CHAPTER 2

Drug Profile
2.1. METOPROLOL SUCCINATE (MS)

Metoprolol succinate is a cardioselective $\beta_1$-adrenergic blocking agent used for acute myocardial infarction, heart failure, angina pectoris and mild to moderate hypertension. It may also be used for supraventricular and tachyarrhythmias and prophylaxis for migraine headaches. Metoprolol is structurally similar to bisoprolol, acebutolol and atenolol in that it has two substituents in the $para$ position of the benzene ring. The $\beta_1$-selectivity of these agents is thought to be due in part to the large substituents in the $para$ position. At low doses, metoprolol selectively blocks cardiac $\beta_1$-adrenergic receptors with little activity against $\beta_2$-adrenergic receptors of the lungs and vascular smooth muscle (Anisree G.S. et al., 2011). Receptor selectivity decreases with higher doses. Unlike propranolol and pindolol, metoprolol does not exhibit membrane-stabilizing or intrinsic sympathomimetic activity. Membrane-stabilizing effects are only observed at doses much higher than those needed for $\beta$-adrenergic blocking activity. Metoprolol possesses a single chiral centre and is administered as a racemic mixture.

2.2. Physicochemical properties

The chemical name for metoprolol succinate is di-(±)-1-(isopropylamine)-3-[$p$-(2-methoxyethyl) phenoxy]-2-propanol succinate and the formula is as (Phale M. D. et al., 2009):

![Chemical structure](image)

Metoprolol succinate is a white crystalline powder, having the molecular weight 267.364 g/mol. Its half life 3-7 hours and melting point is 136-137°C. Bioavailability of MS is 60%, and the protein binding is 12%. pKa value and Log P value are 9.68 and 1.6 respectively. % loss on drying is less than 0.5%. It should be stored at or below 25°C.

It 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.
2.3. Dose
Initial dose : 12.50 mg orally once a day
Maintenance dose : 12.50 mg to 90 mg orally twice a day
Maximum dose : 100 mg per day

2.4. Pharmacodynamics
Pharmacological action anti-hypertensive, antianginal, antiarrhythmic. Blocks mainly beta\(_1\)-adrenoceptors of the heart has no intrinsic sympathomimetic and membrane stabilizing activity (Kaduskar D. et al., 2010). Reduces cardiac output and Garden, slows the heart rate, decreases the stimulating effect of catecholamines on the myocardium during physical exercise and mental overexertion, and warns reflex orthostatic tachycardia. Antihypertensive effect is due to a decrease in cardiac output and renin synthesis, inhibition of renin-angiotensin system and the CNS, the restoration of baro-receptor sensitivity and, ultimately, a decrease in peripheral sympathetic effects (Gohel M. C. et al., 2009).

2.4.1. Mechanism of action
Metoprolol competes with adrenergic neurotransmitters such as catecholamines for binding at Beta\(_1\)-adrenergic receptors in the heart. Beta\(_1\)-receptor blockade results in a decrease in heart rate, cardiac output, and blood pressure.

2.5. Pharmacokinetics
2.5.1. Absorption Metoprolol is completely absorbed after oral administration. The systemic bioavailability of metoprolol from a single oral dose is approximately 50%, owing to an extensive first-pass effect (Kannan K. et al., 2010).

2.5.2. Distribution The plasma protein binding of metoprolol is low, approximately 5-12% and has a volume of distribution of 5.6 L/kg. Metoprolol plasma concentration is achieved over a dosage interval of 24 hours. The release rate is independent of physiological factors such as pH, food and peristalsis.

2.5.3. Metabolism Metoprolol undergoes oxidative metabolism in the liver primarily by the CYP2D6 isoenzyme. The three main metabolites have been identified, though none of them have a clinically significant β-blocking effect. As a rule over 95% of an oral dose can be recover in the urine (Gami S.V.et al., 2011). About 5% of the given dose is excreted in the urine in unchanged form.

2.5.4. Excretion The elimination half-life of metoprolol in plasma averages 3.5 hours (extremes: 1 and 9 hours). The total clearance rate is approximately 1 litre/minute (Ramkanth S..et al., 2010).
2.6. Other Drug Interactions

a. Antiarrhythmic agents- Beta-blockers may enhance the negative inotropic and negative dromotropic effect of antiarrhythmic agents. Digitalis glycosides, in association with beta-blockers, may increase atrioventricular conduction time and may induce bradycardia.

b. Prostaglandin synthetase inhibiting agents- Concomitant treatment with indomethacin or other prostaglandin synthetase inhibiting agents may decrease the antihypertensive effect of beta-blockers.

c. Antidiabetics- The dosages of oral antidiabetics may have to be readjusted in patients receiving beta-blockers.

d. Antihistamines- Plasma levels of metoprolol may be raised by co-administration of compounds metabolised by CYP2D6 eg. Antihistamines.

e. Calcium antagonists- Increased negative inotropic and chronotropic effects may occur when metoprolol is given together with calcium antagonists of the verapamil and diltiazem type.

f. Anaesthetics- In patients receiving beta-blocker therapy, inhalation anaesthetics enhance the cardiodepressant effect.

g. Rifampicin & Alcohol- The plasma concentration of metoprolol is lowered by rifampicin and may be raised by alcohol and hydralazine.

2.7. Adverse Effects

a. Central Nervous System- Fatigue, Dizziness, headache, Paraesthesiae, muscle cramps.

b. Gastrointestinal- Nausea, abdominal pain, diarrhoea, constipation, vomiting.

c. Haematologic- Thrombocytopenia.

d. Hepatic- Liver function test abnormalities, Hepatitis.

e. Metabolism- Weight gain.

f. Musculoskeletal- Arthralgia.

g. Psychiatric- Depression, concentration impaired, somnolence or insomnia, nightmares, Nervousness, anxiety, impotence / sexual dysfunction, Amnesia / memory impairment, confusion, hallucinations.

h. Respiratory- Dyspnoea on exertion, Bronchospasm, Rhinitis.

i. Sense organs- Disturbances of vision, dry and/or irritated eyes, conjunctivitis, tinnitus, taste disturbances.
j. **Skin**- Rash, increased sweating, Loss of hair, Photosensitivity reactions, aggravated psoriasis.

### 2.8. Recent work on metoprolol succinate

Gastroretentive controlled release system of metoprolol succinate in the form of tablet was formulated tablet to increase gastric residence time leading to improved drug bioavailability. Sodium alginate and NaCMC in different combinations was used, and evaluate the tablet for mass, thickness, hardness, drug content and floating properties. Dissolution study for 24 hrs was carried out and found controlled release of metoprolol with floating for 16 hrs (Boldhane et al., 2010). Mucoadhesive buccal tablets of metoprolol tartrate were prepared using carbopol-934, HPMC and sodium carboxymethyl cellulose, and characterized the formulations for physiochemical parameters, in vitro release study and in vivo studies. The formulation containing HPMC and carbopol in the ratio 1:2 showed best mucoadhesive performance and in vitro release profile (Ramana et al., 2007). Colon targeted tablets for metoprolol succinate using kondagou gum as a polymer and PVP K-30 as binder was developed, and coated with shellac as an enteric coat polymer and evaluated for enteric coat test. The optimized formulation showed negligible difference in release mechanism as well as release kinetics when stability study was done for 3 months at 40°C (Srujana et al., 2011). Floating sustained-release matrices of metoprolol succinate using Gelucire 43/01 and Gelucire 44/14 was developed by a melt-solidification technique. Prepared matrices were evaluated for in vitro and in vivo characteristics. The Gelucire 43/01 is an appropriate carrier for the development of sustained-release floating drug delivery systems and Gelucire 44/14, a highly hydrophilic and lipophilic balance (HLB) excipient, acts as release enhancer (Suresh et al., 2010). Floating-Mucoadhesive tablets were developed using directly compressible polymers such as HPMC K4M, HPMC K15M, Sodium CMC and Carbopol 940P, utilizing both the concepts of adhesiveness and of flotation and evaluated for buoyancy test, mucoadhesion force, swelling study, drug content, Ex vivo mucoadhesion strength and in vitro release profile (Panigrahay et al., 2011). Osmotically controlled oral tablets of metoprolol succinate were formulated using different concentration of mannitol, by wet granulation technique. The tablet was coated with cellulose acetate, and evaluated for hardness, weight variation, and drug release study. On increasing the concentration of osmogen the rate of drug
release follows zero order kinetics (Mothilal et al., 2010). Matrix type transdermal film of metoprolol tartrate was developed using different ratio of Eudragit RL-100 and polyvinyl pyrrolidone K-30. The films were evaluated for in vitro by drug release studies, skin permeation studies and drug-excipients interaction analysis. On the basis of in vitro drug release and skin permeation performance, formulation containing Eudragit and polyvinyl pyrrolidone in the ratio of 8:2 was found to be better than the other formulations (Aqil et al., 2003). Floating pulsatile drug delivery system of metoprolol tartrate was developed. The rapid release core tablet (RRCT) was prepared by using superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of HPMC E5, E15, and E50 and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. Developed formulations were evaluated for their physical characteristics, drug content, in vitro disintegration time, in vitro drug release profile, floating lag time, floating time and in vivo X-ray study (Salunkhe et al., 2011). Time-controlled release formulation of metoprolol succinate based on a pulsatile multiparticulate (pellets) drug delivery system was developed. The formulation was intended to be administered in the evening at 22:00 hours to evaluate symptoms of cardiovascular disease that are experienced in the early morning hours (from 04:00 to 06:00). Drug layering followed by a swelling layer and finally by an insoluble coat application was done using a sanmour fluid bed processor (Jagdale et al., 2011). Buccoadhesive tablets of Metoprolol tartrate were prepared using combination of natural polymers such as sodium carboxy methyl cellulose, gum karaya, xanthan gum and locust bean gum. Buccal tablets were evaluated by different parameters and the results revealed that formulation containing combination of xanthan gum and locust bean gum in 2:1 ratio exhibited complete drug release in 45 min. but poor drug permeation (Hirlekar et al., 2010). Transdermal films of metoprolol tartarate were prepared by solvent casting method using polymers such as ethyl cellulose, poly vinyl alcohol, Eudragit RL100, Eudragit L100. Di-n-butylphthalate was used as plasticizer. In-vitro drug release kinetics was studied using Franz-diffusion cell and found that the drug release followed zero order kinetics. The combination of polymer can potentially be optimized to develop an effective transdermal system (Anilreddy et al., 2010). The buccoadhesive tablets of metoprolol tartrate were prepared and characterized for physicochemical properties, bioadhesive strength, and in vitro drug release. The
formulation containing 1:1.25 ratios of drug and polymer exhibited optimum drug release (Velmurugan et al., 2011). Oral sustained tablets of Metoprolol succinate by wet granulation method using natural hydrophilic gums such as karaya gum (KG) and xanthan gum (XG) as a release modifier were developed, and evaluated the tablets for weight physico-chemical characteristics and in vitro dissolution. Among the formulations studied, formulation containing combination of KG and XG (2:8) having concentration of 20% showed sustained release of drug for 12hrs with cumulative percent release of 99.24% (Deshmukh et al., 2009). A simple, specific, accurate, and precise reverse phase liquid chromatographic method (RP-HPLC) for the estimation of metoprolol succinate from bulk drugs was developed and validated. The linearity of the method was good (r > 0.998), as also were intra-day and inter-day precision (RSD <2%). The results showed that proposed method is successfully applied for the quantitative determination of metoprolol succinate in bulk drugs (Phale et al., 2009).

β-adrenoceptor blocking and antihypertensive effects of chronic once daily treatment with conventional metoprolol 200 mg, two 'long-acting' formulations of metoprolol 200 mg and atenolol 100 mg in a cross-over study in 12 hypertensive patients concurrently receiving diuretic therapy was compared. after twenty-four hours after dosing only atenolol treatment was consistently associated with a reduction in both exercise heart rate (P < 0.001) and blood pressure (P < 0.02) when compared with placebo (Ramsay et al., 1985).

Extended release matrix tablets of metoprolol succinate were formulated using HPMC, Ethyl Cellulose, Lactose Monohydrate and magnesium stearate. Release kinetics evaluated by using USP II (Paddle) dissolution apparatus. In-vitro swelling studies revealed that, the drug release governed by swelling of polymer and it is non-fickian or transport anomalous diffusion (Kaduskar et al., 2010). Modified release tablet of metoprolol succinate using HPMC and xanthan gum as a matrixing agent was fabricated. The in vitro drug dissolution study was carried out in pH 6.8 phosphate buffer employing paddle rotated at 50 rpm. The similarity factor (f2) was calculated for selection of best batch. The desired drug release pattern can be obtained by using a proper combination of HPMC (high gelling ability) and xanthan gum (quick gelling tendency) (Gohel et al., 2009). A simple, rapid and selective HPLC method has been developed for quantization of Amlodipine Besylate and Metoprolol succinate from bulk drug and pharmaceutical formulations. The linearity was in the concentration range of 2.5 to 15 µg/ml for
Amlodipine Besylate and 25 to 150 µg/ml for Metoprolol succinate, with good linearity response greater than 0.999 (Rao et al., 2010). In vitro in vivo correlation of metoprolol tartrate sustained release capsules was investigated. They prepared non pareil seeds and coated with metoprolol tartrate using polyvinyl pyrrolidone and iso-propyl alcohol. Correlation of in vitro in vivo study was confirmed by plotting the graph between percentages absorbed in vivo versus the percentage released in vitro at the same time (Kannan et al., 2010). A high-performance reversed-phase liquid chromatographic method was developed for quantification of metoprolol tartrate (MT) in human plasma using C_{18} column and acetonitrile–water–triethylamine 18:81:1 (v/v) as mobile phase. The method can be successfully used for analysis of MT in human plasma during pharmacokinetic studies (Aqil et al., 2007).
References


2.9. CARVEDILOL (CR)
Carvedilol is a non-selective beta blocker indicated in the treatment of mild to moderate congestive heart failure (CHF). It blocks $\beta_1$ and $\beta_2$ adrenergic receptors as well as the $\alpha_1$ adrenergic receptors.

2.10. Physicochemical properties
It is described chemically as: $C_{24}H_{26}N_2O_4$. Carvedilol is chemically [3-(9H-carbazol-4-yloxy)-2-hydroxypropyl][2-(2-methoxyphenoxy)ethyl]amine and the formula is as (Yadav et al., 2009):

![Chemical structure of Carvedilol](image)

Carvedilol is also known as Carvedilolum [Latin]. It is a white crystalline powder, having the molecular weight 406.47. Its half life 6-10 hours and melting point is 113-121°C. Bioavailability of CR is 25-35 %, and the protein binding is 98%. pKa value and Log P value are 7.8 and 3.42 respectively. % loss on drying is less than 0.5%. It should be stored at or below 25°C and protect from moisture.

It is can be easily soluble or dissolved in dimethyl sulfoxide. It is also easily soluble in methanol as well as methylene chloride. Isopropanol and ethanol can partially dissolve the Carvedilol. Ethyl ether can also partially dissolve Carvedilol. However, these active pharmaceutical ingredients cannot be dissolved in water, intestinal fluids or gastric fluids (Mishra, 2011).

2.11. Dose
Initial dose: 12.5 mg orally twice a day with food
Maintenance dose: 6.25 mg to 25 mg orally twice a day
Maximum dose: 80 mg per day

2.12. Pharmacodynamics
Carvedilol is a non-selective beta-adrenergic blocking agent with alpha1-blocking activity and is indicated for the treatment of hypertension and mild or moderate
(NYHA class II or III) heart failure of ischemic or cardiomyopathic origin. Carvedilol is a racemic mixture in which non-selective β-adrenoreceptor blocking activity is present in the S(-) enantiomer and α-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol has no intrinsic sympathomimetic activity. The effect of carvedilol β-adrenoreceptor blocking activity has been demonstrated in animal and human studies showing that carvedilol reduces cardiac output in normal subjects; reduces exercise-and/or isoproterenol-induced tachycardia and reduces reflex orthostatic tachycardia.

2.12.1. Mechanism of action
Carvedilol is a racemic mixture in which non-selective beta-adrenoreceptor blocking activity is present in the S(-) enantiomer and alpha-adrenergic blocking activity is present in both R(+) and S(-) enantiomers at equal potency. Carvedilol β-adrenergic receptor blocking ability decreases the heart rate, myocardial contractility, and myocardial oxygen demand. Carvedilol also decreases systemic vascular resistance via its alpha adrenergic receptor blocking properties. Carvedilol and its metabolite (a less potent beta blocker, but more potent antioxidant) have been shown to restore the inotropic responsiveness to Ca²⁺ in OH⁻ free radical-treated myocardium. Carvedilol and its metabolites also prevent OH⁻ radical-induced decrease in sarcoplasmic reticulum Ca²⁺-ATPase activity. Therefore, carvedilol and its metabolites may be beneficial in chronic heart failure by preventing free radical damage (Nucci, 2005).

2.13. Pharmacokinetics

2.13.1. Absorption Carvedilol is rapidly and extensively absorbed following oral administration. The absolute bioavailability of carvedilol is approximately 25% (Sripalakit, 2010). Plasma levels peak approximately one hour after an oral dose. Carvedilol undergoes stereoselective first-pass metabolism with plasma levels of R(+)carvedilol approximately two to fourfold higher than S(-)-carvedilol following oral administration in healthy subjects. Plasma levels increase in a dose proportional manner.

2.13.2. Distribution Greater than 98% of carvedilol is bound to plasma proteins, primarily albumin. Carvedilol is highly lipophilic; the volume of distribution is approximately 2 L/kg and is increased in patients with liver disease. When used as directed, carvedilol is unlikely to accumulate during long-term treatment.
2.13.3. Metabolism In all animal species studied, and also in humans, carvedilol is extensively metabolised into a variety of metabolites which are mainly excreted in the bile. The first-pass effect after oral administration amounts to about 60 to 75%; entero-hepatic circulation of carvedilol and/or its metabolites has been shown in animals.

The major P450 enzymes responsible for the metabolism of both R(+) and (S-) carvedilol in human liver microsomes were identified as CYP2D6 and CYP2C9, and to a lesser extent CYP3A4, CYP2C19 and CYP2E1.

Carvedilol is only responsible for alpha-blocking activity, it would be anticipated that, on average, poor metabolisers of debrisoquine would have greater alpha-blockade after carvedilol administration with little change in beta-blocking activity, compared to extensive metabolisers.

2.13.4. Excretion After oral administration, the elimination half-life of carvedilol is approximately six to ten hours. Plasma clearance ranges from 500 to 700 mL/minute. Elimination is mainly biliary, with the primary route of excretion being via the faeces. A minor portion is eliminated via the kidneys. The pharmacokinetics of carvedilol is affected by age.

2.14. Other Drug Interactions

a. Digoxin Digoxin plasma concentrations are increased by about 15% when digoxin and carvedilol are administered concomitantly. Both digoxin and carvedilol slow AV conduction. Therefore, increased monitoring of digoxin is recommended when initiating, adjusting or discontinuing carvedilol.

b. Catecholamine depleting agents Patients treated with both carvedilol and a drug that can deplete catecholamines (e.g. reserpine and monoamine oxidase inhibitors) should be observed closely for signs of hypotension and/or severe bradycardia.

c. Cyclosporin A modest increase in mean through cyclosporin concentration has been observed following initiation of Carvedilol treatment in renal transplant patients suffering from chronic vascular rejection. It is recommended that cyclosporin concentrations be monitored closely after initiation of carvedilol therapy and that the dose of cyclosporin be adjusted as appropriate.

d. Clonidine Administration of clonidine with agents with beta-blocking properties may potentiate blood pressure and heart rate lowering effects.
e. **Calcium channel blockers** When Carvedilol is to be administered orally with calcium channel blockers of the verapamil or diltiazem type, it is recommended that ECG and blood pressure be monitored.

f. **Antiarrhythmic drugs** Care should be taken when prescribing beta-blockers with antiarrhythmic drugs. Interactions have been reported during concomitant beta-blocker therapy with antiarrhythmic drugs.

g. **Insulin or oral hypoglycaemics** Agents with beta-blocking properties may enhance the blood sugar reducing effect of insulin and oral hypoglycaemics. Therefore, in patients taking insulin or oral hypoglycaemics, regular monitoring of blood glucose is recommended.

### 2.15. Adverse Effects

a. **Body as a whole:** Asthenia, Sudden death, abdominal pain, Infection, Pain in extremity, Back pain, Accidental injury

b. **Cardiovascular system:** Heart failure, Hypotension, Chest pain, Bradycardia, Syncope (including presyncope), Angina pectoris, Atrial fibrillation, Ventricular tachycardia, Hypertension, Unstable angina pectoris, Myocardial infarct, Ventricular fibrillation.

c. **Nervous system:** Dizziness, Headache.

d. **Gastrointestinal:** Diarrhoea, Nausea.

e. **Haematology:** Anaemia.

f. **Metabolic:** Weight gain, Peripheral oedema, Generalised oedema, Hyperglycaemia, Gout, Diabetes mellitus.

g. **Musculoskeletal system:** Muscle cramps.

h. **Respiratory system:** Upper respiratory infection, Dyspnoea, Bronchitis, Cough increased, Lung disorder, Pneumonia.

i. **Urogenital system:** Kidney function abnormal, Urinary tract infection.

j. **Vision:** Blurred vision.

### 2.16. Recent work on Carvedilol

Nanoparticles of carvedilol with Eudragit E 100 were prepared by nanoprecipitation method using polymeric stabilizer Poloxamer 407, and characterized for encapsulation efficiency, particle size and in-vitro release. The feasibility of formulating carvedilol-loaded Eudragit E100 nanoparticles for the treatment of hypertension (Yadav et al., 2009). The stability of carvedilol using two aqueous solutions and one aqueous suspension was studied. Samples were stored at 4, 25 and
40°C for 0, 3, 7, 14, 28 and 56 days and tested through high performance liquid chromatography (HPLC). Carvedilol stayed stable in the acidic aqueous solution at the three different temperatures during 56 days, but the other was not stable at different temperature (Chiappetta et al., 2010). A method for the determination of carvedilol in human plasma was developed using high performance liquid chromatography with mass spectrometer (HPLC-MS). Deproteinized the plasma samples and injected the supernatant directly onto the HPLC column (C18). Curve was linear over the range of 2 to 100ng/ml and method was acceptable (Lee et al., 2010).

Buccal mucoadhesive patches of carvedilol were prepared using HPMC K15 and carbopol 940P. The patches were evaluated and found that patches exhibited drug release in the range of 77-97% in 8 hrs and the data of in-vitro release were fed into Higuchi and Korsmeyer-Peppas models (Kumar et al., 2011). Matrix type transdermal patches of carvedilol were developed using polymeric combination of PVP and ethyl cellulose (EC) by solvent casting method over a backing membrane of PVA. The in-vitro drug release and permeation studies indicated that the required rate can be adjusted by proper ratio of PVP and EC (De et al., 2011).

A simple, sensitive and reliable method for simultaneous quantification of Carvedilol and its metabolite 4-Hydroxyphenyl Carvedilol in human plasma was developed by using High-throughput liquid Chromatography–tandem mass spectrometric method. The validated method was successfully applied to bioavailability and bioequivalence study (Chandiran et al., 2011). Mucoadhesive buccal tablets of carvedilol in the forms of monolayered tablets were established using Sodium methyl cellulose (NaCMC), sodium alginate and Methocel K15M as bioadhesive polymers to impart mucoadhesion. Buccal tablets were evaluated by different parameters. Tablets of carvedilol can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bio availability of carvedilol (Kumar et al., 2010).

Transdermal drug delivery systems of carvedilol was formulated using HPMC and Eudragit as polymer while di-butyl phthalate as plasticizer. The in-vitro permeation studies indicated that matrix patches containing HPMC and Eudragid in the ratio of 1:4 shows better release (Dey et al., 2010). A rapid, sensitive and specific method to quantify carvedilol in human plasma was described using metoprolol as the internal standard (IS). The IS from plasma was extracted using a diethyl-ether solvent. The extracts were analyzed by a high performance liquid chromatography coupled to electrospray tandem mass spectrometry (HPLC–MS/MS). The study was conducted using an open, randomized,
two-period crossover design with a 2-week wash-out interval (Nucci et al., 2005). *In vitro* dissolution rate of carvedilol was increased by co-grinding technique using various carriers, namely lactose, corn starch, treated agar, microcrystalline cellulose. The prepared co-ground mixtures were evaluated for drug content, *in vitro* dissolution characteristics and short-term stability. The co-ground mixtures prepared with a drug-carrier ratio of 1:9 using microcrystalline cellulose and treated agar respectively, showed promising results in enhancing the dissolution rate of carvedilol (Swamy et al., 2010). A sensitive, simple and selective spectrofluorimetric method was developed for the determination of carvedilol (CA) in pharmaceutical formulation and a biological fluid. The proposed method was successfully applied to the analysis of commercial tablets (Sayed et al., 2010). Matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations was developed by the solvent evaporation technique. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations with minimal fluctuations and improved bioavailability of 71% in comparison with oral administration (Ubaidulla et al., 2007). A new and rapid ultraviolet spectroscopic method was developed for the estimation of carvedilol in pure form and in their formulations. The absorbance of carvedilol was at 241 nm in the wavelength range of 200-350 nm. The developed method was accurate, sensitive, precise and reproducible. It may be directly applied for the estimation of drug content in pharmaceutical formulations (Theivarasu et al., 2010). Mucoadhesive buccal patches of carvedilol were formulated by solvent casting method using chitosan, HPMC, and NaCMC as mucoadhesive polymers, patches were characterized and the optimized patch promising drug delivery system in maintaining buccal cavity hygiene and used for controlled release of drug (Patel et al., 2011). A new, simple and sensitive spectrophotometric method in ultraviolet region was developed for the determination of carvedilol in bulk and pharmaceutical formulations. Carvedilol exhibited maximum absorbance at 285 nm with apparent molar absorptivity of $15.4 \times 10^3 \mu g/ml$ (Jain et al., 2005). Two simple, specific, accurate and precise methods namely RP-HPLC and HPTLC were developed for the estimation of carvedilol in bulk and pharmaceutical formulations. For the HPLC method the ratio of phosphate buffer, acetonitrile and methanol was used as mobile phase. The proposed methods were successfully used for the determination of carvedilol in marketed preparations (Patel et al., 2006).
References


Lee H.J., Kim S. H. and Lee S. H., Rapid and sensitive carvedilol assay in human plasma using a high performance liquid chromatography with mass spectrometer


