Chapter 3

LITERATURE SURVEY -
DILTIAZEM HYDROCHLORIDE
Literature Survey - Diltiazem Hydrochloride

Diltiazem HCl (DL) belongs to the benzothiazepine class of compounds. It was first synthesized in the laboratories of Tanabe Seiyaku Co. Japan and was granted its first patent in 1969.

Chemical name, formula and molecular weight

(2S-cis)-3-(acetyloxy-5-[2-(dimethylamino) ethyl]-2, 3-dihydro-2-(4-methoxy-phenyl)-1, 5-benzothiazepin-4(5H)-one monohydrochloride.

Molecular formula – C_{22}H_{26}N_{2}O_{4}S HCl
Molecular weight - 450 g/mole

Structure -

![Chemical Structure of Diltiazem Hydrochloride](image)

Physical Properties

DL is a white to off white crystalline powder. It is odourless and has a bitter taste.

Melting Point - 207.5 - 212°C

UV max - 205, 236nm

Solubility- The solubility at 25°C of DL in a variety of solvents is presented in table 3.1
TABLE 3.1: Solubility of DL in various solvents at 25°C

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroform</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Formic Acid</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Methanol</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Water</td>
<td>Freely soluble</td>
</tr>
<tr>
<td>Dehydrated Alcohol</td>
<td>Sparingly soluble</td>
</tr>
<tr>
<td>Benzene</td>
<td>Practically in soluble</td>
</tr>
<tr>
<td>Ether</td>
<td>In soluble</td>
</tr>
</tbody>
</table>

**CAS Numbers**

- Diltiazem: 42399-41-7
- Diltiazem hydrochloride: 33286-22-5
- Diltiazem malate: 144604-00-2

**Pharmacology**

DL has pharmacological actions similar to those of other calcium-channel blocking agents (e.g., nifedipine, and verapamil). The principal physiologic action of DL is to inhibit the transmembrane influx of extra cellular calcium ions across the membranes of myocardial cells and vascular smooth muscle cells, without changing serum calcium concentrations.

Calcium plays important roles in the excitation-contraction coupling processes of the heart and vascular smooth muscle cells and in the electrical discharge of the specialized conduction cells of the heart. The membranes of these cells contain numerous channels that carry a slow inward current and that are selective for calcium. Activation of these slow calcium channels contributes to the plateau phase (phase 2) of the action potential of cardiac and vascular smooth muscle cells.

The exact mechanism whereby DL inhibits calcium ion influx across the slow calcium channels is not known, but the drug is thought to interfere with the release of calcium from the sarcoplasmic reticulum.
By inhibiting calcium influx, DL inhibits the contractile processes of cardiac and vascular smooth muscle, thereby dilating the main coronary and systemic arteries. In patients with Prinzmetal variant angina (vasospastic angina), inhibition of spontaneous and ergonovine-induced coronary artery spasm by DL results in increased myocardial oxygen delivery. Dilation of systemic arteries by DL results in a decrease in total peripheral resistance, systemic blood pressure and after load of the heart and, at high doses (e.g., 210 mg), an increase in the cardiac index. Decreases in peripheral vascular resistance usually occur without orthostatic decreases in blood pressure or tachycardia; however, orthostatic hypotension has occurred occasionally when the upright position was assumed suddenly. The reduction in after load, seen at rest and with exercise, and its resultant decrease in myocardial oxygen consumption, are thought to be responsible for the effects of DL in patients with chronic stable angina pectoris. DL also appears to reduce left ventricular mass and wall thickness that is associated with hypertension.

**Pharmacokinetics**

In all studies described in the Pharmacokinetics section, DL was administered as the hydrochloride salt. Pharmacokinetic data of DL are given in table 3.2.

**Absorption**—Approximately 80% of an oral dose of DL is rapidly absorbed from the GI tract following oral administration of conventional tablets of the drug. Only about 40% of an oral dose reaches systemic circulation as unchanged drug since DL undergoes extensive metabolism on first pass through the liver. Oral bioavailability and average plasma concentrations at steady state reportedly are equivalent following oral administration of DL dosages of 120 mg twice daily as
extended-release capsules or 60 mg 4 times daily as conventional tablets; however, peak plasma concentration at steady state is lower and the time to peak concentrations is longer with extended-release capsules. An extended-release tablet formulation of the drug (not commercially available in the US) also has been shown to be bioequivalent to conventional DL tablets. The oral bioavailability of the dual-release at steady state is about 95% when compared with that of conventional DL tablets. Oral bioavailability of DL hydrochloride increases disproportionately with increasing doses; as the dose of conventional tablets increases from 60 mg to 120 mg or the dosage of extended-release capsules increases from 120 to 240 mg daily (60 to 120 mg twice daily), oral bioavailability of the drug approximately triples, and as the dosage of extended-release capsules increase from 240 to 360 mg daily, the oral bioavailability approximately doubles. Food does not appear to affect the extent of absorption of dual-release DL capsules; however, rate of absorption may be increased if the dual-release or extended-release capsules (Dilacor XR) are taken with a high-fat meal. Peak serum concentrations usually are reached within 2-3, 4-11, or 10-14 hours after oral administration of conventional tablets, extended-release capsules, or dual-release capsules of the drug, respectively. Considerable interindividual variations in plasma concentrations attained have been reported with a specific oral dose of DL. Plasma concentrations of 50 - 200 ng/mL appear to be required for antianginal effect. The manufacturer of DL dual-release capsules states that the dual-release capsules administered once daily provide 24-hour blood pressure control.

**Distribution**- About 70-85% of DL is bound to plasma proteins, but only 35-40% is bound to albumin. DL is distributed into milk, apparently in concentration approximately equal to maternal serum concentrations.
Elimination- In healthy individuals, DL has a plasma half-life of 3.5-10 hours; however, plasma half-life of unidentified metabolites may be increased to about 20 hours. Elimination of the drug appears to be a first-order process. Plasma half-life of the drug may be increased in geriatric patients, but is unchanged or only slightly increased, in patients with renal impairment. DL is rapidly and almost completely metabolized in the liver via deacetylation, N-demethylation, and O-demethylation to one active and at least 5 inactive metabolites; the drug and its metabolites also undergo glucuronide and/or sulfate conjugation. About 10-35% of DL is metabolized to deacetyl diltiazem, which has 25-50% of the coronary vasodilating activity of DL. Approximately 2-4% of a dose of the drug is excreted in urine unchanged. The remainder of the drug is eliminated in urine and bile, mainly as metabolites.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa</td>
<td>7.7</td>
<td>T(_{1/2})</td>
<td>3 to 5 hours</td>
</tr>
<tr>
<td>Log P</td>
<td>2.7</td>
<td>CL</td>
<td>1000 ml/min</td>
</tr>
<tr>
<td>Oral absorption</td>
<td>100 %</td>
<td>AU</td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td>T(_{\text{max}})</td>
<td>3 hours</td>
<td>Dose</td>
<td>180 to 360 mg/day</td>
</tr>
<tr>
<td>Vd</td>
<td>4.5 l/kg</td>
<td></td>
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</tr>
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</table>

Uses

DL is used in the management of Prinzmetal variant angina, chronic stable angina pectoris, and hypertension.
Dosage

Angina- For the management of Prinzmetal variant angina or chronic stable angina pectoris, the usual initial adult dosage of DL as conventional tablets is 30 mg 4 times daily. Generally, dosage is gradually increased at 1- to 2-day intervals until optimum control of angina is obtained. The average optimum adult dosage range for DL tablets appears to be 180-360 mg daily given in 3 or 4 divided doses.

Hypertension- For the management of hypertension in adults receiving DL as monotherapy, the usual initial dosage as extended-release capsules (Cardizem SR) is 60-120mg twice daily and as dual-release capsules (Cardizem CD) or extended-release capsules (Dilacor XR) is 180-240 mg once daily.(PDR Generics, 1996; The Merck Index, 1996; Physicians Genrx, 1996; Martindaie, 1999; Hardman JG, 1996, Cardizem CD, package insert)

Literature Review

Pellets Based Formulations

Geoghegan et. al. (1989), developed a controlled release pellet formulation of DL comprising of core containing DL in association with an organic acid (fumaric acid) and a multilayered membrane containing water soluble synthetic polymer (Eudragit RS 12.5% in acetone/isoProH 140 parts) and optionally a film forming water soluble polymer (Eudragit RL 12.5% in acetone/isoProH 10 parts and isoProH 50 parts). The amount of DL released after 2, 4, 8 and 24 hr was 2.3, 17.7, 49 and 95.7% respectively. Time of peak effect of 14 hr was observed in volunteers when 240 mg dose was given.

Geogheganand co-workers (1990) developed controlled release pellets DL for once daily administration. The pellet core was prepared using DL, fumaric acid (or
adipic acid), and talc using a coating solution of polyvinylpyrrolidone (or other water soluble polymer or a combination of water soluble and a minor proportion of water insoluble polymer). The core was coated by spraying solutions of Eudragit RS and RL. The prepared pellets could be compressed into tablets using a binder (e.g. microcrystalline cellulose) maintaining the same release pattern or filled into capsules. An initial rapid release of DL could be obtained by combining rapid release pellets with coated pellets. The bioavailability and other pharmacokinetic parameters of the drug after single oral administration were consistent with once a day requirement.

Appelgren and co-workers (1991) prepared sustained release multiple unit dosage form for once or twice a day administration. DL was administered in the form of uncoated multiple unit dose granule. The granules were coated with a mixture of ethylcellulose and an anionic polymer which dissolves at pH ≥ 5. The coating mixture contained 20-40 parts per weight anionic polymer in relation to 60-80 parts per weight of ethyl cellulose.

Hendrickson and co-workers (1992) used coated beads to obtain controlled release formulation of DL for once a day oral administration. Central cores consisted of DL and sugar. The cores were coated with various amounts of Eudragit RS 30D and Eudragit RL 30D to obtain rapid release and slow release beads respectively. A mixture of these two types of beadles filled into capsules was found to be suitable for once a day administration in antihypertensive treatment.

Eicehl et. al. (1992), prepared a delayed release pharmaceutical preparation of DL in which two batches were combined in a dosage form, the long acting batch and the short acting batch. A half of the core prepared by coating a dispersion containing DL, hydroxypropyl methylcellulose, microcrystalline cellulose, magnesium stearate in
water and the other half of beads were coated with a dispersion containing Eudragit NE 30D, Eudragit RSL 30D, sodium lauryl sulphate and magnesium stearate in water. A mixture of the beads showed a two tiered release profile in dissolution test performed accordingly to USP basket method.

Follonier et al. (1992), examined the effects of different parameters such as type, drug/polymer ratio, and pellet size on the release of DL from hot melt extruded pellets. Additional cationic hydrocolloids or enteric polymers were incorporated in order to approach zero order release kinetics.

Buxton and co-workers (1993) prepared controlled release coated spheroids containing DL. The (0.85 - 1.7mm) were coated with a film coat of ethylcellulose N10, colloidal anhydrous silica, dibutyl sebacate, polysorbate 80, dichloromethane and methanol. DL containing controlled release spheroids were film coated with a dispersion of hydrochlorothiazide and hydroxylpropyl methylcellulose. DL release was not affected by application of hydrochlorothiazide layer.

Buxton and co-workers (1993) prepared a controlled release formulation comprising of spheroids containing DL and a spheronizing agent. DL and microcrystalline cellulose were mixed, wet granulated and extruded to make spheroids. The spheroids were coated with a film of ethylcellulose, colloidal silica, dibutyl sebacate, polysorbate 80.

Sherman and co-workers (1996) developed a pharmaceutical formulation containing DL suitable for once daily oral administration. It comprised of a blend of beads having three different dissolution profiles. Core beads were made by the extrusion and spheronization process containing 90% of drug, the balance being microcrystalline cellulose together with methylcellulose as a binder. The core beads
were then coated with a coating composition containing Eudragit RS 30D along with plasticizer and talc. Capsules filled with these beads showed 100% after 12 hr.

**Matrix Based Formulations**

Altevogt, et. al. (1989), proclaimed an once a day tablet formulations of DL using hydrogenated castor oil and stearic acid as hydrophobic filler to control release pattern of the tablets. DL, lactose, hydrogenated castor oil and stearic acid were heated to 60° and then cooled and granulated with sodium carboxymethylcellulose. The tablets showed more than 60% drug dissolution after 5 hr during in-vitro studies.

Chang and co-workers (1990) developed sustained release tablets comprising of DL in hydrophobic matrix and water-soluble film coating. The tablets contained DL, glycerylmonostearate, confectioner's sugar, microcrystalline cellulose, povidone, magnesium stearate, hydroxypropyl methylcellulose (2% solution 50 cps), Polyethylene glycol and color dispersion. The percentage drug dissolved in 24 hr was found to be 90%.

Kristmundsdottir et. al. (1995), studied the influence of excipient on drug release (DL) from chitosan matrix tablets. The effect of different concentrations of lactose, sodium lauryl sulphate, sodium alginate, carbopol 934 P, citric acid and hydroxypropyl methylcellulose on drug release profiles was studied. Sustained release was obtained in all the cases. Both the type and amount of excipient used influence the drug release.

Xu Ping (1995) developed a new type of complex reservoir - matrix system for the controlled delivery of DL. The capsule type device contained (i) an appropriate amount of the drug in a compartment; (ii) a swelling-controlled membrane which was prepared by mixing polymeric materials with another appropriate amount of the drug.
and (iii) a water soluble gelatin capsule as a container. The swelling controlled membranes were prepared from poly (2-hydroxy-ethyl methacrylate) hydrogels. The effect of pH on the swelling of the hydrogels was studied. In-vitro dissolution testing was carried out to evaluate the release of the drug. Zero order release kinetics was obtained over a period of 12 hr.

Galiatsatos and co-workers (1996) used blends of poly(2-hydroxyethyl methacrylate) PHEMA, polyethylene glycol (PEG), ethylene oxide-propylene oxide block polymer (P(EO-PO), and DMSO to study the release of DL from the matrixes. The duration of zero order release increased from 1-4 hr with only a 10% increase in amount of copolymer. For blends containing > 15% copolymer a decrease in the zero order interval was more gradual.

Kuhrts et. al. (1996), prepared a sustained release drug delivery employing a powdered hydrocolloid gum obtainable from higher plants. An oral delivery pharmaceutical composition for achieving sustained release of a drug includes (a) 20-90% of a pharmaceutically acceptable hydrocolloid gum (b) 5-30% another excipient that aids in sustained release and (c) a therapeutically effective amount of a drug. The mean particle size of the gum is about 150 μm or less. A caplet contained DL 240, guar gum 490, hydroxypropyl methylcellulose 39 and stearic acid 16 mg.

**Osmotically Controlled Formulations**

Haslam and co-workers (1989) prepared an osmotic pump for controlled release diltiazem L-malate comprising of core containing a therapeutically effective amount of drug and an effective buffering agent (sodium bitarate). The core was surrounded by a rate controlling water soluble wall prepared from polymer permeable to water but impermeable to solute and a pH insensitive pore forming additive
dispersed throughout the wall in an amount of 1.0 to 60% of total wall weight. Tablet cores prepared from sodium bitartrate and polyvinylpyrrolidone were coated with solution containing cellulose acetate, sorbitol and polyethylene glycol 400 and dried. The drug release profile in hydrochloride (pH 1.2), water and 0.05 M phosphate buffer (pH 7.5) were very similar. About 50% drug was released after 6-7.5 hr in all three media.

Appel (1991) and his team utilized ethylcellulose (Aquacoat) to achieve controlled release of DL from tablets. Plasticizers and urea, a pore forming agent, were added and the release profiles were examined. The drug dissolution was found to be dependent on thickness of coating, concentration of pore forming agent and type and concentration of plasticizer.

McClellan and co-workers (1991) investigated an osmotic pump for conversion of first order to zero order kinetics using DL as a model drug. The presence of NaCl (1M) markedly decreased the solubility of DL. Devices were prepared with cores that contained DL and sufficient NaCl granules coated with microporous cellulose acetate butyrate film to maintain a 1M NaCl concentration with in the drug compartment over 16 hr period. In-vivo percent DL absorbed profiles were superimposable with in-vitro release profile in beagle dogs.

**Floating Formulations**

Hou and co-workers (1991a, b) prepared sustained release intragastric floating tablets of DL based on polyvinylpyrrolidone and polyvinyl alcohol. The tablets were buoyant on the gastric juice and DL was slowly released from them. In the absorption study in dogs, the plasma DL concentration after oral administration was determined using HPLC. They reported that steady and lasting drug concentration could be
maintained with floating tablets. They also explored the potential of tablet based on chitosan and DL. The unique advantage of chitosan matrix was that they gradually swelled and floated in acid medium (pH 1.2). When a capsule was administered orally to dog, the plasma concentration reached the maximum level in 2 hr after oral administration. The tablets did not give a sharp peak but produced a sustained plateau of drug.

**Miscellaneous Formulations**

Horiuchi and co-workers (1990) evaluated release characteristics of two ethyl β-cyclodextrins (diethyl β-cyclodextrin and triethyl β-cyclodextrin) as sustained release drug carriers using DL. The release rate of DL was significantly retarded from the complexes. Effect of pH, rotating speed and additive in dissolution medium were investigated. Release rate of DL can be controlled by combining the ethylated β-cyclodextrin complexes with parent β-cyclodextrin complex in different mixing ratios. No decrease in area under plasma concentration was produced for a long time when administered to dogs.

Carli and co-workers (1991) prepared delivery system containing DL loaded onto particles of crosslinked water insoluble but swellable nonionic polymer (e.g., crosslinked β-cyclodextrin, crosspovidone) and coated with an water insoluble but slightly water permeable polymer (e.g., Eudragit RS 100). The system showed prolonged drug release of greater than 24 hr.

Ishino et al. (1992), prepared an orally applicable pulsatile drug delivery system in dry coated tablet form using DL. The coating consisted of polyvinylchloride, hydrogenated castor oil, and polyethylene glycol. The tablets exhibited a typical pulsatile pattern with a 7 hr lag phase. This dosage form was orally
tested in beagle dogs. The drug was released in gastrointestinal tract as effectiveness in the in vitro tests.

Noda and co-workers (1992) prepared controlled release preparation comprising of core containing DL and a coating layer containing Eudragit RS 100, water repellant salt (calcium stearate) and plasticizer (triethyl citrate). The preparation released DL in sigmoid type dissolution pattern irrespective of pH of dissolution media. The study in dog revealed that higher plasma concentration was maintained for a long time (30 hr) after a lag period of 8 hr.

Kristmundsdottir and co-workers (1996) prepared microparticles containing DL by spray drying technique using Eudragit Rs and RL as coating materials. Release pattern of DL was not affected by microparticles structure. They concluded that the drug release could be controlled by choice of polymer type and production conditions during spray drying.

In Vivo Studies

Uekama et. al. (1987), prepared complex of DL with ethylated β-cyclodextrins to prepare sustained release tablets of DL. A considerable increase in area under plasma concentration curve (AUC, upto 48 hr) was observed in comparison to conventional DL tablets (with starch as diluent) following oral administration in rats.

Du Souichet et. al. (1990), studied the influence of food on bioavailability of DL conventional and slow release tablets. It was concluded that food does not influence bioavailability of slow or conventional release formulation.

Herpin (1990) compared the effect of two dosage of sustained release DL (240 and 300 mg). Both formulations were given once a day for 21 days in placebo controlled blind study in 38 patients. The reduction in clinical blood pressure
appeared to be similar in both dosage forms and placebo groups, whereas the ambulatory blood pressure profile was significantly lowered only in patients receiving dosage form containing 300 mg of DL.

Thiercelinet. et. al. (1990), prepared sustained release micro granules of DL. Bioavailability studies were performed after single dose administration and after repeated dose administration. The bioavailability was compared with conventional formulation (Tildiem). A relative bioavailability of 1.06, prolongation of Tmax (7.16 versus 2.46 hr) and longer final half life (11.8 versus 5.6) were observed following single dose administration. Repeated administration of sustained release DL (240 mg daily) and repeated administration of conventional preparation of DL (120 mg every 12 hr over a period of 6 days) showed a relative bioavailability of 0.9, and lowering effect on Cmax of 191 versus 230 ng/ml and statistically equivalent minimum concentrations of 62 ng/ml versus 74 ng/ml. Concurrent food intake increased the bioavailability of DL by 28%. Microgranules at a dose of 300 mg yielded an effective and well tolerated concentration (80-200 ng/ml) with a single dose regimen.

Sulton and co-workers (1990) studied the pharmacokinetics of two extended release osmotic formulation of DL in beagle dogs following oral administration of 110 mg of drug in extended release tablet form and oral dosing of 55 mg solution. Both the formulations had similar bioavailability (F) as DL solution. The two extended release formulations designed with different in-vitro release profiles, reflected these differences in vivo with nearly identical in-vitro and in-vivo release profiles.

Klokkers-Bethke and co-workers (1991) prepared a multiple unit drug delivery system for positioned release in the gastrointestinal tract. The in-vivo targeting properties of two formulations containing 120 mg od drug per capsule were
investigated in a bioavailability study. The Tmax values were 7.3 ± 5.0 hr; and the relative AUC values were 100% and 60%.

Zentner and co-workers (1991) studied the drug release kinetics from controlled porosity osmotic pumps that have been effectively manipulated using either solubility or resin modulation methods. Solubility of DL was reduced for an extended period of 12-14 hr using controlled release sodium chloride elements into core tablet formulations. Other formulations contained poly(4-vinyl pyridine), an positively charged anion exchange resin. In both cases zero order and pH-independent release was seen.

WilDinget et al. (1991), studied the in vivo behaviour of a sustained release multiparticulate form of DL (240 mg) by gamma scintilography in eight subjects under fasting or fed condition. The gastric emptying of the pellet formulation was significantly influenced by the presence of food. The type of oral formulation (i.e. solution or pellets) appeared to affect the rate, but not the extent, of absorption with the relative bioavailability (pellets to solution) being greater than 90%.

Dange and co-workers (1992) studied the pharmacokinetics and pharmacodynamics of DL in 8 healthy Indian adults. DL was administered as single dose (60 mg) of 2 formulation viz., immediate release (IR) and modified release (MR). It was observed that MR formulation of DL had better pharmacokinetic and dynamic profile as compared to IR formulation.

Christrup and co-workers (1992) studied the single dose and steady state pharmacokinetics of DL administered in two different commercial formulations. The Area Under the Curve (AUC) values following single dose administration of Cardil and Cardizem were 678 and 948.6 ng/hr ml. The area under the curve in steady state
of Cardil and Cardizem were 880.1 and 1056.8 ng/hr ml respectively. The $T_{\text{max}}$ values were 2.9 hr and 6.8 hr.

Gu and co-workers (1992) studied the pharmacokinetics and dynamics of DL floating tablets in 8 healthy volunteers. Each subject received 90 mg DL floating and normal tablets in crossover design. The half-life of the floating and normal tablets was reported as 6.4 and 2.3 hr, and $C_{\text{max}}$ were found to be 56 and 96 ng/ml respectively. Area under the curve of both the products was found to be similar, suggesting same bioavailability. The duration of hypotension was longer with the floating tablet.

Caramella and co-workers (1993) studied the in-vitro/in-vivo correlation of six preparations i.e. three multiple unit dosage forms micropellets in capsules (D, E, and G), matrix tablet (B) and two non-disintegrating tablets (A and C, commercial products). A and C showed mean dissolution time (MDT) 1.34 and 1.44 hr and $t_d$ 91 and 92 min respectively. For prolonged release formulations (B, E, D and G), MDT ranged between 2.28 and 4.23 hr and $t_d$ ranged between 149 and 291 min. Mean residence time (MRT) was found to be 8.68 and 6.47 for A and C respectively and it ranged between 9.62 and 11.27 hr for the prolonged release preparations. High variability between various formulations was found for $C_{\text{max}}$ and area under the curve values. No relationships could be established.

Murata and co-workers (1994) studied the in vivo performance of multiparticulate sustained release DL preparations coated with ethylcellulose in dogs. The bioavailability of the formulation was comparable with that of conventional DL tablet. The plasma concentration was analyzed with a two fraction absorption model. Almost all of the slow release fraction reached the colon within 5 hr of administration. In-vivo release profile of DL from the sustained release preparation was calculated by the Wagner-Nelson method. A close correlation of in vivo release profiles was found.
Matsuo and co-workers (1996) prepared delayed release tablets containing 30 mg DL and compressed CM-L2 (14 cps), CM-L3 (27 cps), or CM-L4 (95 cps), CM type hydroxy ethylcellulose and investigated the in-vitro dissolution in media pH 1.2 and 6.8 and in vivo pharmacokinetics. DL was rapidly released from tablets after a lag time of several hr in all cases. Lag time increased as viscosity increases and there was little difference in lag time between two dissolution media. Rate of water uptake was greater in CM-L4 than in CM-L3 and CM-L2. Time to peak effect (T_max) and mean residence time from 0-24 hr of the tablets significantly increased as the viscosity increases. Values of area under the curve were the same, C_max values decreased with prolongation of lag time. In vivo and in vitro release profiles were generally similar and lag times also corresponded well.