Objectives of the study

Chapter — 3
3.1 Objectives

Main objectives of carrying out the study were to

- Develop and evaluate a HBS system in the form of single unit capsule for the modified release of celecoxib, metformin and amoxycillin using various low-density polymers.
- Assess the in vivo buoyancy of the optimized HBS systems using gamma scintigraphy.
- Assess the pharmacokinetic parameters of the optimized formulation and its comparison with a conventional formulation.
- Find out the location of the capsule after predetermined time intervals using gamma scintigraphic techniques.

3.2 Selection of the drugs and rationale of the study

For the selection of an ideal drug candidate to be formulated into a HBS system certain properties are desirable:

- Physicochemical properties
  - Aqueous solubility should be limited
  - Drug should be stable in gastro intestinal tract
  - PKs should be favorable.
- Biological properties
  - Either half-life should be low or high GI residence time should be required to enhance bioavailability.
  - Once a day formulation is desired.
  - Absorption site is specifically proximal small intestine.
With the aim to provide sustained, site-specific delivery and absorption enhancement, HBS systems of the selected drugs were designed. Metformin is an anti hyperglycemic agent, which improves glucose tolerance in type II diabetes. It has been reported that the absolute bioavailability of metformin when given orally is 50-60 %. Biological half-life of metformin is 1.5-1.6 hrs. The main site of its absorption is proximal small intestines and it has poor colonic absorption (Marathe et al., 2000). A HBS system is planned for metformin as such a system when administered would remain buoyant on the gastric fluids for a prolonged period of time and the drug would be available in the dissolved form at the main site of its absorption i.e., proximal small intestines. In this way it stands an advantage over conventional dosage form, which needs to be administered twice or thrice a day.

Celecoxib, a class II drug of BCS classification, is reported to be 22-40 % bioavailable with conventional capsule dosage form. Paulson et al., 2000 reported that if the gastric residence time of celecoxib can be prolonged its bioavailability could be enhanced. In the present study it was aimed to prolong the gastric residence time of celecoxib by designing a HBS in the form of single unit floating capsule, which would be retained in the stomach by the virtue of attaining a density of less than that of gastric fluids.

Amoxicillin is a broad-spectrum antibiotic, which is widely used as a combination drug in the drug regimen for the treatment of Helicobacter pylori. A HBS system designed for amoxicillin would increase the contact time of drug with GI mucosa where this bacterium is found in abundance. Plasma half-life of 1 hour and its acid stability makes it an even better candidate to be designed as a HBS system. Thus amoxicillin is one of the best candidates for local delivery in gastric mucosa.
3.3 Choice and selection of drug

3.3.1 Amoxicillin trihydrate: a drug profile (Florey, 1976)

1. Description

Name: Amoxicillin trihydrate  
Molecular formula: $C_{16}H_{18}N_3O_5$S.3$H_2$O  
Molecular structure:  

![Molecular structure of Amoxicillin trihydrate]

Chemical name: 6-[D(-)- $\alpha$- amino-$\beta$-hydroxyphenyl acetamido) penicillanic acid trihydrate  
Molecular weight: 419.96

2. Appearance, color, odour

Amoxicillin trihydrate is a white to off-white free flowing crystalline powder. It has a typical penicillin odour described as sulfurous type.

3. Physical Properties

Melting range: It browns at 90° C and degrades between 216-218° C.
Solubility: Its solubility in water is 4 mg/ml, in methanol it is 7.5 mg/ml and in ethanol it is 3.4 g/ml. It is practically insoluble in chloroform ether, hexane, and benzene and in fixed oils. It is soluble in dilute solutions of acids and alkali hydroxides.

pH: A 0.2 % w/v solution has a pH between 3.5-5.5.

4. Identification: (Indian Pharmacopoeia 1996)

The infrared absorption spectrum should be concordant with the reference spectrum of amoxycillin trihydrate.

5. Storage

It should be stored in airtight container at a temperature not exceeding 30° C.

6. Mechanism of action (Tripathi, 1999)

All β-lactam antibiotics act by interfering with the synthesis of bacterial cell wall. They inhibit the enzyme transpeptidase so that the cross-linking (which provides stability and rigidity of the cell wall) does not take place. When bacteria divide in the presence of a β-lactam antibiotic, cell wall deficient forms, which are capable of multiplying, result. Since the interior of the bacterium is hyper osmotic, these cell wall deficient forms swell and burst, thus leading to bacterial lysis. Lytic effects of these antibiotics may also be due to depression of some bacterial anti-lysins, which normally function during cell division. The peptidoglycan cell wall is unique of bacteria. Higher animals synthesize no such substance. This is why penicillins are practically non toxic to man.

7. Pharmacology

Amoxycillin is an orally active member of the penicillin family. The penicillin nucleus consists of a thiazolidine ring connected to a lactam ring. In case of amoxycillin, the benzyl ring in the side chain extends the range of anti microbial activity into the Gram-negative bacteria.
8. Spectrum of activity

Amoxycillin is a bactericidal for both Gram positive and Gram negative organisms since it is destroyed by β-lactamase. The drug is ineffective in most *staphylococcus* infections. Most strains of *meningococcus*, *pneumococcus* and *gonococcus* are sensitive to amoxycillin. Amoxycillin was initially very effective against *haemophilus influenzae* but 6-12% of organisms isolated are now resistant to amoxycillin particularly in children. Similarly an increasing percentage of *salmonella sp*, *E. coli*, *Proteus mirabilis* and *shigella* species are not sensitive to amoxycillin. Amoxycillin is not usually effective against *Klebsiella*, *Pseudomonas* or *Actinobacter*. *Streptococcus virdians* and *listeria monocytogenes* remain sensitive to low concentrations of amoxycillin.

9. Method of analysis (Florey, 1976)

a) A spectrophotometric method for analysis of amoxycillin involves formation of amoxycillin penicillinic acid in presence of acid and cuprous ions and measurement of its UV absorption 320 nm.

b) A spectrofluorometric method is based on the reaction with formaldehyde and measurement at 430 nm after excitation at 366 nm.

c) A fluorescamine assay has been proposed for ampicillin which also determines 14 ng/ml at pH 6.5 to 7.5 and is also applicable to amoxycillin

10. Pharmacokinetics

Amoxycillin is more acid stable than benzyl penicillin, so that more of the total oral dose reaches the small intestine. It has an oral absorption of 90% and attains a peak serum level 10 mg/litre with a 500 mg oral dose. Peak levels are attained 1 to 2 hours after dosing. Food has no significant influence on the absorption of amoxycillin. Plasma half-life of amoxycillin is around 1 hour.
Amoxycillin is rapidly distributed throughout the body, and like ampicillin it penetrates the uninflammed meninges poorly. The volume of distribution is 0.31 kg /body weight. Plasma protein binding is 20%.

Elimination of amoxycillin occurs via the kidney by glomerular filtration and tubular secretion. A small amount (10-20%) of the drug is metabolized by hydrolysis of β-lactam ring in penicilloic acid, which is excreted in the urine.

11. Therapeutic uses

a) Amoxycillin trihydrate is used in the treatment of following conditions:
   b) Urinary tract infections
   c) Otitis media
   d) Respiratory tract infection
   e) Enteric infections
   f) Bacterial meningitis
   g) Gram negative septicemia
   h) Gonorrhoea
   i) Infective endocarditis
   j) Periodontal diseases

12. Contraindications

a) Penicillin hypersensitivity
   b) Glandular fever and lymphatic lymphoma
   c) Bacterial resistance

13. Adverse reactions

Potentially life threatening effects- anaphylactic shock may occur in very rare occasions
Acute overdosage: Overdosage will produce very high urinary concentrations, more so after parenteral administration. Problems are unlikely if adequate fluid intake and urinary output are maintained, however, crystalluria is a possibility.

Severe/irreversible: amoxycillin causes hypersensitivity reactions similar to those induced by benzylpenicillin and ampicillin including rashes and fever. Convulsions may possibly occur if large i.v. doses are given.

14. High-risk groups

Neonates

Children

Pregnant women

The elderly

Concurrent disease such as renal disease

Drug interactions

Potentially hazardous interaction- none is known

Other significant interactions - the simultaneous use of amoxycillin and an oral contraceptive might be expected to cause breakthrough bleeding or pregnancy in rare occasions, because of reduced absorption due to diarrhoea.

15. Dosage forms

Amoxycillin is available in oral and parenteral forms as various generic and licensed formulations

a) Capsules containing 250 and 500 mg, amoxycillin as trihydrate

b) Tablets containing 500 mg dispersible amoxycillin trihydrate

c) Syrup and syrup forte containing, 125 and 250 mg amoxycillin trihydrate per 5 ml after reconstitution with water.

d) Pediatrics suspension containing 125 mg amoxycillin trihydrate per 1.25 ml after reconstitution.
e) Injection as 250 mg, 500 mg and 1 g vials of amoxycillin sodium to be reconstituted with water for injection.

3.3.2 Metformin hydrochloride: a drug profile

1. Description

   Name: Metformin hydrochloride
   Molecular formula: \( \text{C}_4\text{H}_{11}\text{N}_5\cdot\text{HCl} \)
   Molecular structure:

   \[
   \begin{align*}
   &\text{H}_3\text{C} \\
   &\text{N} - \text{C} - \text{NH} - \text{C} - \text{NH}_2 \cdot \text{HCl} \\
   &\text{H}_3\text{C} \quad \text{NH} \quad \text{NH}
   \end{align*}
   \]

   Chemical name: 1,1-dimethylbiguanide hydrochloride
   Molecular weight: 165.62

2. Appearance, color, odour

   Metformin hydrochloride is a white crystalline powder. It is hygroscopic in nature.

3. Physical Properties

   Melting range: Melts between 222° C and 226° C
   Solubility: Freely soluble in water; slightly soluble in ethanol (95%); practically insoluble in acetone, in chloroform, in dichloromethane and in ether.
   pH: 6.68 (1% aqueous solution)
4. Identification: (British Pharmacopoeia 1999)

The infrared absorption spectrum should be concordant with the reference spectrum of metformin hydrochloride.

5. Storage

It should be stored in well-closed container.

6. Mechanism of Action

The mechanism of action involves binding of a apolar biguanide hydrocarbon side chain to membrane phosphoipids, evoking a change in electrostatic surface potential. Metformin potentiates insulin action mainly by post receptor mechanism. In this way metformin ameliorates insulin resistance and insulin independent effects on muscular glucose uptake. Metformin also improves the blood lipoprotein profile.

7. Pharmacology

Metformin reduces elevated blood glucose concentrations in patients with diabetes, but it does not increase insulin secretion. Augmentation of muscular glucose uptake and utilization, reduction of increased hepatic glucose production through an antigluconeogenic action leads to blood glucose lowering effect.

8. Pharmacokinetics

Metformin is incompletely absorbed, fecal recovery being about 30% of an oral dose. The absorption is slower than elimination. Oral bioavailability of usual doses is 50-60%. Although the absorption occurs over a whole range of intestines, the major part of drug appears to be absorbed from a confined area in upper part of intestine.

The distribution of metformin is rapid. Metformin is not bound to plasma proteins. The plasma elimination half-life ranges from 1.5-4.5 hours. It is excreted unmetabolized in the urine.

9. Therapeutic uses

Type II diabetes (non insulin dependent diabetes NIDDM)
Objectives of the study

Type 1 diabetes (insulin dependent diabetes IDDM as an adjuvant therapy in combination with insulin)

Obesity and insulin resistance

Hyperlipoproteinemia

10. Contraindications

Impaired renal function

Acute complications (severe infection, major operation, trauma)

Before X-ray examination with iodinated contrast media

Liver damage

Alcoholism

Deficiencies of vitamin B₁₂, folic acid and iron

Ketosis-prone diabetes

Severe cardiovascular disease

General ill health

Diabetes with significant late complications (nephropathy, retinopathy)

11. Adverse reactions

Lactic acidosis

Vitamin B₁₂ and folate malabsorption

Hypoglycemia

12. High-risk groups

Neonates

Children

Pregnant women

The elderly concurrent disease
13. Method of analysis

a) Metformin concentrations were determined by an HPLC method applying a 100 RP-18 column. The detection was at 234 nm, and phenformin was applied as the internal standard. The mobile phase consisted of 0.01M Na₂HPO₄ solution (pH 6.5), methanol, and acetonitrile (20:3:6, v/v). The quantitation limit was 100 ng/ml. Intra assay and inter assay coefficients of variation were 5 and 9%, respectively (Stepensky et al., 2002).

b) Weigh and powder 20 tablets. Shake a quantity of the powder containing 0.1 g of Metformin Hydrochloride with 70 ml of water for 15 minutes, dilute to 100 ml with water and filter, discarding the first 20 ml. Dilute 10 ml of the filtrate to 100 ml with water and dilute 10 ml of the resulting solution to 100 ml with water. Measure the absorbance of the resulting solution at the maximum at 232 nm, Appendix II B. Calculate the content of the C₄H₁₁N₅.HCl taking 798 as the value of A (1%, 1 cm) at the maximum at 232 nm (British Pharmacopoeia 1999).

14. Dosage forms

Metformin is available in market as the following preparation.

a) As immediate release tablets 500 and 850 mg.

b) Extended release tablets 500 and 1000 mg.
3.3.3 Celecoxib: a drug profile

1. Description

Name: Celecoxib
Molecular formula: C\textsubscript{17}H\textsubscript{14}F\textsubscript{3}N\textsubscript{3}O\textsubscript{2}S

Chemical name: (4-(5-(4- methylphenyl) -3-(trifluoromethyl) -1H-pyrazol-1-yl) benzenesulfonamide)

Molecular weight: 381.38
CAS No.: 169590-42-5

2. Appearance, color, odour

Celecoxib is a white powder, diaryl substituted pyrazole. The crystal shape of drug is rhomboid.


Melting range: 157-9°C
Solubility: It is very poorly soluble in water but soluble in organic solvents like acetone and acetonitrile.
pH: 6.68 (1% aqueous solution)

4. Storage

It should be stored in well-closed container.

5. Mechanism of Action

Celecoxib is a cyclooxygenase (COX) inhibitor that exhibits relative in vitro and ex vivo selectivity for COX-2 over COX-1 (Srinivasu et al., 2002).

All Non steroidal anti-inflammatory drugs (NSAIDs) act by inhibiting the catalytic activity of cyclooxygenase (COX) and thereby prostaglandins and thromboxane production (Vane, 1971). COX exists as 2 isoenzymes: constitutive COX-1 and inducible COX-2 (Fu et al., 1990). Products derived from COX-1 activity are involved in physiological functions such as GI mucosal protection, platelet function and regulation of renal haemodynamics and electrolyte balance. In contrast COX-2 catalyses the production of prostaglandins (PG) that mediate pain and inflammatory processes. Conventional NSAIDS inhibit both isoenzymes to varying degrees. At therapeutic concentrations these agents exert their analgesic and anti inflammatory properties through inhibition of COX-2, whereas adverse events result from COX-1 inhibition (Crofford, 1997).

Celecoxib, is the first of its class, the COX-2 specific inhibitors, to be approved for its role in the treatment of osteoarthritis and rheumatoid arthritis.

6. Pharmacodynamic Properties

Celecoxib is a cyclooxygenase (COX) inhibitor that exhibits clinically meaningful relative selectivity for COX-2 over COX-1 (Penning et al., 1997).

a) Anti-inflammatory and Analgesic Effects.

Celecoxib exhibited similar anti-inflammatory and analgesic effects to comparator NSAIDs (indomethacin, naproxen, piroxicam) in rodent models. Repeated (twice daily
for 10 days) administration of celecoxib reduced the local oedematous response to footpad injection of *mycobacterium butyricum* in the adjuvant induced arthritis model of chronic inflammation. In a model of carrageenan-induced acute inflammation and pain, prophylactic administration of single oral doses of celecoxib reduced paw volume and withdrawal latency to thermal stimuli. Oral celecoxib 30 mg/kg was also effective in reducing the carrageenan-induced elevation in CSFPGE2 levels to baseline when administered either prophylactically or therapeutically (2 hours before and 3 hours after injection with carrageenan, respectively).

b) Ulcerogenic potential

Celecoxib produced less GI damage than comparator NSAIDs in a single dose study in rats with gastric damage and after repeated administration in dogs and volunteers with endoscopically normal GI mucosa.

In a fasted rat model, oral celecoxib at single doses of up to 200 mg/kg showed no evidence of acute gastric damage. Additionally, gastric glandular mucosal damage was not reported after repeated dosage of up to 600 mg/kg/day over 10 days. In dogs, no GI injury was reported after 13 weeks administration of celecoxib at supra therapeutic doses (plasma concentrations 16-fold higher than at therapeutic concentrations). In contrast, evidence of GI injury was present after 2 weeks treatment with nabumetone at therapeutic and meloxicam at 3 times therapeutic concentrations.

c) Platelet Function

Conventional NSAIDs interfere with haemostasis by inhibiting COX-1 mediated platelet activation and their use has been associated with a low incidence of bleeding events. Although NSAID associated GI bleeding results primarily from mucosal injury, systemic coagulopathy may be contributory. Spontaneous bleeding outside the GI
tract or during surgical procedures may occur with use of aspirin and other NSAIDs. (Schefer, 1999)

Single and multiple administration of celecoxib at supratherapeutic dosages up to 1200 mg/day (600 mg twice daily) had no significant effect on collagen and arachidionate induced platelet aggregation or bleeding time in humans. In contrast, ibuprofen 800 mg (single dose), aspirin 650 mg (5 days twice daily administration) and naproxen 500 mg (7 days twice daily administration) produced significant inhibition of platelet aggregation. Moreover, naproxen increased bleeding time by seconds at all time points after final dosage (Leese et al., 2000).

d) Renal Function

In states of compromised renal function (e.g., cardiorenal disease, dehydration, ageing) in which COX activity provides a greater contribution (than in healthy individuals) to maintain renal haemodynamic function. Use of NSAIDs may blunt PG mediated compensatory mechanisms. Accordingly fluid and electrolyte disturbances, acute renal dysfunction, nephrotic syndrome and renal papillary necrosis may occur during NSAID use. (Whelton, 1999)

7. Pharmacokinetic Properties

The pharmacokinetics of celecoxib has been investigated in healthy volunteers. A mean peak plasma celecoxib concentration of 705 g/L (1.85 mol/L) was reached 2.8 hours after a single 200 mg dose in volunteers under fasting conditions $C_{max}$ and the area under the plasma concentration time curve increased in a dose proportional manner over the therapeutic dose range of 100 to 200 mg. At higher doses, less than proportional increases were observed. Clinically significant alterations in pharmacokinetic properties were not observed when celecoxib was administered with food.
Celecoxib is 97.4% bound to plasma proteins (Susan et al., 2001) and does not show preferential distribution between erythrocytes and plasma. The apparent volume of distribution at steady state of approximately 400 L suggests extensive tissue distribution, although definitive distribution studies are not available.

Celecoxib undergoes extensive hepatic metabolism, predominantly via cytochrome P450 (CYP) 2C9 (Karim et al., 1997). Three metabolites, all lacking COX-1 and COX-2 activity, have been identified in human plasma. The methyl group of celecoxib is oxidized to the hydroxymethyl metabolite followed by further oxidation of the hydroxyl metabolite to the carboxylic acid. After a single oral dose of celecoxib 300 mg to volunteers 27.1% of the administered drug was recovered in urine and 57.6% in faeces. Unchanged celecoxib accounted for 2.6% of faecal recovery. In volunteers the mean effective half-life of celecoxib was 11.2 hours after a single 200 mg dose. The low solubility of celecoxib appears to prolong absorption. The apparent plasma clearance was 27.7 L/h. The absolute bioavailability of celecoxib was higher when given as a solution (64%-88%) compared to capsules (22%-40%) (Susan et al., 2001).

8. Dosage and Administration

Celecoxib is indicated for relief of the signs of rheumatoid arthritis in adults. For patients with osteoarthritis, the recommended oral dosage is 200 mg/day, in 1 or 2 doses. The recommended oral dosage in adult patients with rheumatoid arthritis is 100 to 200 mg twice daily. Celecoxib can be taken without regard to mealtime and the lowest dosage should be sought for each patient. Celecoxib dosage of 100 to 400 mg has been used in clinical trials of post-operative pain management.

The recommended dosage of celecoxib should be reduced by approximately 50% in patients with moderate hepatic impairment. Although dosage adjustments are not

Objectives of the study
generally necessary in the elderly, therapy should be initiated at the lowest dosage for patients weighing less than 50%.

9. Contraindications and warnings

Celecoxib is contraindicated in patients with a history of asthma, urticaria or allergic-type reactions after administration of aspirin or other NSAIDs, or in those who have demonstrated allergic-type reactions to sulfonamides. Use of celecoxib should be avoided during the third trimester of pregnancy as it may cause premature closing of the ductus arteriosus.

As a result of reports of oedema in some patients taking celecoxib, use of this drug should proceed with caution in patients with fluid retention, hypertension or heart failure. Celecoxib should also be used with caution in patients with pre-existing asthma or advanced kidney disease and when initiating treatment in patients with considerable dehydration.

10. Drug Interactions

Anticoagulant activity should be monitored after initiating or changing celecoxib therapy in patients receiving warfarin or similar agents, as these patients are at increased risk of bleeding complications. Although a 15 day study indicated that conadministration of celecoxib for one week did not alter the pharmacokinetics of anticoagulant effect of warfarin, rare increase in prothrombin time in patients receiving concomitant celecoxib and warfarin have been identified in postmarketing reports (Karim et al., 1997). Patients on lithium treatment should be closely monitored when celecoxib is introduced or withdrawn. Celecoxib should be introduced at the lowest recommended dose in patients receiving fluconazole, and coadministration with other inhibitors of CYP2C9 should proceed with caution as these drugs have the potential to inhibit the metabolism of celecoxib. As celecoxib is an inhibitor of
CYP2C6, there is a potential for interaction with drug metabolism by this enzyme. Diminished antihypertensive effects of ACE inhibitors and reduced natriuretic effects of frusemide (furosemide) and thiazides have been reported during NSAID treatments and these interactions should be considered in patients taking concomitant celecoxib.

11. Methods of Analysis

a) Spectrophotometric method

Saha et al., 2002 reported a UV method for preparation of calibration curve and estimation of celecoxib from commercial capsule formulation.

A stock solution of celecoxib was prepared by dissolving 10 mg of drug in 100 ml of 50% v/v acetonitrile sodium phosphate buffer (pH 5.6) to get a final concentration of 100 mg/ml. The $\lambda_{\text{max}}$ of celecoxib was determined by scanning a suitable dilution of the stock. The $\lambda_{\text{max}}$ was found to be 251 nm.

Commercial capsules were taken randomly. 20 capsules were weighed and contents were thoroughly mixed and an accurately weighed aliquot amount (equivalent to 5 mg of celecoxib) was transferred to a series of 25 ml volumetric flasks (five in each case) and volume was made using 50% v/v acetonitrile sodium phosphate buffer (pH 5.6). From the absorbance values the drug content per capsule (on an average weight basis) was calculated.

b) HPLC Method

Saha et al., 2002 have also reported a HPLC method for celecoxib.

A stock solution (100 mg/ml) of pure drug was prepared by dissolving 5 mg celecoxib in 50 ml of 65:35 acetonitrile: water mixture 1 ml of this solution was transferred to 10 ml volumetric flask and the volume was made to obtain a solution of 10 mg/ml.
this solution, concentration of 100, 200, 400, 600, 800 and 1000 ng/ml were made in series in 10 ml volumetric flasks.

Chromatographic column used was a reverse phase 4.6 X 250 mm, C8 HPLC column with 5 mm particles. Flow rate of mobile phase was 1.25 ml/min. Injection volume was 20 μl. The eluate was analyzed at a wavelength of 230 nm.

Commercial capsule formulations were taken for estimation of celecoxib. From the area under the curve the drug content per capsule was calculated.

c) Chromatographic method

A micellar electrokinetic chromatographic method was developed, for the quantification of celecoxib, by Srinivasu et al., 2002.

Capillary electrophoresis was performed using an Agilent CE system (Agilent Technologies, Waldbronn Germany) with built in diode array detector (able to deliver upto 30 KV). An extended light path capillary with a 50 mm inner diameter used was of 48.5 cm length. Detection wavelength was set at 252 nm. The background buffer consisted of 25 mm aqueous borate buffer at pH 9.3.

Assay of celecoxib in formulation sample was carried out. The contents of four capsules were finely grounded in a mortar and pestle. The ground material equivalent to 40 mg of celecoxib was weighed and transferred to a volumetric flask and extracted into acetonitrile by vortex mixing followed by ultra sonication. This solution was used as a stock solution to prepare test solutions.

12. Dosage forms

Celecoxib is available as oral capsules as 100, 200 and 400 mg.
3.4 Selection of Polymers

The selection of polymers was done on the basis of following characteristics that are expected of an ideal polymer for gastroretentive system:

a) The polymer and its degradation products should be nontoxic and nonabsorbable from the gastrointestinal tract.

b) It should be non-irritant to the mucous membrane.

c) It should have a specific density of less than 1 gm/ml so that the polymer may float on the surface of the gastric media.

d) It should not be soluble at the pH of the gastric media (pH 1.2-3)

e) It should allow easy incorporation of the drug and offer no hindrance to its release.

f) The polymer should not decompose on storage or during the shelf life of the dosage form.

g) The cost of the polymer should not be high so that the prepared dosage form remains competitive.

The following polymers were selected for the present study on the basis of their floating performance, chemical functionality and molecular weight:

1. Hydroxypropyl methyl cellulose-K4 M

2. Polyethylene oxide (WSR 60K, 301, 303)

3. Eudragit-RL 100
Objectives of the study

1. Hydroxypropyl methyl cellulose (HPMC) (Harwood, 1994)
   It is mixed alkyl hydroxyalkyl cellulose ether and may be regarded as the propylene glycol ether of methyl cellulose.

Synonyms: Methocel, Metolose, Pharmacoat, E464, HPMC

Empirical Formula: \( \text{C}_6\text{H}_{15}\text{O}_6\cdot(\text{C}_6\text{H}_{18}\text{O}_6)_{8}\cdot\text{C}_6\text{H}_{10}\text{O}_5 \)

Structure:

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether.

Grades: Methocel E5, E15, E50, E4M, F50, K100, K4M, K15M, K100M

Description: An odorless, tasteless, white or creamy-white fibrous or granular powder.

Molecular Weight: Approx. 86,000

Density (bulk): 0.25-0.70 g/cm³

Viscosity: HPMC E-15 Cps (2 % aqueous solution)

HPMC E-4M - 4000 Cps (2 % aqueous solution)

HPMC K4M - 4000 Cps (2 % aqueous solution)

pH: 6.0 – 8.0 (1 % aqueous solution)

Solubility: Soluble in cold water, forming a viscous colloidal solution, insoluble in alcohol, ether and chloroform, but soluble in mixtures of methyl alcohol and
methylene chloride. Certain grades are soluble in aqueous acetone, mixtures of methylene chloride and isopropyl alcohol and other organic solvents.

**Stability:** Very stable in dry conditions. Solutions are stable at pH 3.0 – 11.0. Aqueous solutions are liable to be affected by micro-organisms.

**Incompatibility:** Extreme pH conditions; oxidizing materials.

**Safety:** Human and animal feeding studies have shown HPMC to be safe.

**Applications:** It is a suspending, viscosity increasing and film forming agent. It is also used as a tablet binder and as an adhesive ointment ingredient. The E-grades are generally suitable as film formers while the K-grades are used as thickeners.

2. **Polyethylene oxide (PEO)** (Schmitt, 1994)

**Appearance:** White Powder

**Molecular Weight:** 4,000,000-6,000,000

**Structural Formula:** \( [-\text{CH}_2\text{CH}_2\text{O-}]_n \)

**Description:** PEO is a water-soluble very mild non-ionic polymer compatible with most excipients.

**Viscosity:** (5% w/w solution) @ 25°C

- 50-250 cps for m. wt. 210,000
- 200-2500 cps for m. wt. 400,000
- 2500-5500 cps for m. wt. 1,00,000

**Viscosity** (0.5% w/w solution) @ 25°C

- 250-430 cps for m. wt. 4,400,000
- 600-800 cps for m. wt. 7,200,000

**Usage:** Polyethylene oxide resins are high molecular weight homopolymers produced by the heterogeneous catalytic polymerisation of ethylene oxide.
Polyethylene oxide can be used as long fibre dispersing agent in the manufacture of paper, an adhesive, friction reduction agent, flocculating agent, thickening agent, lubricant and oil field producing. It has excellent film forming properties.

3. Polymethacrylates (Eudragit-S 100, Eudragit-RL 100) (Chang and Shukla, 1994)

Synonym: Methacrylic acid, Eudragit

Chemical Name: Copolymers synthesized from dimethylaminoethyl methacrylate and other neutral methacrylic esters.

Molecular Weight: ≥ 100,000

Structure:

\[
\begin{align*}
\text{Type L and S:} & \quad R_1, R_3 = \text{-CH}_3 \\
& \quad R_2 = \text{-H} \\
& \quad R_4 = \text{CH}_3 \\
\text{Type RL and RS:} & \quad R_1 = \text{-H, -CH}_3 \\
& \quad R_2 = \text{-CH}_3, \text{-C}_2\text{H}_5 \\
& \quad R_3 = \text{-CH}_3 \\
& \quad R_4 = \text{-CH}_2\text{CH}_2\text{N (CH}_3\text{)}^+\text{Cl}^- \\
\end{align*}
\]

Description: Polymethacrylates are film coatings and matrix structures based on polymeric methacrylates. They are synthetic cationic and anionic polymers of...
Objectives of the study

dimethylaminoethylmethacrylates, methacrylic acid and methacrylic acid esters in varying ratios.

Type L (easily soluble in intestinal fluid) is 50 % methacrylic acid and Type S (barely soluble in intestinal fluid) is 30 % methacrylic acid; both are anionic polymers of methacrylic acid and methacrylic acid ester in different ratios.

Type RS (5 % trimethylammonium methacrylate chloride) and Type RL (10 % trimethylammonium methacrylate chloride) are copolymers of acrylic and methacrylic acid esters containing some quaternary ammonium groups.

Type L soluble in polar organic solvents, such as alcohols (ethanol, isopropanol), acetone and mixtures of these with esters, chloroform, etc. Insoluble in water, petroleum, ether, etc. Does not swell at pH<6.5; soluble at pH>7.

Types RL and RS soluble in isopropanol and ethanol in combination with acetone or methylene chloride; also in methanol, chloroform, trichlorethylene, ethyl acetate and glycol monomethyl ether. Barely soluble in pure isopropanol or carbon tetrachloride. Insoluble in petroleum ether or light petroleum. Swells in aqueous media: the amount of water absorbed depends on the pH of the solution and the type (RL swells more than RS due to its higher concentration of hydrophilic quaternary groups.

Stability: Dry powder forms appear to be stable at room temperature.

Application: Eudragit L and S are employed as film coating agents resistant to gastric fluid with different solubilities (L<pH 6, S>pH 7). Eudragit RL and RS form water insoluble film coats for delayed-release products. Permeability is dependent upon pH. Eudragit RL film coats are more permeable than those of Eudragit RS.
3. Plan of Work

In an attempt to develop single unit floating/ hydrodynamically balanced capsules of metformin, celecoxib and amoxycillin, the following plan of work was envisaged.

1. Characterization of Drugs
   a) Physical properties
   b) Identification tests
      i. Chemical tests
      ii. UV spectral analysis
      iii. FT-IR analysis
      iv. HPLC analysis

2. Analytical methodologies for selected drugs
   a) Determination of absorption spectra.
   b) Preparation of calibration curves.
   c) To study the interference of polymers with the analytical methods.

3. Selection of polymers for preparation of floatable capsules on the basis of floatation studies of various drug polymer combinations

4. Formulation of floatable capsules by using different polymer ratios.

5. Evaluation of hydrodynamically balanced capsules by \emph{in vitro} drug release studies.

6. Optimization of formulation on the basis of floatation / release rate studies.

7. Radiolabeling of drugs to determine the \emph{in vivo} buoyancy by gamma scintigraphy.

8. Interaction studies of the optimized capsules by
   a) FT-IR studies
   b) UV studies

9. Evaluation of optimized capsules for
   a) General appearance
Objectives of the study

b) Weight variation
c) Content uniformity
d) Stability studies

10. *In vivo* buoyancy studies in rabbits by gamma scintigraphy.
11. Determination of pharmacokinetic parameters of the optimized formulation in rabbits using gamma scintigraphic studies.