Several studies have demonstrated circadian rhythmicity for all body functions. Incidence of several cardiovascular events, like myocardial infarction, stroke and sudden cardiac death, also exhibit circadian rhythm (1, 2). These events are often observed early in the morning as the blood pressure (BP) rises significantly just before waking hours and declines to its lowest value around midnight (3). Lower concentrations of anti-hypertensive drugs during sleep are recommended because excessive reduction in blood pressure during sleep might predispose elderly hypertensive patients to ischaemic cerebrovascular disease (4). Conventional drug delivery systems seem inappropriate to address such medical needs by way of administering drugs, since there is a sharp rise in

In view of the circadian rhythm of cardiovascular diseases, a delayed-onset extended-release (DOER) formulation of metoprolol tartrate (MT) was prepared. This was achieved through dissolution-guided optimization of the proportion of Methocel K4M and Methocel K15M. Core erosion ratio was greater than 50 %, thereby showing steady release of the drug after the lag time until complete dissolution. Optimized formulation produced a lag phase of 6 h followed by complete release of 98.7 ± 2.1 % in 24 h. Water uptake study revealed that Methocel K15M has lower water uptake (30 ± 1 %) than Methocel K4M (40 ± 2 %) after 24 h. Axial swelling of polymers was higher than swelling in the radial direction. Drug-polymer interaction study precludes any interaction between drug and polymer. Such a drug delivery system may provide a viable alternative for effective management of hypertension and other related disorders. This work also proposes an approach to attain DOER for a hydrophilic drug by using a hydrophilic swellable polymer in press coat.

Keywords: metoprolol tartrate, delayed-onset extended-release (DOER), core erosion ratio

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BP during early hours. However, if these drugs are delivered as sustained release formulations (5), there is a likelihood of excessive reduction in blood pressure during night time. Therefore, there is need to design a delayed-onset extended-release (DOER) system of antihypertensive drugs so that their administration at bedtime would warrant drug release within the therapeutic level in the morning. Chronopharmaceuticals are synonymous with time-delayed-release dosage forms with the onset of release after a pre-programmed time interval (6).

Since β-blockers such as metoprolol (MT) and carvedilol specifically block the sympathetic drive, they may be particularly effective for suppressing the morning blood pressure surge (7); therefore, MT, which is therapeutically indicated in conditions such as hypertension or angina, was chosen as the model drug in the present study. It belongs to BCS class I having a half-life of 3–7 h and plasma protein binding of 12%.

The purpose of this study was to prepare a DOER system of MT by preparing compression-coated core tablets for once a day administration that would provide the desired lag time of about 6 h followed by sustained release over a period of 24 h. Apart from the *in vitro* dissolution test, the *in vitro* core erosion test, effect of rotation speed, effect of pH and water uptake test were also carried out to understand the behaviour of DOER system in different environments.

**EXPERIMENTAL**

**Materials**

Metoprolol tartrate was obtained as a gift sample from Astra Zeneca, India. Hydroxypropyl methylcelluloses HPMC (50 mPa s) and Methocel (K4M, E4M, and K15M with viscosity of the order of 4 and 15 Pa s) were obtained as gift samples from Colorcon Asia Pvt. Limited, India. Commercial tablets of metoprolol (sustained release, 50 mg, Astra Zeneca, India) were procured from a local retail pharmacy. All the excipients were of pharmacopoeial grade and other chemicals used were of analytical grade.

**Preparation of the core part of press coated tablets**

Press coated tablet formulations (TM1-TM9) were designed as per the composition given in Table I. Core was first prepared by dry mixing of weighed amounts of MT, lactose, and HPMC via screening through a 2-mm pore size sieve. The powder mixture obtained was then subjected to wet granulation using isopropyl alcohol with Methocel E4M as binder. The granules obtained by passing the wet mass through a sieve of pore size 2.38-mm were compressed after air drying at room temperature and addition of suitable amounts of talc and magnesium stearate as glidant and lubricant, respectively. The blend was compressed into tablets using a single punch tablet machine (Jyoti Scientific Industries, India) with 8-mm round and flat faced punches.

**Preparation of press coated core tablets**

Coat granulations were prepared prior to preparing complete press coated tablets, using isopropyl alcohol as granulating vehicle. The granules obtained by passing the
wet mass through a sieve of pore size 2.38-mm and air drying at room temperature were used to prepare press coated tablets by placing the core tablet in the centre of the die cavity with coat granulations carefully placed in equal proportions both above and below the core tablet. The contents were then compressed using 11-mm round, flat faced punches using a single punch tablet machine.

Drug-excipient interaction study

**Infrared spectroscopy (FTIR).** – Infrared spectra of pure MT, physical mixture of the drug and polymers, Methocel K4M, Methocel K15M and the tablet were recorded (Jasco FTIR-410, Japan). All the discs were prepared in a KBr press.

**Differential scanning calorimetry (DSC).** – Thermograms for five samples, i.e., pure MT, physical mixture of the drug and polymers, Methocel K4M, Methocel K15M and the tablet were recorded using Shimadzu DSC-60 (Japan). The samples were hermetically sealed in aluminium pans and heated at a constant rate of 10 °C min⁻¹ over the temperature range of 40–200 °C.
Characterization of coated core tablets

Drug content uniformity. – All the coated tablets were subjected to the test for drug content uniformity as mentioned in Indian Pharmacopoeia (8).

Compressibility test. – To evaluate the compressibility and compactibility, a blend of coat polymer granules (Methocel K4M and Methocel K15M) were compressed as per earlier mentioned conditions and the tensile strength of the six tablets was calculated (9).

Water uptake. – Water uptake of the compression coated tablets comprising of different grades of HPMC was determined in triplicates.

Swelling. – Swelling behaviour of tablets was determined in 0.1 mol L\(^{-1}\) hydrochloric acid (pH 1.2) and phosphate buffer (pH 6.8) as dissolution media. Tablets were immersed in the dissolution medium and the swollen part of each tablet was measured. Percent swelling was then calculated (10).

In vitro core erosion. – In vitro core erosion test was performed on six coated tablets to find the extent of water penetration into the core part of the tablet (11).

In vitro drug dissolution. – The USP type 2 (paddle type) apparatus (12) (Labindia DS 8000, India) was used to determine the amount of MT released from compression coated core tablets. The paddle rotation speed and temperature were 50 rpm and 37 ± 0.5 °C, respectively. The dissolution medium was 750 mL of 0.1 mol L\(^{-1}\) HCl (pH 1.2) for initial 2 h, subsequent to which 250 mL of 0.2 mol L\(^{-1}\) trisodium phosphate dodecahydrate was added to make the phosphate buffer pH 6.8 up to 24 h. Samples were withdrawn at specific time intervals and analyzed at 272 nm using a UV spectrophotometer (Shimadzu UV-1601, Japan).

Effect of pH and rotation speed on the release profile. – Dissolution test was carried out for TM7 in three different dissolution media, 0.1 mol L\(^{-1}\) HCl (pH 1.2) and phosphate buffers, pH 6.8 and pH 7.4, for 0–2, 2–8 and 8–24 h, respectively. Dissolution tests were also performed at varying rotation speeds of 50, 75 and 100 rpm to evaluate effects of the rotation speed on the lag period as well as the drug release behavior.

Effect of different viscosity grades of HPMC. – Two grades of HPMC, Methocel K4M and Methocel K15M, were selected and tablets were prepared by varying the amount of polymer in the press coat while keeping the inner core part the same with respect both to mass and composition. The effect of different viscosity grades of HPMC was recorded with respect to changes in the dissolution profile.

Kinetic assessment of drug dissolution. – The fitness of zero-order, first-order and Higuchi (13) kinetic models was assessed by the coefficient of determination of the curve between the time and amount of drug released. The Korsmeyer-Peppas model was also applied to find out the mechanism of drug release (14). Drug release, from simple swellable systems may be described by the well known Korsmeyer-Peppas kinetic equation:

\[
\frac{M_t}{M_{\infty}} = kt^n
\]
where $M_t$ and $M_{\infty}$ are the amounts of drug released at time $t$ and the overall amount released, respectively, whereas $k$ is the release rate constant and $n$ is the release exponent indicative of the release mechanism. When $n$ is 0.45, the diffusion phenomenon dominates and when $n$ value reaches 0.89 and above, it may be characterized by the case II relaxation release transport and super case II transport. Values of $n$ between 0.45 and 0.89 can be regarded as indicators of anomalous transport.

RESULTS AND DISCUSSION

Drug-excipient interaction study

The IR spectra of MT showed the predominant peak (cm$^{-1}$) at 3346.85 for N-H stretching of amino group, 2934.16 for C-H stretching of methyl group, 1512.88 for aromatic ring, 1245.79 for C-O stretching in aromatic ether, 1111.76 for C-O stretching in aliphatic ether, 1298.82 for C-O stretching in secondary alcohol and 821.53 for 1,4-disubstituted benzene. IR spectra of the physical mixture, Methocel K4M, Methocel K15M and the tablet retained all the characteristic peaks of MT and those of Methocel K4M and Methocel K15M with the absence of any additional peaks (Fig. 1). These observations preclude possible interactions between the drug and polymers.

![Fig. 1. FTIR spectra of: a) pure MT, b) physical mixture of drug and polymers, c) Methocel K4M, d) Methocel K15M, and e) tablet.](image-url)
DSC thermogram of metoprolol tartrate showed a sharp endothermic peak at 123.13 °C corresponding to its melting point with 567.17 mJ g\(^{-1}\) heat of fusion. DSC thermogram of the physical mixture showed MT endotherm at 123.30 °C with characteristic peaks for the polymers. Tablet formulation showed a shift in peak (123.12 to 116.08 °C). This may be attributed to partial loss of the crystalline character of the drug upon processing (Fig. 2). The absence of any significant change in thermal behavior endorsed the suitability of the drug with selected polymers.

**Compressibility and compactibility.** – Tensile strength of the coat polymer indicates its compressibility and compactibility for press coat formation. The tensile strength of HPMC was found to be 13.2 ± 0.8 kg cm\(^{-2}\), thereby showing its practical applicability and good compressibility, which is in concordance with previous results (6).

**Water uptake and swelling.** – Methocel K15M has lower water uptake (30 ± 1 %) than Methocel K4M (40 ± 2 %) after 24 h though the initial water uptake was the same (about 10 %) in both cases. These results are in consonance with previous studies (15).

Axial and radial swelling of the polymeric coat on compression coated tablets showed maximum radial swelling of 300 ± 5 and 362 ± 6 % in 0.1 mol L\(^{-1}\) HCl (pH 1.2) and phosphate buffer (pH 6.8), respectively, while axial swelling was 525 ± 8 and 563 ± 9 % in the same media after 24 h. Axial swelling was found to be higher than swelling in the radial direction, probably due to the release of stress developed during powder compaction along axial direction. These findings were similar to those reported by Dahlberg et al. (16).

In vitro core erosion. – The core erosion ratios of all formulations (TM1 to TM9) were 53, 57, 51, 57, 58, 60, 56, 53 and 52 %, respectively, all found to be greater than 50 %, thereby showing a steady release of drug after the lag time until complete dissolution. Therefore, tablet probably absorbs water during its transit through the lumen, thereby allowing drug release in the colon in spite of lower amount of water available there for solubilizing the drug. These results were found to be in consonance with a previous study by Sawada et al. (11), which also demonstrated that water soluble excipients like lactose monohydrate dissolve to enhance water penetration into the core part.
In vitro drug dissolution. – The drug content uniformity was found to be in the range of 99–102 % of MT in all formulations. All the formulations (TM1-TM9) subjected to the in vitro dissolution study were swollen. When Methocel K4M alone was used as a press coat polymer (TM1, TM2 and TM3), it was unable to provide the desirable lag period and sustainability with respect to release (Fig. 3). However, when only Methocel K15M was used in the press coat (TM4, TM5 and TM6), it was unable to release the drug at all, probably because of a thicker gel like network that was formed due to swelling (Fig. 3). However, blending of these two polymers (28.5 % of Methocel K4M and 14.2 % of Methocel K15M) in the press coat (TM7) produced a lag phase of 6 h, followed by complete release of 98.7 ± 2.1 % in 24 h (Fig. 3). However, tablets prepared with amounts of Methocel K4M lower than 28.5 % in the press coat (TM9) showed a reduction in the lag phase. On the other hand, lowering the amount of Methocel K15M below 14.2 % in the press coat (TM8) compromised the sustainability and lag time for release probably because the lag time got prolonged on increasing the press coat polymer viscosity, which in turn delayed the process of dissolution and/or erosion. However, lowering of the press coat viscosity probably formed a thinner hydrogel layer, thereby facilitating diffusion of the highly soluble drug like MT through the gel layer in a sustained manner for a prolonged period of time. On this basis, tablet formulation TM7 was considered to be optimized, since diffusion of the drug through the formed gel layer and erosion of the gel layer resulted in the drug release process.

The pH of GIT varies from 1.2 to 8.0 during the tablet transit from the stomach to the colon. Therefore it was imperative to understand the effect of dissolution medium pH on the release pattern of the drug. In the acidic pH of the stomach (pH 1.2), there was a lag in drug release, which continued even when pH of the medium was raised to pH 6.8 up to 6 h (% of drug release 9.3 ± 1.1). About 99.6 ± 1.7 % of the drug was released after 24 h upon subsequent change of pH to 7.4, which was explicit in a sustained release fashion (Fig. 4).

To further understand how peristaltic motion of GIT may affect the pattern of release from the formulation, an in vitro test was performed at different speeds of the rotating paddle. There was a reduction in the lag period with increasing rotating speed be-

![Fig. 3. Dissolution profile of compression-coated core tablets and the commercial tablet. Mean ± SEM, n = 3.](image)
cause of the initial fast diffusion of dissolved drug and easy erosion of the outer layer of the tablet, followed by full gelling of the polymer for complete drug release. However, the overall drug release remained the same with increasing paddle speed.

When a once-a-day tablet formulation of metoprolol available in the market was subjected to in vitro release under the experimental conditions, the drug released in a sustained manner without showing any delayed onset/lag period. In contrast, the administration of MT as a DOER system (TM7) at bedtime can be expected to release the drug after an approximately 6 h lag period at about 4–5 am in the morning and continue to provide MT in the therapeutic range for the rest of the day.

**Kinetic assessment of drug dissolution.** – The coefficient of determination for zero-order ($R^2$) was found to be 0.9786; the values were for the first-order, Higuchi and Korsmeyer-Peppas models, 0.7824, 0.9674, and 0.9461, respectively. They are indicating better correlation with zero-order release, thereby reflecting constant drug release from formulation TM7 up to 24 h. The value of exponent $n$ for Korsmeyer-Peppas model cannot be correlated clearly in this case as $n$ value of 0.1229 fails to interpret the exact mechanism of drug release. These results were found to be in concurrence with literature, which states the absence of any correlation between the $n$ value and diffusion guided release for drug delivery systems based on HPMC (17).

**CONCLUSIONS**

Press-coated core tablets of metoprolol tartrate prepared by conventional pharmaceutical processes using different viscosity grades of HPMC showed excellent time-delayed release of the drug. An optimal lag period in both acidic and basic environments, due to the initial swelling of polymers, followed by complete drug release in a controlled manner could be obtained owing mainly to diffusion through the swollen polymer and in part to the slow erosion of the core. Thus, the delayed-onset extended-release system
of metoprolol may be beneficial for alleviating the symptoms of hypertension and related cardiovascular diseases. The results are not only encouraging but they also promise effective management of such diseases through this novel approach after suitable trials in animal models and human beings.

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Vodeći računa o cirkadijanom ritmu kardiovaskularnih bolesti, pripravljene su formulacije metoprolol tartarata (MT) s odgođenim i produljenim oslobađanjem (DOER). Optimizacija je provedena praćenjem oslobađanja pri čemu je mijenjan omjer hidroksi-propilmetil celuloze Methocela K4M i Methocela K15M. Erozija obložnog sloja bila je veća od 50 %, što pokazuje ujednačeno oslobađanje ljekovite tvari nakon početne odgođene faze do potpunog oslobađanja. U optimiziranoj formulaciji oslobađanje je započelo nakon 6 h, nakon čega slijedi potpuno oslobađanje (98.7 ± 2.1 %) tijekom 24 h. Nakon 24 h ulazak vode u Methocel K15M bio je manji (30 ± 1 %) nego u Methocel K4M (40 ± 2 %). Aksijalno bubrenje polimera bilo je značajnije nego radijalno bubrenje. Nije zapažena interakcija lijeka i polimera. Opisani sustav za isporuku lijekova može biti korisna alternativa za učinkovitu terapiju hipertenzije i srodnih poremećaja. DOER s ovojnicom od hidrofilnih polimera koji bubre upotrebijev je i za druge hidrofilne lijekove.

**Ključne riječi:** metoprolol tartarat, odgođeno i produljeno oslobađanje (DOER), erozija ovojnice

**S A Z E T A K**

Priprava i vrednovanje tableta metoprolol tartarata s odgođenim i produljenim oslobađanjem koristeći hidrofilne polimere koji bubre

SUBHASH CHAND DADARWAL, SARIKA MADAN i SHYAM SUNDER AGRAWAL

Vodeći računa o cirkadijanom ritmu kardiovaskularnih bolesti, pripravljene su formulacije metoprolol tartarata (MT) s odgođenim i produljenim oslobađanjem (DOER). Optimizacija je provedena praćenjem oslobađanja pri čemu je mijenjan omjer hidroksi-propilmetil celuloze Methocela K4M i Methocela K15M. Erozija obložnog sloja bila je veća od 50 %, što pokazuje ujednačeno oslobađanje ljekovite tvari nakon početne odgođene faze do potpunog oslobađanja. U optimiziranoj formulaciji oslobađanje je započelo nakon 6 h, nakon čega slijedi potpuno oslobađanje (98.7 ± 2.1 %) tijekom 24 h. Nakon 24 h ulazak vode u Methocel K15M bio je manji (30 ± 1 %) nego u Methocel K4M (40 ± 2 %). Aksijalno bubrenje polimera bilo je značajnije nego radijalno bubrenje. Nije zapažena interakcija lijeka i polimera. Opisani sustav za isporuku lijekova može biti korisna alternativa za učinkovitu terapiju hipertenzije i srodnih poremećaja. DOER s ovojnicom od hidrofilnih polimera koji bubre upotrebijev je i za druge hidrofilne lijekove.

**Ključne riječi:** metoprolol tartarat, odgođeno i produljeno oslobađanje (DOER), erozija ovojnice

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