/w) postulating that such stabilization will protect the drug till released in the colon. Captopril (9.5% by weight of the core) mixed with the stabilization mixture, microcrystalline cellulose, cornstarch and stearic acid. The mixture was then compressed to form the tablet cores which could also be in form of beads. The core tablets were coated with a mixture of methacrylic acid copolymer, acetyltri-n-butyl citrate (as a plasticiser) and glidant. An overcoat composed of a part of the drug (62.5% by weight of the overcoat) and water soluble polymer (HPC, 37.5% w/w) was further applied on to the surface of the coated tablets. The overcoat is responsible for the immediate release of the drug prior administration. The inner coat could be either enteric or delayed type depending on the material used. Authors claimed that captopril is converted into metabolites such as disulfide and mixed disulfides at the pH of the colon (5–7.5) and at least portion of captopril will be available from the pH-stabilized formulation upon the release into the colonic region of the GIT which, in turn, result in improved bioavailability. However, it is believed that ascor-

bic acid stabilizes captopril in solution by acting as antioxidant, in one hand, and by decreasing the pH of the medium on the other hand (Nahata et al., 1994). Unfortunately data regarding the in vitro release pattern of such tablets are not available due to the nature of the published patent.

The release profile from the coated tablets could be further delayed either by modification of the tablet core or the tablet coat. Such modifications include addition of hydrophobic material (mainly polymer) to form the tablet core and/or complex formation of the drug with a carrier. The tablet coat could be modified by making use of the multiple coating of different polymers, or the use of polymer combination to form one coat or incorporation of inert materials within the tablet coat (Rowe, 1986).

2.2. Beadlets

The technique of preparing beadlets from the drug and various polymers beside other inert materials contained in hard gelatin capsules has also been described in the literature to deliver captopril. Beadlets prepared from captopril (27 part by weight), citric acid (30 part by weight) and microcrystalline cellulose (34 part by weight), and filled into hard gelatin capsules were found to release the drug in vitro slowly for up to 6 h during a study conducted by Joshi et al. (1988). They showed that the release pattern of the beadlets could be modified further by coating them using seal coat composed of HPMC and PEG (8.3 and 2.8 part by weight, respectively) and an outer barrier coat composed of ethyl cellulose and acetylated glycerides (4.2 and 1.3 part by weight, respectively).

2.3. Hydrophobic tablets

Incorporation of hydrophobic materials within tablets composed of water soluble drugs is believed to extend the release of drug within GIT. Captopril mixed with chitosan (both were 47% by weight), lactose magnesium stearate and then compressed into tablets, showed a zero order release kinetics for up to 8 h when tested in vitro in neutral and acidic media (Thakur and Jain, 1988).

2.4. Pulsatile delivery system

These are recently developed systems which are able to deliver the drug to specific area within the GIT depending on the nature of the device used and the GI transit time. Wilding et al. (1992), reported a study in which captopril was administered to eight male volunteers by means of a pulsatile delivery system designed to release the drug in the colonic region of GIT. The system consisted of an insoluble capsule body containing 25 mg captopril powder and 5 mg^{III} in (1-Mbq)-labeled diethylenetriamine pentaacetic acid (DTPA). The contents were sealed into the capsule body by means of hydrogel plug which absorbs water and swells in the presence of aqueous fluids and ejected from the capsule, thereby, releasing the contents (Rashid, 1990). In spite of the fact that the delivery system used was capable of releasing 75% of the drug in 6 h, it failed to improve the drug availability upon in vivo administration where it revealed area under plasma concentration time curve (AUC) for captopril only account for 1/16 of that revealed by the conventional tablets under the same conditions. Such failure was contributed to the instability of the drug in the colonic region of the GIT.

2.5. Microcapsules

It is one method, among others, used to control the drug release where the viscosity and the concentration of the polymers used to form the microcapsules are the drug release rate determinants (Deasy et al., 1984). Four different viscosity grades of ethyl cellulose were used to prepare captopril microcapsules by means of temperature induced coacervation from cyclohexane (Singh and Robinson, 1988). Tablets, obtained by direct compression of the formed granules, showed in vitro captopril release of 80–96% up to 12 h, moreover, the release was of biphasic type which account for a rapid initial release followed by slow release one.

2.6. Semisolid matrix systems

The techniques and objectives of these systems are the same as that of hydrophobic tablets where the nature of the hydrophobic material being the main difference. In these systems, the hydrophobic materials (drug carriers) are in the semisolid state. The drug mixed with the liquified carrier (by means of heat) and the obtained semisolid mixture (on cooling) filled into hard gelatin capsule to form the semisolid matrix capsules. In a study conducted by Seta et al. (1988a), captopril heated with a mixture of soybean oil and glyceryl monostearate and filled into hard gelatin capsules showed higher plasma captopril level for long time when administered to beagle dogs compared to coated slow release granules of the drug under the same non fasting condition. Authors claimed that, due to its rheological properties, semisolid matrix easily adhere to the GIT which resulted in slow transition rate in the GIT, moreover, the oily base acted as a barrier for captopril from being attacked by food components. However, captopril plasma AUC in case of the semisolid matrix was only half that of the conventional drug tablets under the sane test conditions. In a follow up study and by making use of ascorbic acid as an oxidant, authors were able to show that the described semisolid capsules were capable to maintain adequate blood level of captopril up to 8.5 h (Seta et al., 1988b). Furthermore, the capsules were found to be efficient, in human, for 12 h and requires twice a day doses (Seta et al., 1988c).

2.7. Floating tablets and capsules

These systems will float on gastric content for desired period of time during which the drug will be entirely released from the device. Various attempts have been made to develop floating systems among which the so called 'hydrodynamically balanced system (HBSTM)' developed by Sheth and Tossounian (1984) where formulation of the drug with gel-forming hydrocolloid meant to remain buoyant on stomach contents. Such system when becomes in contact with gastric fluid will swell and attain specific gravity lesser than that of the gastric juice. These systems are useful for drug that acting locally in the proximal GIT or for drugs suffering stability in the intestinal fluids. Captopril is one drug from the later category. Matharu and Singhavi (1992) described floating capsules to deliver captopril. A mixture of two grades of hydroxy propyl methyl cellulose (HPMC 4K and HPMC 15K), each in the range of 7–28% w/w of the prescription, and microcrystalline cellulose (MCC), in range of 20.8–31.4% w/w, were mixed, beside the drug (28% w/w) and filled into hard gelatin capsules to form the floating capsules. These capsules were found to act as a floating device in artificial gastric fluids and the authors were able to sustain the release of captopril for a period up to 8 h during USP/NF in vitro dissolution method. Moreover, the release rate of the drug was found to be dependant on the concentration and the viscosity grade of the polymers used.

2.8. Bioadhesive systems

In recent years, the development of bioadhesive controlled release systems has been the subject of large number of studies (Peppas and Buri, 1985; Longer and Robinson, 1986) Some of these systems are already o the pharmaceutical market. Bioadhesion based upon the adhesive capacity of some polymers with glycoproteins (mucins) of the surface epithelium of the GIT and so the name mucoadhesive. These systems are candidate for buccal, sublingual, ocular, rectal, vaginal, oral and nasal administration of drugs. Among the adhesive polymers used, anionic polymers were found to form the strongest adhesion to the mucin (Leung and Robinson, 1988). The aim of application of such technique to deliver drugs is based on the fact that bioadhesion will enhance the gastric residence time and localize the dosage form onto specific physiological area for optimum absorption and hence efficient therapy.

There are very few reports concern with the use of mucoadhesive systems to deliver captopril.

DeCrosta et al. (1987) used dry granulation technique to formulate mucoadhesive tablets of captopril, where carbopol 934P (as mucoadhesive substance in range of 55–75% by weight of the tablet) was mixed with captopril (25–35% w/w)

and stearic acid (as lubricant) and the blended mixture was dry granulated and compressed into tablets. The tablets claimed to sustain the release of the drug for up to 16 h. Authors interpreted the slow release mechanism being mainly due to the gelling properties of carbopol which caused a diffusional barrier to the drug release.

The same technique has been described by Matharu and Singhavi (1992) in which captopril (25% w/w) blended with lactose and wet granulated with solution of retarding polymers (either ethyl cellulose or Eudragit RS 100) in isopropyl alcohol. The obtained dry granules were blended with polyacrylic acid cross linked with 0.001% ethylene glycol (as bioadhesive polymer, 43–47% w/w) and magnesium stearate and compressed into tablets. They prepared other tablets using dry granulation of a mixture composed of the drug (25% w/w), carbopol 934P (57% w/w), lactose and magnesium stearate then compressed into tablets. In both cases authors were able to show in vitro sustained release of captopril from the investigated tablets where 60–80% of the drug being released up to 8 h period of time through out the investigated series of tablets. They did not mention the mucoadhesion properties of the tablets, however, they interpreted the slow release mechanism being related to the viscosity grade and amount of the polymers used, moreover, they showed that ethyl cellulose is stronger retardant compared to eudragit RS 100. Based on the fact that captopril does not exhibit 'window-effect' of absorption and the drug bioavailability is affected by the presence of food, authors hypothesized that such mucoadhesive tablets could possibly protect the drug from being attacked by food components. Same hypothesis has been mentioned before (Seta et al., 1988a).

3. Discussion

As has been shown, the technique of coated tablets and/or multilayered tablets sustained the release of captopril for a limited period of time. Suitability of such systems for once or even twice a day administration is doubtful. This is simply due to their inability to localize he drug release in the absorption area within the GIT for a long period of time, although they successively sustained the release of the drug. In turn, this could be attributed to the short GIT residence time of these formulations. Even if the drug is considered to be efficiently delivered by these systems through out the GIT, considerable amounts will be released in the lower part of the GIT where the drug shows the poorest absorption due to the instability of the drug at the pH of this part (Wilding et al., 1992). It is obvious that stabilization of the drug in its dosage form will bring some benefits regarding its bioavailability. Such stabilization could be held by means of addition of antioxidants, complexing agents and buffers. On other words, stabilization of the drug in the formulation should be accompanied by enhancement of the gastric residence of the dosage form. It is the picture in case of the semisolid matrix formulations where authors were able to formulate captopril controlled release dosage form being applicable for twice a day administration by making use of ascorbic acid to stabilize the drug and, moreover, the nature of the used system enabled the drug to adhere on to the gastric content and so decrease the transition rate of the drug through the GIT.

In case of hydrophobic tablets, although the release pattern of captopril complied with the desired zero order kinetics for controlled release formulations, the release period was comparatively short. It is the same situation with captopril beads formulations. Furthermore, lack of gastric residence enhancement will add to the problems encountered with these systems to regard them as efficient delivery systems to control the in vivo release of captopril. The same is applicable with captopril microcapsules formulation.

Pulse released formulation of captopril when tested in vivo revealed bioavailability of 1/16 of that of conventional tablets similarly administered. This may be attributed to the nature of the used pulse released device which aimed to release the drug in the colonic region of the GIT. Apparently, upper small intestine is permeable to captopril and it is not the case with the colon (Hu and Amidon, 1988). However, even so the system used is directed to pulse released the drug in the proxi-

mal small intestine, from which the drug is adequately absorbed, another problem will be encountered since the drug is subjected to the dose dumping phenomenon (being freely water soluble) and so the drug will attain very high blood level which will exaggerate the pharmacological side effects of the drug which is against the strategy upon which the aim of controlled release dosage forms is based.

With regard to the floating systems reviewed here, the in vitro sustained release was up to 8 h which is comparatively short time, moreover, gastric retention of these systems depends on gastric motility, pH and presence of food. It is somewhat 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 (Ingani et al., 1987) and, furthermore, they are of value when food effects are encountered. Due to the lack of the in vivo data concerned with these systems, It is unfair to justify their suitability and efficiency for delivering captopril in a sustained release dosage form.

Prolongation of the residence time of the dosage form to produce once or twice a day dose application, in case of the bioadhesive systems, is faced with different difficulties. Such difficulties, as suggested by Lehr et al. (1992) being attributed to the fact that both the acidic environment and thick mucus in the stomach prevent the bioadhesion bond formation, moreover, the adhesive agent can adhere to other content of the GIT and the mucus itself can deactivate the mucoadhesive surface due to the high turn over of the mucus resulting in difficulty in retaining the bioadhesive system in its site.

4. Conclusion

As has been seen for the different captopril controlled release dosage forms reviewed here, claims to meet the requirements of optimum drug delivery are mostly based on in vitro data only. Other formulations were studied in single group of animals or human. Indeed, presence of in vivo set of experiments along with in vitro release tests will definitely add ease to make a decision regarding suitability and efficiency of the developed system to deliver the drug in a sustain manner. Some formulation are encouraging showing that it is possible to formulate a controlled release dosage form capable to sustain the release of captopril after a single oral administration as far as the drug stability is considered as the main important factor during formulation, this is beside the drug residence time in the GIT, localization of the dosage form and the type of the ingredient used. Only by considering these factors collectively, it is feasible to formulate a controlled release dosage form to deliver captopril, however, extensive investigations are required to examine these factors and to determine their role in such developed controlled release dosage form to deliver captopril. It is of interest to mention that most of these developed formulations reflected the use of polymers as the release controlling agent which may be attributed to the biocompatibility of these materials. Surprisingly, despite of all these performed research work, there are likely to be no well established captopril controlled release dosage forms reported to be in the drug market.

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