CHAPTER 1

INTRODUCTION
INTRODUCTION

Dosage forms are drug delivery systems. Drugs are converted to dosage forms using one or more materials referred as Excipients. They are usually pharmacologically inert material used for achieving certain objectives like modifying appearance, handling property, physical property, improving stability, packaging characteristics or modifying therapeutic characteristics. The cost of dosage form is directly related to the choice of excipients. A large number of excipients from the plants, animals or mineral sources are available in which carbohydrate containing excipients have their own place due to variety of properties like binding agent, suspending agent, granule forming, coating material, easily dispersible material, emulsifying agent and increased viscosity of aqueous solutions etc.

Natural carbohydrate polymers are hydrocolloids, used as gel forming components, tablet binders, sweeteners, flavoring agents, granulating, coating, taste masking, easily dispersible product making material and easy to swallow composition.

Carbohydrates are used in modern dosage forms for release control also, in the form of matrix material, encapsulating excipients, coating material or carrier to target the drug to the tissues.

Plantago Ovata is a traditional plant which is used in Ayurveda, home remedy, and modern medicine for its laxative and cathartic properties. India is a major source of its global production. It is mainly cultivated in North Gujarat and North – West Rajasthan, covering an area of approximately 16,000 hectares. In India approximately 50,000 hectares of land is used for its cultivation which produces approximately 50000 tonnes of seeds annually. India exports psyllium husk worth 75 million USD per annum.

Plantago Ovata husk and seeds contain mucilage which is present in the epidermis of the seed. Chemically it consists of pentosan and aldobionic acid. The product of hydrolysis are D-xylose, L- arabinose, aldobiuronic acid, galacturonic acid, rhamnose, fixed oil, accubin, glycoside, sugars, sterols, proteins are also important constituents of the drug.
Investigations on plantago ovata are interesting from formulations point of view. Till date 57 patents have been granted on its various aspects like process of sterilization of psyllium seed\textsuperscript{21}, dietary fibres\textsuperscript{22,55}, soil conditioning\textsuperscript{23}, microwave muffins\textsuperscript{24}, dehusking process\textsuperscript{25}, R-T-E cereal\textsuperscript{26}, oral re-hydrating agent\textsuperscript{27}, tissue sealant\textsuperscript{28}, wound treatment\textsuperscript{29,53}, cleaning process\textsuperscript{30}, littering clumpable material\textsuperscript{31}, fat reducing product material\textsuperscript{32,50,56}, with lipase inhibitor\textsuperscript{33}, hydro-colloidal gum\textsuperscript{34,60}, gel-fraction\textsuperscript{35,52,54}, modulated aerosol\textsuperscript{36}, isolation of mucilage\textsuperscript{37}, multiplication of earthworms\textsuperscript{38}, reducing viscosity\textsuperscript{57}, core formulations\textsuperscript{39}, bioavailability testing\textsuperscript{51,59}, containing pioglitazone hydrochloride and a biguanide, e.g. Metformin.

Little attempt has been made to utilize plantago ovata in pharmaceutical formulations indicates its potential in designing conventional and new formulations. Very little attempt has been made to chemically modify plantago ovata husk\textsuperscript{40,61}, however abundant literature is available regarding carbohydrate modification\textsuperscript{41,61}. Taking into consideration the possibility of chemical modification of one or more hydroxyl group of husk, possibility lies in obtaining new material and exploring their use in designing new formulations\textsuperscript{42,43,62}. 
REFERENCES


CHAPTER 1.1

INTRODUCTION TO MODIFIED RELEASED DOSAGE FORMS
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The success of modified or controlled released systems for a number of drugs has provided unprecedented impetus for this dosage form. With development of new techniques and methodology coupled with advanced technology and with ever increasing pressure to find novel clinically viable dosage forms for old and new drugs, it has become almost mandatory to examine this dosage forms for practically every drug in pharmaceutical research and development.

1.1.1 Advantages of controlled and modified realised dosage forms

As control release dosage forms are often more expensive than conventional formulations\(^1\), they cannot be justified unless they offer practical or clinical advantages:

1. Reduction in dosing frequency.
2. Reduced fluctuation in circulating levels.
3. Increase patient’s compliance.
4. Avoidance of night dosing.
5. More uniform effects.
6. Reduction in GIT Irritation and other dose.

1.1.2 Disadvantages of controlled and modified realised dosage forms

1. Costly.
2. Unpredictable and often poor in-vivo correlation.
3. Dose dumping.
4. Reduced potential for dose adjustment.
5. Increase potential for first pass clearance and poor systemic availability.
1.1.3 Characteristics that make a drug unsuitable for controlled release

1. Very short elimination half life.
2. Long elimination half life.
3. Narrow therapeutic index.
4. Large dose.
5. Poor absorption.
6. Active absorption.
7. Low or slow solubility.
8. Extensive first pass clearance.
9. Time course of circulating drug levels different to that of pharmacological effect.

1.1.4 Approaches used to retard drug release

1. Capsules of polymeric material filled with solid or liquid drug/suspension wherein drug release is controlled by diffusion through the capsule wall.
2. A heterogeneous dispersion of drug particles in a solid matrix (biodegradable/non-biodegradable) which control drug release by diffusion through the matrix by erosion of matrix or combination of both.
3. A laminate of drug and polymeric material made by coating a film of bio/non biodegradable material with the solid drug and then forming the film into a “sealed sandwich” wherein drug release is by diffusion, erosion or both.
4. A heterogeneous dispersion or solution of drug in a water swellable hydrogen matrix which controls drug release by slow surface to centre. Swelling of the matrix by water and subsequent diffusion of the drug from the water swollen part of the matrix.
5. Liquid-liquid encapsulation of the drug in the viscous solution of the polymer.
6. Pumps that either mechanically or chemically (osmotic pressure) provide the drug in a controlled manner.

7. Drug coated micro pellets as floating delivery systems slowly releasing the drug for an extended time in the gastric juice.

8. At a constant rate, bio-adhesive delivery systems that adhere in GIT and drug were released.

9. Chemical bonding of drug to polymer backbone which control drug release by hydrolysis.

10. Formation of macromolecular structures of the drug via ionic and covalent linkage which controls drug release by hydrolysis, thermodynamic dissociations, or microbial degradation.
1.1.5 Drug release characteristics from oral controlled released formulations

Fig 1.1: Schematic presentation of four major types of drug release characteristic from release formulations
1.1.6 Hydrophilic matrix system

Hydrophilic matrix drug delivery systems are widely used to control drug release because of their flexibility to obtain desirable drug release profiles, cost effectiveness, and broad Food and Drug Administration (FDA) acceptance. These systems consist of hydrophilic polymer, drug and other excipient distributed throughout the matrix. This system is dependent on polymer wetting, polymer hydration, and polymer dissolution for drug release. At the same time, other soluble excipient or drug substances will also wet, dissolve and diffuse out of the matrix while insoluble excipient or drug substances will be held in place until the surrounding polymer/excipient/drug complex erodes or dissolves away.

The release of a drug from a matrix system is influenced by factors relating to the physicochemical properties of the drug substance and to the dosage forms. The properties of drug substance influencing the dissolution rate and subsequent bioavailability include solubility, particle size distribution, crystalline, polymorphism, state of hydration, and complexation.

Several studies have reported on the effect of formulation composition and processing parameters on the properties of hydrophilic matrix tablets processing parameters such as processing procedure, compression force and tablet characteristics (shape, size, surface area and hardness) have been investigated. The molecular weight distribution (viscosity), concentration, degree of substitution, and particle size of polymeric carriers have shown to influence on drug release. Incorporation of additives such as surfactants, ion-exchange resins, or ionic additives to modify polymer gelling and pH adjusting agents have been reported to modify the release profiles of the drug from the matrix tablet formulation therefore expected after addition of soluble lactose increased the dissolution of water soluble drugs.

Matrix-mini tablets offer advantages over conventional pellets as up-scaling of pelletization process is problematic. For wax based mini pellets prior to tableting, melt granulation in a hot stage screw extruder and milling are required. Drug release can be successfully modulated using mixtures of different starches, microcrystalline wax and drug.
Another approach to drug delivery design comprises of a compressed drug disc encased in a polymeric coat and containing an electrolyte\textsuperscript{22}. On exposure to dissolution media, ionic interactions occur and a texturally variable matrix is manifested. The sum of diffusion/dissolution rates, diffusion path length and erosion rate of controlled drug release from such matrices determine the pharmacokinetics. Weakly basic drugs or salts demonstrate pH dependent solubility. To overcome problems of decreasing drug release with pH changes as observed in conventional tablets, addition of organic acids like fumaric or succinic assists in maintaining low pH in the micro-environment within the matrix. Constant drug release can be obtained even in phosphate buffer\textsuperscript{23}.

The release profiles of drug from hydrophilic matrices have been studied\textsuperscript{24} X-ray and DSC identified the ionic bonding between drug and matrix. The interaction is found to be insensitive to pH but affected by ionic strength. In case of proteinaceous matrices like egg albumin or bovine serum albumin, the protein conformation, and nature (folding, denaturation, solubility) significantly affect matrix behaviour and drug release\textsuperscript{25}.

To control the release of a highly water soluble drug the use of a hydrophobic matrix like hydrogenated vegetable oil is undertaken\textsuperscript{26}. The release mechanism from such matrices seems to obey both root time kinetics and first–order behaviour. The effect geometry has a significant effect on the drug release rate.

1.1.7 Hydrophilic polymer used

In particular, water–soluble cellulose ethers (e.g., hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC) have been extensively studied for this application. Other hydrophilic polymers also find frequent use, including polyethylene oxide, polyvinyl alcohols, carbopol and numbers polysaccharides such as xanthan gum, chitosan, elagin acid, pectin, guar, gum and ispaghula.
1.1.8 REFERENCES:


CHAPTER 1.2

INTRODUCTION TO DICLOFENAC SODIUM
Diclofenac is a phenyl acetic acid derivative and is a potent synthetic non-steroidal anti-inflammatory drug (NSAID). It has mainly analgesic, antipyretic and anti-inflammatory action.

1.2.1 Description

(a) Generic Name : Diclofenac

(b) Synonyms : Voltaren, Voltarol, Voldol, Voveran, Orthophen

(c) Chemical name : 2-(2, 6-dichlorophenyl)amino)benzene acetic acid monosodium salt (O-(2,6-dichloroaniline) phenyl) aminophenylacetate Sodium O-(2,6 dichlorophenyl) amino Phenyl acetate

(d) Empirical Formula : C_{14}H_{10}Cl_{2}NO_{2}Na

(e) Molecular Weight : 318.13

(f) Element Composition : C-52.85%

H-3.17%

Cl-22.29%

Na-7.27%

N-4.40%

O-10.06%

(g) Structural Formula : 

(h) Appearance : It is white to off-white in colour, odourless, crystalline, and slightly hygroscopic in nature.
1.2.2 Physical properties

(a) Solubility: It is soluble in water, alcohol, and acetone and phosphate buffer. It is insoluble in acids, cyclohexane, acetonitrile and chloroform. Table 1.2.1 shows the solubility of Diclofenac in different solvents.

(b) Melting Point: 283°-285°C

(c) Stability: It can be frozen for at least two weeks without degradation in biological fluid (serum). Diclofenac is also stable at 130°C for 8hr.

Table 1.2.1 Solubility of Diclofenac

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Temperature</th>
<th>Solubility/mg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deionised water(pH5.2)</td>
<td>RT</td>
<td>&gt;9</td>
</tr>
<tr>
<td>Methanol</td>
<td>RT</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Acetone</td>
<td>RT</td>
<td>6</td>
</tr>
<tr>
<td>Acetonitrile</td>
<td>RT</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>RT</td>
<td>&lt;1</td>
</tr>
<tr>
<td>pH1.1(HCL)</td>
<td>RT</td>
<td>&lt;1</td>
</tr>
<tr>
<td>pH7.2 (phosphate buffer)</td>
<td>RT</td>
<td>6</td>
</tr>
</tbody>
</table>

(d) Dissociation Constant: The pKa is 4.2 in aqueous solution at 30°C.

(e) Partition Co-efficient: The octanol-water partition coefficient at 25°C reported as 4 to 4.17.
1.2.3 Pharmacology

(a) Properties

Diclofenac is a potent non-steroidal anti-inflammatory drug with pronounced analgesic, antipyretic and anti-inflammatory properties. Its potency is much greater than that of indomethacin, naproxen, and phenylbutanol. Diclofenac appears to reduce intra-cellular concentration of free arachidonate in leukocytes by altering the release or uptake of the fatty acids.

(b) Mechanism of action

Diclofenac inhibits cyclo-oxygenase enzyme. It inhibits the conversion of arachidonic acid to unstable endoperoxide intermediate, prostaglandin E1, a reaction catalyzed by cyclo-oxygenase. Thus it inhibits the production of prostaglandin content of human serum, urine and synovial fluid of arthritic knee joint, thereby acting as a potent anti-inflammatory agent.

(c) Pharmacokinetics and Metabolism

(i) Absorption:

Absorption of diclofenac is almost complete from solution by oral and intramuscular route. Absorption may vary according to the specific dosage forms used. Intake of food delays but does not reduce absorption after administration of enteric coated tablets, but this effect is of no clinical significance during long term treatment.

Peak plasma concentration ($C_{\text{max}}$) and area under plasma concentration-time curve (AUC) is dose related in the range of 25 mg to 150 mg. Slow release tablets may take up to 17 hrs to dissolve. First pass metabolism reduces oral bioavailability to 50% - 60%. There is no accumulation during multiple dosing. The drug accumulates in synovial fluid after oral administration, which may explain its considerably longer duration of action than the plasma life. 

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### Type of dosage form

<table>
<thead>
<tr>
<th>Type of dosage form</th>
<th>Cmax (mg/ml)</th>
<th>Tmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Uncoated tablet-50 mg</td>
<td>1.0</td>
<td>10-30 min</td>
</tr>
<tr>
<td>2. Enteric coated tablet</td>
<td>1.5</td>
<td>1.5-2.5 hr</td>
</tr>
</tbody>
</table>

### Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Mean concentration</th>
<th>Mean concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 2hr (mg/ml)</td>
<td>At 7hr (mg/ml)</td>
</tr>
<tr>
<td>1. Plasma</td>
<td>300</td>
<td>52</td>
</tr>
<tr>
<td>2. Synovial fluid</td>
<td>200</td>
<td>205</td>
</tr>
</tbody>
</table>

(ii) **Protein Binding and Distribution:**

At therapeutic concentration, the drug is extensively bound to plasma protein (Albumin 99.7%) apart from liver, bile and kidney, highest levels of diclofenac are found in blood, heart and lung. Diclofenac crosses the placenta in animals but human datas are not available.

(iii) **Metabolism:**

Diclofenac is metabolised in the liver. The principle metabolite is 4’Hydroxyl diclofenac, which has about 0.033 to 0.025 activity of diclofenac.

(iv) **Excretion:**

Diclofenac and its metabolites are excreted through bile (33%) and urine (67%). The concentration of unchanged drug in urine is about 0.7% the clearance rate is reported as $4.2 \pm 0.9$ ml/min. And elimination rate as 1.2 to 1.8 hr. The volume of distribution ($V_d$) is reported as $0.17 \pm 0.11$ ltr./kg.
(v) Biological Half Life:

It is reported as 4 hr.

(d) Adverse effects\textsuperscript{3,5}

The most common adverse effects occurring with diclofenac are gastrointestinal irritation, peptic ulceration and gastrointestinal bleeding due to inhibition of cyclooxygenase enzyme. In acute toxicity studies transaminase activities in plasma occurs in about 15% of patients. The elevations in diclofenac was found to cause gastric lesions in lower dose (12 mg/kg). Elevation of hepatic transaminase are usually reversible and are only rarely associated with clinical evidence of hepatic disease. Transaminase activities should be evaluated during the first 8 weeks of therapy and the drug should be discontinued if abnormal values persist or if other signs or symptoms developes, other unwanted responses of Diclofenac include central nervous system effects, skin rashes, allergic reaction, edema, headache and drowsiness. Hypertensive reactions, abnormality of liver function tests, impairment of renal function, agranulocitosis and thrombocytopenia are rarely observed.

(e) Contraindications\textsuperscript{3}

Children, nursing mothers or pregnant women should not use Diclofenac. It is also contraindicated in individuals with ulcerative lesions or renal disease.

(f) Therapeutic uses\textsuperscript{3,4}

Diclofenac is mainly used for the long-term symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondilitis. It is also used for short-term treatment of acute musculoskeletal injury, acute painful shoulder, acute renal colic, post-operative pain and dysmenorrhea.
(g) **Dose**

**For adults:**
- Oral : 75 to 150 mg daily in divided dose.
- Intramuscular : 75 mg once/twice daily
- Rectally : 100 mg

**For Children:**
- Orally or rectally : 1-3 mg/kg body weight.
  
  Daily in divided doses.

It is used intramuscularly in renal colic at a dose of 75 mg repeated once after 30 minutes if necessary. For children, the suggested oral or rectal dose for Juvenile chronic arthritis is 1 to 3 mg/kg of body weight in divided doses.

(h) **Dosage forms**

It is available as enteric coated tablets, sustained release tablets, suppositories, intramuscular injection, eye drops and gels\textsuperscript{23}.  

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### Proprietary preparations

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Name of Preparation</th>
<th>Name of Company</th>
<th>Content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A) Tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol</td>
<td>Geigy, U.K.</td>
<td>25/50</td>
</tr>
<tr>
<td>2</td>
<td>Voveran</td>
<td>Ciba Geigy, Bombay</td>
<td>25/50</td>
</tr>
<tr>
<td>3</td>
<td>Diclomex</td>
<td>Torrent, Ahmedabad</td>
<td>25/50</td>
</tr>
<tr>
<td>4</td>
<td>Dysonac</td>
<td>SG Pharma, Bombay</td>
<td>25/50</td>
</tr>
<tr>
<td>5</td>
<td>Relaxyl</td>
<td>Franco India, Bombay</td>
<td>25/50</td>
</tr>
<tr>
<td>6</td>
<td>Diclofen</td>
<td>P &amp; B Lab, Bombay</td>
<td>25/50</td>
</tr>
<tr>
<td>(B) Sustained Release Tablets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol Retard</td>
<td>Geigy, U.K.</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Voltaren</td>
<td>Spain, Italy</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Voveran SR</td>
<td>Ciba Geigy, Bombay</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Diclonec</td>
<td>Lupin</td>
<td>100</td>
</tr>
<tr>
<td>(C) Suppositories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Modified Release</td>
<td>Japan</td>
<td>25</td>
</tr>
<tr>
<td>(D) Gels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Voltarol Emugel</td>
<td>Geigy</td>
<td>1%</td>
</tr>
</tbody>
</table>
1.2.5 Methods Analysis

(a) Ultraviolet spectrophotometer determination\textsuperscript{1,11,12}

This method is based on the measurement of absorption of appropriately diluted Diclofenac solution in ultra violet light in a 1 cm matched quartz tube. Beers Law is obeyed in the concentration range of 3 to 30 µg/ml Diclofenac. With this method one can also analyze derivatives of Diclofenac.

(b) Colorimetric determination\textsuperscript{9}

This is a sensitive method based on the reaction of Diclofenac with potassium ferricyanide (1% w/v) in basic medium. The yellow colour developed after addition of sodium hydroxide (6% w/v) shows maximum absorbance at 450 nm. The beers curve shows linear relation in the concentration range of 2 to 10 µg/ml of Diclofenac.

(c) Determination of Diclofenac through the formation of charge transfer complex with chlorine:

A colorimetric method based on formation of a colours charge transfer complex between the drug and chlorine. The complex formed in ethanol shows maximum absorbance at 545nm. The Beers law is observed in concentration of 0.08 µg/ml.

(d) Gas liquid chromatography\textsuperscript{1}

This method was used to analyze Diclofenac and its metabolites using electron capture detector. Before injecting in to the column, Diclofenac or its metabolites are derivatized into the indolones or the methyl esters. The various columns used are coated with barium carbonate and satirically coated with Carbowax 40M; 3% OV-17 Gas-Chrom Q on 80-120 mesh glass beads;3% JXR (methyl silicone) on Gas-Chrom Q; 1.5% Silicone OV-17 on Shimalite W AW DMCS, 80-100 mesh.
(e) **High performance liquid chromatography**

Diclofenac was detected at 254nm on the basis of chromatographic methods on C-18 reverse phase columns using mobile phase consisting of methanol, acetic acid, and water. The recovery was 98–102% and relative standard deviation was 0.23–0.42%. Diclofenac was estimated in pharmaceutical formulations and urine samples with HPLC.

(f) **Nuclear magnetic resonance**

Proton magnetic method to quantify diclofenac in tablet form has been described. Diclofenac has a well-defined sharp peak (at 3.62 ppm) which was chosen for quantitative measurement. Internal standard used was anhydrous sodium acetate (1.85ppm). The amount of diclofenac can be calculated by comparing the peak ratio of diclofenac to that of the internal standard.

(g) **Electrophoresis**

Capillary zone electrophoresis has been used for the determination of diclofenac in commercial tablets, erythrocytes and urine samples. The method has been found to be faster than liquid chromatography.
1.2.6 REFERENCES:


5. Martindale, the extra pharmacopoeia, the pharmaceutical press, UK, 1999, XXXII, p31.


CHAPTER 1.3

INTRODUCTION TO METOPROLOL
Metoprolol (LOPRESSOR, others) is a $\beta_1$-selective antagonist lacking intrinsic symphathomimetic activity\textsuperscript{20}.

**1.3.1 DESCRIPTION\textsuperscript{3}**

(a) Generic Name : Metoprolol

(b) Synonyms : Lopressor

(c) Chemical name : 1-(4-(2-methoxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol.

(d) Empirical Formula : (C\textsubscript{15}H\textsubscript{25}NO\textsubscript{3})\textsubscript{2}, C\textsubscript{4}H\textsubscript{6}O\textsubscript{6}

(e) Molecular Weight : 684.8

(f) Element Composition : Heavy metals (2.3.13). 2.0 g complies with the limit test for Heavy metals, Method A (10 ppm). Sulphated ash (2.3.18). Not more than 0.1 per cent. Loss on drying (2.4.19). Not more than 0.5% determined on 1.0 g by drying in an oven at 105°.

(g) Structural Formula :

\[
\begin{align*}
\text{O} & \quad \text{NHCH(CH}_3\text{)}_2 \\
\text{CH}_2\text{CH}_2\text{OCH}_3 & \quad \text{OH} \\
\end{align*}
\]

1-(4-(2-methoxyethyl)phenoxy)-3-(isopropylamino)propan-2-ol

(h) Appearance : A white crystalline powder or colourless crystals.
1.3.2 PHYSICAL PROPERTIES

(a) Solubility : Lipid Solubility, Moderate
(b) Melting Point : 120°C
(d) Dissociation Constant : The pka is 4.2 in aqueous solution at 30°C

1.3.3 PHARMACOLOGY

(a) Properties²,³

Metoprolol shows membrane-stabilizing activity. Despite almost complete GI absorption, its bioavailability is relatively low because of first-pass metabolism. Plasma concentrations vary widely, which may relate to genetically determined differences in hepatic CYP2D6 activity. The $t_{1/2}$ of metoprolol (3–4 hrs) can double in CYP2D6 poor metabolizers, who have a 5 times higher risk for developing adverse effects compare to normal metabolizers. An extended release formulation (TOPROL XL) is available for once-daily administration.

For hypertension, the usual initial dose is 100 mg/day, increasing at weekly intervals until optimal reduction of blood pressure is achieved. If the drug is taken only once daily, confirm that blood pressure is controlled for the entire 24hrs period. Metoprolol generally is used in two divided doses for the treatment of stable angina. For the initial treatment of patients with acute myocardial infarction²¹, an intravenous formulation of metoprolol tartrate is available; initiate oral dosing as soon as the clinical situation permits. Metoprolol generally is contraindicated for the treatment of acute MI in patients with heart rates 45 beats/min, heart block greater than first degree (PR interval $\geq$0.24sec.), systolic blood pressure 100mmHg, or moderate-to-severe heart failure. Metoprolol is also effective in chronic heart failure²¹, ²⁴.
(b) Mechanism of Action\textsuperscript{4,5}

All of the blockers exert equilibrium-competitive antagonism of the actions of catecholamines and other adrenomimetics at receptors. Probably the best recognized action of these compounds that is not mediated by a receptor is depression of cellular membrane excitability. This effect has been described as a membrane stabilizing action, a quinidine like effect, or a local anesthetic effect. This action is not too surprising in view of the structural similarities between blockers and local anesthetics. However, with the usual therapeutic doses, the actions of the receptor blocking agents\textsuperscript{22} appear almost entirely accounted for their receptor antagonism.

Because the receptors of the heart are primarily of the 1 type and those in the pulmonary and vascular smooth muscle are 2 receptors, 1-selective antagonists are frequently referred to as cardioselective blockers.

(c) Pharmacokinetics and Metabolism

(i) Absorption:

Absorption, Metabolism, and Excretion of Propranolol (Inderal) is suitable for both parental and oral administration. Absorption from the gastrointestinal tract is extensive. The peak therapeutic effect after oral administration occurs in 1 to 1.5 hours. The plasma half-life of propranolol is approximately 3 hours. The drug is concentrated in the lungs and to a lesser extent in the liver, brain, kidneys, and heart. Binding to plasma proteins is extensive (90%). The liver is the chief organ involved in the metabolism of propranolol, and the drug is subject to a significant degree of first-pass metabolism\textsuperscript{17}. At least eight metabolites have been recovered from the urine, the major excretory route. The pharmacokinetic profile of metoprolol (Lopressor) is similar to that of propranolol\textsuperscript{18}. Metoprolol is readily and rapidly absorbed after oral
administration and is subject to a significant amount of first-pass metabolism by the liver. Curiously, the duration of metoprolol’s action is longer than one would predict from its plasma half-life, which ranges from 0.5 to 2.5 hrs. The degree of binding of metoprolol to plasma proteins is modest (10%). The extensive distribution of metoprolol to the lungs and kidney is typical of a moderately lipophilic drug. Metoprolol undergoes considerable metabolism; only 3% to 10% of an administered dose is recovered as unchanged drug. The metabolites are essentially inactive as receptor blocking agents and are eliminated primarily by renal excretion. Small amounts of the drug are present in the feces.

(d) **Adverse Effects and Precautions:**

The most common adverse effects of β receptor antagonists arise as pharmacological consequences of blockade of β receptors; serious adverse effects unrelated to β receptor blockade are rare.

(i) **Cardiovascular System:**

β receptor blockade may cause or exacerbate heart failure in patients with compensated heart failure, acute myocardial infarction, or cardiomegaly. Nonetheless, chronic administration of β receptor antagonists is efficacious in prolonging life in the therapy of heart failure in selected patients. The bradycardia caused by β antagonists may cause life-threatening brady-arrhythmias in patients with partial or complete AV conduction defects. Particular caution is indicated in patients who are taking other drugs, such as verapamil or various antiarrhythmic agents, which may impair sinus-node function or AV conduction.

Some patients complain of cold extremities while taking β blockers. Symptoms of peripheral vascular disease may worsen (though uncommon), or Raynaud’s phenomenon may develop.

After prolonged β blockade, there is enhanced sensitivity to β adrenergic stimulation when the β blocker is withdrawn abruptly, possibly related to up regulation of β
receptors during β blockade. Thus, abrupt discontinuation of β receptor antagonists after long-term treatment can exacerbate angina and may increase the risk of sudden death. Optimal strategies for discontinuation of β blockers are not known, but it is prudent to decrease the dose gradually (over several weeks) and to restrict exercise during this period.

(ii) **Pulmonary Function:**

A major adverse effect of β receptor antagonists is the bronchoconstriction resulting from blockade of β₂ receptors in bronchial smooth muscle. β blockers may cause a life-threatening increase in airway resistance in patients with bronchospastic disease. β₁ selective antagonists or those with intrinsic sympathomimetic activity at β₂ adrenergic receptors may be somewhat less likely to induce bronchospasm; however, the selectivity of current β₁ blockers is modest, and these drugs should be avoided if possible in patients with asthma.

(iii) **CNS:**

CNS-related adverse effects may include fatigue, sleep disturbances (including insomnia and nightmares), and depression. There is no clear correlation between the incidence of the adverse effects of β receptor antagonists and their lipophilicity.

(iv) **Metabolism:**

β adrenergic blockade may blunt recognition of hypoglycemia and may delay recovery from insulin-induced hypoglycemia. β receptor antagonists should be used with caution in diabetic patients who are prone to hypoglycemic reactions; β₁ selective agents may be preferable.

(v) **Miscellaneous:**
Despite anecdotal evidence, the incidence of sexual dysfunction in hypertensive males treated with β receptor antagonists is not clearly defined. Information about the safety of β antagonists during pregnancy still is limited.

(vi) **Overdose:**

Manifestations of poisoning with β receptor antagonists depend on the pharmacological properties of the ingested drug. Hypotension, bradycardia, prolonged AV conduction times, and widened QRS complexes are common manifestations. Seizures and depression may occur. Hypoglycemia is rare, and bronchospasm is uncommon in the absence of pulmonary disease. Significant bradycardia should be treated with atropine, but a cardiac pacemaker often is required. Large doses of isoproterenol or a receptor agonist may be necessary to treat hypotension.

(vii) **Drug Interactions:**

Aluminum salts, cholestyramine, and cholesterol may decrease absorption of β blockers. Phenytoin, rifampin, and phenobarbital, as well as smoking, induce hepatic biotransformation enzymes and may decrease plasma concentrations of β receptor antagonists that are metabolized extensively (e.g., propranolol). Cimetidine and hydralazine may increase bioavailability of propranolol and metoprolol by affecting hepatic blood flow. β receptor antagonists can impair the clearance of lidocaine. Other drug interactions have pharmacodynamic explanations. For example, β antagonists and Ca\(^{2+}\) channel blockers have additive effects on the cardiac conducting system. Additive effects on blood pressure between β blockers and other antihypertensive agents often are employed.

**Drugs Acting at Synaptic and Neuro effector Junctional Sites Adrenergic Agonists and Antagonists:**

Clinical advantage: The antihypertensive effects of β receptor antagonists can be opposed by Indomethacin and other NSAIDs.
(f) **THERAPEUTIC USES**

(i) **Cardiovascular Diseases:**

β receptor antagonists are used extensively in the treatment of hypertension, angina and acute coronary syndromes, and congestive heart failure\(^\text{24}\). These drugs also are used frequently in the treatment of supraventricular and ventricular arrhythmias\(^\text{25}\).

(ii) **Myocardial Infarction:**

β receptor antagonists lacking intrinsic sympathomimetic activity, administered during the early phases of acute myocardial infarction and continued long-term, may decrease mortality by 25%.

(iii) **Congestive Heart Failure:**

The reflex sympathetic responses to heart failure may stress the failing heart and exacerbate the progression of the disease, and blocking those responses is beneficial. β receptor antagonists are highly effective treatment for all grades of heart failure\(^\text{24}\) secondary to left ventricular systolic dysfunction\(^\text{31}\). The drugs improve myocardial function and the quality of life, and prolong life. Thus, β blockers have moved from being contraindicated to being the standard of care in many settings of heart failure\(^\text{26}\).

(iv) **Use of β antagonists in other cardiovascular Diseases:**

β receptor antagonists, particularly propranolol are used in the treatment of hypertrophic obstructive cardiomyopathy, for relieving angina, palpitations, and syncope. β blockers also may attenuate catecholamine-induced cardiomyopathy in
pheochromocytoma\textsuperscript{27,31}. β blockers are used frequently in the medical management of acute dissecting aortic aneurysm; their usefulness comes from reduction in the force of myocardial\textsuperscript{32} contraction and in dP/dt. Patients with Marfan’s syndrome may develop progressive dilation of the aorta, which may lead to aortic dissection and regurgitation, a major cause of death in these patients; chronic treatment with propranolol may slow the progression of aortic dilation and its complications\textsuperscript{39}.

(v) **Glaucoma:**

β receptor antagonists are very useful in the treatment of chronic open-angle glaucoma. Six drugs currently are available: carteolol (Ocupress, others), betaxolol (Betaoptic, others), levobunolol (Betagan, others), metipranolol (Optipranolol, others), timolol (Timoptic, others), and levobetaxolol (Betaxon). Timolol, levobunolol, carteolol, and metipranolol are nonselective; betaxolol and levobetaxolol are β\textsubscript{1} selective; none has significant membrane-stabilizing or intrinsic sympathomimetic activity. Topically administered β blockers have little or no effect on pupil size or accommodation and are devoid of blurred vision and night blindness often seen with miotics. These agents decrease the production of aqueous humor, which appears to be the mechanism for their clinical effectiveness. This helps in the treatment of glaucoma\textsuperscript{41}.

(vi) **Other Uses:**

β receptor antagonists control many of the cardiovascular signs and symptoms of hyperthyroidism and are useful adjuvants to more definitive therapy. Propranolol, timolol, and metoprolol are effective for the prophylaxis of migraine\textsuperscript{23}; the mechanism of this effect is not known; these drugs are not useful for treating acute migraine attacks. By reducing signs of increased sympathetic activity (tachycardia, muscle tremors, etc.), propranolol and other β blockers are effective in controlling acute panic symptoms in individuals who are required to perform in public or in other anxiety-provoking situations\textsuperscript{28, 41, 45}. Propranolol also may be useful in the treatment of essential tremor. β blockers may be of some value in the treatment of patients undergoing withdrawal from alcohol or those with akathisia\textsuperscript{29}. Propranolol and
nadolol are efficacious in the primary prevention of variceal bleeding in patients with portal hypertension caused by hepatic cirrhosis.42,48.

(g) Dose

For adults:  
Orally :  100mg orally in 1 or 2 divided doses.
Intravenous :  5 mg/ml inj.
Intramuscular :  75mg once/twice daily
Rectally :  100mg

For Children:  
Orally :  1 to 2 mg/kg/day.
Max dose orally :  6mg/kg/day.

h) Dosage forms :  It is available as tablet form.

1.3.4 METHODS ANALYSIS

Tests Appearance of solution.

A 2.0% w/v solution is clear and not more intensely coloured than reference solution BS8.

pH 6.0 to 7.0 determined in a 2.0% w/v solution.

Specific optical rotation: +7.0° to +10.0°, determined at 20°C in a 2.0% w/v solution.

Related substances: Determine by thin-layer chromatography coating the plate with silica gel G. Mobile phase. Chloroform: Pour 200ml of chloroform in the developing chamber containing several beakers, each containing 45ml of strong ammonia solution and saturate for 1½ hours by lining the walls with absorbent paper. Test solution. Dissolve 0.2g of the substance under examination in 10ml of
chloroform. Reference solution (a): Add 0.01% w/v solution of the substance under examination in chloroform. Reference solution (b): Add 0.004% w/v solution of the substance under examination in chloroform.

Apply to the plate 20µl of each solution. After development, dry the plate in air. Place the plate in a chamber of chlorine gas prepared by adding 5ml of 5M hydrochloric acid to a beaker containing 0.5g of potassium permanganate, and let the plate remain in the chamber for about a minute. Remove the plate from the chamber; allow standing for a few minutes and spraying it with a 0.5% w/v solution of potassium iodide in starch solution. Any secondary spot in the chromatogram obtained with the test solution is not more intense than the spot in the chromatogram obtained with reference solution (a) and not more than one such spot is more intense than the spot in the chromatogram obtained with reference solution (b).
1.3.5 REFERENCES:

1. Therapeutic Guidelines: Cardiovascular. **2003**.


51. Goodman and Gilman’s the pharmacological basic of therapeutics, Mcgraw Hill publishing Division, 2001,X, p709.
52. Indian Pharmacopoeia, Publication and Informatics Directorate,Ministry of Health and Family Welfare, Controller of Publications, Govt. of India,Delhi, V,1996, p480.


CHAPTER 1.4

INTRODUCTION TO RANITIDINE
The H₂ receptor antagonist Ranitidine was the first truly effective drug for the therapy of acid-peptic disease, and their long history of safety and efficacy eventually led to their availability without a prescription. Increasingly, proton pump inhibitors (some also available OTC) are replacing the H₂ receptor antagonists in clinical practice.  

1.4.1 DESCRIPTION

(a) Generic Name : Ranitidine
(b) Synonyms : ZANTAC
(c) Chemical name : N-[2-[[5-[(dimethylamino) methyl] furan-2-yl] Methyl] thio] ethyl]-N-methyl-2-nitroethene-1, 1-diamine
(d) Empirical Formula : C₁₃H₂₂N₄O₃S, HCl
(e) Molecular Weight : 350.9
(g) Structural Formula :

(h) Appearance : A white to pale yellow crystalline powder
1.4.2 PHYSICAL PROPERTIES:

(a) Solubility : Water, Ethanol, Methanol
(b) Melting Point : 69°-70°C
(c) Dissociation Constant : 8.2 and 8.7
(e) Partition Co-efficient : 0.0630201

1.4.3 PHARMACOLOGY

(a) Properties\textsuperscript{1,2}:

Ranitidine, a histamine H\textsubscript{2}-receptor antagonistic is now well established as a potent inhibitor of gastric acid secretion, effective in the treatment and prophylaxis of gastrointestinal lesions aggravated by gastric acid secretion.

(b) Mechanism of Action\textsuperscript{1}:

The H\textsubscript{2} receptor antagonists inhibit acid production by reversibly competing with histamine for binding to H\textsubscript{2} receptors on the basolateral membrane of parietal cells. Four different H\textsubscript{2} receptor antagonists, who differ mainly in their pharmacokinetics and propensity to cause drug interactions, are available. These drugs are less potent than proton pump inhibitors but still suppress 24-hour gastric acid secretion by \(
\approx \)
70\%. The H\textsubscript{2} receptor antagonists predominantly inhibit basal acid secretion, which accounts for their efficacy in suppressing nocturnal acid secretion. Because the most important determinant of duodenal ulcer healing is the level of nocturnal acidity, evening dosing of H\textsubscript{2} receptor antagonists is adequate therapy in most instances. All four H\textsubscript{2} receptor antagonists are available as prescription and over-the-counter formulations for oral administration. Intravenous and intramuscular preparations of cimetidine, ranitidine, and famotidine also are available. When the oral or nasogastric routes are not an option, these drugs can be given in intermittent intravenous boluses or by continuous intravenous infusion.
(c) **Pharmacokinetics and Metabolism:**

The H$_2$ receptor antagonists are rapidly absorbed after oral administration, with peak serum concentrations within 1–3 hours. Therapeutic levels are achieved rapidly after intravenous dosing and are maintained for 6–8 hours (ranitidine). Unlike proton pump inhibitors, only a small percentage of H$_2$ receptor antagonists are protein-bound. Liver disease per se is not an indication for dose adjustment. The kidneys excrete these drugs and their metabolites by filtration and renal tubular secretion, and it is important to reduce doses of H$_2$ receptor antagonists in patients with decreased creatinine clearance. Neither hemodialysis nor peritoneal dialysis clears significant amounts of the drugs.

(d) **Contraindications:**

The H$_2$ receptor antagonists generally with well tolerance, at a low (<3%) incidence of adverse effects; including diarrhoea, headache, drowsiness, fatigue, muscular pain and constipation. Less common adverse effects include those affecting the CNS (confusion, delirium, hallucinations, slurred speech, and headaches), which occur primarily with intravenous administration or in elderly subjects. Long-term use of cimetidine at high doses decreases testosterone binding to the androgen receptor and inhibits a CYP that hydroxylates estradiol. Clinically, these effects can cause galactorrhea in women and gynecomastia, reduced sperm count, and impotence in men. Several reports have associated H$_2$ receptor antagonists with various blood dyscrasias, including thrombocytopenia. H$_2$ receptor antagonists cross the placenta.

(e) **Therapeutic uses**

The major therapeutic indications for H$_2$ receptor antagonists are to promote healing of gastric and duodenal ulcers, to treat uncomplicated GERD, and to prevent the occurrence of stress ulcers.
(f) **Dose**

**For adults:**
- Oral: 150 to 3000 mg daily in divided dose.
- Parenteral: 50 mg intramuscular once/twice daily.

(g) **Dosage forms**

It is available in tablet and injection.

### 1.4.4 METHODS ANALYSIS:

Determine by thin-layer chromatography, coating the plate with silica gel GF254 mobile phase. A mixture of 25 volumes of ethyl acetate, 15 volumes of 2-propanol, 4 volumes of strong ammonia solution and 2 volumes of water makes a test solution. Test solution (a): Dissolve 0.22 g of the substance under examination in 10 ml of methanol. Test solution (b). Dilute 1 ml of test solution (a) to 100 ml with methanol. Reference solution (a): Weigh accurately a quantity of ranitidine hydrochloride reference solution in methanol, and dilute with methanol to obtain a solution containing a known concentration of about 0.022% w/v. Reference solution (b): Dilute 10 ml of reference solution (a) to 20 ml with methanol. Reference solution (c): Dilute 30 ml of reference solution (a) to 100 ml with methanol. Reference solution (d): Dilute 5 ml of reference solution (a) to 100 ml with methanol. Reference solution (e): Weigh accurately a quantity of ranitidine hydrochloride related compound-A reference solution in methanol, and dilute with methanol to obtain a solution containing a known concentration of about 0.127% w/v. Reference solution (f): Weigh accurately a quantity of ranitidine hydrochloride related compound-B Reference solution in methanol, and dilute with methanol to obtain a solution containing a known concentration of about 0.1% w/v. Apply to the plate 10 μl of each solution except reference solution (e). Apply separately an additional 10 μl of the test solution and on top of this application, apply 10 μl of reference solution (e). After development, dry the plate in air and expose it to iodine vapours in a closed chamber until the spots are revealed. Any spot in the chromatogram obtained with the test solution corresponding to the principal spot in the chromatogram obtained with reference solution (f) is not more intense than that of the principal spot in the chromatogram obtained with reference solution (b) (0.5%) and no other spot in the chromatogram obtained with the test solution is more intense than the principal spot in the chromatogram obtained.
with reference solution (c) (0.3%). The sum of the intensities of all the secondary spots in the chromatogram obtained with the test solution does not exceed 1%.
1.4.5. REFERENCES


51. Goodman and Gilman’s the pharmacological basic of therapeutics, Mcgraw Hill publishing Division, X, 2001, p709.


CHAPTER 1.5

INTRODUCTION TO ISPAGHULA
Natural carbohydrates have been popularly used as a material for centuries in all kinds of pharmaceutical applications. It is the world’s most abundant renewable and biodegradable polymer. Ispaghula has been popularly used as therapeutic agent for the treatment of constipation, diarrhoea, irritable syndrome, inflammatory bowel disease, ulcerative colitis, colon cancer, diabetes and hypercholesterolemia.

The uniqueness of the chemical structures and macromolecular configurations of mucilage obtain from the ispaghula (plantago ovata forskal) has attracted carbohydrate chemists in last decade, as the hydrogel produced by it is rigid, difficult to break and to dissolve. Ironically solubility and flexibility are very important criteria for materials to be used in pharmacy. To meet these criteria chemical modifications of ispaghula husk mucilage is indispensable so that it can be transformed into carrier for new drug delivery system, as a low cost non-conventional source for using pharmaceutical formulations as an “Excipient”\(^1\), which can improve its procesability and performance for specific application in the broad field of pharmacy. The use of natural carbohydrates in the medicine field must adhere to very rigid standards. They must be non-toxic, non-carcinogenic, biocompatible and no way injurious to the biological environment. Being natural carbohydrate polymer of natural origin, ispaghula has gained acceptance for its therapeutic action and food applications and enjoyed U.S. general recognition as safe laxative, food additive, ready to eat cereal material etc. Exploitation of ispaghula husk mucilage as an “Excipient”\(^1\) and its innovative, non-conventional applications, chemical derivatization, use of its derivative in modern fashion of drug designing has become a room for inventions for research scholar. Gums and mucilage are naturally occurring biopolymers, finding increasing applications in pharmaceutical and biotechnology industry. It has been used successfully for many years in the food and pharmaceutical industry as thickening agents, as gelling agents, and as a colloidal stabilizer. Mucilage also has several unique properties that have enabled it to be used as a matrix for entrapment and/or delivery of variety of drugs, proteins and cells.
The mucilage, by itself or by its gelling property\textsuperscript{3,4,5} can be employed in pharmaceutical industry, health promotion and treatment. It has been used potentially as a carrier for drug delivery to the gastrointestinal tract, such as matrix tablets, gel beads, film-coated dosage form. This review will discuss the important chemical reactions, its chemistry and in general characteristics of mucilage and its gel forming nature, its physical, chemical, mechanical properties and their pharmaceutical applications.

Being a naturally occurring polysaccharide, in recent year it has gained increased importance in industrial applications. The benefits of natural carbohydrates are also more and more appreciated by the scientists and consumers from various industries due to its inertness, biocompatibility and biodegradability.

Ispaghula is a valuable crop of pharmaceutical utility. It is cultivated on a large scale in North Gujarat. India is the largest producer and exporter of ispaghula seeds and seed husk, which are valued for their rich mucilaginous content.

**Synonyms:** Ispaghula, Psyllium\textsuperscript{3,4,5}

### 1.5.1 History of psyllium\textsuperscript{3}:

Genus plantago comprises of 200 species, of which 10 occur in India (Wealth of India, 1969). However plantago ovata is the main source of ispaghula seed and husk for use in medicine. It is the plant of west Asian origin, introduced into India during Muslims settlement in Middle Ages\textsuperscript{1,2}. The name ispaghula is derived from two Persian words ‘Isap’ and ‘ghol’ meaning a horse ear, referring to the characteristic shape of its seed\textsuperscript{5}. Minor source of the seed and husk is plantago psyllium, earlier cultivated in France, but now given up by France, which also imports sizeable quantities of ispaghula from India. Plantago major, plantago lanceolata, plantago pumilla, plantago coronopus, plantago argentia and plantago lagopus are also produced in smaller quantities but none of these find use in pharmaceutical industry. Seed husk is mild laxative, emollient and demulcent. It is considered as a safe laxative particularly beneficial in cases of habitual constipation, chronic diarrhoea and dysentery. It does not irritate the intestine and is specific in its use when mucous membrane is disturbed by inflammatory infections. The swelling property is attributed
to the presence of a polysaccharide (glycane). Since ancient age systems of medicines, a traditional plant known as ‘Ispaghula’ is widely used as home remedy in all cultures, in various kinds of diseases, conditions like chronic constipation, diarrhoea, inflammation of mucous membrane of GI and genitourinary tracts, duodenal ulcer, gonorrhoea, piles, etc., as bulk forming, non-irritant laxative drug, demulcent, as a cervical dilator etc.

1.5.2 Botanical source

Ispaghula husk consists of the dried coat of plantago ovate (Forskal) and is obtained by crushing the seeds and separating by winnowing. Ispaghula husk consists of the episperm and collapsed adjacent layers removed from the seeds of plantago ovate Forsk.

Family: Plantaginaceae

ISPAGHULA: The word ‘Ispaghula’ is derived from Persian language, there the word ‘Isap’ means ‘horse’ and ‘Ghula’ means ‘ear’, as the seeds of the genus plantago (includes more than 200 species) is looks like shape of the ear of the horse, the dried ripe seeds of plantago afra (plantago psyllium), plantago indica (plantago arenaria) and plantago ovata belongs to family plantaginaceae are used in medicine. The U.S National Formualry includes all three species under the name of heading ‘plantago seed. The British Pharmacopoiea describes the seeds of the first two species under the title ‘psyllium’ and the husks of seeds of the plantago ovata are included under the heading of ‘Ispaghula husk’. The latter consists of the epidermis and the adjacent layers removed from the ripe seeds. The seeds of plantago afra and plantago indica are known in commerce as Spanish or French psyllium, while those of plantago ovata are known as blond psyllium, ispaghula, spogel seeds or plantagae seeds. Some of the most important characters are given in the table ahead:
TABLE 1: Differences between different species of Ispaghula\textsuperscript{3,4,5}

<table>
<thead>
<tr>
<th></th>
<th>P. afra</th>
<th>P. indica</th>
<th>P. ovata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>France, Spain, Cuba</td>
<td>Mediterranean Europe, Egypt</td>
<td>Pakistan, India</td>
</tr>
<tr>
<td>Colour</td>
<td>Glossy; deep brown</td>
<td>Dull; blackish-brown</td>
<td>Dull; pinkish grey-brown</td>
</tr>
<tr>
<td>Shape</td>
<td>Boat-shaped; outline elongated ovate</td>
<td>Boat-shaped; outline elliptical</td>
<td>Boat-shaped; outline ovate</td>
</tr>
<tr>
<td>Length</td>
<td>2.0-3.0 mm</td>
<td>2.0-3.0 mm</td>
<td>1.5-3.5 mm</td>
</tr>
<tr>
<td>Weight of 100 seeds</td>
<td>0.09-0.10 g</td>
<td>0.12-0.14 g</td>
<td>0.15-0.19 g</td>
</tr>
<tr>
<td>Swelling index</td>
<td>NLT 10</td>
<td>NTL 10</td>
<td>NTL 9; husk NTL 40</td>
</tr>
</tbody>
</table>

All the seeds contain mucilage in the epidermis of the taste. The seeds may be evaluated by measuring the volume of mucilage produced after shaking the seeds with water and allowing to stand, known as “Swelling index”\textsuperscript{3,4,5}, this is defined in the B.P. as the volume in adhering mucilage, after it has swollen in an aqueous liquid for 4 hours. The drug is treated with 1.0ml ethanol (96%) and 25ml water in a graduated cylinder, shaken every 10min for 1hr and allowed to stand as specified. In some instances, as with linseed and psyllium seed where the mucilage is in a layer near the surface of cases such as marshmallow root where the mucilage is distributed throughout the tissues, the powdered drug is used. Examples are: Agar-10, Fenugreek-6, Ficus-6.0, Ispaghula husk-40(determined on 0.1g powder), Ispaghula seed-9, Linseed-4 (whole drug) and -4.5 (powdered drug), Marshmallow-10. Some variations in the method of determination have given rise to other terminology. Thus skyrme and Wallis in their original work on seeds of plantago species, in 1936 used the term Swelling factor (24hrs standing period) and the B.P. (1993) cites Swelling power in respect of ispaghula husk (variation in shaking procedure and standing time). Yet again, for Iceland moss. The B.P. 2000 cites Swelling value. Two fractions have been separated from the mucilage of ispaghula; one is soluble in cold water, and the other is soluble in hot water giving a highly viscous solution which gels on cooling. On hydrolysis fractions yield D-xylose, L-arabinose and aldobiouronic acid. The seeds...
also contain fixed oil, aucubin glycoside, various bases, sugars and protein. The aucubin glycoside content differs appreciably in different seed samples and species.

1.5.3 Geographical source\textsuperscript{3,4,5}

Ispaghula is largely cultivated in India, France and Persia. In India, it is cultivated in Gujarat, Punjab, and South Rajasthan\textsuperscript{3, 4}. Majority of the industries for processing of husk are located in North Gujarat. In Maharashtra, it is found to be grown successfully near Pune. About 30 thousand hectares of area is said to be under cultivation for the drug in India.

(a) Allied Drugs:\textsuperscript{3,4,5}

Plantago major is reportedly used as a medicinal substitute for plantago ovata; the seed oil contains an unusual hydroxyolefinic acid. Wild seeds of plantago ovata and related species are reported to contain less mucilage than the cultivated variety. Plantago asiatica, a species used in Chinese medicine, which contains mucilage the backbone chain which is composed of B-1, 4–linked D- Xylopyranose residues having three kinds of branches.

(b) Adulterants:\textsuperscript{3,4,5}

Seeds are adulterated with the seeds of plantago lanceolata. These seeds are oblong, elliptical in shape and yellowish–brown in colour.
1.5.4. Chemical nature

Seeds contain about 10% mucilage, which is present in the epidermis of the testa. Protein free amino acids and fixed oil are present in endosperm and embryo. Fixed oil contains unsaturated fatty acids and β-sitosterol. The husk contains mainly mucilage. It contains ≤ 2% organic matter. Mucilage is colloidal in nature. It is composed of at least two polysaccharides. D-xylose, L-arabinose, D-galacturonic acid and L-rhamnose are commonly found polysaccharides depends on uronic content.

(a) Cold water fraction:

The fraction soluble in cold water contains higher uronic acid [uronic anhydride (20%)] and lower pentosan (52%). The cold water fraction yields xylose, aldobiouronic acid, L-arabinose on hydrolysis.

(b) Hot water fraction:

Fraction soluble in hot water (90% to 95%) contains 3% uronic acid and 90% pentosan. The hot water fraction form highly viscous solution which forms gel on cooling. On hydrolysis, it yields D-xylose, L-arabinose, aldoburonic acid and D-galactose.
Chemical Structure of mucilage of ispaghula husk
(a) **Distinction from gum acacia**: 

Dissolve 1g in 20ml water by shaking and add 0.5ml hydrogen peroxide solution and 0.5ml of a 1% w/v solution of benzidine in ethanol, shake and allow standing, no blue colour is produced.

(b) **Distinction from Karaya and Ghatti gum**:

Ten ml of a 0.5% w/v solution in water gives precipitate with 5ml of 20% w/v solution of lead acetate.

(c) **Distinction from tragacanth gum**:

Ten ml of a 0.5% w/v solution in water gives precipitate with 2ml of 3%w/v solution of barium hydroxide.

1.5.5 **CHEMICAL MODIFICATION**:

The biological & biomedical applications of polymeric material have greatly increased recently. Of these, bio-based materials, or biopolymers, are used to repair, restore, or replaced damaged or diseased tissue or to interface with the physiological environment. A natural carbohydrate is an excellent candidate for these areas of application. The development of chemical modification methods of carbohydrates with various reagents has included reactions with by functional compound that leads to crosslinked polymers thus larger molecular aggregate with different rheological behaviour, or insoluble products with a wide range of swelling characteristics, may be synthesized. The insoluble cross-linked polysaccharides have found several applications, e.g., in chromatography, gel filtration, well known examples of this chemicals modifications are cross-linked dextrans (Sephadex) and agaroses (Sepharose). Natural carbohydrates being a high-molecular-weight biopolymers, supramolecule, syndiotactic, polysaccharides may have one or more primary or /and secondary hydroxyl groups which are readily available for chemical modification reactions to alter its mechanical, physical and solution properties. The possible
reactions, sites for this type of chemical modifications are explained here by taking one of the example of naturally occurring biopolymeric material cellulose as follow (figure-2). The chemical reactivity of cellulose is determined to a large extent by the structure of its solid state. Cellulose possesses one primary and two secondary hydroxyl groups. Like any hydroxyl-containing compound, these hydroxyl groups can undergo addition, substitution, and oxidation reaction. Once the hydroxyl groups on the chain unit are made accessible, they offer a verity of possibilities for making useful derivatives. These derivatives can be made by etherification, esterification, cross-linking, or graft co-polymerization. There are various schemes for the derivatization is as per figures shown below by taking one of the examples of polysaccharide-cellulose.

![Scheme 1](image1.png)

Scheme 1

Cellulose + Acid \[\xrightarrow{\text{Catalyst}}\] Cellulose ester + Water

Scheme 2
Scheme 5
Scheme 8
Scheme 9
Much emphasis has been placed on the chemical modifications of naturally occurring bioadhesive materials nowadays, as it is useful material from the viewpoint of the high potential of these polysaccharide. In many cases, the chemically modified molecules show greater activity than the original polymeric material.

Polysaccharides and their derivatives have found numerous applications in a variety of fields including the paper and textile, food, cosmetics, and chemical and pharmaceutical industries. The high potential for exploiting these natural biopolymers with their broad range of structural, functional and physico-chemical properties, in various applications has provided the stimulus for the search for new or modified polysaccharides.

Various steps involved in the preparation of partially methylated alditol acetates (PMAAs) from glycoprotein-derived carbohydrates were improved to obtain the derivatives in a rapid manner with excellent yields. Carbohydrates were permethylated in dimethyl sulfoxide (DMSO), using a fine suspension of sodium hydroxide and methyl iodide (CH$_3$I). The fine suspension of NaOH was prepared conveniently from commercially available 50% aqueous NaOH in DMSO by sonication and washing the precipitate with DMSO. Methylation of ovalbumin and fetuin glycopeptides using the fine suspension of NaOH and CH$_3$I was complete within 5 min, and the methylation reaction did not generate any non-sugar artifacts. Methylated carbohydrates without any purification were hydrolyzed in a mixture of volatile organic acids, which permitted rapid removal of the acids from samples by evaporation. Acetylation of partially methylated alditols with acetic anhydride for 2–4 hrs at ambient temperature using 4-N, N$'$-dimethylaminopyridine as a catalyst and the reaction was free from generating non-sugar reaction artifacts. The reaction time course for methylation, hydrolysis, and acetylation was determined to obtain optimum reaction conditions for preparation of the PMAAs. The procedure facilitated rapid identification and quantification of PMAAs due to diminished reaction artifacts and the quality of the chromatogram depended only on the purity of starting material and the reagents used for the methylation analysis. Utility of these simple methods for rapid methylation analysis was demonstrated in the characterization of
oligosaccharides isolated in small amounts using a carbohydrate analyser.

The chemical reactivity of mucilage can be determined by the structural fragment of the section of the mucilage structure of plantago ovata forsk (Kennedy and White, Bioactive Carbohydrates), which can be an influential role in the preparation of mucilage derivatives, as shown in the figures. Mucilage possesses one primary hydroxyl group per unit of β dextro xylopyranose units, these hydroxyl group can undergo reactions like oxidation, reduction, methylation, sulfonation, esterification, etherification, attachment of cystein etc. As a result of the inductive effects of neighbouring substitutions the acidity, tendency to dissolve and gelling property will change. Hence depending on the reaction medium whether acid or alkaline, the reactivity of hydroxyl group varies. For example, for etherification of hydroxyl groups conducted in an alkaline medium, CH$_2$OH of α-l-arabinofuranose is the most readily etherified first, on the contrary for esterification; the hydroxyl group of mucilage is also available.

Once the hydroxyl group of the mucilage backbone structure is available for the chemical modification, they offer a variety of possibilities for making useful derivatives. The properties of chemically modified mucilage derivatives will be depends on the type of the reactions which can be use for the modification of mucilage of ispaghula, distribution, uniformity, and the substitution of the groups. The average number of hydroxyl groups replaced by the chemical modification reactions is the degree of substitution (DS).

Modified derivatives can be used in the fields of pharmacy, medicine, cosmetics and food. Practical applications of such kinds of natural carbohydrates like cellulose, starch, etc. are widely used in the same manners and the same industries. A systematic flowchart for mucilage derivative preparations can form a new window for research scholars.
A new drug delivery modality can be developed based on drug encapsulation in polymeric micelles followed by a controlled release at the site triggered by ultrasound focused on the tumor. Ultrasound not only released drug from micelles but also enhanced the local uptake of both free and encapsulated drug by tumor cells, thus providing effective drug targeting. The significant success of in-vitro studies of this new drug delivery technique warranted extending studies to animal experiments. The results of the in-vitro studies of the above technique and summarized and the first in vivo experiments using colon cancer in rats are reported/monitored using doxorubicin (DOX) and ruboxyl (RB) release from micelles under continuous wave (CW) or pulsed ultrasound in the frequency range of 20KHz to 3MHz. The measurements were based on the decrease of the fluorescence intensity when drug was transferred from the micelle core to aqueous environment. Native natural carbohydrate may not be suitable in some controlled drug delivery system, as many drugs are released too fast from system based on this, due to substantial swelling, enzymatic degradation of native carbohydrate in biological systems. Various kinds of polysaccharides in particularly starch. Starch is utmost important as sizing agent in the textile industry, pharmaceutical industry, printing industry and for the finishing in various industries. However the properties of natives starch is not always optimal compared to the properties required for the particular applications. One of the problems is the very large molecular size instability of viscous solution, under varying temperature and its susceptibility to microbial degradation.

Consequently chemical modification of starch has become an important tool to overcome the problems and creates starches having altered characteristics, compare to native starch. Common treatments are acid treatments oxidation, etherification, quaternization, grafting, cross-linking, preparation of poly-vinyl-starch composites, etc. There are thus an increasing interest in and used for methods capable of introducing oxidative changes of various kinds in polysaccharides, by using aqueous medium, phenol oxidizing enzyme enhancing agent, peroxidase enzyme etc. The relevance of studying the effect of chemical modification on the functional and structural properties of polysaccharides lies in the design of new molecules with altered physicochemical properties. The modified molecule can be use in designing new drugs delivery system which has ability to modify the rheological properties of
the parent native polysaccharide in aqueous or organic solution. Though the
derivatization has become popular in practice carbohydrate, research chemists has to
increase more resistance towards hydrolysis and enzymatic lysis than native plain
carbohydrate. Typically starch derivatives are more resistant to enzymatic lysis than
native starch. Recently, starch derivatives have been studied for using oral drug
delivery systems. For example cross-linked starch, starch-g-polyacrylic acid
copolymer and starch/ethylene –vinyl alcohol copolymer have already been reported
as anti-phlogistic and peptide drug delivery systems. For example, native sago starch
needs to be modified to improve its quality for its specific industrial applications
which can improve gelling capacity, stability at various temperature, and solubility.
Hydroxypropylation and cross-linked have been studied. The effect of
hydroxypropylation and crosslinking on dual-modified sago starch properties has
been reported and discussed. The invention based on oxidation process of a hydroxyl
group of sugar monomer of an oligo-or a polysaccharide in an aqueous medium with a
phenol oxidizing enzyme and an enhancing agent, whereby an oligo- or a
polysaccharide with altered characteristics compared to the native oligo- or
polysaccharide is created. . Lacquer polysaccharides (LP) were isolated from the sap
of lac tree (Rhus vernicifera). Its derivatives, carboxymethyl LP, sulfated LP and
debranching LP were prepared. Their structure was analyzed by GPC, FT-IR and
NMR spectroscopy. The sugar components of carboxymethyl and sulfated LP a
hardly changed, but the molecular weight of the former decreased. Several cross-
linking methods for derivatization are available including irradiation in the U.V.
region this method shows effect on enzymatic activity and on that remaining after
storage of the samples with immobilized enzyme was studied; both were seen to be
related with the cross-linking density of final polymer. The immobilized enzyme was
more resistant than the soluble enzyme to inactivation by hydrogen peroxide at neutral
pH and provided good yields after thermal treatment cinnamic carbohydrate esters;
new polymeric supports for the Immobilization of horseradish peroxide. The
usefulness of ricin as a research tool is handicapped by its extremely biohazardous
nature. In this work, ricin toxicity has been reduced by chemical modification of
carboxyl groups using 1-ethyl-3 (3-dimethylaminopropyl) carbodiimide and (©)
glycine methyl ester. The reaction was carried out in 8M urea and in the presence of
0.1M lactose to protect the groups involved in saccharide binding. Together with
carboxyl groups, tyrosine residues were also modified. The maximum modification
achieved was 13 carboxyl groups and 7 tyrosines/molecule (about 30% of total carboxyls and tyrosines). The modification did not alter substantially the strength and specificity of the carbohydrate binding ability of the lectin, as observed by hemaglutination tests and by inhibition assays with different carbohydrate structures. However, the LD 50 decreased 90-fold when the highest modification was achieved. Therefore, the modified lectin can be used more safely in the study of galactose-containing carbohydrates. Several types of chemical modifications are available in general natural carbohydrates like starch, cellulose, chitosan etc.

In the present invention dietary fibres are widely used in hypoglycemic, hypolipidemic and slimming diets. It is probable that their ingestion coincides with the oral administration of drugs and a modification of their pharmacokinetics can appear. Garcia and coworkers have studied the influence of two soluble fibres (guar gum and psyllium) on the pharmacokinetics of ethinylestradiol (EE) when they were administered together to female rabbits via the oral route. Three groups of rabbits were used. All animals received 1mg/kg of EE; this compound was administered alone.

1.5.6 Official tests

1. Identification:

a) Ispaghula husk consists of pinkish-beige fragments or flakes up to about 2mm long and 1mm wide, some showing a light brown spot corresponding to the location of the embryo before it was removed from the seed. The material swells rapidly in water, forming stiff mucilage.

b) The powdered ispaghula is pale yellow in colour. Examine the powder under microscope using lactic acid reagent. The powder shows mainly fragments of the episperm with polygonal cells filled with mucilage; fragments of the inner layers of the testa with brownish thin walled cells often associated with the outer layers of the endosperm. Examine under a microscope using 50% v/v solution of glycerol. The powder shows occasional starch granules, single or in groups of two to four, measuring 3µ to 25µ in diameter.
c) Examine by TLC using silica gel plate. The chromatogram obtained with the test solution shows two orange-pink zones (arabinose and xylose) and a yellow (galactose) similar in position and colour to the zones in the chromatograms obtained with the references solutions.

2. **Swelling index**: Not less than 40, determined on 1g of the powdered drug.

3. **Total Ash**: Not more than 4.0%

4. **Acid Insoluble Ash**: 0.45%

5. **Loss on drying**: Not more than 12% determined on 1.0g of the powdered drug by drying in an oven at 100°C to 105°C for 2h.

6. **Microbial limits**: The total combined mold and yeast count does not exceed 1000/g and it meets the requirement of the test for absence of Salmonellas species and E. Coli.

7. **Insect infestation**: Husk not more than 100 insect fragments, including mites and psocids. Powder not more than 4000 insect fragments including mites and psocids.

8. **Heavy extraneous matter**: Not more than 1.1%

9. **Light extraneous matter**: Not more than 1.5%.

10. **Storage**: Store in a well-closed container; protected from light, moisture and from attack by insects and rodents.
1.5.7 Pharmacological activity

The dietary fibres from ispaghula seeds or husk, which are not digested or absorbed by the body, have high affinity for water. When these fibres come in contact with water in the intestine, a gel is formed that lubricates the bowel. In this manner, mucilage and the remaining fibrous content help in the expulsion of the intestinal bacteria in the gut and pass unchanged. The mucilage absorbs irritating products of gastrointestinal digestion and bacterial and other toxins. The bulking effect of psyllium also works to rid the colon of toxic substances, including heavy metals as it acts almost as a sponge to soak them off the walls of the intestine. This spongy action has a dual advantage as it can decrease hunger when taken with meals, so used in slimming process too.

1.5.7.1 Therapeutic uses and administrations

Traditionally ispaghula is widely used for medicinal purposes such as a bulk laxative, lipase inhibitor and hypolipidemic agent in arthritis constipation, skin diseases and in cosmetic preparations. It is also used in management of chronic non-specific diarrhoea in childhood and for internally fed patients. Its activity has been found comparable to misoprostol and loperamide for its antidiarrhoeal activity. Administration of ispaghula is also beneficial in reducing gastrointestinal side effects of administered drugs. It has been reported that ispaghula is capable of reducing post-prandial blood glucose levels in type-II diabetes; noninsulin dependent diabetes with hyperlipidamemia and improves insulin sensitivity. Co administration of ispaghula with other drugs results in changes of oral bioavailability and pharmacokinetic parameters.

It is taken immediately after mixing with water or other fluid in dose up to 10g. The seeds are considered cooling and diuretic for gastric and duodenal ulcers and urinogenital disorders. The seeds are given either as a decoration or infusion of powder with sugar. An emollient poultice made from the seeds mixed with oil is used against gout. Ispaghula has been reported to lower serum cholesterol concentration in patients with mild to moderate hypercholesterolemia. Optimum dose of 2-5g daily.
has been suggested in irritable bowel syndrome. It has been claimed that seed mucilage is used in cosmetics and as a stabilizer in ice cream manufacture. Recently ispaghula husk is also used in anti-obesity formulations along with other gums. Theories concerning how this is accomplished include the ability of water soluble fibre to increase the excretion of cholesterol through the bowel, to inhibit its synthesis in the liver, to bind to and absorb bile acids in the intestine. Ispaghula husk is also reported to reduce gallstone formation.

(a) Medicinal efficacy of psyllium / Ispaghula:

Psyllium has been reported for the treatment of constipation, diarrhoea, and irritable bowel syndrome, inflammatory bowel disease-ulcerative colitis, colon cancer, diabetes and hypercholesterolemia. Constipation can be defined as infrequent or hard pellet stools or difficulty in evacuating stool. This drug increases the frequency and weight of stools, softens hard stools, and reduces pains at defecation. A recent study demonstrated its superior effect compared with sodium docusate, psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight and ameliorating chronic diarrhoea. Psyllium is a common ingredient in bulk laxative products, and several studies suggest that psyllium may provide benefits for treating constipation. The gelatinious mass of psyllium promotes peristalsis, hydration of the feces, provides a laxative exertion, relieves chronic constipation and produces a soft stool: as it lubricates, softens and increase fecal volume and viscosity. It may also relieve irritable bowel syndrome, diverticulities, mucus colitis, cystitis, gastrointestinal ulcers and diarrhoea. Psyllium is an excellent source of fibre, which also has a direct action on the bowel. Acting like a bottle brush, psyllium cleanses the bowel and promoting peristaltic action of the muscles, motivates bowel movement. When using psyllium it is necessary to drink plenty of water, so that the psyllium is able to swell, absorbing water to develop the mucilage action. Studies have shown that psyllium is more beneficial than bran, in maintaining regularity. First-line treatment for patients complaining of chronic constipation may involve the use of osmotic laxatives, lubricating agents, dietary fibre, bulk-forming agents, or evacuants. The choice depends on whether the clinical context is suggestive of slow transit or evacuation disorders. During one study, it was found that the majority of the stool
collected after psyllium dose, was gelatinous and the gel fraction isolated from stool contained 75% of carbohydrates was xylose (64%) and arabinose (27%), the same sugars in psyllium.

(b) Constipation:

Psyllium is one of the most widely used bulking agents worldwide. A recent study demonstrated its superior effect compared with sodium docusate. Psyllium has been shown to have the paradoxical property of both improving constipation by increasing stool weight and ameliorating chronic diarrhoea. Several studies suggest that psyllium may provide benefits for treating constipation. There is a scientific basis for psyllium working as a mild laxative. Psyllium is renowned for its mucilaginous properties and, when the seeds are soaked in water, they increase from 8 to 14 times, their original size. This gelatinous mass promotes peristalsis, hydration of the feces, provides a laxative exertion, relieves chronic constipation and produces a soft stool. First-line treatment for patients complaining of chronic constipation may involve the use of osmotic laxatives, lubricating agents, dietary fibre, bulk-forming agents or rectal evacuants the choice depends on whether the clinical context is suggestive of slow transit or evacuation disorders. Being a structural component of the plant, psyllium forms a matrix that resists hydrolysis so that absorption of free arabinose during passage through the stomach and small intestine amounts to less than 5%. Similarly, psyllium also resists colonic bacterial degradation.

(c) Diarrhoea:

Wenzl and co-workers have concluded that the normal intestine delivers stools that defer widely in quantity but maintain percent faecal water within a narrower range. Stools looseness in diarrhoea is determined by the ratio of faecal water to water holding capacity of insoluble solids. Psyllium increases the number of normal stools and decreases the number of liquid stools. Psyllium delays gastric emptying, probably by increasing meal viscosity and reduce the acceleration of colon transit, possibly by delaying the production of gaseous fermentation products. A combination of psyllium and calcium seems to be cheap and effective alternative to conventional treatment of
chronic diarrhoea. Faecal consistency was markedly different in psyllium calves as compare with control. Infection with enterotoxigenic E.Coli (ETEC) induces secretory diarrhoea by stimulating net secretion of fluid and electrolytes. Psyllium ameliorates ETEC-induced diarrhoea and prevents the enhanced secretory responses to calcium-mediated agonists that occur in ETEC-infected piglet jejunum. A major placebo effect occurs in patients with painful irritable bowel syndrome and is probably responsible for the efficacy of psyllium. Supplementation with dietary fibre from psyllium or gum Arabic was associated with a decrease in the percentage of inconsistent stools and an improvement of stools consistency did not appear to be related to unfermented dietary fibre Treatment of PI-associated diarrhoea is largely nonspecific. Agents for which some efficacy has been shown for treatment of PI-associated diarrhoea include oat bran, psyllium, loperamite, calcium carbonate, SP-303, and pancrelipase faecal consistency of two 6 years old male sibling Amur leopards (Panthera pardus orientails) suffering from the acute diarrhoea steadily improved after treatment with oral metronidazole, tylosin tartarate and psyllium fibre Treatment of chronic idiopathic large bowel diarrhoea in dogs with a highly digestible diet and soluble fibre has been reported.

(d) Ulcerative colitis (Crohn’s disease):

The two primary sites for Crohn’s disease are the ileum, which is the last portion of the small bowel (ileitis, regional enteritis), and the colon (Crohn’s colitis). The condition begins as small microscopic nests of inflammation which persist and smolder. The lining of the bowel can then become ulcerated and the bowel wall thickened. Eventually, the bowel may become narrowed or obstructed and surgery would be needed. A small number of studies have examined the ability of psyllium to maintain remission in ulcerative colitis. Dietary fibre has been proven to be beneficial in maintaining remission in human ulcerative colitis, an effect related with an increased luminal production of short-chain fatty acids (SCFA). Dietary fibre supplementation ameliorated colonic damage in HLA-B27
Bowel results in the production of SCFA, which in vivo stimulate cell proliferation, while n-butyrate appears to be antineoplastic in-vitro. The role of dietary fibre during colorectal carcinogenesis might therefore be related to its fermentation to n-butyrate. The ratio of n-butyrate production to total SCFA production from fibre, however, was reduced in patients with colonic cancer and adenomas compared with healthy controls. It may be that the low ratios of colonic n-butyrate formation combined with low-fibre diets increase the risk of colonic neoplasia. Psyllium delayed the fermentation rate of high-amylose cornstarch in the cecum and shifts the fermentation site of starch toward the distal colon, leading to the higher n-butyrate concentration in the distal colon and faeces.

The presence of n-butyrate in the distal colon may be important in the prevention of colon cancer because the majority of tumors in both humans and experimentally induced rodent cancer models occur in the distal colon. The end products of microbial carbohydrate fermentation in the large bowel include SCFA, among which acetate, propionate and n-butyrate are quantitatively most important. SCFA have a range of effects that may be relevant to colonic health. Of these, n-butyrate is of particular interest because it exerts a concentration-dependent slowing of the rate of cancer cell proliferation and promotes expression of differentiation markers in vitro, leading to reversion of cells from a neoplastic to a non-neoplastic phenotype. Fermentation is normally more active in the cecum and proximal colon than in the distal colon. For these reasons, highly fermentable dietary fibres such as pectin, guar gum and oat bran are fully determented in the cecum and proximal colon and do not contribute n-butyrate to the distal colon. This also might be the case for resistant starches such as high-amylose cornstarch (HAS) which has a fast fermentation rate. Therefore, it should be meaningful to establish a method by dietary manipulation to shift the fermentation site of HAS and to increase n-butyrate production in the distal colon and faeces. Such delivery system of starch to the site where the incidence of colon cancer is higher might be of value to better understand the effects of n-butyrate on the large bowel physiology. Physical exercise, use of psyllium and aspirin, reduced risk of colon cancer. Psyllium strongly reduced the tumorigenicity of 1,2-dimethylhydrazine and psyllium-fed rats had the highest faecal aerobic counts, lowest beta-glucuronidase, and highest 7-α-dehydroxylase activities. Psyllium fibre provided colonocytes some protection from deoxycholic acid-induced lysis. Propionic acid, a
product of fibre breakdown, was a potent colonocyte mitogen, suggesting that fibre could indirectly protect the colon by providing colonocyte nutrients.

(f) Irritable bowel syndrome:

Constipation is defined as a symptom chronic constipation-based disorder, for at least 3 months in a year for the dissatisfaction in defecation and characterized by infrequent stools, difficult stool passage or both. On the other hand, the presence of clinically important abdominal discomfort or pain associated with constipation defines IBS with constipation. Intake of psyllium may be effective in alleviating chronic constipation in patients without slow colonic transit or disordered constipation. On the other hand, fibre with lactulose may improve stool consistency in patients with IBS with constipation. In addition, treatment with a combination of psyllium and propantheline was effective, both in relieving symptoms and in the maintenance of remission. Both high-fibre dietary advice and the prescription of fibre as a bulking agent are very common in primary and secondary care management of IBS. IBS patients with constipation may have delayed intestinal transit. Therefore, fibres that accelerate intestinal transit may be beneficial in these patients. The uncertain benefits reported in several clinical studies, however, have led us to reappraise the value of fibre in IBS management. Psyllium seeds showed to be superior to wheat bran with respect to stool frequency and abdominal distension so that it should be preferred in treatment of IBS and constipation. Prior and coworkers have found the optimum dose of psyllium in IBS, 20g/day. Personality factors influence the magnitude of therapeutic response of the psyllium. The easing of bowel dissatisfaction appears to be a major reason for the therapeutic success of psyllium in IBS. There is some correlation between the increase in stool weight and the improvement in symptom score but the whole gut transit time remains unchanged despite alterations in stool weight and patient’s symptoms. It was suggested that psyllium might modify the response to rapidly fermentable, poorly absorbed dietary carbohydrates such as lactose, fructose, and sorbitol, which have been implicated in some studies of IBS. The well-recognized benefit of psyllium in IBS is partly due to its treatment of constipation but psyllium also benefits those with diarrhoea and pain.
(g) **Diabetes:**

Psyllium has been proposed as a possible treatment for high blood sugar levels. Studies in humans suggest moderate reductions in blood sugar levels after a single dose of psyllium, with unclear long-term effects. Water-soluble dietary fibres decrease postprandial glucose concentrations and decrease serum cholesterol concentrations to men with type-2 diabetes. Early or uncontrolled studies suggested that psyllium improved glycemic and lipid control in individuals with type-2 diabetes.

In a carefully controlled crossover study of the effects of psyllium taken immediately before breakfast and dinner compared with the effects of cellulose placebo supplementation in individuals with type 2 diabetes. Postprandial serum glucose values were 14% lower after breakfast, 31% lower after lunch, and 20% lower after dinner with psyllium. High-fibre diets increase peripheral insulin sensitivity in healthy young and old adults. Psyllium has also been shown to significantly reduce postprandial serum glucose and insulin concentrations in nondiabetic individuals.

The ability of soluble fibres to reduce the postprandial glucose response to meals eaten several hours after fibre ingestion (second meal effect) was shown previously in nondiabetic individuals. Several studies indicate that high fibre diets or diets supplemented with soluble fibres such as guar gum, soya or pectin improve metabolic control in many individuals with type-2 diabetes.

(h) **Cholesterol lowering:**

It has been observed that there is a positive association with plasma LDL cholesterol levels and coronary heart disease risk. Intake of dietary fibres known to lower the concentration of LDL in plasma is considered to be highly beneficial. Of the viscous soluble fibres, psyllium husk fibre appears to be one of the most effective with the least adverse effects. Psyllium intake has consistently shown significant reductions in plasma LDL cholesterol levels ranging from 10%-24%. Reports of the use of psyllium, largely in hypercholesterolemia, have suggested that it lowers serum cholesterol as a result of the binding of bile acids in the intestinal lumen and reduced risk of coronary heart disease. The mechanism of action of psyllium’s hypercholesterolemia effects has not been fully elucidated. Psyllium was shown to
stimulate bile acid synthesis by increasing the hydroxylase activity in animal and humans models. Hepatic hydroxylase activity, protein mass, mRNA levels and the rate of transcription are all higher in rats fed cholestyramine, a bile acid sequestrant, and lower in rats fed bile acids.

Psyllium has been shown to coordinately increase hydroxylase activity and mRNA levels in hamsters. A bile acid response element has been identified in the promoter of the hydroxylase gene, suggesting a molecular mechanism involved in transcriptional regulation of hydroxylase. The magnitude of the hypercholesterolemia effect is consistent with findings from a number of studies using hamsters, guinea pigs and rats. Suggested mechanisms for this hypocholesterolemic effect have focused on greater excretion of bile acids and total steroids leading to an up-regulation of bile acid biosynthesis. It is proposed that feeding psyllium causes greater viscosity in the intestine, thus preventing absorption of bile acids and neutral steroids, a phenomenon that has been observed for other viscous sources of dietary fibre.

1.5.7.2. Adverse effects and precautions

Quantities of ispaghula and other bulk laxatives may temporarily increase flatulence and distension. There is a risk of intestinal or oesophageal obstruction and faecal impaction especially if such compounds are swallowed.

1.5.7.3 Hypersensitivity

Often hypersensitivity reactions associates with ingestion or inhalation of ispaghula or psyllium include rhinitis and wheezing acute bronchospasm and urticaria with anaphylaxis. Individuals may become sensitized during occupational exposure to ispaghula or psyllium products. Long term safety and tolerability has been reported by Oliver.
1.5.8 Proprietary names


1.5.9 Pharmaceutical properties of Ispaghula

Ispaghula husk is used as an adjuvant in many formulations such as suspending agent, binding agent, disintegrating agent and sustained release agent due to its swelling and gelling properties. The swelling property of ispaghula husk has been utilised for the formulation of osmotic drug delivery systems\textsuperscript{94, 95}.

(i) Gel formation properties of Ispaghula husk\textsuperscript{96}

Gel forming property of ispaghula has been compared with methylcellulose, sodium-CMC, sodium alginate and starch found to be superior in spreadability, penetration and washability. Gels prepared by hot process are elastic and rigid, those prepared with cold process are soft, smooth and tacky which compare very favourably with other gel bases in their physical characteristics and stability and could be used as base for medicated jellies. It is also used as a gelling material in transdermal drug delivery systems\textsuperscript{97}.

(ii) Binding Properties Ispaghula husk\textsuperscript{98}

Mucilage of husk in hot water possesses better binding action as compared to starch mucilage. It is slightly inferior to methyl cellulose and acacia mucilage.
(iii) **Suspending properties**

The suspending property of husk is superior to sodium alginate and sodium carboxy methylcellulose. The HLB value of the soluble fraction of plantago ovata seed husk dispersion is 9.45.

(iv) **Disintegrating properties of ispaghula husk**

The powder of plantago ovata seed husk appears to be good disintegrating agent for compressed tablets in concentrations ranging from 1-2% of the total weight of the tableting material. It is superior to starch (10%) and methylcellulose (5%) as a disintegrant for some medicaments. Ispaghula husk and mucilage are also used as super disintegrants in the formulation of dispersible tablets.

(v) **Rheological properties of ispaghula**

At lower concentrations ispaghula husk and its mucilage form viscous dispersions in water. Higher concentrations lead to gelling of the dispersion. Pharmaceutical adjuvant influences the syneresis of psyllium seed gum gels.
1.5.10 REFERENCES:


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