Drug content determination of film
Skin irritation tests.
In-vitro Skin permeation test
In-vivo evaluation
Accelerated stability studies

The results are presented in tables and graphically by using various equations governing release kinetics.

2.1 DRUG PROFILE

2.1.1 Drug Profile of Glipizide \(^{41-42}\)

Glipizide contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1-cyclohexyl-3-[4-{2-(5-methylpyrazine-2-carboxamido) ethyl] benzene sulphonyl] urea, calculated with reference to the dried substance.

Name: Glipizide

Synonym: Glydiazinamide

Nomenclature:

1-cyclohexyl-3-{4-[2-(5-methylpyrazine-2-carboxamido) ethyl] benzene sulphonyl] urea

Standards:

Glipizide contains not less than 98.0 per cent and not more than the equivalent of 102.0 % on dry basis.

Molecular Weight:

445.5 g/mol

Molecular Formula:

\( C_{21}H_{27}N_5O_4S \)

Structural Formula:
Appearance:
A white or almost white, crystalline powder

Melting Point:
208°C-229°C

Solubility:
Practically insoluble in water, soluble in methylene chloride, sparingly soluble in acetone and practically insoluble in alcohol
It dissolves in dilute solutions of alkali hydroxides.

Pka:
Glipizide is a weak acid. It has been concluded that it has dissociation constant pKa of 5.9±0.1

Ultra-violet Spectrum:
The ultra violet absorption spectra for Glipizide was determined in 0.01 M Sodium Hydroxide using 1 cm silica cells with a UV Visible spectrophotometer-117 (Systronics, Mumbai). The compound showed a characteristic curve with maxima at 223 nm.

Infra-red Spectrum:
The infrared spectrum of a sample of Glipizide supplied by Dr. Reddy's Laboratories was recorded using potassium bromide disc
method with a FTIR spectrophotometer (Shimadzu Corporation, Japan). The major peaks are at 1033, 1349, 1596 and 3382 cm\(^{-1}\).

**Pharmacokinetics:**

Several factors may modify the kinetics of Glipizide some of which are fibre intake, age, presence of autonomic neuropathy, obesity, renal and hepatic insufficiency.

**Absorption:** Glipizide completely absorbed after oral administration. In the patients with type 2 diabetes Glipizide has absolute bioavailability of 100%. Beginning 2 to 3 h after administration of Glipizide extended-release tablets, plasma drug concentrations gradually rise and reaching maximum concentrations within 6 to 12 h after dosing. The absorption is delayed with food.

**Distribution:** Glipizide binds to plasma proteins (>99%) and crosses the placenta.

**Metabolism:** Glipizide is metabolized almost completely in the liver.

**Half Life:** Plasma half-life: 2 to 4 h

**Excretion:** Urine (60% to 80%, 91% to 97% as metabolites); feces (11%)

**Protein Binding:** About 98% binds with plasma proteins.

**Uses:** Glipizide is indicated in the management of patients with NIDDM who have not responded adequately to diet, physical activity and weight loss.

**Dose:** Adults: Initial: 5 mg/day; adjust dosage at 2.5-5 mg daily increments as determined by blood glucose response at intervals of several days.
Immediate release tablet: Maximum recommended once-daily dose: 15 mg; maximum recommended total daily dose: 40 mg

Extended release tablet: Maximum recommended dose: 20 mg

Dosage Form: Tablet: 2.5, 5 and 10 mg

Packaging and Storage: Store below 40°C (104°F), preferably between 15°C and 30°C (59 to 86°F) in a well-closed container, when otherwise specified by manufacturer.

2.1.1.1 Review of Past Work Done on Glipizide:

Jamzad and Reza, 2006, developed monolithic matrix systems with swellable HPMC or erodible polyethylene oxide. The results indicated that the drug release by erosion and swelling.

Ashok et al., 2009, enhanced the solubility and impart a controlled release of Glipizide by complexing with β-cyclodextrin and matrixing with poly Ethylene Oxide in the form of tablets. They concluded that the formulation releases Glipizide compleately in controlled manner.

Hosmani et al., 2009, Glipizide mucoadhesive microspheres prepared by Polycarbophil and Sodium Alginate. They concluded that polycarbophill and sodium alginate had highly significant effects on dependent variables.

Chowdary and Rao, 2003, microcapsules of glipizide were prepared using sodium alginate, sodium CMC, MC, Carbopol and HPMC as coat
materials. Glipizide release from the dosage form was slow and extended over longer periods of time and depended on composition of the coat\textsuperscript{46}.

\textbf{Nanjappa et al., 2007}, glipizide lipospheres were developed by the emulsification phase separation technique using paraffin wax and stearic acid as retardants. The optimized liposphere formulation developed was found to produce sustained anti-diabetic activity following oral administration in rats\textsuperscript{47}.

\textbf{Patel et al., 2005}, formulated and mucoadhesive microspheres of glipizide using chitosan by simple emulsification phase separation technique using glutaraldehyde as a cross-linking agent. The drug release was also sustained for more than 12 h. \textit{In vivo} testing of the mucoadhesive microspheres to albino Wistar rats demonstrated significant hypoglycemic effects\textsuperscript{48}.

\textbf{Bennet et al., 2005}, evaluated Glipizide patches in healthy cats. Glipizide was detected in all treated cats. The results indicated that transdermal administration of glipizide is not equivalent to oral administration. They concluded that transdermal administration of glipizide cannot be recommended for clinical use at that time\textsuperscript{49}.

\textbf{Ouyang et al., 2005}, osmotic pump (OP) of metformin hydrochloride (MT) and glipizide (GZ) developed. Sodium carbonate was used to modulate the solubility of GZ within the core and MT was not only one of
the active ingredients but also the osmotic agent. The OP had a good sustained effect in comparison with the conventional product.$^{50}$

**Radhika et al., 2009,** developed a new monolithic matrix tablet to completely deliver glipizide using HPMC K 100 and Eudragit L 100. The results suggested that the formulated tablets of glipizide showed improved efficacy compared with marketed one.$^{51}$

**Thrombose et al., 1999,** demonstrated that the asymmetric membrane capsule can be used to deliver a poorly water soluble Glipizide with a pH sensitive solubility. The drug was solubilized with the use of a pH-controlling excipient and prolonged release of glipizide was acheived.$^{52}$

**Jolly et al., 2008,** examined *in vitro–in vivo* for glipizide sustained-release matrices prepared by using EC, MCC, HPMC, xanthan gum, guar gum, Starch 1500 and lactose. They concluded that proper selection of polymers will control the release of Glipizide.$^{53}$

**Kajal et al., 2009,** investigated the effect of chemical enhancers on the release of glipizide through transdermal matrix patch using L-menthol, oleic acid and n-octanol. The patches were prepared with EC and PVP as polymers and Di-Butyl phthalate as plasticizer. They observed these chemical enhancers decreased the percentage release.$^{54}$
Mona, 1998, mucoadhesive buccal film of glipizide were prepared by using HPMC, Sod CMC, carbopol-934P and Eudragit RL-100. The formulations were found to be suitable for preparing buccal films.

Chowdary and Sundari, 2003, Matrix tablets of glipizide were formulated using sodium CMC and HPMC, and with and without EC. Tablets formulated employing sodium CMC or HPMC and with EC provided slow release of glipizide over a period of 12 h.

2.1.1.2 Review of past work done on Glipizide TDDS:

Srinivas et al., 2005, investigated glipizide matrix transdermal systems using EC/PVP and Eudragit RL-100/Eudragit RS-100. The transdermal route exhibited negligible skin irritation and produced better improvement with all the tested in vivo parameters compared to oral administration.

Ammar et al., 2006, prepared Glipizide tablets with β-cyclodextrin (β-CyD), dimethyl-β-cyclodextrin (DM-β-CyD), hydroxypropyl-β-cyclodextrin (HP-β-CyD) and hydroxypropyl-γ-cyclodextrin (HP-γ-CyD). Several percutaneous formulations of the drug and the prepared complexes in different bases (o/w emulsion, polyethylene glycol, carboxymethyl cellulose and Carbopol) were developed. The results indicated the feasibility of using glipizide for transdermal delivery.
Shu Yen et al., 2007, evaluated the transdermal permeability of pentoxifylline gel prepared with carbomer 934 and HPLC. A 3% Azone and 5% propylene glycol were used as collaborative enhancers. The transdermal processes of pentoxifylline fits to a zero-order kinetic equation and have a good in-vitro-in-vivo correlation.

NOTE: Very few attempts have been made on Glipizide transdermal drug delivery systems.

2.1.2 Drug Profile of Glimepiride: 60, 61

Glimepiride contains not less than 98.0 per cent and not more than the equivalent of 102.0 per cent of 1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea, calculated with reference to the dried substance.

Name: Glimepiride

Nomenclature:

1-[[p-[2-(3-ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulfonyl]-3-(trans-4-methyl cyclohexyl) urea

Molecular Weight:

490.617 g/mol

Molecular Formula:

C_{24}H_{34}N_{4}O_{5}S

Structural Formula:
Appearance:
It is a yellowish white, crystalline, odourless odourless powder.

Melting Point:
207°C

Solubility:
Glimepiride is practically insoluble in water

Pka:
Glimepiride is a weak acid. It has been concluded that it has dissociation constant 6.2 ± 0.1 at 37°C

Ultra-violet Spectrum:
The ultra violet absorption spectra for Glipizide was determined in 0.01 M Sodium Hydroxide using 1 cm silica cells with a UV Visible spectrophotometer-117 (Systronics, Mumbai). The compound showed a characteristic curve with maxima at 230 nm.

Infra-red Spectrum:
The infrared spectrum of a sample of Glimepiride supplied by Dr. Reddy’s Laboratories was recorded using potassium bromide disc method with a FTIR spectrometer (Shimadzu Corporation, Japan). The major peaks are at 1056, 1349, 1594 and 3387cm⁻¹.
Several factors may modify the kinetics of Glimepiride some of which are fibre intake, age, presence of autonomic neuropathy, obesity, renal and hepatic insufficiency.

**Absorption:**

80-100% of an oral dose of Glimepiride is absorbed from the GI tract. The drug is absorbed equally from the stomach, duodenum and ascending colon. Peak plasma concentrations will reach in 1.5-2 h. Food does not significantly affect absorption of Glipizide. Following an oral administration of Glimepiride to normal fasting subjects, a rise in plasma concentrations of insulin and the associated fall in plasma glucose occurred in 15-60 min reaching peak effect in 1-2 h.

**Distribution:**

Glimepiride binds to plasma proteins (over 99.5%) more strongly. As Glimepiride crosses the placenta tends to occur in neonates whose mothers have been taking sulphonyl ureas upon the time of delivery have chances of developing hypoglycemia.

**Metabolism:**

Glimepiride is completely metabolized by oxidation mechanism after IV or oral dose. Cytochrome P450 II C9 found to involve in the detoxification of Glimepiride to M1 then to M2. M1 possesses 1/3rd of the pharmacological activity when compared to its parent molecule in an animal model.

**Half Life:** Plasma half-life: 5 h

**Excretion:** Urine & Fecal
**Protein Binding:** In plasma >99.5%

**Uses:**

Hypoglycemic agent in patients with noninsulin-dependent diabetes mellitus (NIDDM)

**Dose:**

1-4 mg PO qd, Start: 1-2 mg PO qd, incr. 1-2 mg/day q1-2wk; Max: 8 mg/day; Info: give w/ first main meal

**Dosage Form:**

Tablets: 1, 2, 3, 4, 6 and 8 mg tablets.

**Packaging and Storage:**

Store below 40°C (104°F), preferably between 15°C and 30°C (59 to 86°F) in a well-closed container, when otherwise specified by manufacturer.

**2.1.2.1 Review of Past Work Done on Glimepiride:**

**Ammar et al., 2008,** studied the effect of complexation of glimepiride with beta-cyclodextrin and its derivatives (HP-beta-CyD and SBE-beta-CyD) in presence of different concentrations of water-soluble polymers (HPMC, PVP, PEG 4000 and PEG 6000) on the dissolution rate of the drug. The results revealed that the dissolution rate of the drug from these ternary systems is highly dependent on polymer type and concentration. The dissolution rate of the drug from ternary systems containing PEG 4000 or PEG 6000 seems to be generally higher than from systems containing HPMC or PVP62.
**Cho et al., 2009**, ethylene-vinyl acetate (EVA) matrix containing glimepiride was prepared as a potential transdermal drug delivery system using quinupramine as permeation enhancer and concluded that an EVA matrix containing a permeation enhancer can be used for the transdermal controlled delivery of glimepiride$^{63}$.

**NOTE:** Very few attempts have been made on Glimepiride Controlled drug delivery systems

### 2.1.2.2 Past work done on Glimepiride transdermal patches

**Ammar et al., 2008**, chitosan polymer was utilized in developing transdermal films for glimepiride by the inclusion of beta-cyclodextrin (beta-CyD) as well as the use of several conventional penetration enhancers. *In vivo* studies on diabetic rats for selected formulae revealed a marked therapeutic efficacy sustained for about 48 h. The above-mentioned results shed light on feasibility of utilizing chitosan as an effective, safe transdermal delivery system for glimepiride$^{64}$.

**Yao et al., 2007**, studied pharmaceutical characterization, the pharmacokinetics and relative bioavailability of glimepiride gel-matrix
controlled-release patch in rats. The glimepiride-TDDS showed a slower, longer and smoother serum concentration-time profile, as compared with conventional oral administration in both absorption and elimination phase. As a result, it was evident that the patch exhibited good controlled-release properties\textsuperscript{68}.

\textbf{NOTE:} \textit{Very few attempts have been made on Glimepiride transdermal drug delivery systems.}

\section*{2.2 POLYMER PROFILES}
\subsection*{2.2.1 Profile of Aloe barbadensis miller \textsuperscript{66-70}}
\textbf{Description:}

It is a shrub with thick, fleshy leaves.

\textbf{Composition:}

Anthracene derivatives, 2-alkylchromones, Flavonoids

\textbf{Characters:}

Minute, acicular crystals, or a microcrystalline powder, varying in color from yellow to yellowish-brown, odourless or possessing a slight odour of Aloes, a characteristic bitter taste and permanent in the air.

\textbf{Dose:}

0.5 to 2 gr or 0.03 to 0.12 g.
Properties:

The dried leaves contain anthranoids (produces a laxative effect). It restrains stationary contractions and animate propulsive contractions in the colon result in acceleration in intestinal passage and reduced liquid absorption.

pH:

4.4 to 4.7.

Fig. 2.1 Aloe barbadensis miller leaf

Chemical composition:

Table 2.1: Summary of the chemical composition of Aloe barbadensis miller leaf pulp and exudates

<table>
<thead>
<tr>
<th>Class</th>
<th>Compounds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthraquinones/</td>
<td>Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid</td>
</tr>
<tr>
<td>Anthrones</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Pure mann, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, xylan, cellulose</td>
</tr>
<tr>
<td>Chromones</td>
<td>8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol, 8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, nealoesin A</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxygenase</td>
</tr>
<tr>
<td>Category</td>
<td>Compounds/Components</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Cyclooxygenase, superoxide dismutase lipase, oxidase, phosphoenolpyruvate carboxylase</td>
<td>Inorganic compounds Calcium, chlorine, chromium, copper, iron, magnesium, zinc, manganese, potassium, phosphorous, sodium,</td>
</tr>
<tr>
<td>Arachidonic acid, γ-linolenic acid, steroids (campesterol, cholesterol, β-sitosterol), triglycerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid</td>
<td>Miscellaneous including organic compounds and lipids</td>
</tr>
<tr>
<td>Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine</td>
<td>Non-essential &amp; essential amino acids</td>
</tr>
<tr>
<td>Lectins, lectin-like substance</td>
<td>Proteins</td>
</tr>
<tr>
<td>Saccharides</td>
<td>Vitamin B1, B2, B6, C, β-carotene, choline, folic acid, α-tocopherol</td>
</tr>
</tbody>
</table>

**Uses:**

Antiseptic, analgesic, anti-inflammatory and hepato protective activities. To treat wounds, herpes, ringworm, gastroenteritis, colitis, enterocolitis, vaginitis, cervicitis, scurvy, cholera, dysentery, gonorrhea, syphilis, measles, chicken pox, scarlet fevers, eczema, psoriasis, seborrheic dermatitis, erysipelas, athlete's foot, the stinging insects, spiders, scorpions, snakes, allergies, indigestion, heartburn, gastritis, duodenal ulcers, hemorrhoids, constipation and sunburn. Aloe has Immunomodulatory and anti-cancer effects etc.

**Contraindications:**
Inflamed intestinal diseases like ulcerative colitis, intestinal obstruction, appendicitis and abdominal pain

**Side Effects:**

Potassium loss with long-term use and in combination with corticosteroids and thiazide diuretics

**Administration:**

Multiple forms are available for oral use. Use smallest dosage to overcome constipation. Not advisable for long term use (>1-2 weeks) without medical advice.

**2.2.1.1 Past work done on Aloe barbadensis miller**

Ayesha *et al.*, 2008, studied anti diabetic properties of A. vera (300 mg/kg body wt) in streptozotocin-induced diabetic rats71.

Grover, 2002, Aloe vera, Ficus bengalenesis and other 45 plants were screened for hypoglycemic actions. All plants have shown varying degree of hypoglycemic and anti-hyperglycemic activity72.

Beppu *et al.*, 1993, two different components were separated from Aloe arborescens var. natalensis Berger, which exhibit hypoglycaemic activity in spontaneously diabetic mice and normal mice73.
Subbiah et al., 2006, examined the potential antihyperlipidaemic efficacy of the ethanolic extract from Aloe vera leaf gel in streptozotocin induced diabetic rats with a dose of 300 mg/kg per day for a period of 21 days. They concluded a scientific rationale for the use of Aloe vera as an antidiabetic agent.

Al Awadi, 1987, A blood glucose lowering extract of a mixture of five plants were studied. Only the extracts of myrrh and aloe gums effectively increased glucose tolerance in both normal and diabetic rats. The remaining components, gum olibanum, Nigella sativa seeds and gum assafoetida were without effect.

Josias, 2008, studied the wound healing, antifungal activity, hypoglycemic or antidiabetic effects antiinflammatory, anticancer, immunomodulatory and gastroprotective properties. A. vera to enhance the intestinal absorption and bioavailability of co-administered compounds as well as enhancement of skin permeation. In addition, important pharmaceutical applications such as the use of the dried A. vera gel powder as an excipient in sustained release pharmaceutical dosage forms will be outlined.

Yagi et al., 2009, Aloe vera L. high molecular weight fractions (AHM) containing less than 10 ppm of barbaloin and polysaccharide (MW: 1,000KD) with glycoprotein, verectin (MW 29KD), were prepared by patented hyper-dry system in combination of freeze-dry technique with micro wave and far infrared radiation. AHM produced significant decrease in blood glucose level sustained for 6 weeks of the start of the study. Significant decrease in triglycerides was only observed 4 weeks after treatment and continued thereafter.

Agarry et al., 2005, comparative antimicrobial activities of the gel and ethanolic leaf extract of Aloe vera were tested against Staphylococcus aureus, Pseudomonas aeruginosa, Trichophyton mentagrophytes, T.
schoeleinii, Microsporium canis and Candida albicans. Antimicrobial susceptibility test showed that both the gel and the leaf inhibited the growth of microbes used\textsuperscript{78}.

**Dilip et al., 2008**, compared the antimicrobial effectiveness aloe vera tooth gel and the toothpastes were equally effective against Candida albicans, Streptococcus mutans, Lactobacillus acidophilus, Enterococcus faecalis, Prevotella intermedia and Peptostreptococcus anaerobius. Aloe vera tooth gel demonstrated enhanced antibacterial effect against S. mitis\textsuperscript{79}.

**Arun and Muthu, 2008**, investigated the Aloe vera phyto chemical compounds and antimicrobial activity of different extracts on Aspergillus flavus and Aspergillus niger. The maximum antifungal activity was observed in acetone extracts when compared other extracts. Aloe vera plant extract with acetone can be used as antimicrobial agents\textsuperscript{80}.

**Saeed et al., 2004**, studied the antibacterial, anti-inflammatory and antiseptic activities of Aloe barbadensis extracts\textsuperscript{81}.

**Beppu et al., 2006**, carried out three experimental trials to determine antidiabetic effects of Aloe arborescens Miller components in streptozotocin induced diabetes mice.

**Harhaji et al., 2007**, demonstrated the capacity of an herbal anthraquinone aloe emodin to reduce the cytotoxicity of the proinflammatory cytokine tumor necrosis factor (TNF) towards L929 mouse fibrosarcoma and U251 human glioma cell lines.\textsuperscript{83}

**Chitra et al., 1998**, studied the wound healing actions in diabetic rats and reported these effects may be due to the reported hypoglycemic effects of the aloe gel\textsuperscript{84}.
Po Lin et al., 2002, investigated the anticancer effect of aloe-emodin in two human liver cancer cell lines, Hep G2 and Hep 3B. We observed that aloe-emodin inhibited cell proliferation and induced apoptosis in both examined cell lines, but with different the antiproliferative mechanisms. These findings suggest that aloeemodin may be useful in liver cancer prevention.

Paolo et al., 2009, studied Aloe for anticancer activity and its antineoplastic property is due to at least three different mechanisms, based on antiproliferative, immunostimulatory and antioxidant effects. The antiproliferative action is determined by anthracenic and antraquinonic molecules, while the immunostimulating activity is mainly due to acemannan. This study seems to suggest that Aloe may be successfully associated with chemotherapy to increase its efficacy in terms of both tumor regression rate and survival time.

Acevedo et al., 2004, Aloe-emodin (1,8-dihydroy-3-[hydroxymethyl]-anthraquione) purified from Aloe vera leaves has been reported to have antitumor activity. These results support the hypothesis that aloe-emodin represents a novel antitumor chemotherapeutic drug.

Louise and Charles, 2007, study in vitro the potential of Aloe Vera juice as a skin permeation enhancer. Saturated solutions of caffeine, colchicine, mefenamic acid, oxybutynin, and quinine were prepared at 32 °C in Aloe Vera juice and water (control) and used to dose porcine ear skin mounted in Franz diffusion cells with water as receptor phase. Receptor phase samples were taken over a 48 h period and permeants determined by reverse-phase HPLC and observed skin permeability actions.
Chou et al., 2009, suggested aloe-emodin (AE) liposomal formulation as enhancer in transdermal delivery of AE (anti cancer). Experimental data demonstrate the feasibility of applying liposome to deliver AE in clinical therapy.

NOTE: No attempts have been made on Aloe barbadensis miller as Controlled release polymer

2.2.2 Profile of Guar gum: 90-95

Synonyms:

E412; Galactosol; guar flour; jaguar gum; Meprogat; Meyprodor; Meyprofin; Meyproguar

Empirical Formula:

(C₆H₁₂O₆)ₙ

Molecular Weight:

220 000 g/mol

Structural Formula:
Guar gum consists of linear chains of (1,4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1,6) linkages. The ratio of D-galactose to D-mannose is between 1:1.4 and 1:2.

**Functional Category:**

Suspending agent, tablet binder, tablet disintegrant, viscosity-increasing agent.

**Applications in Pharmaceutical Formulation or Technology:**

Guar gum is used in cosmetics, food products and pharmaceutical formulations. In pharmaceuticals, guar gum is used in tablets as a binder and disintegrant and in oral and topical products as a suspending, thickening and stabilizing agent. Recent studies have examined the use of guar gum for colonic drug delivery. Guar gum has been used as part of the diet in diabetes mellitus patients.

**Table 2.2: Main uses of Guar gum**

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emulsion stabilizer</td>
<td>1</td>
</tr>
<tr>
<td>Tablet binder</td>
<td>Up to 10</td>
</tr>
<tr>
<td>Thickener for lotions and creams</td>
<td>Up to 2.5</td>
</tr>
</tbody>
</table>

**Description:**

The USPNF 19 describes guar gum as a gum obtained from the ground endosperms of *Cyamopsis tetragonolobus* (L.) Taub. (Fam. Leguminosae). It is a high molecular weight hydrocolloidal polysaccharide, composed of galactan and mannan units combined through glycoside linkages (galactomannan). The PhEur 2001 similarly describes guar galactomannan as being obtained from the seeds of *Cyamopsis tetragonolobus* (L.) The main components are polysaccharides composed of D-galactose and D-mannose of molecular ratios of 1: 1.4 to 1: 2. The molecules consist of a linear chain of b-(1, 4)-glycosidically
linked manno-pyranoses and single α-(1, 6)-glycosidically linked galactopyranoses. Guar gum is odourless, white to yellowish-white powder and has a bland taste.

Table 2.3: Pharmacopoeial Specifications of Guar gum

<table>
<thead>
<tr>
<th>Test</th>
<th>PhEur 2001</th>
<th>USPNF 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PH (1% w/w solution)</td>
<td>5.5-7.5</td>
<td>—</td>
</tr>
<tr>
<td>Apparent viscosity</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Microbial contamination</td>
<td>+</td>
<td>—</td>
</tr>
<tr>
<td>Loss on drying</td>
<td>15.0%</td>
<td>15.0%</td>
</tr>
<tr>
<td>Ash</td>
<td>1.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Acid-insoluble matter</td>
<td>7.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Arsenic</td>
<td>—</td>
<td>3 ppm</td>
</tr>
<tr>
<td>Lead</td>
<td>—</td>
<td>0.001%</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>—</td>
<td>0.002%</td>
</tr>
<tr>
<td>Protein</td>
<td>5.0%</td>
<td>10.0%</td>
</tr>
<tr>
<td>Starch</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Galactomannans</td>
<td>—</td>
<td>66.0%</td>
</tr>
<tr>
<td>Organic volatile impurities</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>Tragacanth, sterculia gum, agar, alginates and carrageenan</td>
<td>+</td>
<td>—</td>
</tr>
</tbody>
</table>

**Typical Properties:**

**Acidity/alkalinity:**

\[ \text{pH} = 5.0-7.0 \text{ (1% w/v aqueous dispersion)} \]

**Density:**

\[ 1.492 \text{ g/cm}^3 \]

**Solubility:**

Practically insoluble in organic solvents. Guar gum disperses and swells to form a highly viscous solution in water. The optimum rate of
hydration occurs between pH 7.5-9.0. Finely milled powders swell more rapidly and are more difficult to disperse. 2-4h in water develops maximum viscosity at room temperature.

**Viscosity (dynamic):**

4.86 Pas (4860 cP) for 1% w/v dispersion. Viscosity is dependent upon time, temperature, pH, concentration, particle size and rate of agitation.

**Stability and Storage Conditions**

Aqueous guar gum dispersions have a buffering action and are stable between pH 4-10.5 (Prolonged heating reduces the viscosity). Bacteriological stability of guar gum dispersions may be improved by the addition of a mixture of methylparaben (0.15%) and propylparaben (0.02%) as preservatives. Guar gum powder should be stored in a cool and dry place and in a well-closed container.

**Incompatibilities:**

Guar gum is compatible with most other plant hydrocolloids such as tragacanth. It is incompatible with acetone, alcohol, tannins, strong acids and alkalis. Borate ions, in water may prevent the hydration of guar gum. So, further hydration should be prevented. The gel formed can be liquefied by reducing the pH to below pH 7 or by heating. Guar gum may reduce the 1/4th absorption of penicillin V.

**Method of Manufacture:**

Guar gum is obtained from the ground endosperm of the guar plant, *Cyamopsis tetragonolobus* (L.) Taub. (Fam. Leguminosae). The seed hull can be removed (grinding/soaking in sulfuric acid/ soaking in
water/charring). The separated endosperm, containing 80% galactomannan is then ground to different particle sizes depending upon final application.

**Safety:**

Guar gum is widely used in foods and oral and topical pharmaceutical formulations. Excess may cause GI disturbances (flatulence/ diarrhea/ nausea). The daily oral dose of Guar gum is up to 25 g of in patients with diabetes mellitus. The Guar gum swells in the stomach and produce a feeling of fullness. However, it is claimed that premature swelling of guar gum tablets may occur and cause obstruction or damage to the esophagus.

\[
LD_{50} \text{ (hamster, oral): 6.0 g/kg; } LD_{50} \text{ (mouse, oral): 8.1 g/kg}
\]
\[
LD_{50} \text{ (rabbit, oral): 7.0 g/kg; } LD_{50} \text{ (rat, oral): 6.77 g/kg}
\]

**Handling Precautions:**

Observe normal precautions appropriate to the circumstances and quantity of material handled. Guar gum may irritate the eyes. So, eye protection, gloves and a dust mask to be used during its handling.

**2.2.2.1 Past work done on Guar gum**

*Mohini et al., 2005,* prepared guar gum microspheres containing methotrexate (MTX) and characterized for local release of drug in the colon. Guar gum microspheres showed adequate potential in achieving local release of drug in *in vitro* release studies, and this finding was further endorsed with *in vivo* studies96.
Al-Saidan et al., 2004, developed guar gum matrix tablets for oral controlled release of water-soluble diltiazem hydrochloride. Based on the results of in vitro and in vivo studies it was concluded that that guar gum matrix tablets provided oral controlled release of water-soluble diltiazem hydrochloride\(^97\).

Udaya et al., 2003, Polyacrylamide-grafted-guar gum (pAAm-g-GG) was prepared by taking three different ratios of guar gum to acrylamide (1:2, 1:3.5 and 1:5). They concluded that hydrolyzed pAAm-g-GG matrices are pH sensitive and can be used for intestinal drug delivery\(^98\).

Krishnaiah et al., 2002, designed oral controlled drug delivery systems of Trimetazidine dihydrochloride using guar gum in the form of three-layer matrix tablets by using wet granulation technique. The results indicated that guar gum, is a potential carrier in the design of oral controlled drug delivery systems\(^99\).

Senapati, 2006, prepared matrix tablets of phenylpropanolamine using karaya gum and guar gum, alone or in combination with other excipients. They concluded a combination of karaya gum and guar gum exhibited more sustained release than individual gum\(^100\).

Krishnaiah, 2003, developed albendazole colon targeted drug delivery systems using guar gum as a carrier prepared by wet granulation technique using starch paste as a binder. The guar gum matrix tablets
of albendazole showed no change either in physical appearance, drug content\textsuperscript{101}.

Baweja and Misra, 1997, Guar gum and methylated guar gum have been evaluated as hydrophilic matrices for controlled release tablets. Effect of the composition of matrices and the method of preparation of tablets on the drug release kinetics from the guar gum and methylated guar gum matrices have been studied and compared\textsuperscript{102}.

Deshmukh et al., 2009, designed oral controlled release theophylline anhydrous bioadhesive tablets and to optimize the drug release profile and in vitro bioadhesion strength. Different types of natural hydrophilic polymers such as xanthan gum, locust bean gum, guar gum, karaya gum, and their combinations were used to formulate matrix tablets. An increase in the gum concentration increases the drug release profile beyond 12 h\textsuperscript{103}.

\textbf{2.2.3 Profile of Povidone:} \textsuperscript{104-110}

**Nonproprietary Name:**

USP: Povidone  
BP: Povidone

**Functional Category:**

USP: Tablet binder; suspending /or viscosity-increasing agent.  
BP: Pharmaceutical excipient

**Synonyms:**
Polyvidone; polyvinylpyrrolidone; PVP; Kollidon; Plasdone

Chemical Names and CAS Registry Number:

2-Pyrrolidinone, 1-ethenyl-, homopolymer 1-Vinyl-2-pyrrolidinone-polymer [9003-39-8]

Empirical Formula and Molecular Weight:

(C₆H₉NO) n. It is produced as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 g/mol.

Structural Formula:

![Structural Formula](image)

Commercial Availability:

USA: BASF Wyandotte Corp, GAF Corp.

UK: BASF UK Ltd, Becpharm Ltd, Lagden Campbell Chem. Ltd.

Description:

A creamy white, odourless and hygroscopic powder

Typical Properties:

- Acidity/alkalinity: pH = 3.0-7.0 (5% w/v aqueous solution)
- Density (bulk): 0.409 g/cm³; Density (tapped): 0.508 g/cm³
- Density (true): 1.180 g/cm³

Flowability: 20 g/s for povidone K-15; 16 g/s for povidone K-29/32

Melting point: Softens at 150°C
**Particle size distribution:** 90% > 50 µm, 50% > 100 µm, 5% > 200 µm in size for Kollidon 25/30; 90% > 200 µm, 95% > 250 µm in size for Kollidon 90

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

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

**Table 2.4: Dynamic viscosity of 10% w/v aqueous povidone (Kollidon) solutions at 20°C**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dynamic viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K-11/14</td>
<td>1.3-2.3</td>
</tr>
<tr>
<td>K-16/18</td>
<td>1.5-3.5</td>
</tr>
<tr>
<td>K-24/27</td>
<td>3.5-5.5</td>
</tr>
<tr>
<td>K-28/32</td>
<td>5.5-8.5</td>
</tr>
<tr>
<td>K-85/95</td>
<td>300-700</td>
</tr>
</tbody>
</table>

**Table 2.5: Dynamic viscosity of 5% w/v povidone (Kollidon) solutions in ethanol and propan-2-ol at 25°C**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dynamic viscosity (mPa s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ethanol</td>
</tr>
<tr>
<td>K-12PF</td>
<td>1.4</td>
</tr>
<tr>
<td>K-17PF</td>
<td>1.9</td>
</tr>
<tr>
<td>K-25</td>
<td>2.7</td>
</tr>
<tr>
<td>K-30</td>
<td>3.4</td>
</tr>
<tr>
<td>K-90</td>
<td>53.0</td>
</tr>
</tbody>
</table>

**Stability and Storage Conditions:**

Povidone darkens to some extent on heating at 150°C, with reduction in water solubility. It is stable to a short cycle of heat exposure around 110-130°C. Aqueous solutions are susceptible to mold growth and hence require suitable preservatives. Povidone can be stored under ordinary conditions without undergoing decomposition or degradation.
However, since the powder is hygroscopic, it should be stored in a moisture-proof, tight container.

**Incompatibilities:**

Povidone is compatible in solution and with a wide range of inorganic salts, natural and synthetic resins and other chemicals. It forms molecular adducts in solution with sulfathiazole sodium, sodium salicylate, salicylic acid, Phenobarbital, tannin and possibly other compounds.

**Safety:**

Chemically, povidone is inert and non-toxic. The acute oral toxicity in rats and guinea pigs is above 100 g/kg. Prolonged administrations of therapeutic doses are well tolerated without injury. It is free from irritant effects on the skin without any sensitization. It does not irritate the mucous membrane of rabbit eyes. It is not antigenic and does not interfere in antibody formation. It is well tolerated by the upper respiratory tract in inhalation studies.

**Handling Precautions:** No restrictions specified.

**Regulatory Acceptance:** USP XXIII; BP 2000

---

**Table 2.6: Applications of Povidone in Pharmaceutical Formulation or Technology:**

<table>
<thead>
<tr>
<th>Use</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier for drugs</td>
<td>10-25% solution</td>
</tr>
<tr>
<td>Dispersing agent</td>
<td>up to 5% solution</td>
</tr>
<tr>
<td>Suspending or viscosity builder</td>
<td>up to 5% solution</td>
</tr>
<tr>
<td>Tablet binder; tablet diluent; coating agent</td>
<td>0.5 – 5% solution</td>
</tr>
</tbody>
</table>

Povidone is used in the form of a solution as a binder in tablet granulations.

**2.2.3.1 Past work done on Povidone**

Rao et al., 1996, cellulose acetate (CA) and PVP were evaluated for transdermal use. Dibutyl phthalate was used as permeability enhancer. Films composed of CA: PVP (2:1) can be used as rate of controlling membranes for the development of Transdermal Drug Delivery Systems (TDDS) systems using a suitable drug reservoir.¹¹¹
Ghosh and Barik, 2009, developed matrix tablets of aceclofenac, using HPMC, EC and Guar gum by wet granulation method. They concluded that the HPMC matrix tablets provided oral controlled release of aceclofenac.112

Draganoiu et al., 2005, designed polyvinylacetatelpovidone based polymer as a matrix sustained release excipient for propranolol hydrochloride and explored its matrix forming property113.

Raghavendra, 2009, developed sustained release matrix tablets of Tramadol hydrochloride using HPMC and natural gums like Karaya gum (KG) and Carrageenan (CG) 114.

Sahoo et al., 2008, prepared verapamil hydrochloride sustained release tablets with Eudragit RLPO and Kollidon SR. The result indicates that the release of verapamil hydrochloride can be effectively controlled from a tablet containing solid dispersions of Eudragit RLPO115.

Biswajit et al., 2005, designed TDDS of dexamethasone using PVP: EC and Eudragit: PVP. They concluded that PVP–EC polymers are better suited than PVP–Eudragit polymers for the development of TDDS of dexamethasone116.

Nithiyananthan et al., 2009, prepared sustained release matrix tablets of Tamsulosin hydrochloride using HPMC and acheived sustained drug release of Tamsulosin hydrochloride117.

2.2.4 Profile of Ficus bengalensis 118-119

Synonyms

Sanskrit : Nyagrodhah, Vatah

English : Banyan

Hindi : Bat, Bargad
Taxonomical Classification

Kingdom : Plantae – Plants
Subkingdom : Tracheobionta-Vascular plants
Superdivision : Spermatophyta-Seed plants
Division : Magnoliophyta-Flowering plants
Class : magnoliophyta-Dicotyledons
Subclass : Hamamelidae
Order : Urticales
Family : Moraceae-Mulberry family
Genus : Ficus L. – fig
Species : Ficus bengalensis L. – Indian Banyan

Botanical Description

A very large tree reaching 30m high, sending down many aerial roots from the branches and thus extending the growth of the tree indefinitely; young parts softly pubescent. Leaves coriaceous, 10-20 by 5-12.5 cm, ovate or orbicular-ovate to elliptic, obtuse, entire, glabrescent above, glabrous or minutely pubescent beneath, base rounded or subcordate, 3-7 nerved with about 5-7 pairs of lateral nerves above the basal ones and distinct reticulate venation between; peduncles 1.3-5cm long, stout; stipules 2-2.5 cm long. Receptacles about 2cm diameter, sessile in pairs, axillary, globose, puberulous, red when ripe, with 3 broad rounded nearly glabrous coriaceous basal bracts. Male flowers
rather numerous near the mouth of the receptacles, sepals 4, lanceolate. Stamen1. Gall flowers: Perianth as in the male, style short. Fertile flowers: perianth shorter than in the male, style elongate.

**Composition:** Dried, uncooked *Ficus bengalensis* contain nutritional value per 100 g (3.5 oz) Energy 230 kcal (963 kJ)

### Table 2.7: Composition of 100 g of dried fruits of *Ficus bengalensis*

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>57.05 g</td>
</tr>
<tr>
<td>Sugars</td>
<td>38.10 g</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>5.6 g</td>
</tr>
<tr>
<td>Fat</td>
<td>0.56 g</td>
</tr>
<tr>
<td>Protein</td>
<td>3.8 g</td>
</tr>
<tr>
<td>Thiamin (Vit. B1)</td>
<td>0.040 mg</td>
</tr>
<tr>
<td>Riboflavin (Vit. B2)</td>
<td>0.050 mg</td>
</tr>
<tr>
<td>Niacin (Vit. B3)</td>
<td>0.324 mg</td>
</tr>
<tr>
<td>Pantothenic acid (B5)</td>
<td>0.257 mg</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.095 mg</td>
</tr>
<tr>
<td>Folate (Vit. B9)</td>
<td>5 μg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1.8 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>157 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>1.87 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>57 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>65 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>540 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.48 mg</td>
</tr>
</tbody>
</table>

Source: USDA Nutrient database

**Chemical Constituents:**

20-tetratriacontene-2-one, 6-heptatriacontene-10-one, pentatriacontan-5-one, β-sitosterol-alpha-D-glucose and meso-inositol, methyl ethers of leucoanthocyanins-delphinidin-3-O-α-L-rhamnoside (l); pelargonidin-3-
O-α-L-rhamno-side (II) and leucoanthocyanidin, 20- Tetratriaconten-2-one, pentatriacontan-5-one and 6-heptatriacontene-10-one have been isolated from the stem bark of *Ficus bengalensis*.

**Uses:**

- The milky juice is externally applied for pains and bruises and as an anodyne in rheumatism and lumbago. Used to reduce toothache
- The leaves are heated and applied as poultice to abscesses
- The bark is astringent and is used in dysentery, diarrhoea and diabetes
- An infusion of young buds is useful in diarrhoea and dysentery
- The seeds have cooling and tonic actions
- The young tips of hanging roots are effective against obstinate vomiting
- Hypoglycemic effect of the ethanolic extract of the bark of *F. bengalensis* has been observed in normal and alloxan diabetic rabbits
- Free radical scavenging activity of methanolic extract of *Syzygium cumini* seeds, *Ficus bengalensis* bark, a compound Bengalenoside, isolated from *F. bengalensis* extract and Gallic acid isolated from *S. cumini* extract, was studied by DPPH assay method
- Healing Power and Curative Properties, Diarrhoea and Dysentery, Piles, Female Sterility, Leucorrhoea, Teeth Disorders, Rheumatism and Skin Disorders.

**2.2.4.1 Past work done on *Ficus bengalensis*:**

*Subramanian and Misra, 1978,* three ketones, 20-tetraconten-2-one (1), 6-heptatriacontene-10-one (7), pentatriacontan-5-one (13), and
two other compounds, beta-sitosterol-alpha-D-glucose and meso-inositol have been isolated from the stem bark of Ficus bengalensis and their tentative structures were given\textsuperscript{119}.

**Rimi et al., 1994**, hot water extract of Ficus bengalensis was given orally to normal rabbits and rabbits with alloxan induced alloxan-recovered, mildly diabetic and severely diabetic states, at a single dose of 50 mg/kg/day for three days. The extract produced 68\% fall in FBG values in severely diabetic rabbits\textsuperscript{120}.

**Rakesh et al., 2009**, explore scientifically the antidiabetic potential of Ficus bengalensis aerial roots as its bark had already been reported to possess antidiabetic efficacy. The actions of aqueous extract of Ficus bengalensis aerial roots were compared with Glipizide. A dose of 300 mg per kg showed the maximum fall in BGL in normal rats\textsuperscript{121}.

**Singh et al., 2009**, explored antidiabetic potential of Ficus bengalensis aerial roots as its bark had already been reported to possess antidiabetic efficacy. Variable doses of aqueous extract of Ficus bengalensis aerial roots on blood glucose level (BGL) of normal-, sub- and mild-diabetic models have been studied and the results were compared with Glipizide. A dose of 300 mg per kg showed the maximum fall of BGL during FBG in normal rats\textsuperscript{122}.

**Kumar and Augusti, 1989**, isolated a dimethoxy derivative of leucocyandin 3-O-beta-D-galactosyl cellobioside from the bark of F. bengalensis Linn demonstrated antidiabetic action\textsuperscript{123}.
**Cherian and Augusti, 1993,** isolated glycoside of leucopelargonidin from the bark of F. bengalensis demonstrated significant hypoglycemic, hypolipidemic and serum insulin raising effects in moderately diabetic rats with close similarities to the effects of a minimal dose of glibenclamide\textsuperscript{124}.

**Gayathri and Krishnan, 2008,** evaluated the antidiabetic potential of aqueous extract of Ficus bengalensis bark in streptozotocin induced diabetic rats with a dose of 500mg/kg/day\textsuperscript{125}.

**Shukla et al., 1995,** investigated hypocholesterolemic effect of the water extract of the bark of Ficus bengalensis in rabbits\textsuperscript{126}.

**Daniel et al., 1998,** evaluated two flavonoid compounds, viz. 5,7-dimethyl ether of leucopelargonidin 3-0-\(\alpha\)-L rhamnoside and 5,3'-dimethyl ether of leucocyanidin 3-0-\(\alpha\)-D galactosyl cellobioside obtained from the bark of F. bengalensis for antioxidant action in hyperlipidemic rats. The results were compared with the activity of a structurally similar flavonoid, quercetin (known antioxidant). The Ficus compounds showed significant antioxidant effects\textsuperscript{127}.

**NOTE:** No attempts has been made on Ficus bengalensis fruit mucilage as release retardant

**2.2.5 Profile of Ficus carica** \textsuperscript{128-131}

**Introduction to Ficus carica Linn:**

**Synonyms**
Sanskrit : Falgu
English : Common Fig
Hindi : Anjir
Kannada : Anjura
Telugu : Anjur
Malyalam : Atti meer alou (kambi kadhakal)

**Taxonomical Classification:**

Kingdom : Plantae – Plants
Subkingdom : Tracheobionta-Vascular plants
Superdivision : Spermatophyta-Seed plants
Division : Magnoliophyta -Flowering plants
Class : Magnoliopsida-Dicotyledons
Subclass : Hamamelidae
Order : Rosales
Family : Moraceae-Mulberry family
Genus : Ficus
Species : *Ficus carica*

**Botanical Description:**

**Plant:** Warm temperate or sub-tropical small trees or shrubs to 30 ft; trained to stout, wide-headed trees in California. Plants thrive in hot, arid climates -grow in Gulf States, Texas California etc. Several tropical countries like Central America, Caribbean islands; Bermuda, Venezuela, Chile and Argentina grow figs.
**Fruit:** A "syconium" (multiple of druplets) - an inverted inflorescence with swollen receptacle. The opening at the apex is an "ostiole", through which fig wasp crawls to enter, lay eggs and pollinate.

**Composition:** Dried, uncooked *Ficus carica* contain nutritional value per 100 g (3.5 oz) Energy 250 kcal 1046 kJ

**Table 2.8: Composition of 100 g of dried fruits of *Ficus carica***

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>63.87 g</td>
</tr>
<tr>
<td>Sugars</td>
<td>47.92 g</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>9.8 g</td>
</tr>
<tr>
<td>Fat</td>
<td>0.93 g</td>
</tr>
<tr>
<td>Protein</td>
<td>3.30 g</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>1.6</td>
</tr>
<tr>
<td>Thiamin (Vit. B1)</td>
<td>0.085 mg</td>
</tr>
<tr>
<td>Riboflavin (Vit. B2)</td>
<td>0.082 mg</td>
</tr>
<tr>
<td>Niacin (Vit. B3)</td>
<td>0.619 mg</td>
</tr>
<tr>
<td>Pantothenic acid (B5)</td>
<td>0.434 mg</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.106 mg</td>
</tr>
<tr>
<td>Folate (Vit. B9)</td>
<td>9 μg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1.2 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>162 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>2.03 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>68 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>67 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>680 mg</td>
</tr>
<tr>
<td>Sodium</td>
<td>0.8</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.55 mg</td>
</tr>
</tbody>
</table>

Source: USDA Nutrient database

**Uses:**

In those countries where they are plentiful, figs are used as food. Internally they are given in the form of demulcent decoctions in pulmonary and nephritic affections. *Ficus carica* can be taken as food to relieve habitual constipation. Roasted/boiled and break to open, which are used to reduce pus cataplasms in gum-boil.

**2.2.5.1 Past work done on *Ficus carica***
Krishna Mohan et al., 2007, evaluated methanolic extract of Ficus carica leaves for hepatoprotective activity in rats with liver damage induced by carbon tetrachloride. The extract at an oral dose of 500 mg/kg exhibited a significant protective effect by lowering the serum levels of aspartate aminotransferase, alanine aminotransferase, total serum bilirubin and malondialdehyde equivalent, an index of lipid peroxidation of the liver. The activity of extract was also comparable to that of silymarin, a known hepatoprotective.132

Gond and Khadabadi, 2008, extracted shade dried Ficus carica leaves using petroleum ether (60-80°) and tested for antihepatotoxic activity on rats treated with 50 mg/kg of rifampicin orally and got appreciable results133.

Vinson et al., 2005, dried and fresh fruits of Ficus carica were compared for antioxidant activity. The findings suggest that dried fruits should be a greater part of the diet as they are dense in phenol antioxidants and nutrients, most notably fiber.134

NOTE: No attempts has been made on Ficus carica fruit mucilage as release retardant

2.2.6 Profile of Ficus glomerata: 135-139

Synonyms
Sanskrit : Udumbara
English : Cratock, Cluster fig, Country fig, Gular fig
Hindi : Gular
Kannada : Atti
Telgu : Medipandu
Tamil : Alamaram, Peral
Malyalam : Attimeer alou

**Taxonomical Classification:**

Kingdom : Plantae – Plants
Subkingdom : Tracheobionta-Vascular plants
Superdivision : Spermatophyta-Seed plants
Division : Magnoliophyta
Class : Magnoliopsida -Dicotyledons
Subclass : Hamamelidae
Order : Rosales
Family : Moraceae-Mulberry family
Genus : Ficus
Species : F. racemosa
Binomial name : Ficus racemosa
Synonyms : Ficus glomerata Roxb.

**Botanical Description:**

Spreading laticiferous tree, 9.0 to 12.2 m tall, reddish grey bark, alternate leaves, stipules ovate-lanceolate, pubescent, 1.25 to 2.5 cm long, petioles 2.5 to 5.0 cm long. Fruits borne in clusters on the main
trunk and leafless short branches, subglobose or pyriform, 2.5 to 5.0 cm in diameter, red when ripe

**Composition:** Dried, uncooked *Ficus glomerata* contain nutritional value per 100 g (3.5 oz) Energy 275 kcal 1151.4 kJ

**Table 2.9: Composition of 100 g of dried fruits of Ficus glomerata**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrates</td>
<td>59.65 g</td>
</tr>
<tr>
<td>Sugars</td>
<td>45.51 g</td>
</tr>
<tr>
<td>Dietary fiber</td>
<td>7.8 g</td>
</tr>
<tr>
<td>Fat</td>
<td>1.02 g</td>
</tr>
<tr>
<td>Protein</td>
<td>4.50 g</td>
</tr>
<tr>
<td>Thiamin (Vit. B1)</td>
<td>0.090 mg</td>
</tr>
<tr>
<td>Riboflavin (Vit. B2)</td>
<td>0.085 mg</td>
</tr>
<tr>
<td>Niacin (Vit. B3)</td>
<td>0.518 mg</td>
</tr>
<tr>
<td>Pantothenic acid (B5)</td>
<td>0.335 mg</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.156 mg</td>
</tr>
<tr>
<td>Folate (Vit. B9)</td>
<td>12 μg</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>1.5 mg</td>
</tr>
<tr>
<td>Calcium</td>
<td>185 mg</td>
</tr>
<tr>
<td>Iron</td>
<td>2.51 mg</td>
</tr>
<tr>
<td>Magnesium</td>
<td>87 mg</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>52 mg</td>
</tr>
<tr>
<td>Potassium</td>
<td>79 mg</td>
</tr>
<tr>
<td>Zinc</td>
<td>0.48 mg</td>
</tr>
</tbody>
</table>

Source: USDA Nutrient database

**Uses:**

Astringent, stomachic, carminative, anti-cancerous, anti-inflammatory, anti protozoal, hypoglycemic

**2.2.6.1 Past work done on Ficus glomerata**
Muhammad et al., 1988, investigated the effects of powdered Ficus glomerata fruits on blood glucose levels in normal and alloxan-diabetic rabbits. They concluded that plant contains more than one type of hypoglycaemic principles\textsuperscript{140}.

Rao et al., 2008, observes gastroprotective effect of 50% ethanolic extract of F. glomerata fruit was studied in different gastric ulcer models in rats and concluded its gastroprotective activity\textsuperscript{141}.

Joshi and Mohini, 2008, evaluated dose dependent antioxidant activity of aqueous extract of dried bark of Ficus glomerata. The antioxidant activity may be due to flavonoids and phenolics present in the extract\textsuperscript{142}.

Bheemachari et al., 2007, evaluated the effects of latex of Ficus racemosa for antidiarrhoeal potential in rats. The results obtained thus justify and further support the traditional application of the latex as an antidiarrhoeal agent.\textsuperscript{143}

NOTE: No attempts has been made on Ficus glomerata fruit mucilage as release retardant

2.2.7 Profile of Microcrystalline Cellulose \textsuperscript{144-148}
(Grade Used – Avicel PH-105)

**Non-Proprietary Name:**

NF: Microcrystalline cellulose  
BP: Microcrystalline cellulose

**Synonyms:** Cellulose gel; crystalline cellulose; Avicel PH-101, 102

**Functional Category:**

**USP:** Tablet and capsule diluent; tablet disintegrant; suspending and/or viscosity-increasing agent.  
**BP:** Pharmaceutical aid.

**Chemical Name and CAS Registry Number:** Cellulose [900-34-6]  
**Empirical Formula/Molecular Weight:** (C\(_6\)H\(_{10}\)O\(_5\)) \(_n\), \(n=220\) 36,000 (apx)

**Structural Formula:**

\[
\begin{array}{c}
\text{CH}_2\text{OH} \\
\text{H} \\
\text{H} \\
\text{OH} \\
\text{H} \\
\text{OH} \\
\text{H} \\
\text{OH} \\
\end{array}
\]

**Description:**

Purified, partially depolymerized cellulose occurs as a white, odourless, tasteless, crystalline powder composed of porous particles. Available in different particle size grades with different properties i.e. 101 and 102.

**Typical Properties:**

**Density:** The average density of all types of commercially available microcrystalline cellulose is,
Apparent density - 0.28g/cm³
Tap density - 0.43 g/cm³

Particle Size: Commercially microcrystalline cellulose (Avicel pH) is available in four types.

**Table 2.10: Type and average particle size of Micro crystalline Cellulose**

<table>
<thead>
<tr>
<th>Type</th>
<th>Average particle size (µm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH-101</td>
<td>50</td>
</tr>
<tr>
<td>PH-102</td>
<td>100</td>
</tr>
<tr>
<td>PH-103</td>
<td>50</td>
</tr>
<tr>
<td>PH-105</td>
<td>20</td>
</tr>
</tbody>
</table>

Refractive Index:

1.55

Solubility:

Insoluble in water, dilute acids and organic solvents, it slightly soluble in Sodium Hydroxide solution (1 in 20).

Melting range:

260 – 270°C (charring temperature)

Specific surface area:

Avicel (PH-105) 20.7 m²/g; Avicel (PH-102) 10.0 m²/g;
Avicel (PH-103) 11.4 m²/g; Avicel (PH-101) 11.2 m²/g

Stability and Storage Conditions:

Stable, hygroscopic, Store in well-closed container

Incompatibilities:

None cited in the literature.
**Safety:**

Generally regarded as safe

Applications in Pharmaceutical Formulation or Technology Use:
- Tablet binder/ diluent (Wet granulation) -> 5-20% concentration
- Tablet binder/diluent (Direct compression) -> 5-20% concentration
- Tablet disintegrant -> 5-15% concentration
- Tablet glidant -> 5-15% concentration
- Anti-adherent -> 5-20% concentration
- Adsorbent -> 10-30% concentration
- Capsule diluent

### 2.2.8 Profile of Magnesium Stearate

**Non-Proprietary Name:**

NF: Magnesium stearate

BP/EP: Magnesium Stearate

**Synonyms:**

Metallic stearate; magnesium salt

**Functional Category:**

USP: Tablet and/or capsule lubricant

BP/EP: Lubricant; pharmaceutical aid

Others: Glidant; antiadherent

**Chemical Names:**

Octadecanoic acid; Magnesium salt; Magnesium stearate

**CAS Registry Number:** [557-04-0]

**Empirical Formula:** \( \text{C}_{36}\text{H}_{70}\text{MgO}_{4} \)

**Molecular Weight:** 591.3 g/mol
**Structural Formula:**

\[
\begin{align*}
\text{CH}_3\text{(CH}_2\text{)}_{16}\text{COO} & \quad \text{Mg} \\
\text{CH}_3\text{(CH}_2\text{)}_{16}\text{COO} &
\end{align*}
\]

**Description:**

Fine, white, precipitated or milled, impalpable powder of low bulk density, odour and taste are slight but characteristic. The powder is unctuous and readily adheres to the skin.

**Typical Properties:**

- **Density (He):** 1.03 – 1.08 g/cm\(^3\)
- **Bulk volume:** 3.0 – 8.4 ml/g
- **Tapped volume:** 2.5 – 6.2 ml/g
- **Melting point:** 88.5°C

**Solubility:**

It is insoluble in water, alcohol and ether. It slightly soluble in hot alcohol and benzene

**Flowability:** Poorly flowing, cohesive powder.

**Stability and Storage Conditions:**

Stable, non-self-polymerizable

Store in cool, dry place in a well-closed container

**Incompatibilities:**

Acidic substances; alkaline substances; iron salts, strong oxidizing materials.

**Safety:**

Magnesium stearate is described as an inert or nuisance dust. It is classified as non-hazardous by the Department of Transportation Regulations, generally considered not to be a healthy hazard under normal conditions of use. Dust clouds of magnesium stearate may be explosive.

**Applications in Pharmaceutical Formulations:**
In tablets and capsules as lubricant/glidant/anti-adherent (Conc: 0.25-2.0%).

2.3 LITERATURE REVIEW ON CDDS

2.21: Past work done on Controlled drug delivery systems

Manjunatha et al., 2007, prepared diclofenac sodium solid dispersion of immediate release component was prepared using PVP and mannitol carriers by common solvent method, controlled release component was prepared in form of spherical beads by ionotropic gelation technique. The formulations were found to be effective in providing controlled release of drug for a longer period of time.

Reza et al., 2005, designed oral CDDS of verapamil HCl, using natural and semisynthetic polymers (HPMC, tragacanth and acacia) in the forms of 1- and 3-layer matrix tablets. The tablets significantly retarded the drug release.

Bupender, 2006, designed oral controlled release mucoadhesive compressed hydrophilic matrices of atenolol using Carbopol 934P and sodium CMC. The found the optimum formulation with excellent bioadhesive strength and controlled release.

Jain et al., 2008, sustained release tablets of furosemide were fabricated using pectin, guar gum and xanthan gum. The tablet with guar gum exhibited greater swelling index than those with pectin and xanthan gum. A better controlled drug release was obtained with the matrix tablet made-up of the guar gum than with the pectin and xanthan gum. The dissolution profile of furosemide from matrix tablets prepared using different natural polymers were retarded approx 15 h.

Selim et al., 2003, prepared matrix tablets of theophylline, diclofenac sodium and diltiazem HCl using Kollidon SR, Carnauba wax and HPMC-15cps by direct compression process. The results indicated controlled
plasma level of drug can be obtained by combination of these polymers\textsuperscript{158}.

**Panna et al., 2006**, formulated control release oral delivery system using Carbopol 934P and granulation technique in the release of Ibuprofen from matrix tablets by direct compression, wet granulation and dry granulation method at different polymer concentration using lactose, dibasic calcium phosphate, microcrystalline cellulose and starch as diluents. Diluents have appreciable effect on drug release rate only at low polymer concentration\textsuperscript{159}.

**Gedela et al., 2002**, examined the influence of modified gum karaya (MGK) on the oral bioavailability of nimodipine (NM), in comparison with that of gum karaya (GK). They inferred that MGK could be used for the dissolution enhancement of NM\textsuperscript{160}.

**Martin et al., 2006**, investigated CMC on the release properties of theophylline from tablet matrices which were prepared by wet granulation method. They concluded that the drug release mechanism was influenced by both the molecular size of CMC and the presence of polymer additive\textsuperscript{161}.

**Evelyn et al., 2005**, prepared tablets containing theophylline based on a Eudragit RS 30D and NE 30D matrices containing 10\% to 30\% of either of the polymer were produced by compression method. The influence of the different proportions of methacrylic esters was studied\textsuperscript{162}.

**Sriramakamal et al., 2000**, designed and characterized a zero-order bioresorbable reservoir delivery system (BRDS) for diffusional or osmotically controlled delivery of model drugs including macromolecules. The BRDS was manufactured by casting hollow cylindrical poly (lactic acid) (PLA): polyethylene glycol (PEG) membranes on a stainless steel
mold. This study concludes that PEG inclusion at 25°C enables manufacture of uniform, cylindrical PLA membranes of controlled permeability\textsuperscript{163}.

**Perioli et al., 2007**, designed sustained-release mucoadhesive bilayered tablets, using mixtures of mucoadhesive polymers and an inorganic matrix (hydrotalcite), for the topical administration of flurbiprofen in the oral cavity. The first layer, responsible for the tablet retention on the mucosa, was prepared by compression of a cellulose derivative and polyacrylic derivative blend. The second layer, responsible for buccal drug delivery, was obtained by compression of a mixture of the same (first layer) mucoadhesive polymers and hydrotalcite containing flurbiprofen. They achieved satisfactory results means that patient compliance is improved\textsuperscript{164}.

**Mankunatha et al., 2007**, sustained release dosage form of diclofenac sodium containing immediate and controlled release components were designed. Solid dispersion of immediate release component was prepared using PVP and mannitol carriers by common solvent method. Controlled release component was prepared in form of spherical beads by ionotropic gelation technique. The formulations were found to be effective in providing controlled release of drug for a longer period of time\textsuperscript{165}.

**Tiwari et al., 2003**, studied the effect of concentration of hydrophilic (HPMC) and hydrophobic polymers (hydrogenated castor oil and EC) on the release rate of tramadol. Hydrophilic matrix tablets were prepared by wet granulation technique, while hydrophobic (wax) matrix tablets were prepared by melt granulation technique. The effect of EC coating (Surelease) and the presence of lactose and HPMC in the coating composition on the drug release was also investigated. Hydrophobic matrix tablets prepared using HCO were found to be best suited for modulating the delivery of tramadol hydrochloride\textsuperscript{166}.
Rani and Mishra, 2004, fabricated matrix, osmotic matrix and osmotic pump tablets for controlled delivery of diclofenac sodium. The OM and OP tablets, performed better than the matrix tablets. The rate and extent of drug release from matrix tablets with single polymer was significantly different from that of matrix tablet with admixed polymers. Type of porosigenic agents and osmogens also influenced the drug release. It was concluded that the osmotic matrix and osmotic pump tablets could provide more prolonged, controlled and gastrointestinal environmental-independent DS release that may result in an improved therapeutic efficacy and patient compliance

Avachat et al., 2007, developed and characterized an oral controlled release drug delivery system for concomitant administration of diclofenac sodium (DS) and chondroitin sulfate (CS). A hydrophilic matrix-based tablet using different concentrations of hydroxypropylmethylcellulose (HPMC) was developed using wet granulation technique. They concluded that the release of CS and DS can be effectively controlled from a single tablet using HPMC matrix system

Yeole et al., 2006, developed sustained release matrix tablets of diclofenac sodium by using different drug: polymer ratios, such as F1 (1:0.12), F2 (1:0.16), F3 (1:0.20), F4 (1:0.24) and F5 (1:0.28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluent. All the lubricated formulations were compressed using 8 mm flat faced punches. And concluded Xanthan gum can be used as an effective matrix former, to extend the release of diclofenac sodium

Kondaiah and Prakash, 2002, formulated theophylline polymeric matrix tablets for controlled release using sintering technique. The powder of ethylene vinyl acetate copolymer 1802 was prepared by a novel spray technique. Matrix tablets of theophylline in vinyl acetate copolymer were prepared in different drug and polymer ratios using
direct compression and subsequent sintering technique at various temperatures. The cumulative percent of drug released from this tablet formulation is better than two commercial products and comparable to the other one.\(^{170}\)

**Kuksal et al., 2006**, prepared and characterized extended-release matrix tablets of zidovudine using hydrophilic Eudragit RLPO and RSPO alone or their combination with hydrophobic ethyl cellulose. They concluded that the results suggest that the developed sustained-release tablets of zidovudine could perform therapeutically better than conventional dosage forms, leading to improve efficacy and better patient compliance.\(^{171}\)

**Hamdy et al., 2007**, investigated different types and levels of hydrophilic matrixing agents, including methylcellulose (MC), sodium alginate (Alg), and sodium carboxymethylcellulose (CMC), in an attempt to formulate controlled-release matrix tablets containing 25 mg baclofen. The tablets were prepared by wet granulation. They suggested that MC and Alg are good candidates for preparing modified-release baclofen tablet formulations.\(^{172}\)

**Vishnu et al., 2007**, established mucoadhesive buccal devices of propranolol hydrochloride (PRH) in the forms of bilayered and multilayered tablets. The tablets were prepared using sodium carboxymethylcellulose (SCMC) and Carbopol-934 (CP) as bioadhesive polymers to impart mucoadhesion and ethyl cellulose (EC) to act as an impermeable backing layer. The present study concludes that mucoadhesive buccal devices of PRH can be a good way to bypass the extensive hepatic first-pass metabolism and to improve the bioavailability of PRH.\(^{173}\)

**Jaber and Naser, 2004**, designed lithium carbonate (LC) sustained-release tablets. The tablets developed using carbopol (CP), Na CMC and HPMC. The tablets were prepared by either direct compression or wet
granulation. *In vitro* release studies demonstrated that the releases of LC from all formulated sustained matrix tablets were sustained. Na CMC, CP, and HPMC can, therefore, be used to modify release rates of LC in hydrophilic matrix tablets\textsuperscript{174}.

**Dave et al., 2004**, prepared a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and HPMC were evaluated for gel-forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. The effects of citric acid and stearic acid on drug release profile and floating properties were investigated. These studies indicated that the proper balance between a release rate enhancer and a release rate retardant can produce a drug dissolution profile similar to a theoretical dissolution profile\textsuperscript{175}.

**Bashar et al., 2003**, designed pH-dependent swellable and erodable-buffered matrices and to studied the effect of the microenvironment pH on the release pattern of diclofenac sodium. Buffered matrix tablets containing diclofenac sodium, mixed with hydrophilic polymer (HPMC) and pH-dependent solubility polymer (Eudragit L100-55) were prepared with different microenvironment pHs. It was concluded from this study that changing the pH within the matrix influenced the rate of release of the drug without affecting the release pattern\textsuperscript{176}.

**Raghuram et al., 2003**, developed once-daily sustained-release matrix tablets of nicorandil using EC, Eudragit RL-100, Eudragit RS-100 and PVP were used as granulating agents along with hydrophilic matrix materials HPMC, sodium CMC and sodium alginate\textsuperscript{177}.

**Piyakulawat et al., 2007**, polyelectrolyte complex (PEC) hydrogel beads based on chitosan (CS) and carrageenan (CR) have been studied as a controlled release device to deliver sodium diclofenac (DFNa) in the simulated gastrointestinal condition. They concluded the release of drug was controlled by diffusion of DFNa through the hydrogel beads\textsuperscript{178}. 
**Bhalekar et al., 2006,** prepared resinates of verapamil HCl were formulated using Indion resins. Resinates were pelletized using HPMC. Resinate of Indion 254 with 5% HPMC fulfilled USP criteria for extended release verapamil preparation.\(^ {179}\)

### 2.4 LITERATURE REVIEW ON TDDS

**2.22: Past work done on transdermal drug delivery systems**

**Arora et al., 2002,** prepared matrix-type transdermal patches of diclofenac diethylamine using PVP and EC by solvent evaporation technique. And concluded that diclofenac diethylamine can be formulated into the transdermal matrix type patches to sustain its release characteristics and the polymeric composition (PVP/EC, 1:2) was found to be the best choice\(^ {180}\).

**Ehab and Tadros, 2007,** prepared transdermal patches of salbutamol sulfate as ethosomes and classic liposomes containing different cholesterol and dicetylphosphate concentrations. The entrapment efficiency percentage was significantly increased by increasing cholesterol, dicetylphosphate and ethanol concentrations. *In vitro* permeation studies of the prepared gels containing the selected vesicles showed that ethosomal systems were much more efficient at delivering SS into mice skin than were liposomes or aqueous or hydroalcoholic solutions\(^ {181}\).

**Bagyalakshmi et al., 2007,** developed membrane-moderated transdermal systems of ampicillin sodium using HPMC, MC, CAP, chitosan, sodium alginate and sodium CMC in an ethanol: pH 4.7 buffer volatile systems by the solvent evaporation technique with HPMC as the rate-controlling membrane for all the systems. They concluded that
Hydrophilic ampicillin sodium can be developed as a transdermal delivery system with sodium alginate that is an alternative to intravenous administration and has minimal adverse effects\textsuperscript{182}.

**Deepak and Pundarikakshudu, 2003**, designed and evaluated unilaminate transdermal adhesive matrix systems using Eudragit E as the adhesive and rate-controlling polymer. Triethylcitrate (TEC) and dibutylphthalate (DBP) have no influence on the diffusion of bupropion through human cadaver skin when used as plasticizers. Incorporation of succinic acid in the adhesive matrix retarded diffusion due to the formation of rigid cross linking of the polymer, while propylene glycol and myristic acid, alone or in combination, significantly enhanced the flux of bupropion through human cadaver skin\textsuperscript{183}.

**Pandey et al., 2000**, prepared different transdermal nimesulide gels using various gel bases, with an objective to formulate suitable transdermal formulation of nimesulide. The polymers selected were sodium alginate, HPMC, NA CMC and methyl cellulose. And observed Sodium alginate gel containing nimesulide was found to be better in all aspects compared to other gel formulations and this was comparable to the marketed gel\textsuperscript{184}.

**Agarwal and Priya, 2006**, different matrix-type transdermal patches of atenolol and metoprolol tartrate were formulated with PVP, CAP, HPMC phthalate and EC. The patches were formulated using combination of polymers and propylene glycol and 1,8-cineole as plasticizer and
penetration enhancer, respectively. The results indicated that maximum release was obtained at 48 h\textsuperscript{185}.

**Shakeel et al., 2007**, investigated the potential of a nanoemulsion formulation for transdermal delivery of aceclofenac. Various oil-in-water nanoemulsions were prepared by the spontaneous emulsification method. These results suggested that nanoemulsions are potential vehicles for improved transdermal delivery of aceclofenac\textsuperscript{186}.

**Narasimha et al., 2001**, prepared transdermal formulations containing theophylline and salbutamol sulfate (SS) using hydroxypropylmethylcellulose. Theophylline was loaded by adsorption with the aid of the coadsorbate sodium chloride. Theophylline was analyzed in saliva, and salbutamol was analyzed in the blood plasma of guinea pigs. The elimination half-life of the drugs was significantly prolonged compared to that for tablets\textsuperscript{187}.

**Parikh and Ghosh, 2004**, developed a transdermal drug delivery of fluoxetine and permeation studies across human cadaver skin were carried out using Franz diffusion cells. Permeation enhancement was achieved by azone, SR-38 and ethanol. Ethanol at 65% vol/vol was able to increase the permeation of fluoxetine\textsuperscript{188}.

**Isik et al., 2006**, evaluated and compared the in vitro and in vivo transdermal potential of w/o microemulsion (M) and gel (G) bases for diclofenac sodium (DS). The effect of dimethyl sulfoxide (DMSO) as a penetration enhancer was also examined when it was added to the M formulation. The in vitro and in vivo studies showed that M could be a new, alternative dosage form for effective therapy\textsuperscript{189}. 
Aqil et al., 2005, characterized transdermal drug delivery systems of pinacidil monohydrate in vivo by monitoring the effect of the TDDS on blood pressure of methyl prednisolone acetate induced hypertensive rats and concluded that a single patch application of pinacidil TDDS (B-4) can effectively control hypertension in rats for 2 days\textsuperscript{190}.

Prashanth et al., 2004, study concludes that PR in combination with PVP and with incorporation of dibutyl phthalate (30\% w/w) produces smooth flexible films with improved tensile strength and percentage elongation. The release rate of drug from films and permeation across skin increases with increase in drug and PVP loading but is independent of film thickness. Patches containing PR:PVP (7:3) show promise for pharmacokinetic and pharmacodynamic performance evaluation in a suitable animal model\textsuperscript{191}.

Narasimha and Rani, 2000, demonstrated the efficacy of a magnetic field to act as a permeation enhancer. The substitution of chemical enhancers by magnetic field in transdermal delivery systems appears to be possible\textsuperscript{192}.

Malay and Saroj, 2004, investigated and evaluated the biopharmaceutical behaviors of the matrix patch containing trazodone hydrochloride (TZN) following transdermal administration in rabbits. The ex vivo skin permeation study was performed using Keshary-Chien glass diffusion cell and mouse epidermis with intact stratum corneum as membrane. The plasma level of TZN following transdermal application could be maintained for 24 h\textsuperscript{193}.

Yuvaraj and Chetan, 2007, transdermal patches of carvedilol with a HPMC-drug reservoir were prepared by the solvent evaporation technique. In this investigation, the membranes of Eudragit RL100 and Eudragit RS100 were cast to achieve control led release of the drug. The non-ionic surfactants in the patches increased the permeation rate, Span 80 exhibiting better enhancement relative to Tween 80\textsuperscript{194}. 
**Ting Li et al., 2007,** formulated transdermal drug delivery system of indomethacin, MASCOS 10 (polyacrylic acid type) pressure sensitive adhesive was used to prepare a drug-in-adhesive type patch containing a variety of permeation enhancers (i.e. azone, L-menthol, 2-isopropyl-5-methylcyclohexyl heptanoate (M-HEP), isopropyl myristate (IPM), Tween-80 and oleic acid) and concluded, the present data confirm the feasibility of developing indomethacin transdermal patches195.

**Srinivas and Udupa, 2004,** developed the membrane controlled transdermal systems of glibenclamide using drug containing carbopol gel as reservoir and EC, Eudragit RS-100, Eudragit RL-100 and EVA as rate controlling membranes. They revealed that the glibenclamide patches exhibited better control of hyperglycemia than oral glibenclamide administration in mice196.

**Ekapol and Kraisri, 2008,** developed diltiazem hydrochloride patches with HPMC and EC. The influence of enhancers dibutyl phthalate, isopropyl myristate, isopropyl palmitate, N-methyl-2-pyrrolidone, oleic acid, polyethylene glycol 400, propylene glycol and Tween80 on permeation was evaluated. And concluded that the film composed of 8:2 HPMC/EC, 30% DBP and 10% IPM, IPP or Tween80 loaded with 25% diltiazem should be selected for manufacturing transdermal patch 197.

**Ubaidulla et al., 2007,** developed a matrix-type transdermal therapeutic system containing carvedilol with different ratios of hydrophilic and hydrophobic polymeric combinations by the solvent evaporation technique. The bioavailability studies in rats indicated that the carvedilol transdermal patches provided steady-state plasma concentrations and improved bioavailability in comparison with oral administration198.
Sridevi et al., 2000, developed acrylate based TDDS for glibenclamide and evaluated it for its pharmacodynamic performance in streptozotocin induced diabetic male Wistar rats. In diabetic rats, normoglycemic levels were maintained for a period of 24 h after transdermal delivery, an effect comparable to that of oral glibenclamide.