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Formulation and *In Vitro* Evaluation of Metoprolol Succinate Matrix Tablets

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ABSTRACT

Metoprolol succinate is a selective β1 receptor blocking agent used in treatment of hypertension and angina pectoris. In the present investigation an attempt was made to reduce the frequency of dose administration to prevent nocturnal heart attack and to improve the patient compliance by developing extended release matrix tablets of Metoprolol succinate. The extended release formulations from F-1 to F-3 were formulated using the release retarding agents HPMC E 5, HPMC K 100M and Xanthan gum respectively. The formulations from F-4 to F-9 were formulated by using varying concentrations of Xanthan gum and HPMC K 100M. The formulations from F-10 to F-18 were formulated by using Xanthan gum alone as release retarding agent and varying the diluents and diluents concentration. All the formulations were developed by wet granulation method employing PVP K 30 in purified water (10% w/v) as binding agent. All the formulations were evaluated for both official as well as unofficial tests. All the formulations were investigated for *In vitro* drug release studies in pH 6.8 phosphate buffer of volume 500mL in USP paddle apparatus for 20 hrs. The results of dissolution studies indicated that the formulation F-17 containing nearly 48 % w/w of Xanthan gum and 28 % w/w of pregelatinised starch had shown that the drug release pattern as per USP specifications. The release kinetics of the optimized formula F-17 followed Higuchi model and non-fickian transport.

1. INTRODUCTION

Oral drug delivery is the most important method of administering drugs for systemic effects. Nevertheless, it is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. Oral medication is generally considered as one of the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration and cost-effective manufacturing process. The topical route of administration has been employed to deliver drugs to the body for systemic effects but topical route of administration is limited in its ability to allow effective drug absorption for systemic drug action. The parenteral route of administration is important in treating medical emergencies in which the subject is comatose or cannot swallow and in providing various types of maintenance therapy for hospitalized patients.

Tablets and capsules represent unit dosage forms in which one usual dose of the drug has been accurately placed. By comparison, liquid oral dosage forms such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 mL and patient himself can take medication by measuring with tablespoon or other measuring devices. Such dosage measurements are typically in error by a factor ranging from 20 to 50 % when the drug is self administered by the patient.

An immediate release system allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug. Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. For example, a tablet containing a pain killer drug should disintegrate quickly in the gastrointestinal tract to allow a fast uptake into the body [1].

Controlled release systems also offer a sustained release profile but, in contrast to sustained release forms, controlled release systems are designed to lead to predictably constant plasma concentrations, independently of the biological environment of the application site. This means that they are actually controlling the drug concentration in the body, not just the release of the drug from the dosage form, as is the case in a sustained-release system.

The release kinetics is usually zero order. In contrast to sustained release systems, the dose in the therapeutic systems is of less importance than the release rate from the therapeutic system. Ideally the release rate from the dosage form should be the rate determining step for the absorption of the drug and in fact for the drug concentration in the plasma and target site. However, controlled release systems are not necessarily target specific which means that they do not exclusively deliver the drug to the target organ. This may be achieved by so called targeted delivery systems which aim to exploit the characteristics of the drug carrier and the drug target to control the biodistribution of the drug.

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes, drugs in many extended release systems must diffuse through a rate controlling polymeric membrane or matrix. The ability of a drug to diffuse in polymers, its so called diffusivity (diffusion coefficient *D*), is a function of its molecular size (or molecular weight). Generally, values of the diffusion coefficient for drugs of intermediate molecular weight (i.e., 150 to 400 Da) through flexible polymers range from 10^{-6} to 10^{-9} cm^2/sec, with values in the order to 10^{-8} being most common. A value of approximately 10^{-6} is typical for these drugs through water as the medium. For drugs with a molecular weight greater than 500 Da, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify (i.e., less than 10^{-12} cm^2/sec). Thus, high-molecular weight drugs should be expected to display very slow release kinetics in extended release devices using diffusion through polymeric membranes or matrices as the releasing mechanism.

The Bio-Pharmaceutical Classification System (BCS) allows estimation of likely contribution of three major factors solubility, dissolution and intestinal permeability which affect the oral drug absorption. First, if a drug upon chronic administration is capable of either inducing or inhibiting enzyme synthesis, it will be a poor candidate for a SR/CR product because of the difficulty in maintaining uniform blood levels of a drug.

Second, if there is a variable blood level of a drug through either intestinal (or tissue) metabolism or through first pass effect, this will also make formulation of SR dosage form difficult, since most of the process are saturable, the fraction of the drug loss would be dose dependent and that

would result in significant reduction in bioavailability if the drug is slowly released over an extended period of time.

The glomerular capillaries do not permit the passage of plasma protein and drug protein complexes. Hence only unbound drug is eliminated. The elimination half-life of drugs generally increases when the percent of bound drug to plasma increases. Such drugs need not be formulated into sustained/controlled release formulations. Since blood proteins are mostly re-circulated, not eliminated, high drug protein binding can serve as a depot for drug producing a prolonged drug action [2, 3].

2. MATERIALS AND METHODS

These are the type of sustained or controlled drug delivery systems, which release the drug in continuous manner. These release in by both dissolution and diffusion mechanisms. The material most widely used in preparing matrix systems includes both hydrophilic and hydrophobic polymers. Commonly available hydrophilic polymers include Hydroxypropylmethylcellulose (HPMC), Hydroxypropylcellulose (HPC), Hydroxyethylcellulose (HEC), Xanthan gum, Sodium alginate, Poly (ethylene oxide) and cross linked homopolymers and copolymers of Acrylic acid.

Metroprolol succinate was obtained as gift sample from Aarthi Chemicals Private Limited, Xanthin gum from gift sample C. P. Kcl Co. USA, HPMCK 100M, HPMCE 5, microcrystalline cellulose from SD Fine Chem Limited Mumbai, Lactose, PVPK 30 from Himedia Laboratories Private Limited Mumbai, Pregelatinised starch from Dhavan Enterprises, Gujarat, Talc from N. R. Chem Products, Mumbai, Magnesium stearate from Central Drug House Private Limited, Sodium hydroxide from Rankem RF CL Limited, New Delhi, Potassium Dihydroxide Orthophosphate, Phosphoric acid from Spectrum Chemicals Private Limited, Mumbai and Monobasic sodium phosphate from Spectrochem Private Limited Delhi.

Drug profile

Metoprolol succinate

Metoprolol succinate is a β1-selective (cardio selective) adrenoceptor blocking agent.

Chemical name

(±) 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate

Structure of Metoprolol succinate

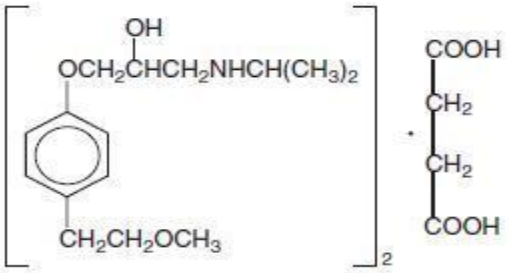

Figure 1. Structure of Metoprolol succinate

Molecular formula: $C_{30}H_{50}N_2O_6.\ (CH_2COOH)_2$

Metoprolol succinate is freely soluble in water; soluble in methanol; sparingly soluble in ethanol; slightly soluble in dichloromethane and 2-propanol; practically insoluble in ethyl acetate, acetone, diethyl ether and heptane.

Laboratory test findings

Clinical laboratory findings may include elevated levels of serum transaminase, alkaline phosphatase, and lactate dehydrogenase.

Drug interactions

Catecholamine depleting drugs

Catecholamine depleting drugs (eg, Reserpine, Monoamine oxidase (MAO) inhibitors) may have an additive effect when given with beta blocking agents. Observe patients treated with Metoprolol succinate extended release tablets plus a catecholamine depletor for evidence of hypotension or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Over dosage

Signs and symptoms

Overdosage of Metoprolol succinate extended release tablets may lead to severe bradycardia, hypotension, and cardiogenic shock. Clinical presentation can also include: atrioventricular block, heart failure, bronchospasm, hypoxia, impairment of consciousness/coma, nausea and vomiting.

Treatment

Consider treating the patient with intensive care. Patients with myocardial infarction or heart failure may be prone to significant hemodynamic instability. Seek consultation with a regional poison control center and a medical toxicologist as needed. Beta-blocker overdose may result in significant resistance to resuscitation with adrenergic agents, including beta-agonists. On the basis of the pharmacological actions of Metoprolol, employ the following measures. There is very limited experience with the use of hemodialysis to remove Metoprolol, however Metoprolol is not highly protein bound.

3. RESULTS AND DISCUSSION

The formulations of Metoprolol succinate were prepared by wet granulation technique using HPMC E5, HPMC K100M and Xanthan gum as release retarding agents in different ratios employing Lactose, Microcrystalline cellulose, Pregelatinised starch as diluents, Sodium CMC as disintegrant, PVP K30 in purified water as binding agent with talc and magnesium stearate as glidant and lubricant.

FTIR was performed for the pure Metoprolol succinate, Xanthan gum, Pregelatinised starch, physical mixture of pure drug: Xanthan gum, physical mixture of pure drug: Pregelatinised starch, physical mixture of pure drug: PVP K30 and physical mixture of pure drug with Xanthan gum, Pregelatinised starch and PVP K30 to detect any sign of interaction which would be reflected by a change in the position or disappearance of any characteristic peaks of the compound (Figure 2-6).

From the Infrared spectral analysis, it was clear that the characteristic absorption peaks of Metoprolol succinate were found in physical mixture of drug and excipients, so it indicates that there was no interaction between drug and excipients. The results of angle of repose were represented in Table 13. The angle of repose values of the formulations were found to be in the range of 29^0.28' to 33^0.54'. The results proved acceptable flow properties of the granules formulated. The results of bulk density, tapped density, compressibility index and Hausner's ratio of granules were represented in Table 16. The bulk densities of the formulations were found to be in the range from 0.401 to 0.423 g/ml. The tapped densities of powders were found to be in the range from 0.455 to 0.488 g/ml. The results of Carr's index and Hausner's ratio values

showed that the formulations F1 to F18 had acceptable flow properties. To investigate the mechanism of drug release, various kinetic models like zero order, first order, Higuchi's and Korsmeyer-peppas equations were applied to the *in vitro* drug release data. The drug release kinetics was performed for all formulations and the results were shown in Table 1. The release kinetics of the optimized formula followed Higuchi model and non-Fickian transport.

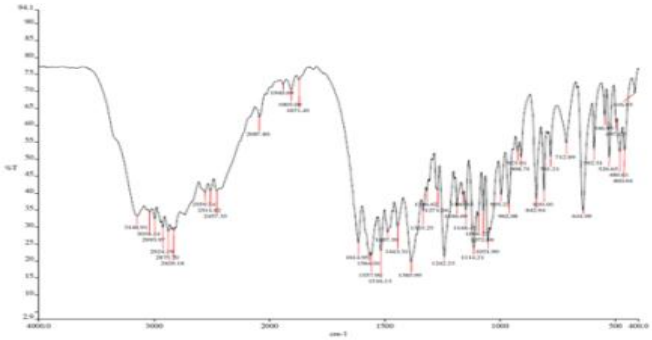

Figure 2. Infra red spectra of pure drug Metoprolol succinate

Table 1: Characteristic peaks of pure Metoprolol succinate

Sl. no.	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~1600	1614.95	Aromatic
2	N-H	Stretching	3310-3140	3148.91	2^0 amine
3	C-O	Stretching	1350-1260	1271.04	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.45	Ether
5	C-O	Stretching	1410-1300	1385.99	Phenoxide

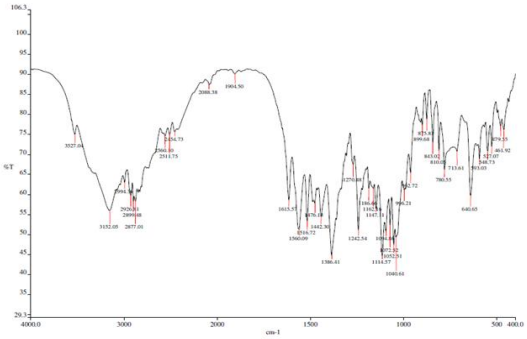

Figure 3. Infra red spectra of Metoprolol succinate + Xanthan gum

Table 2: Characteristic peaks of Metoprolol succinate in mixture of drug + Xanthan gum

Sl. no.	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~1600	1615.17	Aromatic
2	N-H	Stretching	3310-3140	3161.26	2^0 amine
3	C-O	Stretching	1350-1260	1271.08	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.62	Ether
5	C-O	Stretching	1410-1300	1386.54	Phenoxide

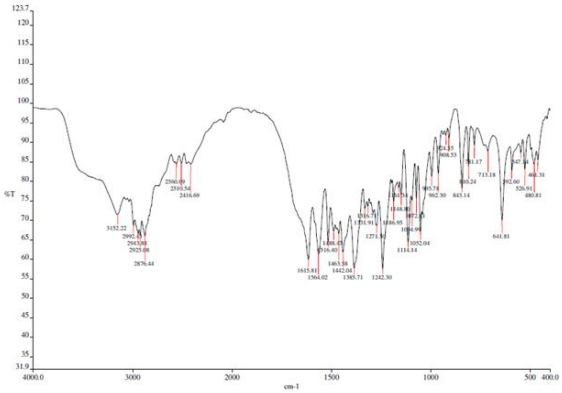

Figure 4. Infra red spectra of Metoprolol succinate + Pregelatinised starch

Table 3: Characteristic peaks of Metoprolol succinate in mixture of drug + Pregelatinised starch

Sl. no.	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~1600	1615.57	Aromatic
2	N-H	Stretching	3310-3140	3152.05	2^0 amine
3	C-O	Stretching	1350-1260	1270.48	2^0 alcohol
4	C-O	Stretching	1150-1070	1147.11	Ether
5	C-O	Stretching	1410-1300	1386.41	Phenoxide

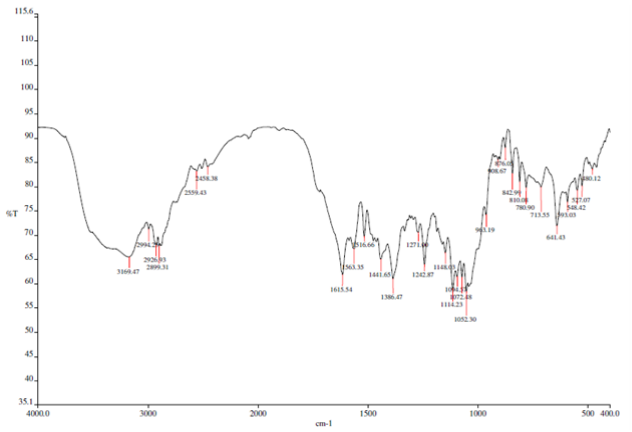

Figure 5. Infra red spectra of Metoprolol succinate + PVP K30

Table 4: Characteristic peaks of Metoprolol succinate in mixture of drug + PVP K30

Sl. no.	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~1600	1615.81	Aromatic
2	N-H	Stretching	3310-3140	3152.22	2^0 amine
3	C-O	Stretching	1350-1260	1271.50	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.80	Ether
5	C-O	Stretching	1410-1300	1316.71	Phenoxide

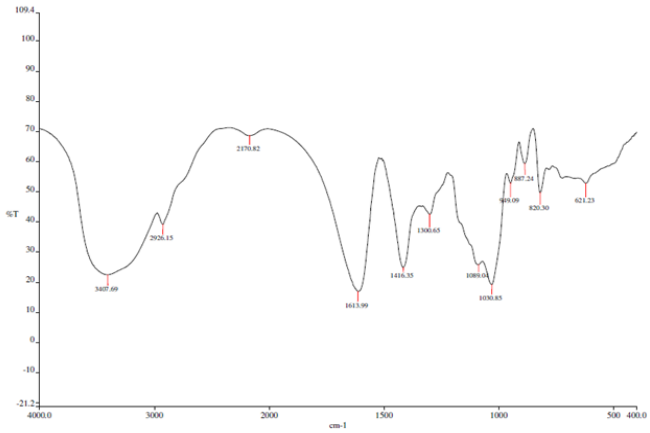

Figure 6. Infra red spectra of Metoprolol succinate + Xanthan gum + Pregelatinised starch + PVP K30

Table 5: Characteristic peaks of Metoprolol succinate in mixture of drug + Pregelatinised starch + Xanthan gum + PVP K30

Sl. no.	Type of bond	Type of vibration	Actual frequency (cm^{-1})	Observed frequency (cm^{-1})	Confirmation
1	C=C	Stretching	~1600	1615.54	Aromatic
2	N-H	Stretching	3310-3140	3169.47	2^0 amine
3	C-O	Stretching	1350-1260	1271.00	2^0 alcohol
4	C-O	Stretching	1150-1070	1148.03	Ether
5	C-O	Stretching	1410-1300	1386.47	Phenoxide

The results of angle of repose were represented in Table 2**.** The angle of repose values of the formulations were found to be in the range of 29^0.28' to 33^0.54'. The results proved acceptable flow properties of the granules formulated. The results of bulk density, tapped density, compressibility index and Hausner's ratio of granules were represented in Table 16. The bulk densities of the formulations were found to be in the range from 0.401 to 0.423 g/ml. The tapped densities of powders were found to be in the range from 0.455 to 0.488 g/ml. The results of Carr's index and Hausner's ratio values showed that the formulations F1 to F18 had acceptable flow properties. The tablets of all the formulations were subjected to unofficial and official quality control tests. The results of weight variation of all formulations were represented in the Table 18. Weight variation was carried out for all the designed formulations and was found to be within the average weight variation limits. The results of hardness of all formulations were represented in the Table 3. The hardness of all the formulations F-1 to F-18 ranged from 4 to 6.5 kg/cm^2 with good mechanical strength. The results of friability of all formulations were represented in the Table 4. The friability values of all formulations were in the range of 0.16 to 0.32 %. The results showed that the formulations are physically stable to mechanical shocks during handling and transportation. The drug content uniformity was performed for all the formulations and the results were shown in Table 5. The uniformity of drug distribution within the batch tablets was confirmed by the assay values of 24.83 to 25.1 mg/tablet for all the formulations. Swelling index describes the amount of water that is contained within the hydrogel at equilibrium and is a function of network structure, hydrophilicity and ionisation of functional

group. Swelling study was performed on all formulations for 20 hrs in pH 6.8 buffer. The results of swelling index were shown in the Table 5. The results showed that the percentage swelling index was proportionate to the polymer concentration. The swelling index of all formulations ranged from 171.77 % to 279.09 %. The swelling index was found to be higher for the tablets prepared with Xanthan gum compared to HPMC K 100M and HPMC E5.

In vitro dissolution studies were performed for all the formulated tablets using USP XXIII tablet dissolution apparatus employing rotating paddle at 50 rpm using 500 mL of pH 6.8 phosphate buffers as dissolution medium and the temperature of dissolution medium was maintained at 37±0.5°C. The results of *in vitro* drug release data are given in Table 3.

As per the results of dissolution studies, the formulations from F1 to F13 showed that the drug release was not within USP limits. The formulations from F14 to F16 showed that the drug release was in the border as per USP limits. The formulation F17 showed that the drug release was within the USP limits [1st hr (NMT 25 %) – 18.34 %, 4th hr (20-40 %) – 33.38 %, 8th hr (40-60 %) – 52.85 %, 20th hr (NLT 80 %) – 87.25 %]. The formulation F18 showed that the drug release was in the border as per USP limits. So the formulation F17 was the optimized formula with desired dissolution pattern as per USP specifications.

To investigate the mechanism of drug release, various kinetic models like zero order, first order, Higuchi's and Korsmeyer-peppas equations were applied to the *in vitro* drug release data. The drug release kinetics was performed for all formulations and the results were shown in Table 1. The release kinetics of the optimized formula was followed Higuchi model and non-Fickian transport.

Metoprolol succinate SR tablets can be formulated with good release profile for a prolonged period of time up to 20 hours by using the polymers like Xanthan gum, HPMC K 100M, HPC EXF and MCC PH 101 as release retarding agents [4]. Microcrystalline cellulose can achieve the tablets with good hardness and also concluded that HPMC K 100 shows better drug control compared to HPMC E 4M [5]. Metoprolol succinate using hydrophilic and hydrophobic polymers by direct compression method and concluded that rate of drug release from matrix tablets was found to decrease with Methocel K 100 alone. Combination of hydrophobic polymer and hydrophilic polymer increases the drug release because of swelling of hydrophilic polymer

was low which helps in migration of the drug from the matrix [6]. Fabricated controlled release matrix tablets using Sodium alginate, HPMC K 15 and concluded that the release rate of drug from matrix tablets can be governed by the granulating fluids, polymers and concentration of polymer employed in the preparation of tablet [7]. Santosh Kumar Narla *et al.*, concluded that Kollidon SR can be utilized for effective production of controlled release Metoprolol succinate matrix tablets by direct compression process using an optimum concentration for desired release profile and with good quality parameters [8].

Chandrasekhar Rangaiah K *et al.*, concluded that tablets of Metoprolol succinate can be made by direct compression method by using K 4M, K 15M, K 100M of HPMC, Sodium stearyl fumerate, colloidal anhydrous silica, MCC as suitable excipients as all they showed the compatibility with the Metoprolol succinate [9]. Mohd Azaruddin *et al.*, designed controlled release matrix tablets of Losartan Potassium using Xanthan gum, HPMC K4M and concluded that the polymer concentration plays a major role in drug release. As the polymer concentration of the tablets increased the drug release was prolonged in a controlled manner [10]. N. N. Rajendran *et al.*, conclusively stated that development of extended release formulation of hydrophilic drugs do not necessitate the inclusion of hydrophobic polymers to hydrophilic polymers and the desired extended release of hydrophilic drugs are also viable with hydrophilic polymer alone [11].

N. Srujana *et al.*, developed oral sustained delivery matrix tablets of Metoprolol succinate using Kondagogu gum and stated that sustained release drug formulation can be prepared using Kondagogu gum, a naturally available, environmental friendly, non-toxic and biodegradable gum as carrier [12]. Dewan T Akhter *et al.*, formulated twice a daily Nifedipine sustained release tablet using Methocel K 15M CR and Methocel K 100LV CR concluded that Methocel K15M CR and Methocel K 100LV CR in combination would be useful in the preparation of sustained release matrix tablets of Nifedipine with desired release profile [13].

CONCLUSION

Oral drug delivery is the most desirable and preferred method of administering drugs for their systemic effects. In recent years, there has been an interest on the development of sustained and controlled release drug delivery systems, as the dosage form covers a wide range of preparations

for the treatment of various diseases and infections. The main interest was to explore a natural polymer as an excipient for the design of pharmaceutical dosage forms. Though a wide variety of polymeric substances like semi-synthetic and synthetic are available to serve as a release retarding agents, there is a need to develop new, safe and effective polymers which has several advantages like biocompatibility, cheap, non-toxic, eco-friendly etc.

In the present work, an investigation was made to use Xanthan gum as a natural polymer in the design of extended release oral drug delivery systems. Metoprolol succinate was chosen as the model drug with the view of formulating extended release tablets to improve its bioavailability. Drug excipient compatibility studies were proved by using FTIR. The extended release tablets of Metoprolol succinate were formulated by wet granulation method. The formulated tablets complied for all the un-official and official tests for the tablets. Release of Metoprolol succinate from the tablets formulated by employing 85 mg of Xanthan gum and 50 mg of Pregelatinised starch showed that the drug release was as per within the USP limits. So the formulation F17 was the optimised formula. The polymer Xanthan gum showed better dissolution control compared to the other polymers like HPMC E5 and HPMC K100M. The diluent (Pregelatinised starch) concentration in formulation F17 was compared with the other diluents like lactose and MCC. The Pregelatinised starch containing formulation showed better dissolution control compared to the formulations containing lactose and MCC as diluents. The release kinetics of optimised formula showed non-Fickian transport and followed Higuchi model.

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