2. Review of Literature

2.1 Literature Research Review

Anita Hafner et.al\textsuperscript{27} prepared conventional and composed promethazine-loaded microspheres by spray drying of chitosan solution systems and double water-in oil-in-water (W/O/W) emulsion systems, respectively. Double emulsions were prepared in two different feed concentrations, with chitosan dissolved in both water phases, and ethylcellulose dissolved in oil phase. Swelling and bioadhesive properties of the microspheres depended on the chitosan content, type and the feed concentration of spray-dried system. Results obtained suggested that better ethylcellulose microcapsules with promethazine in the chitosan matrix were formed when less concentrated emulsion systems were spray-dried. Thus, in case of such a system, with ethylcellulose/chitosan weight ratio of 1:2, prolonged promethazine release was obtained.

Chien N.\textsuperscript{28} Nguyen prepared semisolid matrix capsule formulations of verapamil HCl and diltiazem HCl by hot-melt capsule filling which is an especially appealing and simple way to make sustained-release formulations. Semisolid matrices of Gelucire\textsuperscript{®} 50/13 and stearic acid combination eroded and disintegrated at various rates, depending on the combination of waxes, and drug. The release rates were dependent on storage time (2.5 years) and temperature. Semisolid matrices of combinations of only Gelucire\textsuperscript{®} 50/13 and cetyl alcohol eroded at a rate much less than combinations
of Gelucire® 50/13 and stearic acid. The drug release mechanism from Gelucire® 50/13: stearic acid matrices involved diffusion and erosion, whereas Gelucire® 50/13 and cetyl alcohol matrices exhibited a diffusion mechanism only. A combination of Gelucire® 50/13 with cetyl alcohol is more effective than stearic acid in appropriately extending verapamil HCl release from semisolid matrix capsules. The semisolid matrix formulations studied are sensitive to dissolution stirring speeds.

Go´mez-Burgaz M et al\(^{29}\) prepared Chitosan (CS) and carboxymethylcellulose (CMC) sodium inter polymer complexes by using the novel method “tablets-in-capsule” for stomach drug delivery. They investigated the influence of the molecular weight (M.wt.) of CS and the proportion CS/CMC on physical properties and clarithromycin (CAM) release. Swelling was dependent on CS M.W, on medium pH and on proportion polymer/polymer. Swelling kinetics at pH 1.2, were close to Fickian diffusion, whereas at pH 4.2 were non-Fickian. Furthermore, dissolution medium uptake capacity can be adjusted to an exponential equation at pH 1.2 \((r^2 \geq 0.96)\), and to a linear equation at pH 4.2 \((r^2 \geq 0.99)\), showing that at low pHs the repulsion among ionized chains is higher. CAM release rates have shown to be dependent on pH and on polymer proportion. At pH 1.2, the fastest profile was obtained when using high M.W. CS. Drug diffusion was Fickian, so the process is governed by swelling/eroding. Whereas at pH 4.2, CAM release followed zero-order kinetics with no
influence of M.W. and found that the release is controlled by CAM low solubility.

Ceyda T. S-engel, et al. studied on the development of modified release tablet formulations containing diltiazem hydrochloride loaded microspheres. They prepared ethylcellulose microspheres by emulsion-solvent evaporation technique. And evaluated for the influence of emulsifier type and drug/polymer ratio on production yield, encapsulation efficiency, particle size, surface morphology and in-vitro release characteristics. Suitable microspheres tabletted and were evaluated from the perspective of physical and in-vitro drug release characteristics. It was seen that type and ratio of the excipients played an important role in the tabletting of the microspheres. As a result, two tablet formulations containing 180 mg diltiazem hydrochloride and using either Compritol_888 ATO or Kollidon_SR were designed successfully and maintained drug release for 24 h with zero order and Higuchi kinetics, respectively.

Bolourtchian. N, et al. microencapsulated ibuprofen with Eudragit RS using an o/w emulsion solvent evaporation technique. The effects of three formulation variables including the drug:polymer ratio, emulsifier (polyvinyl alcohol) concentration and organic solvent (chloroform) volume on the entrapment efficiency and microspheres size distribution were examined. The drug release rate from prepared microspheres and the release kinetics were also studied. The results demonstrated that microspheres with good range of particle size can
be prepared, depending on the formulation components. The drug:polymer ratio had a considerable effect on the entrapment efficiency. However, particle size distribution of microspheres was more dependent on the volume of chloroform and polyvinyl alcohol concentration rather than the drug:polymer ratio. The drug release pattern showed a burst effect for all prepared microspheres due to the presence of uncovered drug crystals on the surface. It was shown that the release profiles of all formulations showed good correlation with the Higuchi model of release.

Sultana, S et al\textsuperscript{32} formulated and systematically evaluated in vitro performance of mucoadhesive microspheres of lacidipine for treatment of pylorospasm. For this Lacidipine microspheres containing chitosan were prepared by chemical denaturation using glutaraldehyde as a cross-linking agent. The prepared microspheres were evaluated for physical characteristics such as particle size, particle shape and surface morphology by scanning electron microscopy, drug entrapment efficiency and in vitro mucoadhesion. Results of preliminary trials indicated that the polymer concentration, cross-linking agent and stirring speed had a noticeable effect on size and surface morphology. A central composite design was employed to study the effect of independent variables, polymer concentration (X1), volume of glutaraldehyde (X2), stirring speed (X3) and cross-linking time (X4) on dependent variables, drug entrapment efficiency and percentage mucoadhesion. The entrapment efficiency varied from 14–
40.82% depending upon the polymer concentration, volume of cross-linker and stirring speed. All batches of microspheres exhibited good mucoadhesive property (73–83%) in the in vitro wash-off test. It was observed that polymer concentration and glutaraldehyde volume had a more significant effect on the dependent variables. Maximum entrapment (36.53%) and mucoadhesion (81.33%) was predicted at 3.5% chitosan, 3ml glutaraldehyde, 3000 rpm stirring speed and 75 min cross-linking time under optimized process condition. The selected formulation showed controlled release for more than 6 h. The release followed Higuchi kinetics via a Fickian diffusion.

Lian-Yan Wang, et al\textsuperscript{33} showed that the control of size and size distribution of microspheres is necessary for obtaining repeatable controlled release behavior. They prepared chitosan microspheres by a membrane emulsification technique. Chitosan was dissolved in 1 % aqueous acetic acid containing 0.9 % sodium chloride, which was used as a water phase. A mixture of liquid paraffin and petroleum ether 7:5 (v/v) containing PO-500 emulsifier was used as an oil phase. The water phase was permeated through the uniform pores of a porous glass membrane into the oil phase by the pressure of nitrogen gas to form W/O emulsion. Then GST (Glutaraldehyde Saturated Toluene) as crosslinking agent was slowly dropped into the W/O emulsion to solidify the chitosan droplets. The preparation condition for obtaining uniform-sized microspheres was optimized. The membranes of different pore size were used to prepare microsphere of
different sizes. The smallest chitosan microspheres obtained was 0.4 µm in diameter. This was the first report for preparing the uniform-sized chitosan microspheres by membrane emulsification technique.

Zhou Li et al\textsuperscript{34}, prepared captopril/Chitosan-gelatin net-polymer microspheres (CTP/CGNPMs) using Chitosan (CTS) and gelatin (GT) by the methods of emulsification, cross-linked reagent alone or in combination and microcrystalline cellulose (MCC) added in the process of preparation of microspheres, which aimed to eliminate dose dumping and burst phenomenon of microspheres for the improvement of the therapeutic efficiency and the decrease of the side effects of captopril (CTP). The results indicated that CTP/CGNPMs had a spherical shape, smooth surface and integral structure inside but no adhesive phenomena in the preparation. The size distribution ranged from 220 µm to 280 µm. The CTP release test \textit{in vitro} demonstrated that CTP/CGNPMs played the role of retarding the release of CTP compared with ordinary CTP tablets. The release behaviors of CGNPMs were influenced by preparation conditions such as experimental material ratio (EMR) and composition of cross linking reagents. Among these factors, the EMR (1/4), CLR (FA+SPP) and 0.75\% microcrystalline cellulose (MCC) added to the microspheres. The CTP/CGNPMs had the good characteristics of sustained release of drug and the process of emulsification and cross-linking were simple and stable. The CGNPMs are likely to be an ideal sustained release formulation for water-soluble drugs.
Kiran S. Bhise, et al. investigated the potential use of anionic κ-carrageenan and nonionic hydroxyl propyl methyl cellulose (HPMC, K4) to improve the matrix integrity of directly compressed chitosan tablets containing naproxen sodium, an anionic drug. The influence of buffer pH and drug:polymer ratio on the water uptake, matrix erosion, and drug release were studied. The rapid release of naproxen sodium was seen from matrices containing 100% chitosan due to loss in the matrix cohesiveness; whereas, it was relatively slow for matrices containing optimum concentration of κ-carrageenan. In-situ interaction between oppositely charged moieties resulted in the formation of polyelectrolyte complexes with stoichiometric charge ratios of unity. Fourier transform infrared (FTIR) spectroscopy and powder x-ray diffraction (PXRD) data confirmed the importance of ionic bonds in polyelectrolyte complexation. They found that, ionic interactions between polymers were absent in matrices containing HPMC and the integrity of tablets was improved owing to the presence of viscous gel barrier.

Bahar B. Horoz, et al. investigated the effects of different concentrations of polymer and sucrose stearate, aluminum tristearate as dispersing agents on various properties of microspheres. The yield values of microspheres were over the 78%, and the encapsulation efficiencies were found to be ~73%. Particle sizes of microspheres prepared with aluminum tristearate were between 76 and 448 μm, while that of the microspheres containing sucrose stearate were
between 521 and 2000 μm. Morphological and physicochemical properties of microspheres were investigated by scanning electron microscopy and differential scanning calorimetry (DSC). DSC analysis indicated that verapamil hydrochloride formed a solid solution with acrylic polymers. They performed In vitro release studies using the flow-through cell method. While ~80% of drug was released from the microspheres containing aluminum tristearate in 480 minutes, the same amount of drug was released from microspheres containing sucrose stearate in only 60 minutes. They found that chemical structures and concentrations of the dispersing agents were clearly effective on the physical properties of microspheres and their drug-release characteristics.

Valluru Ravi, et. al developed a formulation of novel colon targeted tablet using chitosan and guar gum as carriers and diltiazem hydrochloride as model drug. The prepared blend of polymer-drug tablets were coated with two layers, inulin as an inner coat followed by shellac as outer coat and were evaluated for properties such as average weight, hardness and coat thickness. In vitro release studies of prepared tablets were carried out for 2 h in pH 1.2 HCl buffer, 3 h in pH 7.4 phosphate buffer and 6 h in simulated colonic fluid (SCF) in order to mimic the conditions from mouth to colon. They observed that, 4% w/v of rat cecal contents in saline phosphate buffer (SCF) incubated for 24 h provides suitable conditions for in vitro evaluation of the formulations prepared. In vitro studies revealed that the tablets coated with inulin and shellac have
controlled the drug release in stomach and small intestinal environment and released maximum amount of drug in the colonic environment. Among the polymers used, chitosan was found to be the suitable polymer for colon targeting. The study revealed that polysaccharides as carriers and inulin and shellac as coating materials can be used effectively for colon targeting of drugs for treating local as well as systemic disorders.

Xiao-yan LI et al\(^{38}\) studied on capsules of alginate and gelatin prepared by extrusion method. The capsules prepared were spherical, smooth-surfaced and non-aggregated with a diameter of \((4.0\pm0.3)\) mm. Four kinds of capsules in simulated gastric fluid (SGF) exhibited shrinkage while the beads eroded accompanied with slight swelling in simulated intestinal fluid (SIF). The pH values affected the stability of the capsules and with the increase in pH, the capsules changed from shrank then swelled and finally, broke into pieces. The capsules behaved differently under different ion intensities and the introduction of gelatin weakened the stability of capsules compared with the alginate ones. Cells of L. casei ATCC 393 could be continuously released from the capsules in the simulated gastrointestinal tract (GIT) and the release amounts and speeds in SIF were much higher and faster than those in SGF.

Paola Perugini, et al\(^{39}\) investigated on the formulation of a biodegradable microparticulate drug delivery system containing clodronate, a bisphosphonate intended for the treatment of bone
diseases. They prepared microspheres with several poly(D,L-lactide-co-glycolide) (PLGA) copolymers of various molecular weights and molar compositions and 1poly(D,L-lactide) (PDLLA) homopolymer by a water-in-oil-in-water (w/o/w) double emulsion solvent evaporation procedure. Critical process parameters and formulation variables (ie, addition of stabilizing agents) were evaluated for their effect on drug encapsulation efficiency and clodronate release rate from microparticles. Well-formed clodronate-loaded microspheres were obtained for all polymers by selecting suitable process parameters (inner water/oil volume ratio 1:16, temperature-raising rate in the solvent evaporation step 1°C/min, 2% wt/vol NaCl in the external aqueous phase). Good yields were obtained in all batches of clodronate microspheres (above 60%); drug encapsulation efficiencies ranged between 49% and 75% depending on the polymer used. Clodronate release from all copolymer microspheres was completed in about 48 hours, while those from PDLLA microspheres required about 20 days. The change of microsphere composition by adding a surfactant such as Span 20 or a viscosing agent such as carboxymethylcellulose extended the long-term release up to 3 months. Clodronate was successfully entrapped in PLGA and PDLLA microspheres, and drug release could be modulated from 48 hours up to 3 months by suitable selection of polymer, composition, additives, and manufacturing conditions.
Patil S.B. and Murthy R. S. R. \(^{40}\) prepared mucoadhesive chitosan microspheres of amlodipine besylate for nasal administration with the aim of avoiding the first pass effect. For this microspheres were prepared by simple emulsification cross linking method to optimize parameters like external phase (mixture of heavy and light liquid paraffin in the ratio of 1:1), stirring rate (1200 rpm), dioctyl sodium sulfosuccinate concentration (0.2% w/v), Chitosan:drug ratio (2:1), volume of crosslinking agent (glutaraldehyde, 1 ml) and time of crosslinking (3 h). The microspheres were evaluated for physical characteristics such as particle size, particle shape and surface morphology by scanning electron microscopy, drug entrapment efficiency, in vitro mucoadhesion, and in vitro drug release characteristics. The microspheres had a mean particle size of 36.47±3.39 µm, suitable for nasal administration. Electron microscopy revealed that microspheres were spherical with nearly smooth surface morphology. Application of in vitro drug release data to various kinetic equations indicated matrix diffusion controlled drug release from chitosan microspheres.

Md. Selim Reza \textit{et al.} \(^{41}\) investigated the effect of plastic, hydrophilic and hydrophobic types of polymers and their content level on the release profile of drug from matrix systems. For this, matrix tablets of theophylline, diclofenac sodium and diltiazem HCl using Kollidon SR, Carnauba wax and Hydroxypropyl methylcellulose (HPMC-15cps) were prepared separately by direct compression
process. Statistically significant differences were found among the drug release profile from different classes of polymeric matrices. The release kinetics was found to be governed by the type and content of polymer in the matrix system. Higher polymeric content (75%) in the matrix decreased the release rate of drug because of increased tortuosity and decreased porosity. At lower polymeric level (25%), the rate and extent of drug release was elevated. Carnauba wax was found to cause the strongest retardation of drug. On the other hand, highest drug release was from HPMC matrices while Kollidon SR gave an intermediate release profile between these two polymers. Release rate was also found to be the function of physico-chemical nature of drug molecule. Theophylline and diltiazem HCl, being soluble in nature, released faster than diclofenac sodium from all matrix systems. The release mechanism was explored and explained with biexponential equation. Release profile showed a tendency to follow zero-order kinetics from HPMC matrix systems whereas Fickian (Case I) transport was predominant mechanism of drug release from Kollidon SR matrix system. The mean dissolution time (MDT) was calculated for all the formulations and the highest MDT value was obtained with Carnauba wax for all the drugs under investigation. They concluded that a controlled plasma level profile of drug can be obtained by judicious combination of polymers and modulation of polymer content in the matrix system.
Jain S K et al. prepared novel mucoadhesive chitosan microspheres of Insulin by emulsification method. Prepared microspheres were characterised for various physicochemical attributes, shape, surface morphology, size and size distribution, drug payload, swelling ability and mucoadhesion. And evaluated for in vitro drug release and in vitro drug permeation through mucosal membrane. Glutaraldehyde crosslinked microspheres showed better reduction of blood glucose level than citric acid crosslinked microspheres. The in vivo performance showed prolonged and controlled release of drug as compared with the conventional dosage form.

Morkhade, D.M. and Joshi S.B investigated a natural gum, dammar as a novel microencapsulating material for sustained drug delivery. For this microparticles of Diltiazem HCL and Ibuprofen were prepared by oil in oil emulsion solvent evaporation method and evaluated for particle size, encapsulation efficiency and in vitro drug release kinetics. They investigated the effect of different gum:drug ratios and solubility of drug on microparticle properties. The increasing gum: drug ratio showed an increase in particle size, encapsulation efficiency and drug release rate in all cases. Drug release profiles of all microparticle followed zero order kinetics. They concluded that, gum dammar can be used successfully to produce discrete and spherical microparticles of Diltiazem HCL and Ibuprofen.
KM Manjunatha et. al \(^{44}\) studied on sustained release dosage form of Diclofenac Sod containing immediate and controlled release components. Solid dispersion of immediate release component was prepared using PVP and mannitol carriers by common solvent method. Controlled release component was prepared in the form of spherical beads by ionotropic gelation technique. The beads were prepared by dispersing drug in solutions of ionic polysaccharides such as chitosan and sod alginate. These dispersions were dropped into solutions of counter ions such as tetrasodium pyrophosphate and calcium chloride, respectively. The beads were also prepared using agar by dropping agar-drug hot solution into a mixture of chilled liquid paraffin and water. Then, diclofenac sod controlled release drug delivery systems were prepared by combining the immediate release and controlled release components in different ratios. The formulations were found to be effective in providing controlled release of drug for a longer period of time. The beads were characterized by SEM and x-ray diffraction studies.

Genta I.et. al.\(^{45}\), investigated on a new method for preparation of chitosan microspheres loaded with a hydrophobic drug, ketoprofen by emulsification/solvent evaporation. Physical cross linking was carried out by dry heating chitosan microspheres at fixed temperatures and for different times. Glutareldehyde at different concentrations was used as a chemical cross linking agent on microspheres constituted by different theoretical ketoprofen/chitosan
ratio (1:2, 1:4, 1:6 w/w). Microspheres were morphologically characterized for shape, surface characteristics and size distribution; chitosan/ketoprofen interaction inside the microsphere was investigated by DSC and powder x-ray diffractometry. Ketoprofen contents inside the microspheres and in vitro drug release profile were also determined.

Bhalekar MR et al formulated resinates of Verapamil HCl using Indion resins. Drug loading process was optimized with respect to drug: resin ratio, pH of loading solution, and particle size of resin. Resinates were characterized using XRPD. In vitro drug release rates from resinate was not adequately sustained. Hence resonates were incorporated in pellets using extrusion spherization to achieve desired release pattern. XRPD studies revealed Verapamil to be present in amorphous form in resonates. Resinate of Indion 254 with 5% HPMC fulfilled USP criteria for extended release Verapamil preparation.

Aridam halder et al. Studied on the suitability of polystyrene-coated (PS-coated) microcapsules of drug-resin complex for achieving prolonged release of diltiazem-HCl, a highly water-soluble drug, in simulated gastric and intestinal fluid. The drug was bound to Indion 254, a cation-exchange resin, and the resulting resinate was microencapsulated with PS using an oil-in-water emulsion-solvent evaporation method. The effect of various formulation parameters on the characteristics of the microcapsules was studied. Mean diameter
and encapsulation efficiency of the microcapsules rose with an increase in the concentration of emulsion stabilizer and the coat/core ratio, while the same characteristics tended to decrease with an increase in the volume of the organic disperse phase. The desorption of drug from the uncoated resinate was quite rapid and independent of the pH of the dissolution media. On the other hand, the drug release from the microcapsules was prolonged for different periods of time depending on the formulation parameters and was also found to be independent of the pH of the dissolution media. Both the encapsulation efficiency and the retardation of drug release were found to be dependent on the uniformity of coating, which in turn was influenced by the formulation parameters. Kinetic studies revealed that the desorption of drug from the resinate obeyed the typical particle diffusion process, whereas the drug release from the microencapsulated resinate followed the diffusion controlled model in accordance with the Higuchi equation. PS appeared to be a suitable polymer to provide prolonged release of diltiazem independent of the pH of the dissolution media.

Hekmatara T., et al studied on microspheres containing diltiazem hydrochloride to perform the thermo analytical examination of the components and microspheres. Thermal analysis is a very frequently used method in the preformulation tests of solid dosage forms. On investigations it was found that the crystalline form of the active agents could not be observed in the drug-loaded chitosan
microspheres, which indicates the molecular dispersion of the drug in the matrix. It was established that the preparation conditions influenced the morphology and size of the particles. Moreover, the sphericity of the microspheres was good. On the basis of investigations, the 1:1 diltiazem hydrochloride–chitosan ratio is suggested as the best ratio.

M.A. Garci’a a, et. al 49 developed HPLC method for the single or simultaneous determination of four calcium channel blockers (CCB), namely diltiazem (DTZ), verapamil (VER), nifedipine (NIF) and nitrendipine (NIT) and their active metabolites demetildiltiazem and deacetildiltiazem (MA and M1), norverapamil (NOR), and dehydronifedipine (DHN). DHN was synthesised in their laboratory and different pH values of the mobile phase were subsequently prepared and tested for chromatographic separation. The detection system and the environmental light conditions were optimised. The best separations of all analytes were obtained using a C18 column and a mobile phase of methanol, 0.04 M ammonium acetate, acetonitrile and triethylamine (2:2:1:0.04 v:v). Quantitation was performed using imipramine (IMI) as the internal standard. For DTZ and its metabolites (M1 and MA), the wavelength chosen was 237 nm; for VER and its metabolite NOR, it was 210 nm; and, finally for NIF and its metabolite DHN and NIT it was 216 nm. When a simultaneous analysis was carried out the wavelength was of 230 nm. The optimum pH was 7.90 and 7.10 when the separation of NIT and DTZ or VER
and NIF were carried out, respectively, and 7.90 when a simultaneous separation was carried out. The detection limit of the assay was less than 8 ng ml\(^{-1}\) for all compounds, with coefficients of variation less than 7\% (for inter- and intra-day) over the concentration range of 1–1000 ng ml\(^{-1}\). The retention times were less than 11 min. When NIF or NIT were studied, it was necessary to use a sodium vapour lamp in order to avoid the photo degradation which takes place under daylight conditions.

Frishman W H\(^{50}\) showed calcium-channel blockers are a safe and effective treatment modality for angina and hypertension. They developed Dilacor XR capsules, a new extended-release formulation of diltiazem, for the treatment of hypertension. Dilacor XR (Rhône-Poulenc Rorer Pharmaceuticals Inc., Collegeville, PA) uses a novel drug delivery system, the Geomatrix (JAGO Research AG, Zollikon, Switzerland) controlled-release system, to deliver diltiazem at a constant rate for 24 hours. The rate of absorption is also slower. As doses of Dilacor XR were increased from 120 mg to 540 mg/day, there were disproportionate increases observed in area under the curve, maximum peak plasma concentration, minimum peak plasma concentration, and average peak plasma concentration. The efficacy data from two clinical trials have confirmed the established efficacy of diltiazem and the 24-hour efficacy of Dilacor XR in the control of mild-to-moderate hypertension. The incidence of adverse effects with Dilacor XR in doses as high as 540 mg/day was generally comparable
to that of placebo. They concluded that this new formulation of diltiazem should significantly facilitate blood pressure control because of better patient compliance with a once daily regimen.

2.2 Drug review

2.2.1 Diltiazem Hydrochloride\textsuperscript{51, 52, 53}.

**Category**

Calcium channel blocker

**Description**

It has peripheral and coronary vasodilator properties. It lowers blood pressure and has some effect on cardiac conduction and is given by mouth in angina pectoris, hypertension and myocardial infarction. It is generally well tolerated although headache, ankle edema, gastrointestinal disturbances and rashes may occur. Occasional impairment of cardiac conduction has been seen.

**Figure: 2.2.1 Chemical structure of diltiazem HCl**

![Chemical structure of diltiazem HCl](image)

**Solubility**
It occurs as white odorless crystalline powder or small crystals. Freely soluble in water, chloroform, formic acid and methyl alcohol. Sparingly soluble in dehydrated alcohol, insoluble in ether.

**Melting point:** 211° C

**Dose**

Initial dose of 60 to 120 mg, twice daily, increased at 14 day intervals as required to a maximum of 360 mg daily.

**Pharmacokinetic Data**

*Oral availability:* 40%

*Urinary excretion:* 2 to 4%

*Bound in plasma:* 78±3%

*Clearance:* 11.8 ± 2.2 ml.min⁻¹kg⁻¹

*Vd:* 3.3 ±1.2

*Half life:* 3 to 5 h

*Peak plasma concentration:* 7.2±4

*Bioavailability:* 40%

**Absorption and Fate**

DH is rapidly and almost completely absorbed from the gastrointestinal tract following the oral administration but undergoes extensive first pass hepatic metabolism. About 80% is bound to
proteins and extensively metabolized in the liver; one of the metabolites, desacetyl diltiazem has been reported to have 25 to 50% of the activity of the parent compound. Approximately 2 to 4% of a dose is excreted in the urine as unchanged and remainder being excreted as metabolites in bile and urine.

**Uses and administration**

In India commercial tablets in 30 mg, 60 mg doses are available. 30 mg tablets are prescribed three times daily or four times daily initially then increasing the dose to 240 mg/day in 3-4 divided doses. Sustained release tablets with 90 mg and 120 mg are also marketed and are prescribed two times daily or as necessary.

In the management of hypertension DH may be given as sustained release capsules or tablets in an initial dose of 60 mg to 120 mg, twice daily, increased at 14 day intervals as required to a maximum of 360 mg daily.

**Brand names:**
2.2.2 Verapamil Hydrochloride 54,55,56.

**Category:** Calcium channel antagonist

**Description**

Verapamil Hydrochloride (VH) occurs as colourless and crystalline powder and produces “antihypertensive effect” by decreasing the vascular resistance and dilatation of the peripheral blood vessels. It causes adverse effects bradycardia, depression of atrioventricular or sinoatrial nodal function, Constipation, hypotension, Nausea, flushing, rashes and arthralgia.

**Molecular formula:** \( \text{C}_{27}\text{H}_{38}\text{N}_{2}\text{O}_{4}\cdot \text{HCl} \)

**Figure:** 2.2.1 Chemical structure of verapamil hydrochloride

**Molecular weight:** 491.07

**Solubility:** Freely soluble in chloroform, soluble in water, sparingly soluble in ethanol, practically insoluble in ether.

**Melting point:** 144\(^\circ\) C
Pharmacokinetic Data\textsuperscript{55}

**Oral availability:** 22±8%

**Urinary excretion:** <3%

**Bound in plasma:** 90±2%

**Clearance:** 15±6 ml.min\(^{-1}\)kg\(^{-1}\)

**Vd:** 5.0±2.1 lit.kg\(^{-1}\)

**Half life:** 4.0±1.5 h

**Peak plasma concentration:** 272 ng/ml

Administration and dosage

The conventional dosage is 40 to 80 mg thrice a day, maximum daily dose 480 mg

Contraindication

It is contraindicated in hypotension, in cardiogenic shock, in marked bradycardia and in uncompensated heart failure, in patients with impaired liver function.

Brand names

Tablets: Calaptin-40mg to 80 mg S.R.120 &240mg (Nicholas Piramal India Ltd.)

Vasopten-40mg to 80 mg (Torrent Pharmaceuticals)
2.3 Polymer Review

2.3.1 Chitosan \(^{57, 58}\)

Chitosan is derived from chitin, nature’s second most abundant polymer after cellulose. It comprises of copolymers of glucosamine and N-acetyl glucosamine derived by partial deacetylation of chitin. Its sugar backbone consists of β-1,4-linked glucosamine with a high degree of N-acetylation. The term chitosan is used to describe a series of chitosan polymers with different molecular weight, viscosity, degree of deacetylation (40%-98%). The principle source of chitin is crustacean, insects and fungi. Conventional chitosan is available both as a base and as a salt eg. Hydrochloride, maleate or glutamate.

**Figure: 2.3.1 Chemical structure of chitosan**

![Chemical structure of chitosan](image)

**Chemical name**: -(1 > 4)2-amino-2-deoxy β - D-glucosamine.

**Physical properties**

Having particle size < 30 μm, density : 1.35 – 1.40 g/cc, pH : 6.5-7.5, pKa : 6.5, Viscosity: <200 m Pa s (1% chitosan in 1 % acetic acid), Molecular weight 50-2000 K Da, insoluble in water, ethanol (95%), organic solvents and neutral or alkali solutions but soluble in acids like acetic, formic, propionic, oxalic and succinic etc.
**Chemical properties**

- It is a cationic polyamine
- High charge density at pH < 6.5
- Adheres to negatively charged surfaces
- Forms gels with polyanions
- High molecular weight, linear polyelectrolyte
- Reactive hydroxyl/amino group

**Biological properties**

- Non toxic
- Biocompatible
- Biodegradable

**Pharmacological properties**

- Hypocholesteolemic
- Wound healing properties
- Antacid and antiulcer activities

**Safety**

It is safe and non toxic and has LD$_{50}$ of 10 g/kg in mice

**Pharmaceutical Applications**

1. As a diluents in direct compression tablets
2. Controlled drug delivery for slow release of drugs from tablets and granules
3. Binder in wet granulation

4. Used as a coat material for the preparation of microcapsules for sustained release of several drugs

5. Chitosan microspheres were used for the delivery of anticancer agents

6. Preparation of films for controlling drug release

7. Bioadhesion: Positive charges on the surface of chitosan could give rise to a strong electrostatic bond on a negatively charged mucosal surface and hence used as a bioadhesive polymer

8. It is an absorption enhancer for nasal or oral drug delivery

9. For site specific drug delivery of peptides and other drugs (stomach or colon)

10. DNA delivery carrier in relation to vaccine delivery or gene therapy

11. Absorption enhancer: for hydrophilic across the intestinal tract

12. Disintegrant in tablet formulation

13. Wetting agents and improvement of dissolution of poorly soluble drug substances
2.3.2 Sodium alginate\textsuperscript{59},

It is the purified carbohydrate product extracted from brown seaweed by the use of dilute alkali. It consists chiefly of the sodium salt of alginic acid, a polyuronic acid composed of Beta-D-Mannuronic acid residues.

**Molecular formula:** \((C_6H_7P_6Na)n\)

**Figure: 2.3.2 Chemical structure of sodium alginate**

![Chemical structure of sodium alginate](image)

**Description**

It occurs as a white or buff powder which is odorless and tasteless. The powder may be coarse or fine.

**Viscosity**

It is slowly soluble in water, forming a viscous, colloidal solution. It is insoluble in alcohol and hydroalcoholic solutions in which the alcohol content is greater than 30 \% by weight. It is also insoluble in other organic solvents and acids where the pH of the resulting solution falls below 3.0.

**Safety**
Numerous studies have indicated sodium alginate to be quite safe. Allergy tests have shown to be nonallergic.

**Incompatibility**

It is incompatible with acridine derivatives, crystal violet, phenyl mercuric nitrate and acetate, calcium salts, alcohol in concentrations greater than 5% and heavy metals.

**Applications**

1. Used as stabilizer in emulsions
2. As suspending agent
3. Tablet disintigrant and tablet binder
4. It is also used as a haemostatic agent in surgical dressings
2.3.3 Methyl Cellulose

Chemical name

Cellulose methyl ether

Structural Formula

Figure: 2.3.3 Chemical structure of Methyl Cellulose

Description

It occurs as white odorless tasteless powder. Swells in cold water and produces a clear to opalescent, viscous, colloidal suspension. Insoluble in hot water, saturated salt solutions, alcohol, ether and chloroform. Soluble in glacial acetic acid and in a mixture of equal volumes of alcohol and chloroform.

Applications

Used as gelling, suspending, thickening, coating, disintegrating and emulsifying agent, may be used to modify disintegration, dissolution patterns.
2.3.4 Sodium Carboxy Methyl Cellulose

Is the sodium salt of a polycarboxymethyl ether of cellulose.

**Synonym:** Cellulose gum, Sodium cellulose glycolate

**Chemical Name:** Cellulose carboxy Methyl ether sodium salt

**Molecular formula:** \((\text{C}_6\text{H}_7\text{O}_6\text{Na})_n\)

**Figure:** 2.3.4 Chemical structure Sodium Carboxy Methyl Cellulose

**Grades:** Carboxy Methyl Cellulose H, M, L.

**Description:** White to faintly yellow, odourless, hygroscopic powder or granular material having a faint paper like taste.

**Molecular weight:** 90,000-700,000.

**Bulk Density:** 0.52 g/cm³

**Viscosity:** 1200 cps (1% aqueous solution)

**pH:** 6.5 – 8.5 (1% aqueous solution)
Solubility: It is practically insoluble in acetone, ethanol, ether and toluene. Easily dispersed in water at all temperature forming clear, colloidal solution

Incompatibility: incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals.

Stability: Stabilized in both the dry state and in solution, causes a decrease in viscosity. The bulk material is stable on storage.

Applications: It is used as an emulsifying, gelling and binding agent. It has been found to possess good bioadhesive strength.

Safety: It is nontoxic, nonirritant material and having LD50 16 gm/kg gp
2.3.5 Poly Vinyl Pyrrolidone

**Synonym:** kollidon; povidon.

**Chemical name:** 1-Ethenyl-2-pyrrolidon homopolymer

**Molecular formula:** (C6H9NO)n

**Figure:** 2.3.5 Chemical structure of Poly Vinyl Pyrrolidone

![Chemical structure of Poly Vinyl Pyrrolidone]

**Description:** Occurs as a fine, white, odorless, hygroscopic powder having pH 3.0-7.0 (5%w/v aq solution). is a water-soluble polymer made from the monomer N-Vinylpyrrolidone.

**Solubility:** freely soluble in acids, chloroform, ethanol, ketones, methanol, and water; practically insoluble in ether, hydrocarbons, and mineral oil.

**Viscosity:** the viscosity of aqueous povidone solutions depends on both the concentration and molecular weight of the polymer employed.

**Applications:** In solution, it has excellent wetting properties and readily forms films. This makes it good as a coating or an additive to
coatings. It is used as binder, emulsifier, disintegrant, dissolution aid and suspending agent.

**Safety:** It is non toxic and non irritant

Estimated acceptable daily intake for the Povidone gum has been set by the WHO at upto 2.5 mg/kg body weight. LD50 (mouse IP): 12G/kg
2.3.6 Xanthan gum

**Synonym:** E415, Corn sugar gum, Keltrol

**Molecular formula:** (C35H49O29)n

**Molecular weight:** 2X10

**Figure:** 2.3.6 Chemical structure of xanthan gum

**Applications**

Widely used in oral and topical formulations, cosmetics and foods as a suspending and stabilizing agent. It is also used as a thickening and emulsifying agent. It is non toxic and compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over a wide pH and temperature range.

Although primarily used as gelling, suspending, thickening and emulsifying agent, xanthan gum has also been used to prepare sustained release matrix tablets. Controlled release tablets of diltiazem HCl prepared using xanthan gum has been reported to
sustain the drug release in a predictable manner and the drug release profiles of these tablets were not affected by pH and agitation rate.

Recent studies have revealed that xanthan gum can also be used as an excipient for spray drying and freeze drying processes for better results.

**Description**

Xanthan gum is a microbial desiccation-resistant polymer prepared commercially by aerobic submerged fermentation from Xanthomonas campestris bacterium. It occurs as a cream or white colored, odorless, free flowing, fine powder.

**Acidity/alkalinity:** pH = 6.0 - 8.0 for a 1% w/v aqueous solution.

**Melting Point:** Chars at 270 C

**Solubility**

Practically insoluble in ethanol and ether; soluble in cold or warm water

**Viscosity:** 1200-1600 mPa s for a 1% w/v aqueous solution at 25 C

**Stability**

Aqueous solutions are stable over a wide pH range (pH 3-12).

The bulk material should be stored in a well closed container in a cool dry place.
**Incompatibility**

Xanthan gum is an anionic material and is not usually compatible with cationic surfactants, polymers, or preservatives as precipitation occurs and it is also incompatible with oxidizing agents.

**Safety**

It is non toxic and non irritant at the levels employed as Pharmaceutical excipient. Acceptable daily intake as per WHO is upto 10 mg/kg body weight.