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Research Article

Development of Sustained Release Capsules Containing "Coated Matrix Granules of Metoprolol Tartrate"

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Abstract. The objective of this investigation was to prepare sustained release capsule containing coated matrix granules of metoprolol tartrate and to study its *in vitro* release and *in vivo* absorption. The design of dosage form was performed by choosing hydrophilic hydroxypropyl methyl cellulose (HPMC K100M) and hydrophobic ethyl cellulose (EC) polymers as matrix builders and Eudragit® RL/RS as coating polymers. Granules were prepared by composing drug with HPMC K100M, EC, dicalcium phosphate by wet granulation method with subsequent coating. Optimized formulation of metoprolol tartrate was formed by using 30% HPMC K100M, 20% EC, and ratio of Eudragit® RS/RL as 97.5:2.5 at 25% coating level. Capsules were filled with free flowing optimized granules of uniform drug content. This extended the release period upto 12 h *in vitro* study. Similarity factor and mean dissolution time were also reported to compare various dissolution profiles. The network formed by HPMC and EC had been coupled satisfactorily with the controlled resistance offered by Eudragit® RS. The release mechanism of capsules followed Korsemeyer–Peppas model that indicated significant contribution of erosion effect of hydrophilic polymer. Biopharmaceutical study of this optimized dosage form in rabbit model showed 10 h prolonged drug release *in vivo*. A close correlation (R^2=0.9434) was established between the *in vitro* release and the *in vivo* absorption of drug. The results suggested that wet granulation with subsequent coating by fluidized bed technique, is a suitable method to formulate sustained release capsules of metoprolol tartrate and it can perform therapeutically better than conventional immediate release dosage form.

KEY WORDS: biopharmaceutical evaluation; coated granules; metoprolol tartrate; sustained release.

INTRODUCTION

The development of sustained release (SR) dosage form has become the subject of interest to many pharmaceutical scientists in recent years (1–4). Among numerous approaches to oral SR formulation, matrix system of dosage form proves to be potential because of their simplicity, ease of manufacturing, low cost, high level of reproducibility, stability, ease of scale up, and process validation (4,5). Development of dosage form depends on chemical nature of the drug/polymers, matrix structure, swelling, diffusion, erosion, release mechanism and the *in vivo* environment (6). Besides these, process variables like method of granulation, shear stress during mixing and viscosity of granulating agent play important role in extended release drug (7,8). Nowadays, various hydrogels (matrix builders) with various degree of substitution are applied according to the characteristics of drug and its pharmacological action to control release of both hydrophilic and hydrophobic medicinal agents from matrix granules (9–16). Hydroxypropyl methyl cellulose (HPMC) and cellulose ether are widely used to control release of drug, usually, by two mechanisms: drug diffusion through swelling and erosion of swollen polymer (17–19). Use of single hydrophilic polymer is not justified in case of highly water-soluble drugs because it diffuses out rapidly through the water-filled pores of matrix. Hydrophobic polymers (glycerides, ethyl cellulose (EC)) are used for such drugs (20–25). Release of drug through the matrix can be further modified by forming coating layer on the granules (4,26–33). Generally, "film coating of tablet" is done to compensate for pH-dependent effect of drugs solubility (34). Eudragit® RS/RL polymers are pH independent, insoluble still swellable in physiological media. Quaternary ammonium groups along with chloride counter ions of Eudragit® RS/RL controls permeability of drugs through this coating layer.

Developing oral-sustained release formulations for highly water-soluble drugs with constant rate of release has become a challenge to the pharmaceutical technologists. Fast release drug generally causes toxicity if not formulated as extended release dosage form. Among various formulation approaches, in controlling the release of water-soluble drugs, the development of sustained release coated granules has a unique advantage of lessening the chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. Most of the researchers have worked on matrix tablets and multilayered matrix tablets. In the present study, a sustained release dosage form (coated

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granules in capsule) of metoprolol tartrate (MT) has been developed that enables less frequent administering of drug (35). At first, matrix granules of MT were formed by appropriate combination of HPMC and EC. Eudragit® RL and RS were chosen to form coating on the granules to extend duration of drug release. The objectives of this work were: (1) to evaluate the physical characters of prepared granules, (2) to elucidate the effect of polymer composition, coating composition on the release kinetics, (3) *in vivo* study in rabbit model.

MATERIALS AND METHODS

Materials

Metoprolol tartrate (98–101% purity) were gift samples from Torrent Labotatories, India. Other excipients: hydroxyl propyl methyl cellulose HPMC K 100 M, EC, HPMC E 5 and di-calciumphosphate, Eudragit® RS, and RL were kindly donated by Dhara Life Science Pvt. Ltd. India. All were of Pharmacopoeial standard (USP/NF). Acetonitrile (high-performance liquid chromatography (HPLC) grade) and methanol (HPLC grade) were procured from M/s. Qualigens Fine Chemicals, Mumbai, India. Immediate release tablets of metoprolol tartrate (METOLAR 25 Tab, Batch No. TB0037, Expiry date: March 2011) were purchased from Cipla limited, India.

Preparation of Sustained Release Matrix Granules

Different batches of granules (MG1, MG2, MG3, and MG4) were prepared according to the composition mentioned in Table I. Accurately weighed quantities of each component were mixed in a double cone blender (Jyoti Scientific Industries, India, Model No.1240). The powder mix was wetted with aqueous solution of HPMC E 5 (7.5%, *w*/*w*). The granules obtained after passing through sieve (12 mesh size) were then dried adequately at 60°C for 30–45 min. The dried granules were sifted manually through 12 mesh screen. The matrix granules in particle size range of 14–20 mesh had been selected. These batches of granules were put under physical characterization and drug release study.

Coating of Sustained Release Matrix Granules

The granules MG3 exhibited extended release up to 4 h. It needed further modification to enhance release period. Matrix granules (14-20 mesh size) were coated stepwise in a fluid-bed coater (Glatt-Powrex, Powrex, Japan). Granules were first spray coated with an aqueous ethanolic solution of HPMC K100M to form intermediate layer. This layer makes 3–6% weight gain to the initial granules to prevent any incompatibility between drug and Eudragit®. MT matrix granules (20% w/w drug loading) were again coated with blends of Eudragit® RS and RL along with plasticizer, triethyl citrate (TEC) (20% *w*/*w*) in a fluidized bed coater. All dispersions were plasticized overnight. The following Eudragit® RS and RL blend ratios were investigated: 85:15, 90:10, 95:5, 97.5:2.5, and 100:0 (*w*/*w*), and this causes 10% weight gain in granules.After coating these granules were marked as batch CMG1, CMG2, CMG3, CMG4, and CMG5. Coated CMG4 batch had sustained the drug release for a longer period of 8 h. In the next step, freshly prepared CMG4 granules were coated until a weight gain of 15%, 25%, and 35% (*w*/*w*) was achieved. These formulations were marked as CMG15, CMG25, and CMG35, respectively. The process parameters were as follows: preheating temperature, 35°C; preheating time, 2 min; inlet temperature of 35–40°C, outlet temperature of 32–34°C, product temperature of 32±2°C; spray rate, 2–3 g/min; atomization pressure, 1.2 bar; volumetric flow rate of air, 100 m^3/h and nozzle diameter of 1.2 mm. After coating the granules were fluidized for 10 min and subsequently cured for 24/48 h at 40°C and 15% relative humidity (RH) and were sieved (12–22 mesh) to remove both agglomerate and fine powder. Next, these coated batches were subjected to physicochemical characterization tests and *in vitro* release study.

Table I. Composition of Sustained Release Matrix Granules of Metoprolol Tartrate

	% Granule weight			
Batch	MT	DCP	HPMC K100M	EC
MG1	20	30	50	00
MG2	20	30	40	10
MG3	20	30	30	20
MG4	20	30	20	30
MG5	20	30	10	40

Characterization of Sustained Release Coated Matrix Granules

Finally optimized granules were evaluated for their micromeritic properties such as particle size, true density, tapped density, Carr's index, and flow properties. Angle of repose,bulk density and tapped density were determined by USP <1174> method. Tapped density was determined by using tapped density tester (Electrolab,India) and Carr's index (CI) was calculated. True density was determined by a Helium densitometer (Shimadzu, Kyoto, Japan). Particle size distribution of the granules was determined by using USP standard sieves (Electrolab, India) and graph was plotted with percentage frequency against sieve size (Fig. 1). The drug content in granules was determined by extracting an accurately weighed amount of powdered granules (100 mg) with water. The solution was filtered through 0.45-μm membrane and absorbance was measured at 274 nm after suitable dilution. To further characterize the drug release process, the mean dissolution time (MDT), and similarity factor of dissolution profiles of commercial product and experimental formulations were calculated according to the following equations:

$$\mathrm{MDT} = \frac{\sum_{i=1}^{n} t_{\mathrm{mid}} * \Delta Q}{\sum_{i=1}^{n} \Delta Q},$$

where i is the sample number, n is the total sampling number considered, t_{mid} is the time at midpoint between t_i and t_i-1 and ΔQ the additional amount of drug dissolved in the period of time t_i and t_i-1.

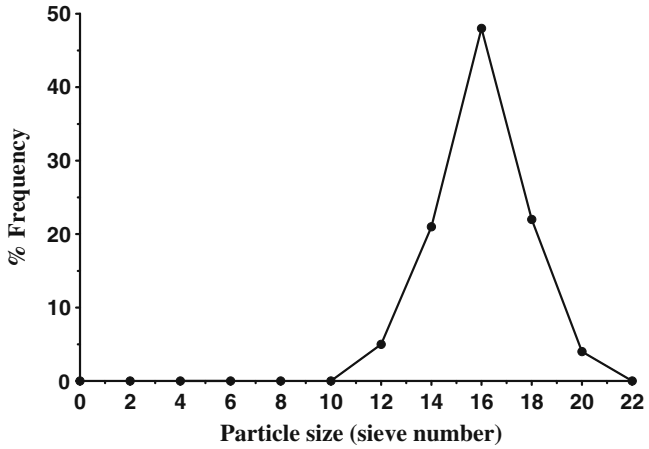

Fig. 1. Frequency distribution plot of SR granules CMG25

Moore and Flanner (36) developed the following equation:

$$f2 = 50\log\left[\left\{1 + (1/n)\sum_{i=1}^{n}(R_i - T_i)^2\right\}^{-0.5}\right] * 100$$

where n is the sampling number, *R*i and *T*i are the percent of drug released from the reference and test products at each time point *i*. f_2 is a measure of similarity between two dissolution profiles. f_2 value greater than 50% represents equivalence of the two curves and when the percent error is zero (*i.e.*, f_2=100), test and drug reference profiles are identical.

Friability. At first fine powder was removed from the granules samples by shaking the samples for 5 min on a sieve of pore size 212 μm. A sample of the residual coarse granules (20 g) was placed in the drum of an Erweka friabulator (Heusenstamm, Germany) rotating at 20 rpm for 10 min. The percentage of dust formed due to the impact was determined and taken as index of friability. The test was performed in the conventional, matrix tablet and coated matrix granules, each in triplicate.

In Vitro Drug Release Studies

The *in vitro* dissolution studies were performed by USP-30 type I dissolution apparatus at 50 rpm. The dissolution medium consisted of 0.1 N hydrochloric acid for first 2 h and the phosphate buffer with pH 6.8 for the next 3 to 12 h (900 mL) and the medium was maintained at 37°C±0.5°C. This simulated the gastrointestinal pH. An aliquot (5 ml) was withdrawn at specific time intervals and replaced with the same volume of fresh medium at same temperature. The withdrawal sample was filtered through 0.45 μm filter paper. Next, its drug content was determined by UV-visible spectrophotometer (Shimadzu, Kyoto, Japan) at 274 nm. It was ascertained that none of the ingredients used in the matrix formulations interfered with the assay of drug (MT). The release studies were conducted in triplicate (8). Mean percent cumulative drug release was plotted against time of release.

Fourier Transform Infrared

The compatibility between drug and polymer was ascertained by Fourier transform infrared FTIR (Perkin Elmer, Model-Paragon 1000 and Sr. No.-39261) study on the drug, polymers, drug-polymer physical mixture and new formulation. Five milligrams of the drug or sample was taken and thoroughly triturated with 100 mg of potassium bromide. The powder was compressed at 20 psi for 10 min on KBr press. A pellet was made out of the mix and introduced into the instrument. The spectrum was recorded in 500–4,000 cm^{-1} and shown in Fig. 2.

Surface Topography by Scanning Electron Microscopy

Granules were removed from the dissolution apparatus at predetermined time intervals and the samples for scanning electron microscopy (SEM) were prepared by lightly sprinkling the granules on a double-sided adhesive tape stuck to a brass stub. The stubs were then coated with gold to a thickness of ~180–200 Å under a nitrogen atmosphere using a gold sputter module in a high vacuum (10^{-2} to 10^{-3} Torr) evaporator. Samples were coated with gold and visualized under scanning electron microscope (Jeol JSM-5200, Tokyo,

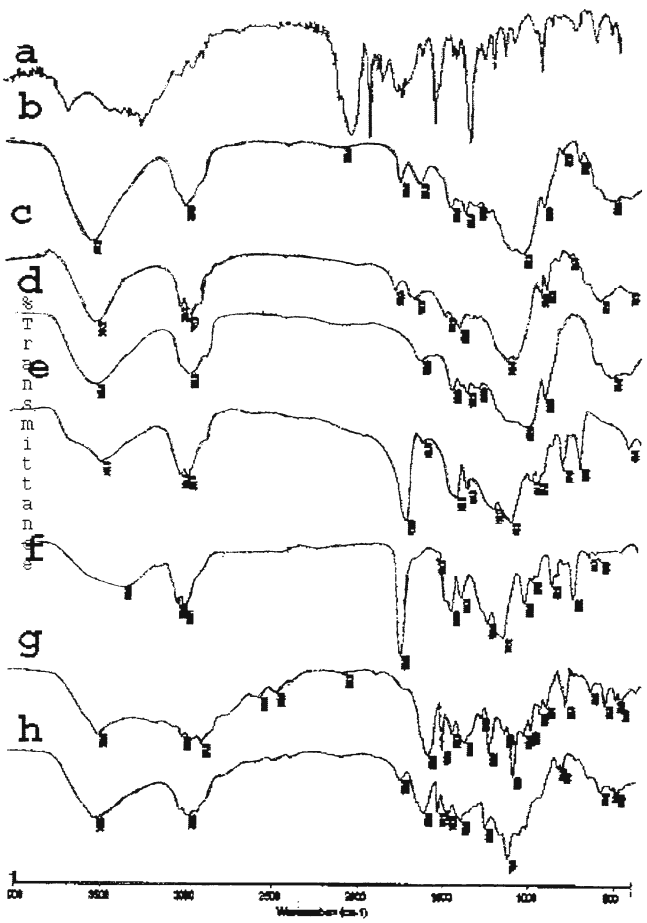

Fig. 2. The FTIR spectra of metoprolol tartrate **a**, HPMC K100M **b**, ethyl cellulose **c**, HPMC E5 **d**, Eudragit® RS **e**, Eudragit® RL **f**, powder mixture **g**, SR granules CMG25 **h**

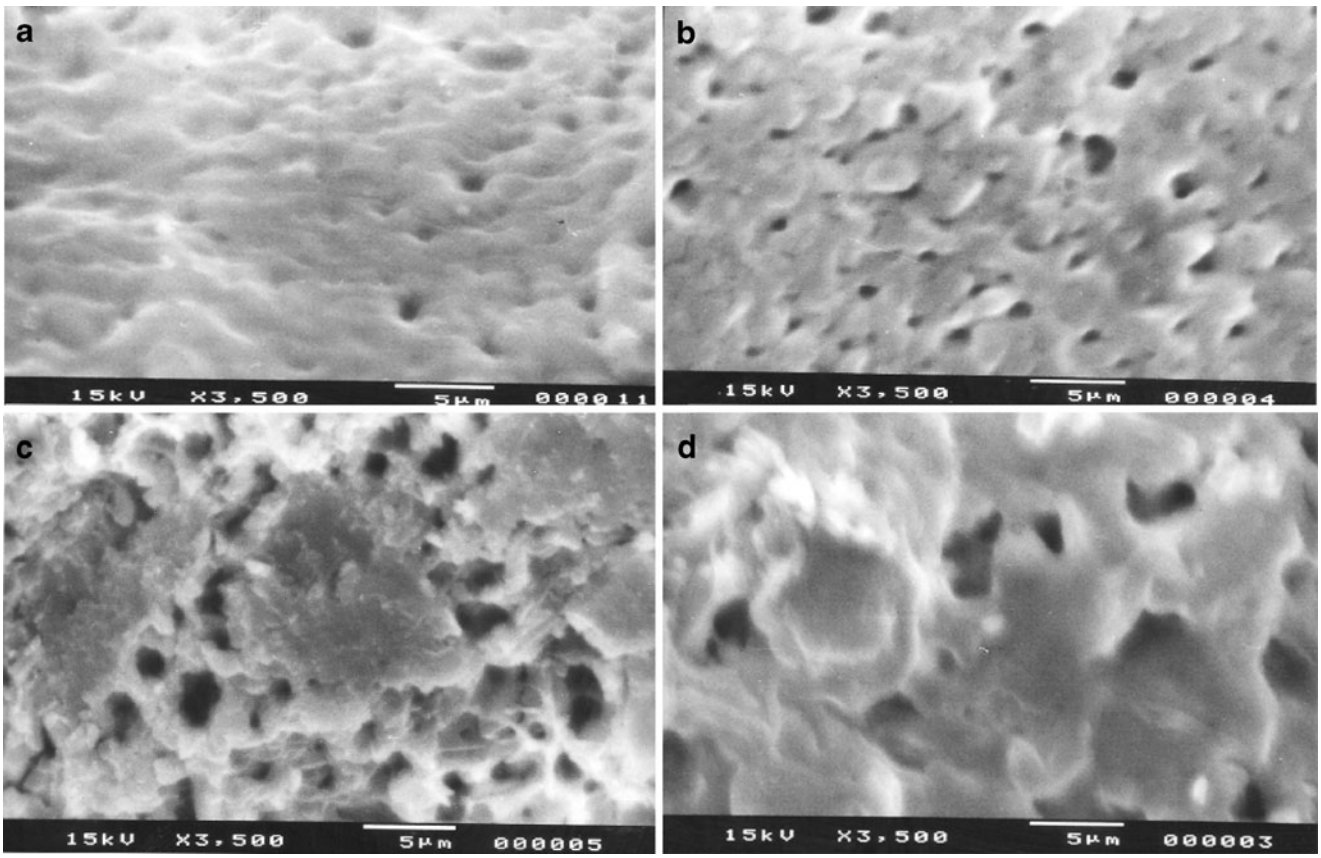

Fig. 3. SEM photomicrographs of optimized SR granules (CMG25) showing surface morphology after 0 h **a**, 2 h **b**, 5 h **c**, and 10 h **d** of dissolution study

Japan). Photomicrographs of coated samples were shown in Fig. 3.

Kinetics and Mechanism of Drug Release

Kinetics of drug release was determined by fitting data to different equations such as zero order (M=kt), first order equation ($M = \ln M_0 + kt$), Higuchi model (M=k$\sqrt{t}$) and Korsemeyer Peppas equation (M=kt^n). A value of n=0.5 indicates case I (Fickian) diffusion,0.5<n<1 is for anomolous (non-Fickian) diffusion, n=1 is for case II transport and n>1 indicates supercase II transport. M is the amount of drug (%) released after time t; M_0 is the amount of drug released at zero time; k is the release rate constant, and n is the exponent. Drug release following particular mechanism is judged by the linearity (R^2) of plot.

Stastical Analysis

The cumulative percent of metoprolol tartrate released from SR capsules (n=6) in the dissolution medium up to 12 h was tested for the statistical significance by using Student's t test. A value of P<0.05 was considered statistically significant.

Stability Studies

Stability studies were conducted on SR capsules of select batch to assess their stability with respect to their physical appearance, drug content and release characteristics after storing at 25°C under 60% relative humidity (RH) and 40°C under 75% RH for 6 months (37).

Biopharmaceutical Evaluation

The *in vivo* study was performed according to the guidelines approved by the "Committee of Purpose of Control and Supervision of Experiments on Animals (CPCSEA)", Ministry of Social Justice and Empowerment, Government of India. The *in vivo* studies were conducted in healthy male albino rabbits weighing 2.2 to 2.5 kg. Rabbits were kept for 1 week in an animal house to acclimatize them and fed a fixed standard diet. Twelve rabbits were divided into two groups of six each and were fasted for 24 h. The first group was fed with 12.5 mg, *i.e.*, exactly half of METOLAR 25 mg tablet (Cipla limited, India), and SR capsules equivalent to 12.5 mg of MT was fed to the second group of animals. Water was allowed *ad libitum* during fasting and throughout the experiment. The formulations were administered to the rabbits with an oral cannula. The rabbits swallowed the formulation without any difficulty. The capsules were put behind the tongue to prevent crushing due to biting. After administration of dose, blood samples (2 ml) were withdrawn carefully from the marginal ear vein at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 h during the study. The total blood collection from a rabbit did not exceed much more than maximum safe bleed, *i.e.*, 6.5–7.5 ml/kg body weight (18). The withdrawn blood samples were transferred to a series of graduated centrifuge tubes containing 0.4 ml of 2.5% *w*/*v*

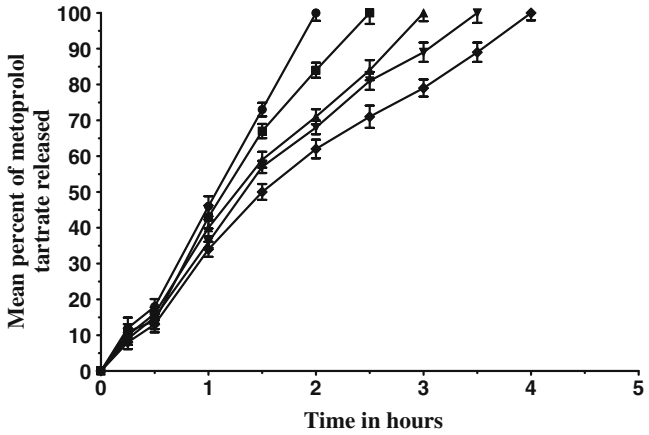

Fig. 4. Profiles show the effects of composition of matrix forming polymers (HPMC, EC) on the *in vitro* drug (MT) release. Data are represented as mean±SD (n=6). *Filled circles* MG1, *filled triangles* MG2, *filled diamonds* MG3, *filled inverted triangles* MG4, *filled squares* MG5

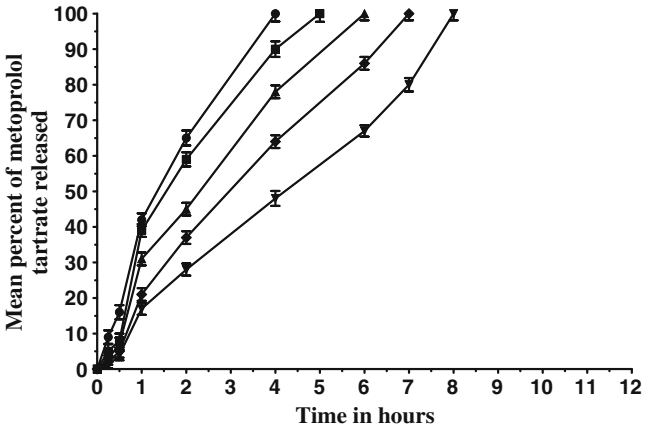

Fig. 5. Profiles show the effects of various ratio of coating materials, Eudragit® (RS, RL) at 10% increase in coating weight on the *in vitro* drug (MT) release. Data are represented as mean±SD (n=6). *Filled squares* CMG1, *filled triangles* CMG2, *filled diamonds* CMG3, *filled inverted triangles* CMG4. *Filled circles* CMG5

sodium citrate solution. The samples were centrifuged at 2,500 rpm for 5 min. The plasma was transferred into another set of sample tubes and frozen until assayed. One plasma sample (without dose of drug) was kept as blank. The sample was filtered through 0.25-μm membrane filter (Millipore). The MT concentration in blood plasma samples was analyzed using HPLC according to the following method. A total 200 μL of plasma sample was mixed with 1 mL of acetonitrile, and centrifuged. The supernatant was evaporated under nitrogen stream, and the residue was dissolved with 300 μL of the HPLC mobile phase and then it was injected into the HPLC column; a reverse-phase column (OSD-AM, 4.6× 150 mm, YMC, Japan) was used. UV detector was used to analyze. A mixture of phosphate buffer (pH 3, containing 0.5% triethylamine): methanol: acetonitrile (90:1:9) was run as mobile phase at a flow rate of 1.4 mL/min (19).

Pharmacokinetic and Statistical Analysis

The maximum plasma concentration (C_{max}) and the time to reach the maximum concentration (t_{max}) were directly obtained from the observed values. The area under the curve up to 24 h after administration (AUC) was calculated by the trapezoidal rule from the observed values. Statistical analysis was performed by the Student's t test and $P<0.05$ was used to indicate statistical significance.

RESULTS AND DISCUSSION

In the present study, uncoated granules (code number, MG1 to MG5) were prepared initially using various compositions (Table I) of matrix forming polymers (HPMC, EC) with the help of granulating agent, HPMC E5. Dicalcium phosphate was used as filler. Figure 1 depicts the distribution of granules according to mesh size as obtained by sieve analysis. It showed normal distribution curve. The mean particle size is 1,000 μm. Next, granules were tested to check dissolution period up to 100% cumulative drug release. Prolonged release of drug was in the order of MG1<MG5< MG2<MG4<MG3.Granules with code number MG3 exhibited extended drug release up to 4 h (Fig. 4). Rate of drug release decreased significantly ($P<0.05$) when 30% HPMC K100 M and 20% EC were used as matrix builder. Gel effect, erosion of matrix polymer and solubility of MT were greatest in MG1 that showed burst effect, *i.e.*, drug release >30% in 1 h. Least gel effect of polymer was observed in MG5 due to high percentage of EC that caused higher diffusion of drug through comparatively more rigid porous channel. EC swells comparatively less than HPMC. Suitable combination of HPMC with EC gave the effect of both hydrophilic and hydrophobic polymer leading to controlled and prolonged release of drug (Fig. 4, MG3). It seems the pores formed by hydrophobic polymer (rigid) were filled by hydrophilic polymer making a well balanced matrix. Enhancement of permeability (HPMC) and retardation of permeation (EC) caused controlled and prolonged release of drug. Chance of dose dumping is caused when >30% drug is released in the first 1 h of dissolution study. MDT was higher in MG3. Thus MG3 had been chosen for the next step of modification.

Table II. Characterization of Coated Granules and SR Capsules of Metoprolol Tartrate

Parameters	CMG15	CMG25	CMG35
Matrix granules			
Angle of repose (°)	27±1.4	25±0.9	28±0.6
Time of flow (g/s)	7.2±0.9	8.5±0.6	9.3±0.5
Bulk density (g/mL)	0.59	0.58	0.55
Tap density (g/mL)	0.65	0.67	0.64
Carr's Index	28±1.1	26.6±0.5	21.3±0.6
Total drug content (%)	98±3.2	99±2.1	98±3.5
Friability (%)	0.25	0.19	0.18
SR capsules			
Weight variation (%)	±2.0	±1.7	±1.9
Content uniformity (%)	99±2.0	99.4±0.8	98±1.1
MDT[a] (h)	2.8±0.2	3.7±0.1	3.9±0.3
f_2	52.95	reference	51.3

[a] MDT indicates mean dissolution time. All values represent mean± SD (n=3)

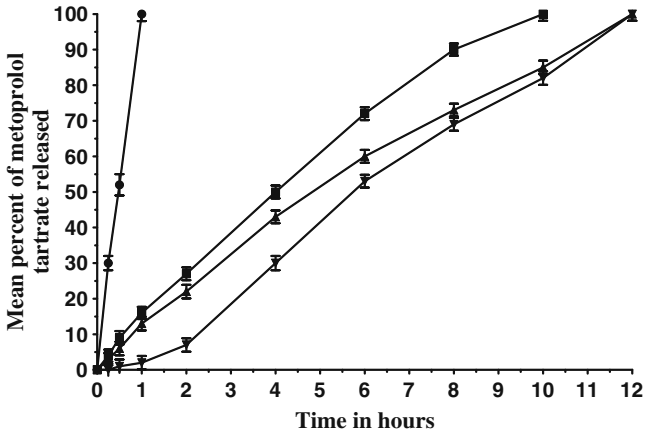

Fig. 6. Profiles show the effects of coating weight% of Eudragit® (RS, RL) at fixed ratio 97.5:2.5) on the *in vitro* drug (MT) release. Data are represented as mean±SD (n=6). *Filled circles* immediate release tablets, *filled squares* CMG15, *filled triangles* CMG25, *filled inverted triangles* CMG35

Allowing 10% increase in weight the granules (MG3) were coated with various mixtures of Eudragit® (RS, RL). TEC (20%) was used as plasticizer. Coated granules were coded as CMG 1 to CMG 5 were put into *in vitro* release study. Figure 5 showed the effect of various ratios of Eudragit® RS and RL on the rate of drug release. Rate of drug release was retarded in the order of CMG5<CMG1<CMG2<CMG3<CMG4. Maximum release period was found in the granules with code number CMG4. The profiles indicated that Eudragit® RL caused greater permeability and Eudragit® RS had a retarding effect on drug release. Minimum effective concentration was not achieved when coating dispersion contained only Eudragit® RS. The coating dispersion containing Eudragit® (RS/RL; 97.5:2.5) released the drug with initial burst release of 28±0.4% MT in 2 h and then it further sustained the drug release upto 8 h with a constant drug release. The role of intermediate subcoating of HPMC K 100 M beneath the coating layer was to ensure uniform concentration of MT in that gelatinous layer and to avoid direct interaction of coating material with initial granule. In Fig. 5, CMG 4 exhibited maximum dissolution period. So, CMG 4 was selected for the next modification to develop sustained release dosage form. Therefore, granules of code CMG 4 were further coated at various coating weight level (*i.e.*, 15%, 25%, and 35% weight gain in granules due to coating) keeping Eudragit® RS/RL ratio as 97.5:2.5. After preparing granules (code no. CMG15, CMG25, and CMG35), these were studied to check dissolution period. This step was found satisfactory. Physical characterization of these granules were performed and tabulated in Table II. Carr index, angle of repose, bulk density indicated that granules had good flow ability. The variation of weight among doses was found minimum. Drug content and variation in weight of capsules were found satisfactory. After preliminary observation of dissolution, capsule was chosen as a dosage form. Next, capsules (size 3, volume 0.3 ml) were filled with the granules containing MT equivalent to 12.5 mg that was calculated already on the basis of body weight. Finally, theoretical drug content in the chosen formulation was 16%, considering 25% weight gain by coating material. Required weight of coated granules in one dose of MT (12.5 mg) was calculated as 78.125 mg. Volume occupied by 78.125 mg granules was 0.135 ml since its bulk density was 580 mg/ml. Excess void volume was maintained to ensure easy filling and uniformity in dose. In Fig. 6 cumulative percentage of drug release from granules in capsules was plotted against time. It indicated that the variation in coating thickness due to increase in weight caused further increase in dissolution period. This type of polymer coatings can be very advantageous for certain types of drugs, *e.g.*, weak bases with pH-dependent solubility like MT. In this set of formulation plasticizer, TEC (20%) had been found to be appropriate. Higher percentage of TEC offered stickiness problem during coating and storage. Drug release was faster because of solubilization of TEC from the coat and that fact made the coating layer more porous, fragile and permeable. The conventional formulation showed complete dissolution in 1 h (0.1 N HCl medium). Capsules containing coated matrix granules of MT showed slow release of drug in comparison to conventional tablet. The successful sustained release formula must show pH independent release so that its absorption is uniform throughout gastrointestinal track.

Both Eudragit® copolymers are insoluble in water but they hydrate in GI fluids independent of pH. Since RS has a lower content of quaternary ammonium groups which are hydrophilic in nature, it displays less water permeability and hydration (or swellability) in comparison with RL (37). Thus absorption of MT starts from upper GIT and continues for 10–12 h up to lower GIT. We observed that formulation CMG 25 extended the dissolution period up to 12 h. Mean dissolution time was higher in CMG 25. The duration for 25%, 50%, and 75% release of MT from capsules containing CMG 25 were found as 2.2±0.14, 5±0.15, 5.2±0.43 and 8.5±0.68 h respectively. Data of f_2 test of similarity indicated dissolution of coated granules were similar within 10%

Table III. Drug Release Kinetic of MT Sustained Release Capsules

Code number	Zero order (M=kt)	First order (lnM=kt)	Higuchi model (M=k$\sqrt{t}$)	Korsemeyer–Peppas model (M=kt^n)
CMG15	K=10.14%/h	K=0.2857 h^{-1}	K=37.37% h$^{-0.5}$	K=14.93% h^{-n}
	R^2=0.9873	R^2=0.811	R^2=0.9885	R^2=0.9962
	n=1		n=0.5	n=0.8614
CMG25	K=8.366%/h	K=0.2554 h^{-1}	K=32.82% hr$^{-0.5}$	K=11.47% h^{-n}
	R^2=0.9897	R^2=0.7935	R^2=0.9896	R^2=0.9996
	n=1		n=0.5	n=0.8983
CMG35	K=8.749%/h	K=0.3788 h^{-1}	K=37.32% h$^{-0.5}$	K=2.62% h^{-n}
	R^2=0.9923	R^2=0.8192	R^2=0.9681	R^2=0.987
	n=1		n=0.5	n=1.55

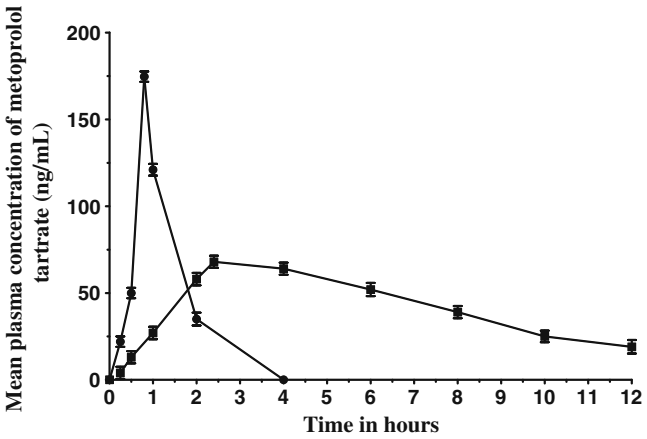

Fig. 7. Profile show mean plasma concentration of metoprolol tartrate against time, following oral administration of immediate release (IR) tablet and capsule (CMG 25) to rabbits. Data are represented as mean±SD (n=6). Filled circles immediate release tablet. *Filled Squares* capsule containing sustained release coated matrix granules CMG25

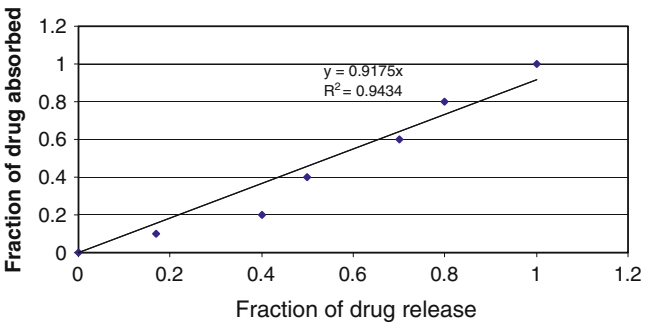

Fig. 8. Fraction of drug absorbed *versus* fraction of drug release (*in vitro–in vivo* correlation for the optimized formulation CMG25)

(Table II), when these showed wide difference against conventional tablet of MT (f_2-10). The finally optimized dosage form did not produce any significant burst effect that indicated a low possibility of dose dependent toxicity (*in vivo*). In case of multi particulate coated granules the chance of dose dumping is very low. Release kinetics was determined by fitting the release data in different established equations (zero order, first order, Higuchi model, Korsemeyer–Peppas equation). Table III shows values of regression coefficient, release constant and exponent n. First order release data was not satisfactory. The data suggested that kinetics of drug release of CMG 25 was best explained by Korsemeyer–Peppas equation (R^2=0.9996, k =11.47, n=0.8983). This indicated combined effect of diffusion and erosion mechanism on the release of drug.

Figure 3 shows photograph of granule (CMG25) by scanning electron microscope which further confirmed both diffusion and erosion mechanisms to be operative during drug release from the optimized batch of SR granules (CMG25). SEM photomicrograph of the granules taken at different time intervals after the dissolution experiment showed that pores had been formed throughout the matrix. SEM photomicrographs of granule surface at different time intervals also showed that the erosion of polymer increased with time. SEM photomicrograph of the surface of fresh granules Fig. 3a did not show any pores. Photomicrographs revealed pores with increasing diameter at 2, 5, and 10 h. These photomicrographs also revealed formation of gelling structure indicating the possibility of swelling of matrix granules Fig. 3c–d. Hence, the formation of both gelling structure and pores in granules indicate the involvement of both erosion and diffusion mechanisms to be responsible for sustaining the release of MT from the formulation. FTIR spectra are reported in Fig. 2. The characteristics bands of pure MT, HPMC K100, HPMC E5, EC, Eudragit® RL, Eudragit® RS were well maintained in both physical mixture and sustained release granules. In CMG25, some smaller bands at 2,549, 2,453, 2,067, 1,050, and 1,000 cm^{-1} were exhibited slightly lower than that of physical mixture, which may be reasonably attributed to the mechanical treatment of the sample. In physical mixture, comparatively weak band at 1,700 cm^{-1} was observed. The absorption bands due to C==O stretch at 1,592 cm^{-1} shifted slightly in comparison to band position as found in other excipients and pure drug. All are showing the bands at 3,300–3,455 cm^{-1} due to OH stretching vibration, 2,900 cm^{-1} due to CH stretching. By matching absorption bands, it was inferred that spectra of CMG25 reflected superimposition of absorption bands of pure drug and other excipients approximately which showed no incompatibility. At the end of storage period, studies were conducted on metoprolol tartrate formulation to assess their stability in terms of their physical appearance, release characteristics and physical integrity under dissolution studies. The formulations after storing at 25°C/60% RH and 40°C/75% RH for 6 months showed no change in physical appearance and very slight change in dissolution pattern. The results of the stability studies indicated that the formulations could provide a minimum shelf life of 2 years (38).

Next, the optimized coated granules filled in capsules were intended for its *in vivo* test in rabbit. Plasma concentration and pharmacokinetic parameters after oral administration of formulated SR coated matrix granules CMG25 and conventional tablet were summarized in Fig. 7 and Table IV. No sustained blood level of MT was evident after oral administration of the conventional formulation. The formulated matrix granules (CMG25) showed significantly lower C_{max} than conventional tablet (p<0.05) and required significantly more time to reach C_{max} (t_{max} 2.4±0.5 h) as compared with conventional tablets (t_{max} 0.8±0.3 h). The AUC increased from 1,259±112.6 ng.h/mL

Table IV. Mean (±SD) Pharmacokinetic Parameters of Metoprolol Tartrate in Rabbits (n=6) Orally Administered with Conventional IR Tablets (Dose 12.5 mg) or SR Capsules CMG25 (Dose 12.5 mg)

Serial no.	Pharmacokinetic parameter	Marked immediate release formulation	Sustained release capsule (CMG25)
1	Peak plasma concentration C_{max} (ng/ml)	174.6±7.2	68.4±5.6
2	Time to reach plasma concentration tmax (h)	0.8±0.3	2.4±0.5
3	Area under the curve AUC0–24 (ng.h/mL)	1,259±112.6	2,127.8±231.6

to 2,127.8±231.6 ng.h/mL (nearly 1.7 times more) for SR capsules. Values of C_{max} and t_{max} clearly indicated that the drug release was sustained to about 12 h after oral administration in rabbits (n=6). CMG25 capsules maintained constant plasma concentration up to about 10 h. The maintenance of plasma concentration for longer duration after administration of new formulation (CMG25) indicates its smooth and extended *in vivo* absorption. *In vitro–in vivo* correlation was determined by plotting a graph (Fig. 8) showing the fraction of drug absorbed *in vivo* versus the fraction of drug released *in vitro*. A high value of correlation coefficient (R^2=0.9434) suggested good correlation between *in vitro–in vivo* data. The slight variation in IVIVC may be attributed to the difference in GIT physiology, pH and transit time of human and rabbits. The pH condition *in vivo* experiment simulates pH in human system. pH values of the contents of different parts of the alimentary tract in rabbits is: stomach 1.9, small intestine 6.0, 6.8, 7.5 at various stages, cecum 6.6, colon 7.2, and that of human is stomach 1–2, duodenum 5.5, small intestine 6–7, distal ileum 7–8, colon 7–7.5 (39). Thus on the basis of the comparative study of GIT of rabbit and human it can be concluded that the pH of GIT is nearly similar. Similar pharmacokinetic and IVIVC can be predicted in humans also. The *in vivo* study of selected SR capsule formulation confirmed its ability to modify the pharmacokinetic behavior of the drug in the desired manner.

Results of the present study demonstrated that appropriate combination of both hydrophilic and hydrophobic polymers can be successfully employed for formulating sustained release capsules of MT. By coating granules with the optimized blends of Eudragit® RS/RL, further control in the drug release was achieved. Capsule is more flexible in comparison to matrix tablet; granules may be used to fill granules of different capacity according to therapeutic need. Physical problems often found in tablet like capping can be avoided here. Moreover, sustained release coated granules have a unique advantage of lessening chance of dose dumping which is a major problem when highly water-soluble drug is formulated as matrix tablets. The investigated sustained release matrix granules in capsule was capable of maintaining constant plasma level of MT up to 10–12 h with high value of "*in vivo in vitro* correlation coefficient" in rabbits. Similar pharmacokinetic results can be predicted in humans also.

CONCLUSION

A new sustained release formulation of metoprolol tartrate has been developed and evaluated for its *in vitro* and *in vivo* drug release. Coating of matrix granules was found to be an effective technique for a highly water-soluble drug—metoprolol tartrate. Bioavailability studies are in progress to assess the usefulness of this formulation in comparison with conventional immediate release metoprolol tartrate formulations on healthy human volunteers.

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