IJPSR (2012), Vol. 3, Issue 06 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 19 February, 2012; received in revised form 20 March, 2012; accepted 23 May, 2012

FORMULATION AND EVALUATION OF CONTROLLED POROSITY OSMOTIC DRUG DELIVERY SYSTEM OF METOPROLOL SUCCINATE

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Keywords:
Metoprolol succinate,
Controlled porosity osmotic tablet,
Zero order,
Release retardant

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ABSTRACT

Controlled porosity osmotic tablet of metoprolol succinate prepared and evaluated in this study. Metoprolol succinate is very high soluble drug, so complete drug release obtained very fast. It is difficult to formulate osmotic tablet of Metoprolol succinate which gives drug release up to 24 hr at zero order. To get desired dissolution profile various formulation parameters like osmogen concentration, level of weight gain and level of pore former concentration were studied. Hypromellose was added as release retardant to reduce its dissolution rate and get drug release up to 24 hr at zero order. As concentration of release retardant increases, dissolution rate decreases. Final optimized formulation with hypromellose was studied for effect of pH of dissolution media, agitation intensity and osmotic pressure of dissolution media. There is no effect of above variables on dissolution confirms that prepared metoprolol succinate tablet gives drug release with osmotic mechanism. Final optimized formulation complies with the USP criteria for the dissolution of metoprolol succinate extended release tablet.

INTRODUCTION: Conventional drug delivery systems have little control over the drug release and so effective concentration at the target site can not be achieved. This kind of dosing pattern may result in unpredictable plasma concentrations.

But oral controlled drug delivery dosage forms provide desired drug release pattern for longer period of time and so the rate and extent of drug absorption from oral controlled drug delivery formulations can be predicated.

However, drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract [1]**.** But drug release from osmotic drug delivery system is not affected by physiological factors.

Controlled porosity osmotic tablet contains core tablet coated with semipermeable membrane which allows active agent to come outside through pores formed in situ. The controlled-porosity osmotic pump has been developed via incorporation of leachable water-soluble small molecules, such as sodium chloride, potassium chloride, urea, and sucrose etc. into major component of film coating material [2-4].

These pore-forming agents are leached when contacted with an aqueous medium, and the pores are created on the surface to allow drug release. Plasticizer can also be used as pore forming agent. Plasticizer has been used to modify not only the mechanical properties but also the thermal property, water absorption behavior, and adhesive property of polymeric films [5].

All of these properties affect the strength of coating films and the integrity of final products, which further affect drug release performance. Many compounds can be acted as a function of plasticizer including poly(ethylene glycol) [6], propylene glycol [7], sorbitol [8], urea [9], oil [10], citrate [11], adipate [12], and phthalate [13], etc.

The release of drug is dominated by thickness of coating films, the level of water-soluble components, the solubility of drug, and the osmotic pressure difference. The advantage of blending of pore-forming agent avoids using high technical laser beam to drill an orifice for drug release, in additional, it is easily fabricated via traditional film coating technique [14].

Candidate drugs for osmotic drug delivery have water solubilities of 50-300 mg/ml. High soluble drugs would show a high release rate that would be zero order release for very small percentage of initial drug load. Thus intrinsic water solubility of many drugs might preclude them from incorporation into osmotic drug delivery system. By modulating the solubility of drug within core, effective drug release can be obtained for even poor candidate drugs for osmotic drug delivery. This approach can be used for conversion of first order profile into zero order profile without altering the chemical structure [15].

Metoprolol succinate is a beta blocker widely used for the treatment of hypertension. Its short biological half-life and thus frequent administration (usually three to four times a day) makes it a suitable candidate for controlled release and/or sustained release (CR/SR) preparations. Metoprolol succinate is a freely water-soluble drug and the release rate of metoprolol succinate from oral osmotic pumps is usually high. Due to high solubility of metoprolol succinate, it would give a high release rate that would be zero order release for very small percentage of initial drug load.

In the present study, solubility of metoprolol succinate was retarded with addition of hypromellose in the system. Hypromellose reduce its solubility and dissolution by swelling matrix mechanism. Prepared osmotic tablet of metoprolol succinate gives drug release for up to 24 hr. by combine matrix and osmotic mechanism.

MATERIALS AND METHODS:

Materials: Metoprolol succinate was obtained from Torrent Pharmaceuticals Ltd, Ahmedabad as a gift sample. It is a white to off white crystalline powder with melting point of 120^{o}C. Sodium chloride (s. d. fine chem., India) was used as osmogent and lactose monohydrate (DMV, India) was used as diluent. Hypromellose (Dow chemicals) was used as release retardant. Povidone (ISP Corporation, India) was used as binder and magnesium stearate (Ferro) was used as lubricant. Cellulose acetate with 39.8% acetyl content (Eastman Chem., USA) was used as semipermeable membrane. PVP (ISP) and PEG 400 (s. d. fine chem.) was used as pore former and plasticizer respectively. The other chemicals used were of analytical grade.

Methods:

Preparation of Core Tablet: Metoprolol succinate, lactose monohydrate, Hypromellose and sodium chloride were sifted through 30# sieve and mixed for 5 min. Dry mix of metoprolol succinate and other excipients was granulated with purified water. Granulated mass was dried at 65ºC in tray dryer till LOD reaches between 1-2%. Dried granules were sized through 0.8 mm sieve and lubricated with magnesium stearate for 5 min. Tablets were compressed with 7.93 mm round concave punches using 16-station rotary tablet press (Cadmach Machinery, Ahmedabad). Tablets were compressed at an average weight of 200 mg and hardness of tablets was kept 5.0-6.0 Kg/cm^2.

Coating of Tablets: Core tablets were coated with semipermeable membrane of 5% solution of cellulose acetate in methelyne chloride/methanol (80:20) mixture. PEG 400 was used as a plasticizer and PVP was used as pore former in semipermeable coating. Coating composition is given table No: 1. Coating was carried out in perforated coating pan (Gans coater, Ganson Limited, Mumbai, India). Core tablets were sprayed with coating solution at following parameters: Pan rpm: 2-8, Inlet temperature: 40-45^{o}C, Atomization pressure: 1.5 Kg/cm^2, Pump rpm: 2-6. Coating was continued till desired weight gain on core tablets was achieved. Coated tablets were dried at 50^{o}C for 24 hr to remove residual solvents.

TABLE 1: COMPOSITION OF EXPERIMENTAL FORMULATION

Ingredients	M1	M2	M3	M4	M5	M6	M7	M8	M9
	Core Tablet Composition (mg/tab)								
Metoprolol succinate	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5	47.5
Lactose monohydrate	75.5	65.5	80.5	60.5	70.5	70.5	70.5	70.5	70.5
Sodium chloride	25	35	30	30	30	30	30	30	30
Hypromellose (K4M)	50	50	40	60	50	50	50	50	50
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total (Core Tablet)	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**	**200**
	Coating Composition (mg/tab)								
Cellulose acetate	15.82	15.82	15.82	15.82	16.42	15.27	12.92	18.72	15.82
PVP	6.02	6.02	6.02	6.02	5.42	6.57	4.92	7.12	6.02
PEG 400	2.16	2.16	2.16	2.16	2.16	2.16	2.16	2.16	2.16
Total (Coated Tablet)	**224**	**224**	**224**	**224**	**224**	**224**	**220**	**228**	**224**

Evaluation of Developed Formulations: Dissolution of coated formulation (n=6) was carried out in pH 6.8 phosphate buffer, 500 ml by using USP dissolution apparatus-II (Electrolab, India) at 50 rpm. Temperature of dissolution media was kept at 37±0.5^{o}C. The samples were withdrawn (10ml) at different time intervals and replaced with 10 ml of fresh media. Samples were withdrawn at 1, 2, 4, 8, 12, 16, 20 and 24 hr for measurement of drug release. Samples were analyzed using UV spectrometer at 280nm.

A. **Effect of pH:** To study the effect of pH on drug release, dissolution study was carried in dissolution media having different pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer. Dissolution apparatus (USP-II) was used for drug release study at 100 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 280nm using UV spectrometer.

B. **Effect of Agitation Intensity:** To study the effect of agitation intensity on drug release, optimized formulation was subjected to dissolution at various rotation speeds. Dissolution was carried out in USP-II (Paddle) at 50, 100 and 150 rpm. The samples (10ml) were withdrawn at predetermined intervals and analyzed at 280nm using UV spectrometer.

C. **Effect of Osmotic Pressure:** To confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride was added in dissolution media. Release studies were carried out in 500 ml of pH 6.8 phosphate buffer using USP-II dissolution apparatus at 50 rpm. To increase the osmotic pressure of dissolution media, sodium chloride (2.5 & 5%) was added. Effect of osmotic pressure created by dissolution media was evaluated by drug release at different time intervals.

RESULTS AND DISCUSSIONS:

1. **Formulation Development:** Osmotic tablet consist of core tablet coated with a rate controlling membrane. Tablet core consists of drug along with release retardant, osmogen, and other conventional excipients to form the core compartment. The core tablet is surrounded by a membrane consisting of a semipermeable polymer and pore former cum plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane is permeable to aqueous fluids but substantially impermeable to the components of the core.

   During operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. The dissolved drug is released through the pores created after leaching of water soluble additive in the membrane. Cellulose acetate was used as water-insoluble polymer. PVP was used as water-soluble plasticizer and pore former. Metoprolol succinate is having high solubility that precludes it from incorporation in osmotic dosage forms. Due to its high solubility, it gives zero order drug release for very small period of time.

Drug release from osmotic tablet was also very fast. So it is required to decrease the dissolution of metoprolol succinate. Release retardant polymer was added in core to reduce its dissolution by swelling. After coming into contact with the aqueous fluids, hypromellose swells and reduce the wettability of metoprolol succinate and extend the dissolution up to 24 hr.

a) **Effect of Osmogen Concentration:** To check the effect of osmogen concentration on drug release, formulations were prepared with different concentration of sodium chloride and all other parameters of tablet kept constant. Quantity of sodium chloride was varied in range of 25 mg/tab to 35 mg/tab. By reducing the concentration of sodium chloride, dissolution rate of metoprolol decreases (**Fig. 1**). Therefore it is concluded that drug release from prepared tablet was done through osmotic pressure. Concentration of sodium chloride is required to be optimized to get the required release profile.

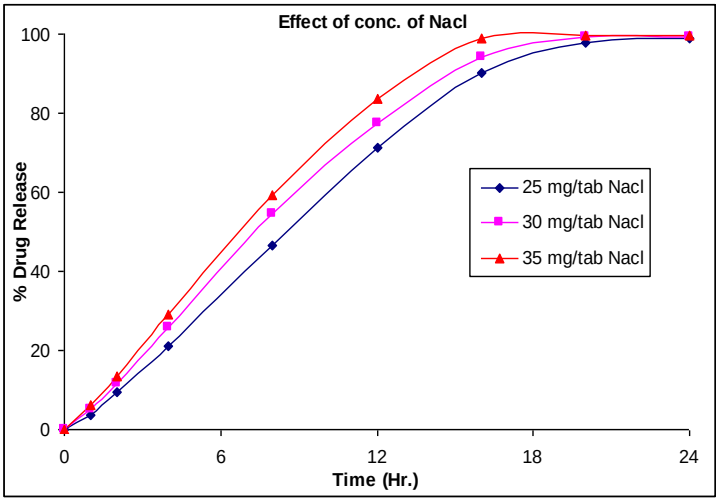

FIG. 1: EFFECT OF OSMOGEN CONCENTRATION

b) **Effect of Release Retardant Concentration:** Highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core and thus extend this technology for delivery of drugs, which otherwise may be poor candidates for osmotic delivery [16-19].

Metoprolol succinate is highly soluble in water. Hypromellose was added in the formulation to reduce the dissolution rate of metoprolol. Different concentration of hypromellose was tried and it was very clearly indicate that drug release rate is dependent on concentration of hypromellose. As the concentration of hypromellose increases, the dissolution rate decreases. Prolonged time drug release can be obtained with formulation containing hypromellose (**Fig. 2**).

Different concentration of hypromellose was tried for desired dissolution profile. At 40 mg/tab hypromellose concentration, dissolution at 8 hr was faster than USP criteria for the dissolution of metoprolol succinate extended release tablet. So concentration of hypromellose was further increased to get the drug release up to 24 hr at zero order release rate. With 50 mg/tab hypromellose concentration, formulation gives drug release as per USP criteria for the dissolution of metoprolol succinate extended release tablet. But with 60 mg/tab hypromellose concentration, dissolution is much slower and dissolution does not comply with the USP criteria for the dissolution of metoprolol succinate extended release tablet.

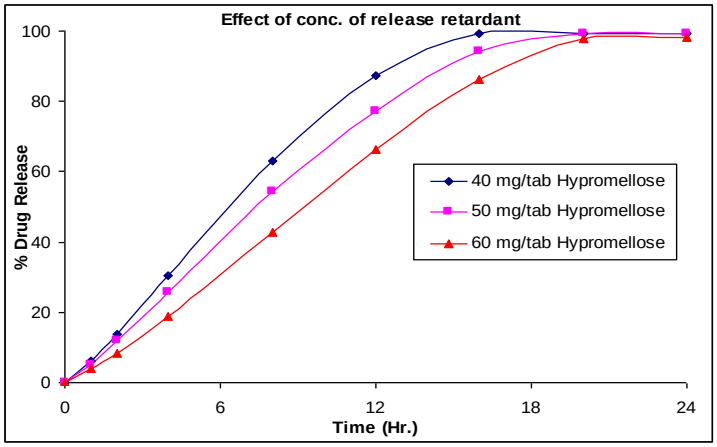

FIG. 2: EFFECT OF RELEASE RETARDANT CONCENTRATION

c) **Effect of Pore Former Concentration:** In controlled porosity osmotic pump, core tablet was coated with semipermeable membrane having pore former. After coming in contact with aqueous media, pore former dissolves and leaches out from the coating which creates microporous membrane around tablet. Drug

release was done through these pores. So concentration of pore former in controlled porosity osmotic pump is important parameter in controlling the release rate. Tablets were coated with different ratios of cellulose acetate/PVP and subject to dissolution after sufficient weight gain achieved. Different concentration of PVP (% of cellulose acetate) like 33%, 38% and 43% were tried (**Fig. 3**). By decreasing the concentration of pore former, drug release was decreased linearly. There is significant effect of pore former concentration on drug release observed.

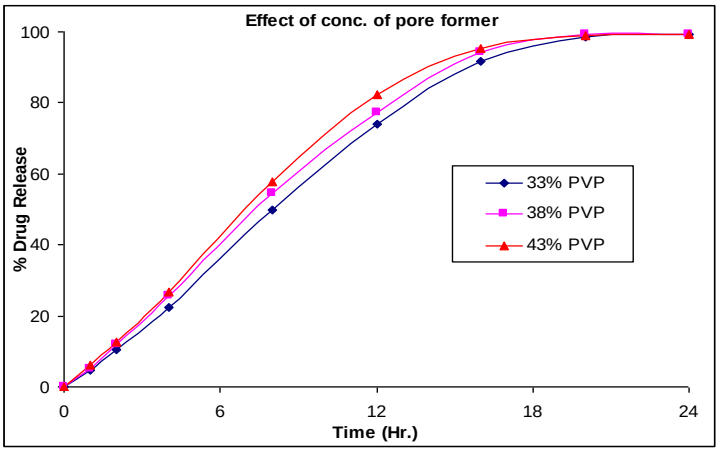

FIG. 3: EFFECT OF PORE FORMER CONCENTRATION

d) **Effect of Coating Weight Gain:** Core tablets were coated with semipermeable membrane of cellulose acetate with different weight gain to identify the effect of coating gain on drug release. Core tablets were coated with 10%, 12% and 14% weight gain and subject to dissolution (**Fig. 4**). There is difference in dissolution observed with different weight gain tablets. With increase in coating weight gain, drug release rate decreased.

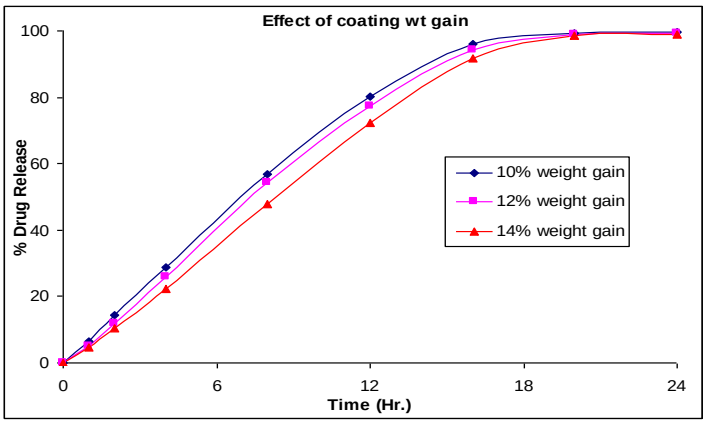

FIG. 4: EFFECT OF COATING WEIGHT GAIN

2. **Performance Evaluation of Optimized Formulation:** Final formulation was evaluated for various dissolution studies to check effect of pH, agitation intensity and osmotic pressure.

In order to study the effect of pH on drug release, dissolution was carried out in media of different pH. Dissolution was carried in 900 ml of 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer in USP-II apparatus (Paddle) at 50 rpm. Drug release for optimized formulation was found similar in all three media. Optimized formulation shows pH independent drug release as per fig.5. The *f*1 and *f*2 values were found to be 1.7 and 90.4 (between 0.1 N HCl and pH 4.5 acetate buffer), 1.0 and 96.3 (between 0.1 N HCl and pH 6.8 phosphate buffer), and 0.8 and 96.7 (between pH 4.5 acetate buffer and pH 6.8 phosphate buffer), respectively.

To study the effect of agitational intensity of the release media, release studies of the optimized formulation was carried out in USP dissolution apparatus type II at varying rotational speed (50, 100, and 150 rpm) in 500 ml of pH 6.8 phosphate buffer. It is clearly evident from **fig. 6,** that the release of metoprolol is independent of the agitation intensity.

Drug release in all three conditions found similar. The *f*1 and *f*2 values were found to be 3.3 and 79.6 (between 50 and 100 rpm), 7.1 and 64.8 (between 50 and 150 rpm), and 3.6 and 77.1 (between 100 and 150 rpm), respectively.

To study the effect of osmotic pressure, release studies of the optimized formulation were conducted in media of different osmotic pressure. The results of release studies in media of different concentration of sodium chloride (2.5% and 5%) showed that the drug release is highly dependent on the osmotic pressure of the release media. Metoprolol release from the formulations decreased as the osmotic pressure of the media increased (**Fig. 7**). The *f*1 and *f*2 values were found to be 15.5 and 49.4 (between without Nacl and 2.5% Nacl), 31.8 and 33.7 (between without Nacl and 5% Nacl), and 19.3 and 47.9 (between 2.5% Nacl and 5% Nacl), respectively.

It was concluded that osmotic pumping is the major mechanism governing drug release from developed formulations [20-23].

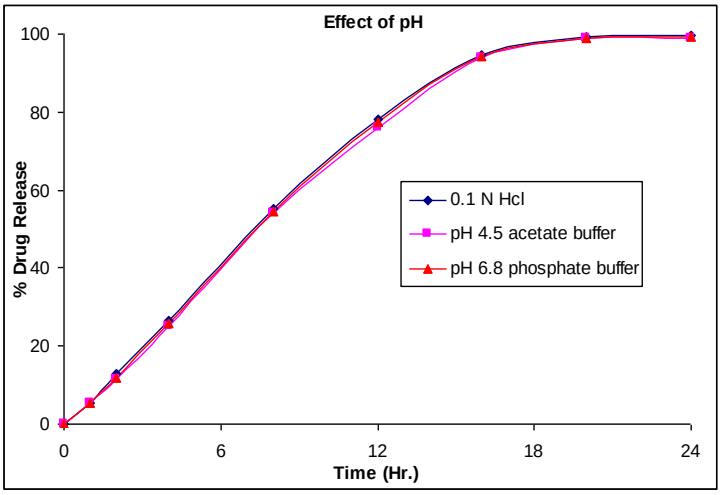

FIG. 5: EFFECT OF pH

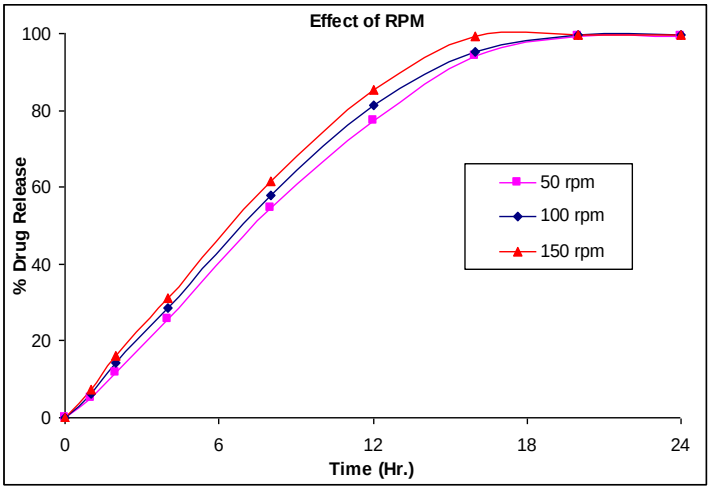

FIG. 6: EFFECT OF RPM

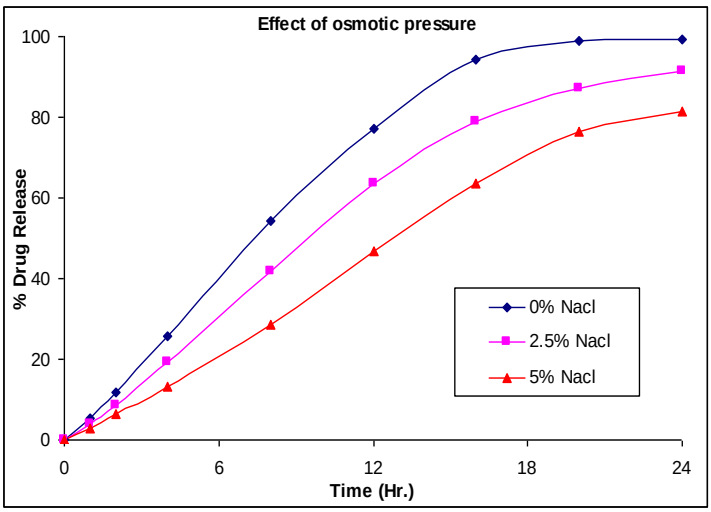

FIG. 7: EFFECT OF OSMOTIC PRESSURE

CONCLUSION: Extended release formulations of metoprolol succinate were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Solubility of active pharmaceutical ingredient is the key factor in development of osmotic dosage form. It is difficult to formulate the osmotic tablet of drugs having very high solubility. Solubility of drug is required to reduce to get desired profile. Level of release retardant (hypromellose) affected the release from the developed formulations. As the concentration of hypromellose increased, release rate was decreased.

Effect of sodium chloride concentration, pore former concentration and weight gain of tablets on dissolution was also checked. Concentration of sodium chloride, pore former increases, dissolution rate of metoprolol succinate also increases. But increase in the tablet weight gain is inversely proportional to the dissolution release rate. The release from the optimized formulations was independent of pH and agitation intensity of the release media, assuring the release from the tablet was independent of pH and hydrodynamic conditions of the body.

Metoprolol succinate release from the developed formulation was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release. Final optimized formulation complies with the USP criteria for the dissolution of metoprolol succinate extended release tablet.

ACKNOWLEDGEMENT: The authors greatly acknowledge Torrent Pharmaceuticals Ltd., Ahmedabad, Gujarat, India, for the gift samples of metoprolol succinate. The authors also acknowledge all for providing gift samples of excipients.

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