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Research paper

Pharmacokinetic evaluation of guar gum-based three-layer matrix tablets for oral controlled delivery of highly soluble metoprolol tartrate as a model drug

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Abstract

The objective of the present study is to carry out pharmacokinetic evaluation of oral controlled release formulation (guar gum-based three-layer matrix tablets) containing highly soluble metoprolol tartrate as a model drug. Six healthy volunteers participated in the study, and a two-way crossover design was followed. The plasma concentration of metoprolol tartrate was estimated by reverse-phase HPLC. The pharmacokinetic parameters were calculated from the plasma concentration of metoprolol tartrate versus time data. The delayed T_{max}, lower C_{max}, decreased K_a, unaltered bioavailability and prolonged $t_{1/2}$ indicated a slow and prolonged release of metoprolol tartrate from guar gum three-layer matrix tablets in comparison with the immediate release tablet dosage form. The results of the study indicated that guar gum three-layer matrix tablets were able to provide oral controlled delivery of highly water-soluble drug such as metoprolol tartrate in humans.

Keywords: Metoprolol tartrate; Guar gum; Three-layered tablets; Oral controlled release; Pharmacokinetic; Humans

1. Introduction

Developing oral controlled release tablets for highly water-soluble drugs with constant release rate has always been a challenge to the pharmaceutical technologist. Most of these highly water-soluble drugs, if not formulated properly, may readily release the drug at a faster rate, and are likely to produce toxic concentration of the drug on oral administration. Though various formulation approaches are used to control the release of water soluble drugs, multi-layer matrix tablets are proving to be potential [1,2]. Metoprolol tartrate, widely used in the treatment of hypertension, angina pectoris, and arrythmias, was chosen as a model drug having high solubility. Several oxidative pathways including α-hydroxylation, O-demethylation and N-dealkylation extensively metabolize the drug [3]. The enhanced therapeutic efficacy of this drug through the provision of constant rate input and maintenance of steady-state blood levels is well documented [4,5]. The broad objective of the present study is to develop and evaluate three-layer matrix tablets for oral controlled delivery of water-soluble metoprolol tartrate using a hydrophilic polymer.

The widely used hydrophilic polymers for sustaining the drug delivery are HPMC, NaCMC, chitosan, HPC, MC, natural gums, etc. A few reports appear in the literature on the use of guar gum, as a carrier, for oral controlled delivery of drugs [6–8]. Earlier, it was reported that guar gum is a potential hydrophilic matrix carrier for oral controlled delivery of drugs with varying solubility [9]. Since metoprolol tartrate is a highly water-soluble drug, it was planned to develop an oral controlled release matrix formulation using guar gum as a carrier. In this context, studies were reported on the design of three-layer guar gum matrix tablets for oral controlled release of metoprolol tartrate [10]. A three-layer guar gum matrix tablet of a highly soluble dug such as metoprolol tartrate containing 50% of guar gum as a release retardant matrix along with

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75 mg of guar gum granules on both sides as rate controlling layers was found to provide the required release rate. Since guar gum is a colon-specific drug carrier [11], the influence of colonic bacterial enzymes on three-layer guar gum matrix tablet was studied [10] by carrying out in vitro drug release studies in simulated colonic conditions (rat caecal content medium). In the presence of rat caecal contents, the three-layer matrix tablets were found intact up to 8 h and the guar gum formulation started disintegrating slowly. At the end of 24 h of the study, the three-layer matrix tablets were found disintegrated into a thick mass and released almost the remaining quantity of metoprolol tartrate in the rat caecal content medium (simulated colonic conditions). After 12 h of dissolution testing, three-layer guar gum tablets released 63.17 ± 0.50% of metoprolol tartrate in rat caecal content medium. This indicates that about 40% of the drug still left over in the formulation after reaching the physiological environment of colon. Even this 40% of metoprolol tartrate is hypothesized to be absorbed slowly due to high colonic residence time and good permeability of the drug through colon [12]. The in vivo performance of these formulations needs to be studied in human volunteers to investigate such a hypothesis. Thus, the present study was carried out to investigate the usefulness of the three-layer guar gum matrix tablets in providing oral controlled drug delivery of a highly soluble metoprolol tartrate in humans.

2. Materials and methods

2.1. Materials

Metoprolol tartrate, diltiazem hydrochloride and rofecoxib were gift samples from M/s Astra-IDL Limited, Bangalore, India, M/s Cheminor Drugs Limited, Hyderabad, India and M/s Torrent Laboratories, Ahmedabad, India, respectively. Guar gum (viscosity of 1% aqueous dispersion is 3725 cps; particle size >75 μm) was obtained from M/s Dabur Research Foundation, India, and was of pharmacopoeia quality (USP/NF). Ammonium dihydrogen phosphate was of analytical grade and supplied by M/s S.D. Fine-Chem Limited, Mumbai, India. Acetonitrile and water used were of high performance liquid chromatography (HPLC) grade (Qualigens). All other reagents used in the study were of AR quality (Qualigens). Other materials used in the study such as hydroxypropylmethlcellulose (HPMC, 15 cps), talc, magnesium stearate and starch were of pharmacopoeia quality (USP/NF). A commercially available immediate release tablet formulation containing 100 mg of metoprolol tartrate was used in the study as a reference formulation.

2.2. Preparation of three-layer guar gum matrix tablets

Three-layer guar gum matrix tablets were prepared by using the method as described earlier [10]. Briefly, it involves compression of 75 mg of granules containing 87% of guar gum on both sides of matrix granule layer containing 50% of guar gum. The composition of the guar gum matrix granules of metoprolol tartrate and release retardant guar gum layer was given in Table 1. Guar gum matrix tablet granules containing 150 mg of metoprolol tartrate were prepared by wet granulation method using 10% w/w of starch as paste. A mixture of talc and magnesium stearate (2:1 ratio) was used as lubricant, and HPMC used as a diluent. Guar gum granules containing 87% of guar gum for layering were also prepared by wet granulation method using 10% w/w of starch as paste.

Table 1
Composition of the three-layer guar gum matrix tablets of metoprolol tartrate

Ingredients	Quantity (mg) present in	
	Guar gum matrix granules of metoprolol tartrate	Release retardant layer of guar gum granules
Metoprolol tartrate	150	–
Guar gum	225	65.25
Starch, as paste	45	7.5
HPMC	16.5	–
Talc	9.0	1.5
Magnesium stearate	4.5	0.75
Total weight (mg)	450	75

Initially the volume of the die cavity (11 mm round, flat and plain) was adjusted equivalent to the weight of three-layer matrix tablet (600 mg). Then pre-weighed amount of guar gum granules equivalent to bottom layer (75 mg) was placed in the die cavity and slightly compressed for uniform spreading. The upper punch was lifted up, and granules of the matrix formulation containing the drug and 50% of guar gum were placed over the bottom layer of guar gum granules in the die cavity and again slightly compressed for uniform spreading. The remaining volume of the die cavity was filled with the pre-weighed amount of guar gum granules equivalent to top layer (75 mg) and compressed with a maximum force of compression on single station tabletting machine to obtain three-layer matrix tablets. Thus the top and bottom layers of the three-layer matrix tablet consisted of release retardant guar gum, and the middle layer consisted of guar gum matrix layer along with metoprolol tartrate (a model drug having high solubility).

2.3. HPLC analysis of metoprolol tartrate in three-layer matrix tablets and dissolution fluids

The quantitative determination of metoprolol tartrate was performed by HPLC. A gradient HPLC (Shimadzu HPLC Class VP series) with two LC-10AT VP pumps, variable wave length programmable UV/VIS Detector SPD-10A VP, CTO-10AS VP Column oven (Shimadzu), SCL-10A VP system controller (Shimadzu), a disposable guard column

LC-18 (Pelliguard™, LC-18, 2 cm, Supelco, Inc., Bellefonte, PA.) and RP C-18 (250 × 4.6 mm^2 I.D, particle size 5 μm; YMC Inc., USA) was used. The HPLC system was equipped with the software 'Class-VP series version 5.03 (Shimadzu)'.

The mobile phase used was a mixture of 0.01 M potassium dihydrogen phosphate, acetonitrile and methanol in the ratio of 55:22.5:22.5. The filtered mobile phase components were pumped at a flow rate of 1.2 ml/min. The column temperature was maintained at 40 °C. The eluent was detected by UV detector at 274 nm, and the data were acquired, stored and analyzed with the software 'Class-VP series version 5.03 (Shimadzu)'. A standard curve was constructed for metoprolol tartrate in the range of 0.1–40 μg/ml using rofecoxib (100 μg/ml) as internal standard. A good linear relationship was observed between the concentration of metoprolol tartrate and the ratio of the peak area of metoprolol tartrate to that of rofecoxib (internal standard) with a high correlation coefficient ($r = 0.9999$). The required studies were carried out to estimate the precision and accuracy of this HPLC method of estimating metoprolol tartrate. The method was found to be precise (intra- and inter-day variation was found to be less than 1%) and accurate (mean recovery 98.8%). The standard curve, constructed as described above, was used for estimating metoprolol tartrate either in three-layer guar gum matrix tablets or dissolution samples.

2.4. Quantitative determination of drug content in three-layer guar gum matrix tablets and reference immediate release tablets of metoprolol tartrate

Both guar gum three-layer matrix tablets and reference immediate release tablets of metoprolol tartrate were tested for their drug content. Ten tablets of either of the formulations were finely powdered, 100 mg of the powders accurately weighed and transferred to 100-ml volumetric flask. Initially about 50 ml of water were added to the volumetric flask and allowed to stand for 6 h with intermittent sonication to ensure complete solubility of the drug. Then the volume was made up with water and the mixture centrifuged. One milliliter of the supernatant liquid was added with 100 μg of rofecoxib (internal standard), the volume made up to 10 ml with water, filtered through 0.2-μm membrane filter and analysed for metoprolol tartrate by HPLC as described above.

2.5. In vitro drug release studies

Metoprolol tartrate three-layer matrix tablets were subjected to in vitro drug release studies in simulated gastric and intestinal fluids to assess their ability in providing the desired controlled drug delivery. Drug release studies were carried out using USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37 ± 0.5 °C) for 2 h in pH 1.2 buffer (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and the experiment continued for another 10 h. At different time intervals, 1 ml of the sample was withdrawn and replaced with 1 ml of pH 7.4 phosphate buffer. One milliliter of dissolution sample was added with 100 μg of rofecoxib (internal standard), the volume made up to 10 ml with water, centrifuged, the supernatant liquid filtered through 0.2-μm membrane filter and analysed for metoprolol tartrate by HPLC as described above. During the drug release studies, all the formulations were observed for physical integrity. The reference immediate release formulation, obtained from the market, was also subjected to in vitro drug release studies (USP apparatus 1, 100 rpm) as per the procedure specified in USP XXIII wherein the dissolution medium was simulated gastric fluid (without enzymes). The dissolution samples were obtained at different time intervals replacing with drug-free dissolution medium.

2.6. In vivo studies in healthy human volunteers

The ethics committee of M/s Sipra Labs Pvt. Ltd, Hyderabad, India approved the protocol of the study which complied with the recommendations of Helsinki Declaration. The approval of the protocol was obtained to conduct the study at M/s Sipra Labs Pvt. Ltd, Hyderabad, India. Six healthy male volunteers (60–70 kg, age between 25 and 30 years) participated in the study, and all were nonsmokers and non-alcoholics. The biochemical examination of the volunteers revealed normal function of the kidney and liver. The nature and purpose of the study were fully explained to them. An informed written consent was obtained from every volunteer. None of the volunteers were on drug treatment one week prior to the participation of the study. The volunteers were free to withdraw from the study under their discretion.

The volunteers were divided into two equal groups (groups-I and -II), and a cross over study was followed. An immediate release tablet dosage form containing 100 mg of metoprolol tartrate was chosen as a reference formulation, and administered orally to three volunteers (group I). The group II ($n = 3$) volunteers were administrated with three-layer guar gum matrix tablet containing 150 mg of metoprolol tartrate. After a washout period of 10 days, group-I volunteers received three-layer guar gum matrix tablet and group-II volunteers received the immediate release tablet. Both the tablet formulations were administered with 150 ml of water after a 12-h overnight fast. Food and drinks were withheld for at least 2 h after dosing. Blood samples were collected from the volunteer's antecubital vein via a hypodermic syringe (rinsed with dilute heparin solution) over a period of 36 h (0, 0.5, 1, 2, 3, 5, 8, 12, 18, 24 and 36 h). The blood samples were immediately centrifuged at 5000 rpm, plasma separated and stored at −40 °C until analysis by HPLC.

2.7. HPLC analysis of metoprolol tartrate in human plasma

The quantitative determination of metoprolol tartrate in human plasma was performed by a reverse phase HPLC using the equipment as described above An aliquot of plasma (0.5 ml) was accurately measured into a 10-ml glass tube with a teflon-lined cap, followed by the addition of 100 μl of diltiazem hydrochloride (internal standard) solution (1 μg/ml) along with 0.1 ml of 1 M sodium hydroxide and 5 ml of dichloromethane as the extracting solvent. After mixing for 20 min by means of a vortex mixer, the mixture was centrifuged at 3000 rpm for 10 min. Four milliliters of the organic layer (dichloromethane) was transferred into a tube and then evaporated at 40 °C to dryness under a gentle stream of nitrogen. The residue was washed with *n*-hexane to remove the lipophilic contaminants before injecting into the HPLC system. This was done by first reconstituting the residue with 100 μl of 1 M acetic acid, followed by the addition of 3 ml of *n*-hexane. The mixture was vortexed for 5 min, the organic layer discarded and remains of *n*-hexane, if any, removed with a stream of nitrogen. Finally, the reconstituted sample was injected into the column (loop volume 20 μl; 150 mm × 4.6 mm I.D., particle size 5 μm; Flexit Inc., Pune, India) through which mobile phase components (acetonitrile:1 M ammonium dihydrogen phosphate, pH adjusted to 4.0) were pumped from the respective reservoirs in the ratio of 50:50 v/v at a flow rate of 0.4 ml/min, which yielded a column back-pressure of 80–110 kg/cm^2. The eluents were monitored at 274 nm, and the sensitivity range of the detector was set at 0.0001 Absorbance Units Full Scale (AUFS). The peak area ratio of metoprolol tartrate to that of internal standard (diltiazem HCl) was determined, and this was used to estimate the plasma concentration of metoprolol tartrate from the regression equation. The regression equation was set up by spiking drug-free plasma with varying amounts of metoprolol tartrate (10–200 ng/0.5 ml) and fixed quantity of internal standard (0.5 μg/0.5 ml), and treating the plasma as described above. The peak area ratio of metoprolol tartrate to internal standard was obtained. A good linear relationship ($r = 0.9997$) was observed between the peak area ratio and plasma concentration of metoprolol tartrate in the range of 10–200 ng/0.5 ml. However, the lower detection limit was found to be 5 ng/0.5 ml. The required studies were carried out to find the inter- and intra-day variation, and accuracy. The inter- and intra-day variation was found to be less than 3% (CV) indicating high precision of the HPLC method. There was a high recovery (89.9–91.5%) of metoprolol tartrate indicating that the HPLC method was highly accurate.

2.8. Pharmacokinetic analysis

The plasma concentration of metoprolol tartrate at different time intervals after oral administration of the tablet formulations to human volunteers was subjected to pharmacokinetic analysis to calculate various parameters such as maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}) and area under the curve ($AUC_{0-\infty}$). The values of C_{max} and T_{max} were directly read from the arithmetic plot of time versus plasma concentration of metoprolol tartrate. The overall elimination rate constant (k_e) was calculated from the slope of the terminal elimination phase of a semi-logarithmic plot of concentration versus time, after subjecting it to linear regression analysis. The elimination half-life was obtained by dividing 0.693 with k_e. The absorption rate constant (k_a) was calculated using method of residuals [13]. The $AUC_{0-\infty}$ was determined by means of trapezoidal rule. The relative bioavailability of metoprolol tartrate from three-layer guar gum matrix tablets in comparison to reference formulation (immediate release dosage form) was calculated by dividing its $AUC_{0-\infty}$ with that of immediate release tablet dosage form after applying dosage correction.

2.9. Statistical analysis

The observed variation in the pharmacokinetic parameters such as $t_{1/2}$, k_a and T_{max} was tested by using analysis of variance (ANOVA) and Duncan's multiple range test with the help of STATISTICA™ computer program (Release 4.5, StatSoft Inc., 1993). The observed difference in mean pharmacokinetic parameters of metoprolol tartrate from three-layer guar gum matrix tablets and immediate release reference tablet dosage form was subjected to paired *t*-test to find the statistical significance. In all the cases, a value of $P < 0.05$ was considered statistically significant.

3. Results and discussion

Metoprolol tartrate (β_1-selective adrenoceptor antagonist) is widely used in the long-term treatment of hypertension and coronary heart diseases [14,15]. Early pharmacokinetic studies have established that it has a relatively short plasma half-life of 3–4 h and its absorption is rapid as well as consistent throughout the gastrointestinal tract including the distal region [16,17]. As a prerequisite, a combination of both these properties makes metoprolol tartrate a suitable candidate for selecting as a model drug for the development of oral controlled release formulation. In addition, the relationship between plasma concentration and β_1-blocking effect (i.e. reduction in exercise-induced tachycardia) is well defined for metoprolol tartrate [18,19]. Maintenance of a steady state plasma concentration of metoprolol tartrate by means of oral controlled drug delivery system improves its therapeutic efficacy and reduces the β_2-mediated adverse effects. Thus, metoprolol tartrate, having high solubility, is an ideal drug candidate for designing oral controlled release dosage form. It was

reported that guar gum in the form of a three-layer matrix tablet could provide oral controlled release of a highly water-soluble drug such as metoprolol tartrate [10]. The present study was carried out to find the in vivo performance of these guar gum formulations in providing in vivo controlled release of highly water-soluble metoprolol tartrate (a model drug) in humans. The three-layer guar gum matrix tablets were prepared using maximum compression force. The hardness of the tablets was 5.63 ± 0.15 kg that could contribute to the control of drug release from the hydrophilic matrix three-layer tablet formulation.

3.1. In vitro drug release studies

Both the three-layer matrix tablets and reference immediate release tablets satisfied the drug content as they contained 98.23 ± 0.67–102.44 ± 0.23% of metoprolol tartrate. When the three-layer guar gum matrix tablets were subjected to in vitro drug release studies, there was a slow drug release and kinetic evaluation of drug release showed that these oral controlled release formulations provided a first order release rate constant of 0.0696 ± 0.02 h^{-1} which is nearer to the required release rate constant of 0.0232 h^{-1} calculated as per the pharmacokinetic parameters of metoprolol tartrate for twice daily administration. However, the reference immediate release tablet formulation was found to release almost all the drug immediately within 1 h (Fig. 1). Thus there existed a clear difference in the in vitro drug release characteristics of guar gum three-layer matrix tablets, which in turn, were expected to provide a slow and prolonged in vivo drug release in humans.

3.2. In vivo evaluation of three-layer guar gum matrix tablets of metoprolol tartrate

The pharmacokinetic parameters T_{max} and $AUC_{0-\infty}$, are related to the rate and extent of absorption, respectively, while C_{max} is related to both the processes [20]. The extent of absorption is a key characteristic of a drug formulation, and therefore the $AUC_{0-\infty}$, is an important parameter for analysis in a comparative bioavailability study. However, the other two parameters, namely T_{max} and C_{max}, are also important features related to the therapeutic use of many drugs [21] and hence also considered in the present pharmacokinetic analysis.

The immediate release metoprolol tartrate tablet formulation was administered at a dose of 100 mg to avoid the possible adverse effects in human volunteers. The mean plasma concentration of metoprolol tartrate following oral administration of guar gum three-layer matrix tablets (dose 150 mg) or immediate release (IR) tablets (dose 100 mg) of metoprolol tartrate were shown in Fig. 2.

The T_{max} of metoprolol tartrate from three-layer matrix tablets was 4.2 ± 1.3 h, and the peak concentration (C_{max})

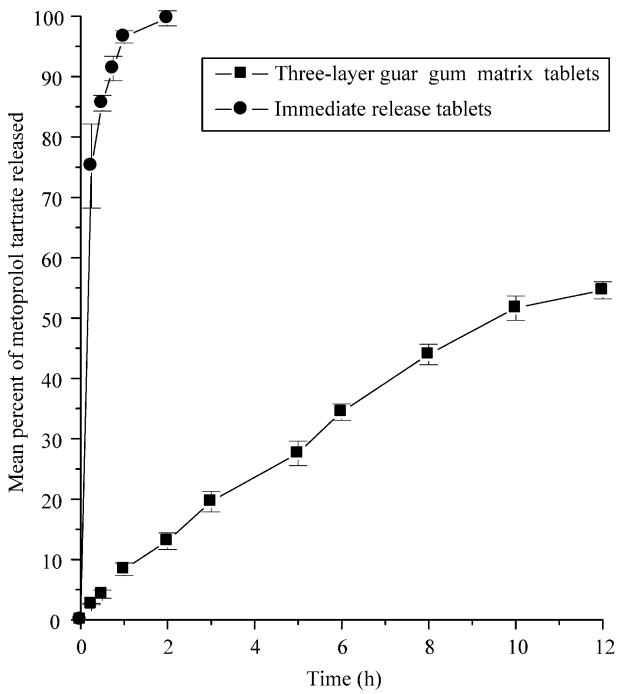

Fig. 1. In vitro dissolution study showing the mean (±SD) percent of metoprolol tartrate released from immediate release (IR) tablet dosage forms ($n = 3$) and three-layer guar gum matrix tablets ($n = 3$) containing 75 mg of guar gum granules as release controlling layer on both sides of guar gum matrix tablets containing 50% of guar gum.

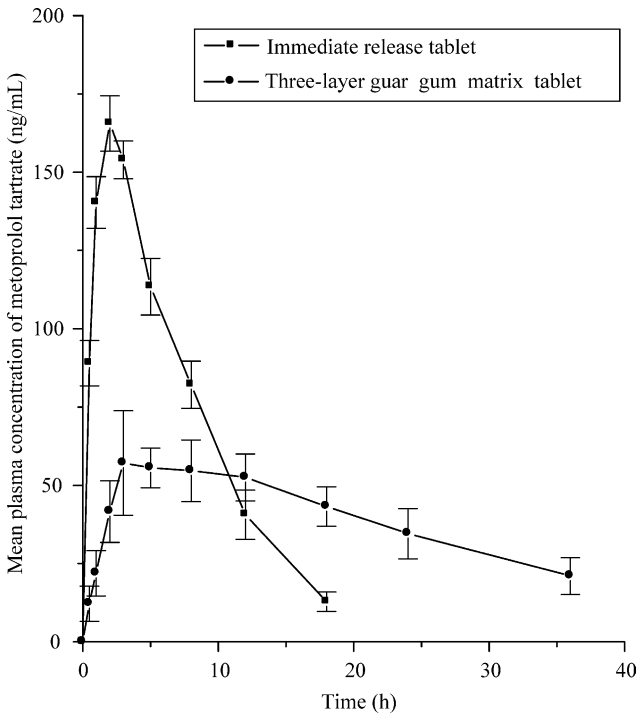

Fig. 2. Mean (±SD) plasma concentration of metoprolol tartrate in human volunteers ($n = 6$) following oral administration of immediate release (IR) tablet dosage forms and three-layer guar gum matrix tablets containing 75 mg of guar gum granules as release controlling layer on both sides of guar gum matrix tablets containing 50% of guar gum.

Table 2
Mean (±SD) pharmacokinetic parameters of metoprolol tartrate in volunteers ($n = 6$) orally administered with conventional IR tablets (dose 100 mg) or three-layer guar gum matrix tablets (dose 150 mg)

Pharmacokinetic parameter	Volunteers ($n = 6$) orally administered with	
	Immediate release formulation	Three-layer matrix formulation
$AUC_{0-\infty}$[a] (ng/ml/h)	1444.1 ± 389.7	2035.6 ± 548.4
Relative bioavailability (%)	–	103.5 ± 13.2
$t_{1/2}$ (h)	4.2 ± 0.9	19.4 ± 2.4**
k_a (1/h)	1.7 ± 0.3	0.6 ± 0.1**
T_{max} (h)	2.0 ± 0.1	4.7 ± 2.0*
C_{max}(ng/ml)	165.5 ± 8.9	61.3 ± 6.3

*Significant at $P < 0.05$; **significant at $P < 0.001$.
[a] Statistical comparison was not made due to difference in the dose administered.

at that time was 61.3 ± 6.3 ng/ml. In case of IR tablets of metoprolol tartrate, the C_{max} was 165.5 ± 8.9 ng/ml, which was significantly ($P < 0.01$) different from that obtained from guar gum three-layer matrix tablets (Table 2). The mean T_{max} value after administration of IR tablets was 2.0 ± 0.1 h, which was significantly different ($P < 0.001$) from that obtained from guar gum three-layer matrix tablets of metoprolol tartrate. The absorption rate constant (k_a) of the drug from immediate release formulation was 1.7 ± 0.3 h^{-1}, and that obtained from guar gum three-layer formulation was 0.6 ± 0.1 h^{-1} wherein the difference in the value of absorption rate constant was statistically significant ($P < 0.001$). Thus the lower C_{max}, prolonged T_{max} and decreased k_a of metoprolol tartrate in human volunteers indicated that the drug release from the three-layer guar gum matrix tablets is slow providing a prolonged and controlled in vivo delivery of the drug. These in vivo absorption characteristics are in confirmation with the observed in vitro drug release rate of the drug from the guar gum three-layer matrix tablets [10].

The area under the plasma metoprolol tartrate concentration versus time curves ($AUC_{0-\infty}$) for the immediate release (dose 100 mg) and guar gum three-layer matrix tablets (dose 150 mg) of metoprolol tartrate were 1444.1 ± 389.7 and 2035.6 ± 548.4 ng/ml/h, respectively (Table 2). The difference in $AUC_{0-\infty}$ might be due to the difference in the dose administered. Earlier report indicated that bioavailability of orally administered metoprolol tartrate increases with increased dose [22]. This shows that $AUC_{0-\infty}$ may increase proportionately with the dose administered. Based on this assumption, the relative bioavailability of metoprolol tartrate from three-layer guar gum matrix tablets against the immediate release tablets was calculated to find the extent of absorption of the drug. There was no difference in the extent of absorption of metoprolol tartrate from guar gum three-layer matrix tablets when compared to immediate release tablets as shown by less than 20% of change in the relative bioavailability (103.5 ± 13.2%) of the drug (Table 2). This indicates that metoprolol tartrate contained in three-layer matrix tablets was completely absorbed.

The elimination half-lives of metoprolol tartrate following oral ingestion of IR and guar gum three-layer matrix tablets were 4.2 ± 0.9 and 19.4 ± 2.4 h, respectively, which were significantly different ($P < 0.001$). Thus the prolonged $t_{1/2}$ is another important indication on the in vivo performance of the controlled release guar gum three-layer matrix tablets in providing a prolonged drug delivery. The immediate release tablet formulation, on fast disintegration followed by fast dissolution, might have resulted in faster absorption and produced high peak concentrations of the drug, and thereby quickly eliminated from the systemic circulation (Table 2).

The in vitro drug release studies showed that the hydrophilic three-layer guar gum matrix tablets of metoprolol tartrate provided slow release of the drug. When tested in human volunteers, the slow and continuous release of the drug from the formulation might have resulted in slow and complete absorption of the drug from stomach and small intestine due to high absorption area. However, on reaching colon, the three-layer matrix tablet might have been disintegrated by colonic bacteria thereby releasing major quantity of the drug, yet resulting in slow absorption of the drug due to less absorption area of the colon. This, in turn, resulted in controlled and prolonged drug concentration in the blood. Thus, the elimination half-life of the drug from guar gum tablets after oral administration is prolonged (Table 2). The in vivo evaluation of guar gum metoprolol tartrate three-layer matrix tablets in human volunteers showed delayed T_{max}, lower C_{max}, decreased k_a, unaltered bioavailability, and prolonged $t_{1/2}$ indicating a slow and prolonged release of metoprolol tartrate from guar gum three-layer matrix tablets.

The β-blocking properties of immediate release and extended release metoprolol formulations were studied by Abrahamsson [23]. It was suggested that controlled release formulations of metoprolol tartrate providing consistent plasma concentration without high peaks are less likely to lose β_1-specificity whereas immediate release metoprolol tartrate tablets producing higher peak plasma concentrations are more likely to have effects on β_2-receptors due to loss of β_1-specificity. Even in the present study, the three-layer metoprolol tartrate matrix tablet dosage form provided a prolonged pseudo-steady state concentration of metoprolol tartrate, in vivo, with minimal fluctuations which in turn may enhance β_1-specificity with minimal β_2-mediated adverse effects. The successful outcome of the present study warrants for further studies in patient volunteers to assess the ability of the above three-layer guar gum matrix formulations of metoprolol tartrate in providing an effective and safe therapy of hypertension.

4. Conclusions

In vivo performance of the guar gum-based three-layer matrix tablet for a highly water-soluble drug (metoprolol tartrate) was studied in healthy human volunteers against an immediate release oral tablet dosage form. The guar gum-based three-layer matrix tablets of highly water-soluble metoprolol tartrate provided pseudo-steady state concentration of the drug in comparison with the immediate release tablet dosage form. The delayed T_{max}, lower C_{max}, decreased k_a, unaltered bioavailability, and prolonged $t_{1/2}$ indicated a slow and prolonged release of metoprolol tartrate from guar gum three-layer matrix tablets. The guar gum three-layer matrix tablets may be useful for long-term constant drug delivery of highly water-soluble drug such as metoprolol tartrate with minimum fluctuations.

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