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A three-layer guar gum matrix tablet for oral controlled delivery of highly soluble metoprolol tartrate

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Abstract

The objective of the study is to design oral controlled drug delivery systems for highly water-soluble drugs using guar gum as a carrier in the form of a three-layer matrix tablet. Metoprolol tartrate was chosen as a model drug because of its high water solubility. Matrix tablets containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum were prepared by wet granulation technique using starch paste as a binder. Three-layer matrix tablets of metoprolol tartrate were prepared by compressing on both sides of guar gum matrix tablet granules of metoprolol tartrate M1, M2 or M3 with either 50 (TL1M1, TL1M2 or TL1M3) or 75 mg (TL2M1, TL2M2 or TL2M3) of guar gum granules as release retardant layers. Both the matrix and three-layer matrix tablets were evaluated for hardness, thickness, drug content uniformity, and subjected to in vitro drug release studies. The amount of metoprolol tartrate released from the matrix and three-layer matrix tablets at different time intervals was estimated by using a HPLC method. Matrix tablets of metoprolol tartrate were unable to provide the required drug release rate. However, the three-layer guar gum matrix tablets (TL2M3) provided the required release rate on par with the theoretical release rate for metoprolol tartrate formulations meant for twice daily administration. The three-layer guar gum matrix tablet (TL2M3) showed no change either in physical appearance, drug content or in dissolution pattern after storage at 40 °C/75% RH for 6 months. The FT-IR study did not show any possibility of metoprolol tartrate/guar gum interaction with the formulation excipients used in the study. The results indicated that guar gum, in the form of three-layer matrix tablets, is a potential carrier in the design of oral controlled drug delivery systems for highly water-soluble drugs such as metoprolol tartrate.

Keywords: Metoprolol tartrate; Three-layer matrix tablets; Controlled drug delivery; Guar gum; Water-soluble drug; Dissolution

1. Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease of administration, high patient compliance, least sterility constraints and flexibility in the design of the dosage form. Hydrophilic polymers are becoming very popular in

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formulating oral controlled release tablets. As the dissolution medium or biological fluid penetrates the dosage form, the polymer material swells and drug molecules begin to move out of the system by diffusion at a rate determined by the nature and composition of the polymer as well as formulation technology. 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 the toxic concentrations, when administered orally.

Metoprolol tartrate, widely used in the treatment of angina pectoris, arrhythmias and hypertension, was chosen as a model drug having high solubility. The enhanced therapeutic efficacy of this drug through the provision of constant rate input and maintenance of steady-state blood levels is well documented (Sandberg et al., 1988; Kendall, 1989). 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 (Regardh et al., 1974; Godbillon et al., 1985). As a prerequisite, a combination of both these properties makes metoprolol tartrate a suitable candidate for development into a controlled release formulation.

Different types of controlled release formulations such as matrix tablets (Eddington et al., 1998), multiple emulsions (Ghosh et al., 1996), iontophoretic application (Okabe et al., 1987), osmotic tablets (Breimer, 1983) and electrolyte-induced peripheral stiffening matrix system (Pillay and Fassihi, 2000) have been developed to improve the clinical efficacy of metoprolol tartrate.

In the recent times, multi-layer matrix tablets are gaining importance in the design of oral controlled drug delivery systems. One or two layers of release retardant polymers are applied on both sides of a matrix tablet such that the swollen hydrophilic polymer controls the drug release after oral administration. These formulations are designed to deliver the drugs at a controlled and predetermined rate, thus maintaining their therapeutically effective concentrations in systemic circulation for prolonged periods of time.

The widely used polymers for sustaining the drug delivery are HPMC, NaCMC, chitosan, HPC, MC, Eudragits, natural gums etc. In the present investigation, it is planned to use guar gum, a naturally occurring and abundantly available polysaccharide, as a release retardant carrier in the design of three-layer matrix tablets for highly water-soluble drugs such as metoprolol tartrate (model drug). A few reports appear in the literature on the use of guar gum, as a carrier, for controlled delivery of drugs (Altaf et al., 1998; Khullar et al., 1998; Jain et al., 1992). Earlier it was reported from our laboratory that guar gum is a potential hydrophilic matrix carrier for controlled delivery of drugs having varying solubility (Krishnaiah et al., 2001). Since metoprolol tartrate is a highly water-soluble drug, it is planned to develop a controlled release matrix formulation using guar gum as a carrier.

Guar gum is a natural non-ionic polysaccharide derived from the seeds of *Cyamopsis tetragonolobus* (Family-Leguminosae). In pharmaceuticals, guar gum is used in solid dosage forms as a binder and disintegrant, and in liquid oral and topical products as a suspending, thickening and stabilizing agent. Therapeutically guar gum is used as part of the diet of the patients suffering from diabetes mellitus. Guar gum on exposure to dissolution fluids gets hydrated and forms a viscous gel layer that slows down further seeping-in of dissolution fluids towards the core of the matrix tablet (Rama Prasad et al., 1998; Krishnaiah et al., 1998a,b, 1999). The strength of the viscous gel layer around the core of the matrix tablets generally depends on several factors such as particle size, force of compression, presence of other excipients, viscosity of the polymer, solubility of the drug etc. This paper describes the development and evaluation of oral controlled drug delivery systems for metoprolol tartrate using guar gum as a carrier in the form of a three-layer matrix tablet.

2. Materials and methods

2.1. Materials

Metoprolol tartrate (98–101% purity) and rofecoxib (98.6–101.4% purity) were gift samples from M/s Astra-IDL Ltd., Bangalore, 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). Acetonitrile (HPLC grade) and methanol (HPLC grade) were obtained from M/s. Qualigens Fine Chemicals, Mumbai, India. Other materials used in the study such as hydroxypropylmethylcellulose (HPMC, 15 cps), talc, magnesium stearate and starch were of pharmacopoeia quality (USP/NF).

2.2. Preparation of metoprolol tartrate matrix tablets

Matrix tablets of metoprolol tartrate were prepared by wet granulation method. A mixture of talc and magnesium stearate (2:1 ratio) was used as lubricant and HPMC was used as diluent. Guar gum was included in the formulation in various proportions. Three matrix formulations were prepared with 30, 40 or 50% of guar gum and were coded as M1, M2 or M3, respectively. The composition of formulations used in the study containing 150 mg of metoprolol tartrate in each case is shown in Table 1. In all the formulations, guar gum was sieved (<250 μm) separately and mixed (planetary mixer, R&D model, Karnawati Engineering Ltd., India) with metoprolol tartrate (<150 μm) and HPMC (<250 μm). The powder mix was granulated with 10% w/w starch paste in the same planetary mixer. The wet mass was passed through a mesh (1680 μm; Multimill, Pharma Fab Industries, India) and the granules were dried at 50 °C for 2 h in a tray drier (Hicon Laboratory Equipment, India). The dried granules were passed through a mesh (1190 μm; Dry granulator, R&D model, Karnawati Engineering Ltd., India) and these granules were lubricated with a mixture of talc and magnesium stearate (2:1) using a cone blender (R&D model, Cadmach Machinery Co. Pvt. Ltd., India). The lubricated granules were compressed at a compression force of 4500–5500 kg using 11 mm round, flat and plain punches on a single station tabletting machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India). Matrix tablets of each composition were tested for their drug content and release characteristics with a suitable number of tablets for each test. The hardness of the matrix tablets was determined by using Monsanto Hardness Tester.

2.3. Preparation of three-layer matrix tablets

Three-layer matrix tablets were prepared by compressing 50 mg of granules containing 87% of guar gum on both sides of matrix granules containing either 30, 40 or 50% of guar gum (coded as TL1M1, TL1M2 or TL1M3, respectively). The other three-layer tablets were prepared by compressing 75 mg of granules containing 87% of guar gum on both sides of matrix granules containing either 30, 40 or 50% of guar gum (coded as TL2M1, TL2M2 or TL2M3, respectively). The preparation of three-layer matrix tablets involved the following steps:

1. Preparation of granules for the matrix tablets.
2. Preparation of guar gum granules for layering.
3. Compression of a layer of either 50 or 75 mg of guar gum granules on both sides of the matrix tablet granules.

Table 1
Composition of metoprolol tartrate matrix tablets containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum

Ingredients	Quantity (mg) present in matrix tablet		
	M1	M2	M3
Metoprolol tartrate	150	150	150
Guar gum	135	180	225
Starch	45	45	45
HPMC	106.5	61.5	16.5
Talc	9.0	9.0	9.0
Magnesium stearate	4.5	4.5	4.5
Total weight (mg)	450	450	450

Table 2
Composition of guar gum granules for three-layer tablets of metoprolol tartrate

Ingredients	Quantity (mg) present in guar gum release retardant layer formulation					
	TL1M1	TL1M2	TL1M3	TL2M1	TL2M2	TL2M3
Guar gum	43.5	43.5	43.5	65.25	65.25	65.25
Starch as paste	5	5	5	7.5	7.5	7.5
Talc	1.0	1.0	1.0	1.5	1.5	1.5
Magnesium stearate	0.5	0.5	0.5	0.75	0.75	0.75
Weight of guar gum granules	50	50	50	75	75	75

Three-layer matrix tablets (TL1M1) containing 50 mg of guar gum granules as release controlling layer on both sides of 30% matrix granules was prepared as follows. Granules of the matrix formulation containing 30% of guar gum (M1) were prepared as described above.

Guar gum granules containing 87% of guar gum for layering were prepared by wet granulation method using 10% w/w of starch as paste. The guar gum and starch paste was mixed well (Planetary mixer, R&D model, Karnawati Engineering Ltd., India) and the resulting wet mass was passed through a mesh (1680 μm; Multimill, Pharma Fab Industries, India) and the granules were dried at 50 °C for 2 h in a tray drier (Hicon Laboratory Equipment, India). The dried granules were passed through a mesh (1190 μm; dry granulator, R&D model, Karnawati Engineering Ltd., India) and these granules were lubricated with a mixture of talc and magnesium stearate (2:1) using a cone blender (R&D model, Cadmach Machinery Co. Pvt. Ltd., India). The composition of guar gum granules used in the study for layering in three-layer matrix tablets is given in Table 2.

Initially the volume of the die cavity (11 mm round, flat and plain) was adjusted equivalent to the weight of three-layer matrix tablets (550 or 600 mg). Then preweighed amount of guar gum granules equivalent to bottom layer (50 or 75 mg) was taken and placed in die cavity and slightly compressed for uniform spreading. The upper punch was lifted up, and granules of the matrix formulation (M1) 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 preweighed amount of guar gum granules equivalent to top layer (50 or 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.

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

The quantitative determination of metoprolol tartrate in guar gum matrix tablets, three-layer matrix tablets and dissolution fluids was performed by a reversed phase high performance liquid chromatography (HPLC). A Shimadzu HPLC system (Shimadzu, Japan) with two LC-10AT VP pumps, a SPD-10A VP variable wavelength UV/Vis detector, a CTO-10AS VP column oven, a SCL-10A VP system controller (Shimadzu) and a RP C-18 column (250×4.6 mm^2 I.D.; particle size 5 μm; YMC, Inc., Wilmington, NC 28403, 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^{-1}. 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^{-1} using rofecoxib (100 μg) 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 analysis of metoprolol tartrate. The standard curve constructed as described above was used for estimating metoprolol tartrate either in the matrix tablets, three-layer matrix tablets or in dissolution fluids.

2.5. Determination of drug content

The metoprolol tartrate guar gum matrix tablets and three-layer matrix tablets were tested for their drug contents. Ten tablets were finely powdered; 100 mg of the powder was accurately weighed and transferred to 100-ml volumetric flask. Initially about 50 ml of triple distilled water (TD 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 TD water and the mixture was centrifuged. One milliliter of the supernatant liquid was added with 100 μg of rofecoxib (internal standard), the volume made upto 10 ml with TD water, filtered through 0.2-μm membrane filter and analyzed for metoprolol tartrate by HPLC as described previously.

2.6. In vitro drug release studies

Metoprolol tartrate matrix tablets and 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 was 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 upto 10 ml with TD water, centrifuged, the supernatant liquid was filtered through 0.2-μm membrane filter and analyzed for metoprolol tartrate by HPLC as described previously. During the drug release studies, all the formulations were observed for physical integrity.

2.7. Drug release studies in rat caecal content medium

Earlier reports indicate the susceptibility of guar gum to the action of colonic bacterial enzymes (Rama Prasad et al., 1998; Krishnaiah et al., 1998a,b, 1999). In this context, it is essential to study the influence of colonic bacterial enzymes on the release of metoprolol tartrate from the guar gum formulations. This was assessed by conducting in vitro drug release studies in rat caecal content medium as reported earlier (Rama Prasad et al., 1998). The rat caecal content was prepared as described previously (Rama Prasad et al., 1998). The care of the rats was in accordance with the institutional guidelines, which were based on Canadian Council on Animal Care (1984).

The drug release studies were carried out using USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37 °C) with slight modifications. A beaker (capacity 150 ml) containing 100 ml of rat caecal content medium was immersed in the water maintained in the 1000 ml vessel, which, in turn, was in the water bath of the apparatus. The swollen matrix tablets contained in the baskets of the apparatus, after completing the dissolution study in 0.1 M HCl (2 h) and pH 7.4 phosphate buffer (3 h) were immersed in the rat caecal content medium. As the caecum is naturally anaerobic, the experiment was carried out with continuous CO_2 supply into the beakers.

At different time intervals, 1 ml of dissolution sample was withdrawn and replaced with 1 ml of

fresh PBS bubbled with CO_2, and the experiment was continued upto 19 h. After the addition of 100 μg of rofecoxib (the internal standard), the volume of the dissolution sample was made upto 10 ml with PBS and centrifuged; the supernatant was filtered through 0.2-μm membrane filter and analyzed for metoprolol tartrate content by HPLC method as described above. Drug release studies were also conducted on metoprolol tartrate matrix tablets after completing in vitro dissolution study in 0.1 M HCl (2 h) and pH 7.4 phosphate buffer (3 h) without rat caecal contents in PBS (control study). The drug content remained either in the mass of the formulation or in swollen formulation was also determined by HPLC to account for the total amount of drug present in the formulation. This ensures the estimation of all the finely suspended drug particles that may be released from the guar gum matrix formulation on erosion by colonic bacteria.

2.8. Kinetics of drug release

The cumulative amount of metoprolol tartrate released from matrix tablets and three-layer matrix tablets at different time intervals was fitted to zero order kinetics using Least-Squares Method of analysis to find out whether the drug release from the formulations is providing a constant drug release. The correlation coefficient between the time and the cumulative amount of drug released was also calculated to find the fitness of the data to zero order kinetics. The fitness of the data to first order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug to be released from the formulations.

The data were also fitted to the model developed by Korsmeyer et al. (1983) in order to find out the drug release mechanism from the formulations. The cumulative percent of drug released from the formulations was plotted against time on log–log scale, and analyzed for linearity using Least-Squares Method. Calculating correlation coefficients between time and the cumulative percent of drug released on log–log scale, tested the fitness of the data.

2.9. Statistical analysis

The cumulative percent of metoprolol tartrate released from guar gum matrix tablets ($n = 3$) in the dissolution medium at 24 h with and without rat caecal contents was compared, and the statistical significance was tested by using Student's t-test. A value of $P < 0.05$ was considered statistically significant.

2.10. Stability studies

Stability studies were conducted on metoprolol tartrate three-layer matrix tablets containing various proportions of guar gum to assess their stability with respect to their physical appearance, drug content and release characteristics after storing at 40 °C/75% RH for 6 months (Mathews, 1999).

2.11. Fourier Transform Infrared Studies (FT-IR)

The FT-IR spectra of metoprolol tartrate, guar gum, powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum (before storage) or powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum (after storage) were obtained (Shimadzu FT-IR system, Japan) after making potassium bromide discs with the sample to detect drug–excipients interaction, if any.

3. Results and discussion

The present study was carried out to develop oral controlled release tablet dosage form for highly water-soluble drug such as metoprolol tartrate. For management of hypertension, the usual effective dose of metoprolol tartrate is 100–300 mg daily in two divided doses. For management of angina pectoris, the usual dose is 100–400 mg in two divided doses. In the present study, 150 mg of metoprolol tartrate was incorporated in the formulations. The required first order release rate constant (kr_1) of metoprolol tartrate from the tablet formulation, for twice daily oral administration, was calculated using the following equation (Lordi, 1989).

$kr_1 = ke(exp(-ke \times Ti)$,

where ke is the elimination rate constant (0.2165 h^{-1}) and Ti, crossing time at which the blood level profiles produced by administration of separate loading and maintenance doses intersect. The value of 'Ti' was in turn calculated using the relationship $Ti = h - Tp$ (where 'h' is the duration of therapy, i.e. 12 h in the present study and Tp is the time taken for maximum plasma concentration, i.e. 1.68 h). Thus, the required first order release rate constant based on the mean pharmacokinetic parameters of the drug in humans (Perry et al., 1996) was found to be 0.0232 h^{-1}. The guar gum formulations developed in the study were subjected to in vitro drug release studies and were optimized till the required first order release rate of metoprolol was obtained.

3.1. In-vitro drug release studies on matrix tablets

In the present study, guar gum was used, as a hydrophilic matrix carrier, in the design of oral controlled drug delivery systems for highly water-soluble drug such as metoprolol tartrate. Guar gum was found to have poor flow properties and low compressibility, and since it is to be incorporated in the matrix tablets in a larger proportion, metoprolol tartrate tablets were prepared by wet granulation technique using starch paste as a binder to impart good flow as well as compressibility.

Good flow of powders/granules is essential in tabletting. The present investigation involves the preparation of three-layer matrix tablets containing high proportion of guar gum and the excipients. Thus, the compressibility and flow properties of the drug and guar gum are likely to influence the compression process in the preparation of three-layer matrix tablets. In view of this, the three-layer matrix tablets were prepared by wet granulation technique using starch paste as a binder. The flow property of pure drug, guar gum and the resulting granules was evaluated by determining angle of repose and Carr's Index.

Angle of repose was determined by the fixed funnel method (Craik, 1958; Train, 1958). A funnel with the end of the stem cut perpendicular to the axis of symmetry was secured with its tip at a given height (H) above a graph paper placed on a flat horizontal surface. The material was carefully poured through the funnel until the apex of the conical pile so formed just touches the tip of the funnel. The mean diameter ($2R$) of the base of the powder cone was determined and the tangent of the angle of repose is given by $\tan \alpha = H/R$, where α is the angle of repose.

Carr's Index relates the poured density of the material to the tapped density and was calculated by using the following relationship:

$$\text{Carr's Index} = \frac{\text{tapped density} - \text{poured density} \times 100}{\text{tapped density}}.$$

Carr's Index values for pure drug, guar gum and granules were determined by measuring the initial volume (V_p) and final volume (V_t) of a known weight (W) of material after subjecting to 100 tappings in a graduated measuring cylinder. From these volumes, the poured density (W/V_p) and the tapped density (W/V_t) values were calculated and were substituted in the above equation to determine Carr's Index.

The angle of repose for pure drugs and guar gum samples could not be obtained since they did not flow at all through the funnel indicating very poor flow properties. The Carr's index of pure metoprolol tartrate and guar gum was found to be 33.71 ± 0.11 and 23.98 ± 0.77, respectively confirming that both the drug and guar gum have poor flow properties. The results of the study warrants the granulation of the drug/gum powder mix for compression into a matrix tablet to give uniform dose. Metoprolol tartrate guar gum matrix granules were prepared by wet granulation method using 10% w/w starch paste as binder.

The improvement in the flow property of the granules has been evaluated by determining angle of repose and Carr's Index as described above. All dried granules were found to be free flowing with an angle of repose ranging from 18 to 25° and Carr's index ranging from 11.21 ± 0.01 to 14.10 ± 0.02 indicating that the desired flow properties were achieved after granulation with starch paste.

Metoprolol tartrate matrix tablets containing different proportions of guar gum along with other additives were prepared by wet granulation method and subjected to various tests such as hardness, thickness, drug content (Table 3) and in vitro drug release studies. The mean values for hardness of the matrix tablets of metoprolol tartrate were in the range of 4.94 ± 0.11–5.11 ± 0.12 kg. The HPLC method used in the study was found to be highly precise ($< 1.4\%$ CV) and accurate (99.8–101.1% recovery). All the matrix tablets satisfied the drug content uniformity as they contained between 98.44 ± 0.83 and $101.44 \pm 0.53\%$ of metoprolol tartrate when assayed by HPLC method as described above. Matrix tablets prepared with different proportion of guar gum were subjected to in vitro drug release studies in pH 1.2 buffer for the first 2 h and in pH 7.4 buffer for another 10 h. When the amount of drug released at different time intervals was fitted to zero and first order kinetics, a better correlation ($r = 0.9537 \pm 0.02$–0.9946 ± 0.01) was observed for first order kinetics when compared to zero order kinetics (Table 4). The first order release rate constants obtained from M1, M2 and M3 formulations were 0.0750 ± 0.01, 0.0680 ± 0.01 and 0.0560 ± 0.02 h^{-1}, respectively. Though a controlled release was observed (Fig. 1), metoprolol matrix tablets could not provide the required release rate (0.0232 h^{-1}). Moreover, the drug release in pH 1.2 buffer was significantly high indicating the need for further control. In order to provide the required control of drug release, it is planned to coat a layer of guar gum as a release retardant polymer on both sides of the guar gum matrix formulations so as to prepare three-layer matrix tablets.

3.2. In-vitro drug release studies on three-layer guar gum matrix tablets

Metoprolol tartrate three-layer matrix tablets with either 50 or 75 mg of guar gum as release retardant layer were formulated and prepared. Guar gum granules containing 87% of guar gum were prepared by wet granulation technique using starch paste as binder. Thus, the three-layer guar gum matrix tablets of metoprolol tartrate contained a middle layer of guar gum and metoprolol with only guar gum in the top and bottom layers. These formulations were tested for hardness and drug content (Table 3), and were subjected to in vitro drug release studies. The mean values for hardness of the three-layer matrix tablets of metoprolol tartrate were in the range of 5.02 ± 0.14–5.63 ± 0.15 kg. All the three-layer matrix tablets satisfied the drug content as they contained 98.23 ± 0.67–$102.44 \pm 0.23\%$ of drug indicating uniform mixing of the guar gum, drug and other formulation excipients.

All the formulations were found swollen and retained their physical integrity till the end of the 12-h dissolution study except that the edges of the swollen formulations were rounded off due to slight erosion of swollen gum. The mean correlation coefficients obtained with all three-layer for-

Table 3
Characteristics of metoprolol tartrate guar gum matrix tablets and guar gum three-layer matrix tablets ($n = 3$)

Tablet formulation	Hardness (kg)	Thickness of tablet (mm)	Drug content (%)
M1	4.94 ± 0.11	3.80 ± 0.01	98.44 ± 0.83
M2	5.08 ± 0.1	3.81 ± 0.01	101.44 ± 0.53
M3	5.11 ± 0.12	3.81 ± 0.01	100.23 ± 0.67
TL1M1	5.02 ± 0.14	4.52 ± 0.01	99.30 ± 0.35
TL1M2	5.13 ± 0.17	5.03 ± 0.01	102.44 ± 0.23
TL1M3	5.24 ± 0.16	4.53 ± 0.01	98.23 ± 0.67
TL2M1	5.56 ± 0.15	5.04 ± 0.01	98.73 ± 1.07
TL2M2	5.63 ± 0.12	4.53 ± 0.01	101.30 ± 0.35
TL2M3	5.59 ± 0.15	5.04 ± 0.01	100.99 ± 0.18

Values shown in the table are mean $\pm$ S.D.

Table 4
In vitro dissolution kinetics of metoprolol tartrate guar gum matrix tablets and guar gum three-layer matrix tablets ($n = 3$)

Tablet formulation	Zero order release rate (mg h^{-1})	First order rate constant (h^{-1})	Kinetic constant (k)	Diffusional exponent (n)
M1	6.277 ± 0.01 ($r = 0.9618 \pm 0.04$)	0.0750 ± 0.01 ($r = 0.9904 \pm 0.012$)	1.566 ± 0.03 ($r = 0.9898 \pm 0.24$)	0.45 ± 0.02
M2	6.181 ± 0.02 ($r = 0.8849 \pm 0.20$)	0.0680 ± 0.01 ($r = 0.9946 \pm 0.01$)	1.523 ± 0.01 ($r = 0.9925 \pm 0.13$)	0.49 ± 0.03
M3	6.137 ± 0.03 ($r = 0.8698 \pm 0.01$)	0.0560 ± 0.02 ($r = 0.9537 \pm 0.02$)	1.500 ± 0.02 ($r = 0.9924 \pm 0.01$)	0.48 ± 0.01
TL1M1	6.013 ± 0.02 ($r = 0.9714 \pm 0.01$)	0.0510 ± 0.01 ($r = 0.9907 \pm 0.01$)	1.491 ± 0.03 ($r = 0.9919 \pm 0.09$)	0.53 ± 0.01
TL1M2	5.350 ± 0.17 ($r = 0.9694 \pm 0.02$)	0.0386 ± 0.02 ($r = 0.9723 \pm 0.11$)	1.472 ± 0.01 ($r = 0.9991 \pm 0.04$)	0.40 ± 0.02
TL1M3	4.929 ± 0.34 ($r = 0.9857 \pm 0.02$)	0.0323 ± 0.02 ($r = 0.9878 \pm 0.01$)	1.416 ± 0.02 ($r = 0.9985 \pm 0.05$)	0.38 ± 0.01
TL2M1	6.005 ± 0.01 ($r = 0.9715 \pm 0.04$)	0.0473 ± 0.03 ($r = 0.9955 \pm 0.02$)	1.372 ± 0.01 ($r = 0.9960 \pm 0.01$)	0.42 ± 0.01
TL2M2	5.151 ± 0.03 ($r = 0.9884 \pm 0.02$)	0.0351 ± 0.01 ($r = 0.9984 \pm 0.01$)	1.255 ± 0.02 ($r = 0.9950 \pm 0.02$)	0.57 ± 0.03
TL2M3	4.782 ± 0.01 ($r = 0.9847 \pm 0.02$)	0.0302 ± 0.02 ($r = 0.9866 \pm 0.04$)	0.788 ± 0.03 ($r = 0.9816 \pm 0.01$)	0.58 ± 0.02

Values shown in the table are mean $\pm$ S.D.

mulations for first order release kinetics were found slightly higher ($r = 0.9537 \pm 0.02$–0.9984 ± 0.01) when compared to those of zero order kinetics ($r = 0.8698 \pm 0.01$–0.9884 ± 0.02) indicating that the drug release from all the formulations followed first order kinetics (Table 4). A better-controlled drug release was observed when a release retardant layer was applied on both sides of the matrix formulations (Figs. 2 and 3). When 50 mg of guar gum was layered on the matrix formulations M1, M2 and M3, the first order release rate constants obtained from TL1M1, TL1M2 and TL1M3 formulations were 0.0510 ± 0.01, 0.0386 ± 0.02 and 0.0323 ± 0.02 h^{-1}, respectively. On further increasing the amount of guar gum layer from 50 to 75 mg on both sides of the middle matrix layer (M1, M2 or M3), the first order release rate constants further reduced to 0.0473 ± 0.03, 0.0351 ± 0.01 and 0.0302 ± 0.02 h^{-1}, respectively in case of TL2M1, TL2M2 and TL2M3 formulations (Table 4). It is evident from these data that the three-layered tablet formulation TL2M3 is providing a release rate constant of 0.0302 ± 0.02 h^{-1} which is nearer to the required release rate constant of 0.0232 h^{-1}.

When the percent of metoprolol tartrate released was plotted against time on log–log scale, the diffusional exponent values (n) ranged from 0.38 ± 0.01 to 0.58 ± 0.02 indicating that metoprolol tartrate release from guar gum matrices followed Fickian diffusion (Table 4). When the hydrophilic guar gum tablets come in contact with the dissolution medium, they take up water and swell forming a viscous gel barrier. In case of guar gum matrix tablets, the initial swelling of the gum may aid dissolution of the freely soluble drugs, and the dissolved drug diffuses out of the swollen gel barrier into the dissolution medium. Unless the swollen gel barrier erodes, further seeping-in of the dissolution medium does not occur. Thus, the release rate of the drug depends on the strength of the gel barrier i.e. the proportion of the hydrophilic guar gum in the matrix tablet, its rate of hydration and viscosity. Guar gum being a hydrophilic polymer was incorporated in the matrix tablets in different proportions to optimize the amount of guar gum needed to provide required release rate. Metoprolol tartrate matrix formulation (M3), in spite of containing higher (50%) proportion of guar gum, could not provide

the required rate of drug release. This might be because of the rapid release of the highly soluble metoprolol tartrate from the surface of the matrix tablet within first 2 h.

Three-layer matrix tablets are based on the idea that the restriction of the matrix area exposed to the dissolution medium may lead to a dual control in the system performance. This is possible for two reasons: (a) matrix hydration rate and consequent swelling are lowered; and (b) the surface through which the drug can be delivered is reduced. These effects, possibly more effective in the initial phase of the dissolution process and less pronounced as swelling proceeds, lead to a linearization of release profile. The drug release mechanism from the three-layer matrix tablets involves the following sequence. In the initial phase, barriers applied to the core are able to delay the interaction of the core with the dissolution medium by reducing the surface available for drug release and by limiting the solvent penetration rate. Thus, in this system the burst effect can be controlled and the area available for drug release can be maintained at a relatively constant

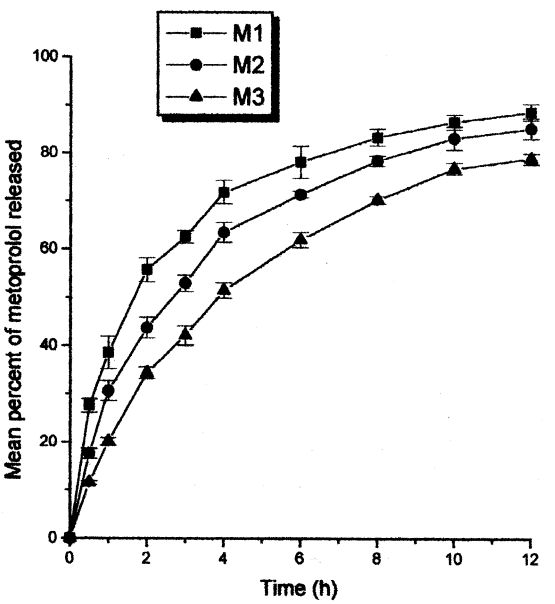

Fig. 1. Mean (± S.D.) percent of metoprolol tartrate released from matrix tablets ($n = 3$) containing either 30 (M1), 40 (M2) or 50% (M3) of guar gum in the dissolution study.

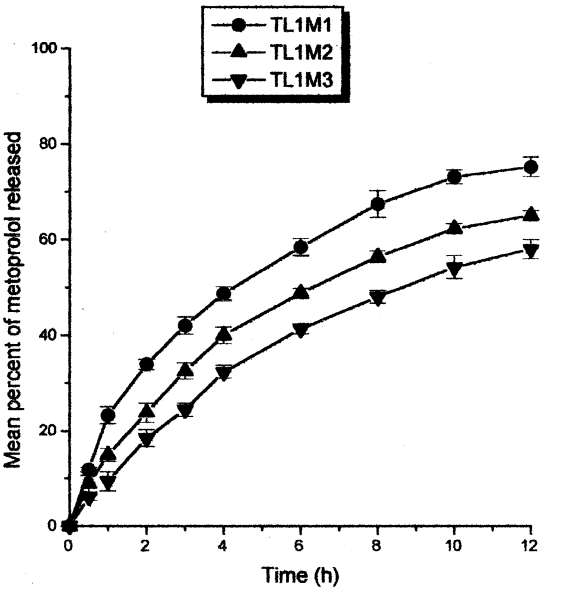

Fig. 2. Mean (± S.D.) percent of metoprolol tartrate released from three-layer matrix tablets ($n = 3$) containing 50 mg of guar gum as release controlling layer on both sides of the matrix tablet containing 30 (TL1M1), 40 (TL1M2) or 50% (TL1M3) of guar gum in the dissolution study.

level during the swelling/erosion processes. During dissolution, barrier layers are progressively eroded and the surface available for the drug release increases. In this way the decrease of the delivery rate due to an increase of the diffusion path length is compensated by the concurrent increase of the area for drug release. After this main release phase, in the last portion of the dissolution process, water can finally reach the core even under the layer, and the matrix can freely swell or dissolve.

3.3. In-vitro drug release studies in rat caecal contents

The In-vivo performance of a controlled release dosage form, especially a hydrophilic matrix tablet, depends on its biodegradability in GI tract. The present study involved the use of guar gum, as a carrier for oral controlled drug delivery, in the form of three-layer matrix tablets. Earlier reports indicate the susceptibility of guar gum to the action of colonic bacterial enzymes (Rama

Prasad et al., 1998; Krishnaiah et al., 1998a,b, 1999). In this context, it is essential to study the influence of colonic bacterial enzymes on metoprolol tartrate release characteristics from the guar gum three-layered matrix tablets. This was assessed by conducting in vitro drug release studies in rat caecal content medium as per the procedure described by Rama Prasad et al. (1998).

Three-layer matrix formulation of metoprolol tartrate containing 75 mg of guar gum as rate controlling layer on both sides of matrix formulation (TL2M3) was found to provide the required release rate in presence of simulated GI fluids. Hence the three-layer matrix tablets (TL2M3) was subjected to in vitro drug release studies in rat caecal content medium to study the influence of colonic bacterial enzymes on the release pattern of TL2M3 formulation. In the presence of rat caecal contents, the three-layer matrix tablets (TL2M3) were found intact upto 8 h and the guar gum formulation started degrading slowly. At the end of 24 h of the study, the three-layer matrix tablets were found disintegrated into a thick mass and

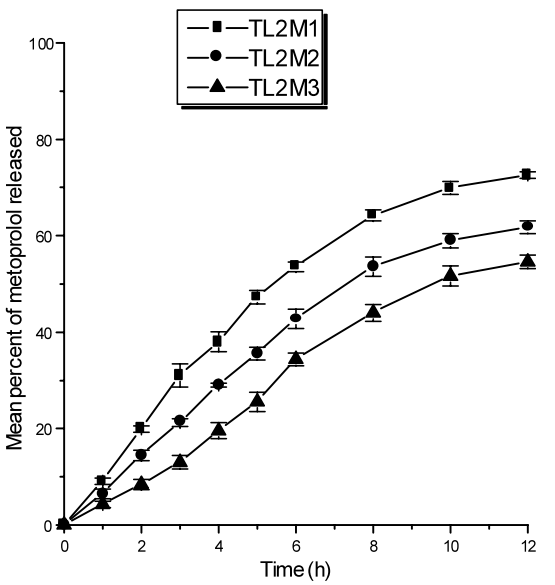

Fig. 3. Mean (± S.D.) percent of metoprolol tartrate released from three-layer matrix tablets ($n = 3$) containing 75 mg of guar gum as release controlling layer on both sides of the matrix tablet containing 30 (TL2M1), 40 (TL2M2) or 50% (TL2M3) of guar gum in the dissolution study.

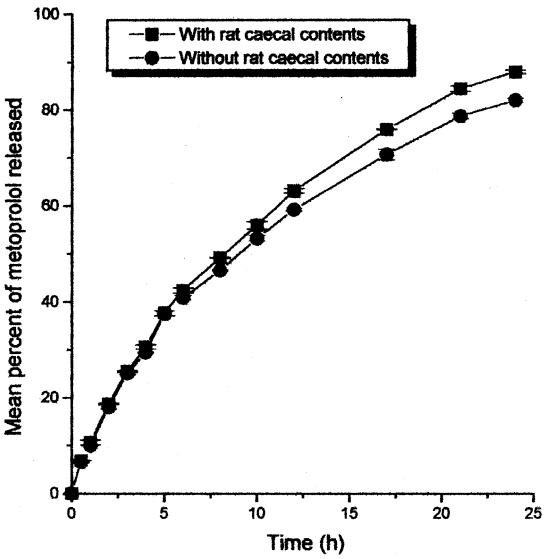

Fig. 4. Mean (± S.D.) percent of metoprolol tartrate released from three-layer matrix tablets ($n = 3$) containing 75 mg of guar gum as release controlling layer on both sides of the matrix tablet containing 50% of guar gum (TL2M3) in the dissolution study with and without rat caecal contents.

released almost the remaining quantity of metoprolol tartrate in the rat caecal content medium (simulated colonic conditions). At the end of 12 h of dissolution testing, three-layer tablet (TL2M3) released $63.17 \pm 0.50\%$ of metoprolol tartrate in rat caecal content medium and $59.28 \pm 0.36\%$ in simulated gastrointestinal fluids (Fig. 4). It is clear that about 40% of the drug is still left over in the formulation after reaching the physiological environment of colon. Since metoprolol tartrate is reported having good permeability through colon (Kinget et al., 1998), the formulation TL2M3 is likely to provide the same extent of first order release rate because of the high colonic residence time thereby providing a slow release of metoprolol tartrate. Thus, guar gum being a colon-specific drug carrier appears to provide oral controlled drug delivery.

3.4. Stability studies

Based on the results of the in vitro drug release studies, three-layer guar gum matrix tablets of metoprolol tartrate are found to provide the re-

quired oral controlled drug delivery. Hence, stability studies were carried out by storing the formulation at 40 °C/75% RH for 6 months (climatic zone IV conditions for accelerated testing) to assess their long-term (2 years) stability. The protocol of the stability studies was in conformation with the recommendation in WHO document for stability testing of products intended for global market (Mathews, 1999). At the end of the storage period, studies were conducted on metoprolol tartrate three-layer matrix tablets to assess their stability with respect to their physical appearance, drug content and release characteristics. The three-layer tablets after storing at 40 °C/75% RH for 6 months (Mathews, 1999) showed no change either in physical appearance, drug content or in dissolution pattern (Table 5). The results of the stability studies indicate that the formulations could provide a minimum shelf life of 2 years (Mathews, 1999).

3.5. FT-IR studies

The FT-IR spectrum of guar gum, metoprolol tartrate, powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum (before storage) and powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum (after storage) is shown in Fig. 5. The slight difference in peak height at 1592 cm^{-1} may be due to the tartrate molecule that has no influence on the metoprolol structure. Based on the spectra obtained with FT-IR spectroscopy, there appears to be no possibility of interaction between metoprolol tartrate and guar gum/other excipients used in the matrix tablets.

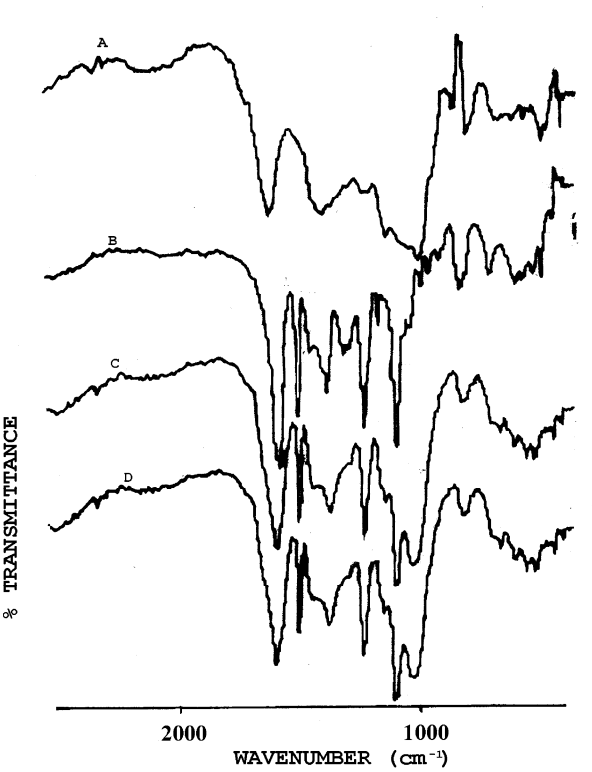

Fig. 5. The FT-IR spectra of guar gum (A), metoprolol tartrate (B), powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum before storage (C) or powdered sample of middle layer of the three-layer matrix tablet coated with 75 mg of guar gum after storage (D).

Table 5
Percent of metoprolol tartrate released from guar gum three-layer matrix tablets ($n = 3$) layered with 75 mg of guar gum granules (TL2M3) in 0.1 M HCl (2 h) and pH 7.4 Sorenson's phosphate buffer (10 h) before and after storage at 40 °C/75% RH for 6 months

Time (h)	Percent of metoprolol tartrate released from TL2M3	
	Before storage	After storage
0	0	0
0.5	4.25 ± 0.6	4.24 ± 0.6
1	7.19 ± 1.3	7.17 ± 1.1
2	11.03 ± 1.3	10.96 ± 1.05
3	17.57 ± 2.0	17.53 ± 1.4
4	22.53 ± 1.3	22.49 ± 1.4
6	35.40 ± 1.7	35.38 ± 1.5
8	43.97 ± 2.0	43.94 ± 1.7
10	51.65 ± 1.4	51.61 ± 1.2
12	54.58 ± 2.3	54.52 ± 2.1

Values shown in the table are mean ± S.D.

4. Conclusions

The present study was carried out to develop oral controlled delivery systems for metoprolol

tartrate using guar gum as a carrier. Guar gum matrix tablets containing various proportions of guar gum were prepared and subjected to in vitro drug release studies. Matrix formulations could not provide the required release of metoprolol tartrate. The first order release rate constants obtained from matrix tablets containing 30, 40 and 50% of guar gum were found to be 0.0750 ± 0.01, 0.0680 ± 0.01 and 0.0560 ± 0.02 h^{-1}, respectively, which were far above the required release rate constant. Hence, guar gum three-layer matrix tablets with either 50 or 75 mg of guar gum layers on both sides of the metoprolol tartrate guar gum matrix containing various proportions of guar gum were prepared and subjected to in vitro drug release studies. The three-layer matrix tablet with 75 mg of guar gum layers on both sides of the metoprolol tartrate matrix formulation containing 50% of guar gum was found to provide the required release rate matching with the theoretical release rate constants calculated on the basis of pharmacokinetic properties of the drug, for metoprolol tartrate tablet formulations meant for twice daily administration. This three-layer guar gum matrix tablet after storing at 40 °C/75% RH for 6 months showed no change either in physical appearance, drug content or in dissolution pattern. Based on the FT-IR studies, there appears to be no possibility of interaction between metoprolol tartrate and guar gum/other excipients used in the tablets. The results clearly indicate that guar gum in the form of three-layer matrix tablet is a potential hydrophilic carrier in the design of oral controlled drug delivery systems for highly soluble drugs. Bioavailability studies are in progress to assess the usefulness of three-layer matrix tablet (TL2M3) in comparison with conventional immediate release metoprolol tartrate tablets.

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References

Altaf, S.A., Yu, K., Parasrampuria, J., Friend, D.R., 1998. Guar gum based sustained release diltiazem. Pharm. Res. 15, 1196–1201.

Breimer, D.D., 1983. Gastrointestinal drug delivery systems. Pharm. Tech. 7, 18–23.

Craik, D.J., 1958. The flow properties of starch powders and mixtures. J. Pharm. Pharmacol. 10, 73.

Eddington, N.D., Marroum, P., Uppoor, R., Hussain, A., 1998. Development and internal validation of an in vitro–in vivo correlation for a hydrophilic metoprolol tartrate extended-release tablet formulation. Pharm. Res. 15, 466–473.

Ghosh, L.K., Sairam, P., Gupta, B.K., 1996. Development and evaluation of an oral controlled release multiple emulsion drug delivery system of a specific beta blocker metoprolol tartrate. Bulletino Chemico Farmaceutico 135, 468–471.

Godbillon, J., Evard, D., Vidon, N., Duval, M., Schoeller, J.P., Bernier, J.J., Hirtz, J., 1985. Investigation of drug absorption from gastrointestinal tract of man. III. Metoprolol in the colon. Br. J. Clin. Pharmacol. 19, 113S–118S.

Jain, N.K., Kulkarni, K., Talwar, N., 1992. Controlled-release tablet formulation of Isoniazid. Pharmazie 47, 277–278.

Kendall, M.J., 1989. Metoprolol-controlled release, zero order kinetics. J. Clin. Pharm. Ther. 24, 159–179.

Khullar, P., Khar, R.K., Agarwal, S.P., 1998. Guar gum as a hydrophilic matrix for preparation of theophylline controlled-release dosage form. Drug Dev. Ind. Pharm. 24, 1095–1099.

Kinget, R., Kalala, W., Vervoort, L., Van den Mooter, G., 1998. Colonic drug targeting. J. Drug Target. 6, 129–149.

Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P., Peppas, N.A., 1983. Mechanisms of solute release from porous hydrophilic polymers. Int. J. Pharm. 15, 25.

Krishnaiah, Y.S.R., Satyanarayana, S., Rama Prasad, Y.V., Narasimha Rao, S., 1998a. Gamma scintigraphic studies on guar gum matrix tablets for colon-specific drug delivery in healthy subjects. J. Controlled Release 55, 245–252.

Krishnaiah, Y.S.R., Satyanarayana, S., Rama Prasad, Y.V., Narasimha Rao, S., 1998b. Evaluation of guar gum as a compression coat for drug targeting to colon. Int. J. Pharm. 171, 137–146.

Krishnaiah, Y.S.R., Satyanarayana, S., Rama Prasad, Y.V., 1999. Studies on guar gum compression coated 5-amino salicylic acid tablets for colon-specific drug delivery. Drug Dev. Ind. Pharm. 25, 651–657.

Krishnaiah, Y.S.R., Rama Rao, T., Ushasree, M., Satyanarayana, S., 2001. A study on the in-vitro evaluation of

guar gum as a carrier for oral controlled drug delivery. Saudi Pharm. J. 9, 98.

Lordi, N.G., 1989. Sustained release dosage forms. In: Lachman, L., Liberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy, 2nd ed. Lea & Febiger, Philadelphia, pp. 430–456.

Mathews, B.R., 1999. Regulatory aspects of stability testing in Europe. Drug Dev. Ind. Pharm. 25, 831–856.

Okabe, K., Yamoguchi, H., Kawai, Y., 1987. New iontophoretic transdermal administration of the beta-blocker-metoprolol. J. Controlled Release 4, 79–85.

Perry, B.M., Raymond, W.R., 1996. Pharmacokinetic Data. In: Goodman & Gilman's The Pharmacological Basis of Therapeutics, IX ed. p. 1760.

Pillay, V., Fassihi, R., 2000. A novel approach for constant rate delivery of highly soluble bioactives from a simple monolithic system. J. Controlled Release 67, 67–78.

Rama Prasad, Y.V., Krishnaiah, Y.S.R., Satyanarayana, S., 1998. In vitro evaluation of guar gum as a carrier for colon-specific drug delivery. J. Controlled Release 51, 281–287.

Regardh, C.-G., Borg, K.O., Johnsson, R., Johnsson, G., Palmer, L., 1974. Pharmacokinetic studies on the selective β_1-receptor antagonist metoprolol in man. J. Pharmacokinet. Biopharm. 2, 347–364.

Sandberg, A., Ragnarsson, G., Jonsson, U.E., Sjogren, J., 1988. Design of a new multiple unit controlled release formulation of metoprolol–metoprolol CR. Eur. J. Clin. Pharmacol. 33, S3–S7.

Train, D., 1958. Some aspects of the property of angle of repose of powders. J. Pharm. Pharmacol. 10, 127T–135T.